Fast-acting antidepressant activity of ketamine: highlights on brain serotonin, glutamate, and GABA neurotransmission in preclinical studies

Thu Ha Pham, Alain M. Gardier *

CESP/UMR-S 1178, Univ. Paris-Sud, Fac. Pharmacie, Inserm, Université Paris-Saclay, Chatenay-Malabry, 92290, France

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ABSTRACT

Ketamine, a non-competitive antagonist of N-methyl-D-aspartate (NMDA) receptor, displays a fast antidepressant activity in treatment-resistant depression and in rodent models of anxiety/depression. A large body of evidence concerning the cellular and molecular mechanisms underlying its fast antidepressant-like activity comes from animal studies. Although structural remodeling of frontocortical/hippocampal neurons has been proposed as critical, the role of excitatory/inhibitory neurotransmitters in this behavioral effect is unclear. Neurochemical and behavioral changes are maintained 24h after ketamine administration, well beyond its plasma elimination half-life. Thus, ketamine is believed to initiate a cascade of cellular mechanisms supporting its fast antidepressant-like activity. To date, the underlying mechanism involves glutamate release, then downstream activation of AMPA receptors, which trigger mammalian target of rapamycin (mTOR)-dependent structural plasticity via brain-derived neurotrophic factor (BDNF) and protein neo-synthesis in the medial prefrontal cortex (mPFC), a brain region strongly involved in ketamine therapeutic effects. However, these mPFC effects are not restricted to glutamatergic pyramidal cells, but extend to other neurotransmitters (GABA, serotonin), glial cells, and brain circuits (mPFC/dorsal raphe nucleus-DRN). It could be also mediated by one or several ketamine metabolites (e.g., (2R,6R)-HNK). The present review focuses on evidence for mPFC neurotransmission abnormalities in major depressive disorder (MDD) and their potential impact on neural circuits (mPFC/DRN). We will integrate these considerations with results from recent preclinical studies showing that ketamine, at antidepressant-relevant doses, induces neuronal adaptations that involve the glutamate-excitatory/GABA-inhibitory balance. Our analyses will help direct future studies to further elucidate the mechanism of action of fast-acting antidepressant drugs, and to inform development of novel, more efficacious therapeutics.

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Contents

1. Introduction

Major depressive disorder (MDD) is a serious, debilitating, life-shortening illness and a leading cause of disability worldwide. According to the World Health Organization, about 350 million people are affected by depression, with a higher risk for females than males (WHO, 2012). MDD is also predicted to be the second leading cause of disease burden in 2020 (Murray & Lopez, 1996).

The current most widely prescribed drugs for MDD treatment, i.e., selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs), display serious limitations such as the delay between drug administration and antidepressant efficacy. Divergent roles of serotonin (5-HT) autoreceptors and heteroreceptors in modulating responses to antidepressant drugs explain, at least in part, this long delay of action (Nautiyal & Hen, 2017). In addition, an up to 30% of resistance and non-response rate has made these current treatments less reliable (Mrazek, Hornberger, Altar, & Degtiar, 2014). More precisely, the response rates to SSRI antidepressant drugs are about one-third after the initial prescription and up to two-thirds after multiple drug trials.

Ketamine, a non-competitive antagonist of the N-methyl-D-aspartate subtype of excitatory amino acid receptor (NMDA-R), is a dissociative anesthetic (Krystal et al., 1994). Clinical studies have demonstrated that it displays antidepressant efficacy in treatment-resistant depression (TRD) (Berman et al., 2000; Zarate Jr. et al., 2006). Different methods have been used for staging TRD (Ruhe, van Rooijen, Spijker, Peeters, & Schene, 2012). Each staging method has its own criteria for treatment duration, classes and number of antidepressant trials, as well as severity of depression. Although there is a lack of consensus regarding these criteria of TRD, failure to respond to more than two classes of antidepressant drugs with adequate dosage and for an adequate duration is typically defined as TRD (McIntyre et al., 2014). More than fifty percent of depressed patients meet this definition (Thomas et al., 2013), among them, those taking monoaminergic antidepressant drugs of the serotonergic/noradrenergic class. However, low response rates to the first antidepressant prescription suggest that there are other strategies/mechanisms of action that may help patients with TRD (Duman & Aghajanian, 2012; Kim & Na, 2016). Ketamine could be one of them.

Twelve randomized clinical trials confirmed that ketamine is the only NMDA-R antagonist to date consistently demonstrating antidepressant efficacy in TRD. Its antidepressant effects following an intravenous infusion are both rapid and robust, even though it has a short-lived action. In most cases, most clinical evidence demonstrates significant effects up to one week with subsequent decreases in response at later time points (see meta-analysis reviews: (Caddy, Giaroli, White, Shergill, & Tracy, 2014; Fond et al., 2014; Newport, et al., 2015; Romeo, Choucha, Fossati, & Rotge, 2015; Xu, Hackett, et al., 2016).

Although downstream neuronal adaptations might be involved in its antidepressant activity (Browne & Lucki, 2013; Sanacora, Zarate, Krystal, & Manji, 2008), the exact mechanisms underlying ketamine's effects remain incompletely resolved. Analyzing in detail brain regions and circuitry involved in its mechanism of action is crucial. It has been postulated that ketamine exerts its therapeutic effect with limited direct interactions with 5-HT systems. Our recent studies performed in BALB/cJ mice suggested evidence of activation of 5-HT neurotransmission in the medial prefrontal cortex (mPFC) (Pham et al., 2017; Pham et al., 2018).

The present review will focus on preclinical data regarding cellular and molecular mechanisms of ketamine underlying its antidepressant-like activity rather than clinical data on ketamine's benefits on TRD.

Indeed, a lot of clinical reviews have already been published, though many of them have used a small number of patients with TRD (see meta-analyses: (Caddy et al., 2015; Kokkinou, Ashok, & Howes, 2018; Papadimitropoulou, Vossen, Karabis, Donatti, & Kubitz, 2017)). In addition, some clinical and biological predictors of ketamine's response are often identical to other therapeutics used in MDD; thus, it is critical to identify more specific clinical biomarkers of this response (Romeo, Choucha, Fossati, & Rotge, 2017).

Preclinical studies have begun to elucidate a working mechanism underlying the rapid antidepressant-like activity of ketamine in animal models/tests of anxiety/depression. Specifically, an initial glutamate burst and activity-dependent synapse formation in the mPFC has been shown (Duman & Aghajanian, 2012; Duman, Aghajanian, Sanacora, & Krystal, 2016; Li et al., 2010). Additionally, the involvement of the balance between excitatory (glutamate, 5-HT) and inhibitory (γ-aminobutyric acid - GABA) neurotransmission within the glutamate mPFC/5-HT dorsal raphe nucleus (DRN) circuitry in rodent studies will be addressed here. Since ketamine is comprised of a mixture of two optical isomers: (S)-ketamine and (R)-ketamine, several active metabolites such as (2R,6R)-hydroxynorketamine (HNK) may also potentially make an important contribution to its antidepressant-like activity (Can et al., 2016). Beyond NMDA-R activation, a possible direct activation of α-amino-3-hyroxy-5-methyl-4-isoxazolepropionic acid receptor subtype (AMPA-R) by (2R,6R)-HNK, the main brain active metabolite (Zanos et al., 2016), is also discussed. Lastly, we also discuss the role of several factors, including species, route and dose of administration, and timing of measures (30 min, 24 h or 7 days prior to testing), which may explain some of the inconsistencies described in the literature.

2. Pharmacodynamics and pharmacokinetics of ketamine

Ketamine is described as a powerful NMDA-R antagonist: in vitro, EC50 = 760 nM, in vivo, ED50 = 4.4 mg/kg in rodents' cortex or hippocampus (Lord et al., 2013; F. Murray et al., 2000). Under physiological conditions and in the presence of extracellular $Mg2_+$, the NMDA channel is closed, due to a decreased permeability to $Ca2_+$ and an inhibition of currents mediated by NMDA-R. This process should theoretically inhibit the ability of ketamine to bind to its phencyclidine-like site (Fig. 1). However, an electrophysiological in vitro study performed in cultured hippocampal neurons has shown that ketamine can still block NMDA-R and reduce post-synaptic currents under physiological conditions (i.e., in the presence of Mg^{2+}) (Gideons, Kavalali, & Monteggia, 2014), which suggests that ketamine readily exceeds the physiologic capacity of the NMDA-R's Mg^{2+}-dependent voltage gating to impede ion flow through the receptor channel.

Ketamine is a racemic mixture containing equal parts of (R)-ketamine and (S)-ketamine. Compared to (R)-ketamine, (S)-ketamine has about four-fold higher analgesic and anesthetic potency, in agreement with its four times higher affinity to NMDA-R (Domino, 2010). (S)-ketamine is considered having twice the therapeutic index of racemic ketamine, which means that adverse effects may be reduced when only half of the usual racemic dose is administered (Muller, Pentyala, Dilger, & Pentyala, 2016).

Ketamine has a short elimination half-life ($t_{1/2}$ = 30 min in mice; (Maxwell et al., 2006)) and is rapidly transformed into various metabolites such as norketamine and HNKs immediately after it enters the body circulation (Can et al., 2016). In our recent study (Pham et al., 2018), we reported that, at 30min following i.p. administration, the plasma concentration of the major brain metabolite, (2R,6R)-HNK is already five
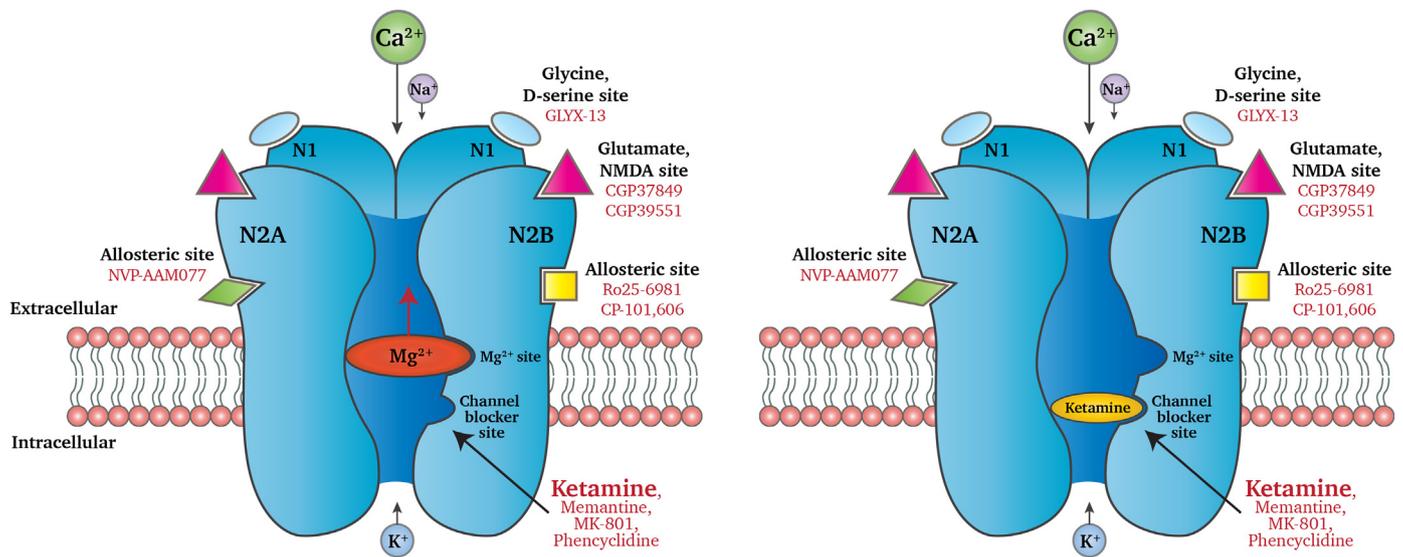
Fig. 1. NMDA receptor channel as target of rapid antidepressant drugs New antidepressant drugs targeting NMDA receptors (NMDA-Rs) have shown promising results in both clinical trials and preclinical studies. Identification of their specific binding sites could help explaining the mechanism of their neurochemical and behavioral effects. NMDA-R is tetrameric ionotropic glutamate receptor, which is composed of four subunits: two GluN1 and two GluN2 (GluN2A and GluN2B). NMDA-R has high permeability for Ca^{2+} ions. A) Under physiological conditions, Mg^{2+} blocks the channel and prevents Ca^{2+} flux into neurons. B) When the channel is open, one Ca^{2+} and one Na^+ ions will enter the pore in exchange for one K^+ ion. NMDA-R can only be activated by a simultaneous binding of glutamate to its site located on the GluN2 subunits, glycine/D-serine being co-agonists that bind to GluN1 subunits. CGP37849 and CGP39551 are known as competitive NMDA-R antagonists that bind to GluN2 subunits. GLYX-13 (rapastinel), formerly known as functional partial agonist of NMDA-R on the glycine-site, but recently being a novel synthetic NMDAR modulator with fast antidepressant effect, which acts by enhancing NMDAR function as opposed to blocking it (Burgdorf et al., 2013). Only a significant depolarization leads to Mg^{2+} release from its binding site and allow other channel blockers to enter into the channel. Ketamine and other channel blockers (e.g., memantine, MK-801) are known to block this channel in an uncompetitive manner, by a specific binding to the phencyclidine-binding site. This channel also possesses allosteric binding sites, located extracellularly, with Ro25-6981 and CP-101,606 (traxoprodil) that bind to GluN2B subunit, and NVP-AAM077 on GluN2A subunit.

times that of racemic ketamine. While norketamine is considered as an NMDA-R antagonist (Ki = 0.6 – 0.9 μM), HNK only shows a moderate inhibition of this receptor in the (2S,6S)- isoform (Ki = 7 μM), but not the (2R,6R)- isoform (Ki >100 μM) (Morris et al., 2017). Interestingly, (2R,6R)-HNK, has been demonstrated to have antidepressant-like activity in rodents, while (2S,6S)-HNK activity is weaker (Zanos et al., 2016). These findings suggest that the focus of antidepressant drug discovery should incorporate mechanisms of not only NMDA-R blockade, but also AMPA-R activation. In fact, the antidepressant activity of the parent drug, ketamine, depends on this AMPA-R activation (Fukumoto, Iijima, & Chaki, 2016; Pham et al., 2017).

3. Quick view of effects of an acute ketamine administration

A sub-anesthetic dose of ketamine impairs prefrontal cortex (PFC) function in rats, which produces symptoms similar to schizophrenia in human. The pioneer experimental work of Moghaddam and colleagues (Moghaddam, Adams, Verma, & Daly, 1997) demonstrated that a single sub-anesthetic dose of ketamine activated glutamatergic neurotransmission in the PFC. Ketamine induced a rapid increase (starting at 40 min after an i.p. injection of 10, 20 or 30 mg/kg, and lasting for 100 min for the 30 mg/kg dose) in extracellular levels of glutamate (Glu_{ext}) as measured by in vivo microdialysis in rats. A single dose of ketamine (20–30 mg/kg, i.p.) also induced a rapid increase in dopamine release in the mPFC, and this effect was blocked by an intra-PFC application of the AMPA-R antagonist, CNQX. Consequently, such an NMDA-R blockade may be involved in the dissociative effects of ketamine.

Thirteen years later, the rapid antidepressant-like activity of ketamine was supported by another pre-clinical study also performed in rats: Li et al. (2010) were the first to suggest that the antidepressant effects of ketamine (10 mg/kg, i.p.) require activation of the mammalian target of rapamycin (mTOR) pathway and induction of synaptogenesis (synaptic formation/maturation) in the mPFC in an AMPA-R-dependent manner. Indeed, AMPA-R activation is required for the antidepressant actions of ketamine because a pretreatment with a selective AMPA-R antagonist, NBQX, blocked the rapid induction of the mTOR signaling

pathway in the mPFC (Li et al., 2010). These authors then investigated the underlying cellular and molecular mechanisms involved in the rapid antidepressant-like activity of ketamine. Using whole-cell voltage clamp in cortical slices from rats that have been chronically stressed, Li et al. (2011) demonstrated that such a low ketamine dose ameliorated chronic stress-induced anhedonia and anxiogenic behaviors and reversed decreases in excitatory postsynaptic current responses in slices of layer V pyramidal neurons in the mPFC.

In addition, the effects of a single dose of ketamine depend upon the inhibitory phosphorylation of glycogen synthase kinase-3 (GSK-3) (Liu et al., 2013). Complementary electrophysiological data have been obtained measuring excitatory postsynaptic current either in cortical or hippocampal slices (Li et al., 2010). Taken together, these data are consistent with the hypothesis that ketamine blocked a subset of NMDA-R located on GABA-releasing interneurons in the mPFC, thus decreasing GABA release, which facilitates glutamate release and the induction of a long-term potentiation (LTP)-like synaptic plasticity (Li et al., 2010). In addition, this indirect disinhibition hypothesis of glutamate signaling suggests that ketamine induces rapid increases in cortical excitability via the selective blockade of inhibitory GABA interneurons, thus increasing glutamate release in the mPFC (Miller, Moran, & Hall, 2016). The subsequent activation of AMPA-R signaling located on glutamatergic neurons has since been described by many authors to explain how ketamine can increase protein synthesis and synaptogenesis, as well as induce a transient cortical disinhibition (see: Duman et al., 2016; Miller et al., 2016; Rantamaki & Yalcin, 2016).

Accumulating evidence suggests that ketamine act through regulation of brain-derived neurotrophic factor (BDNF) signaling. A high prevalence of a less functional Met allele of the Val66Met (rs6265) single nucleotide polymorphism (SNP) in the BDNF gene was found in the general population. In addition, BDNF knock-in mice with Val66Met allele have an impaired ketamine-synaptogenesis in the mPFC. (Liu et al., 2013). In addition, the antidepressant effects of ketamine in Met/Met mice were attenuated in the FST compared to Val/Val or Val/Met carriers. Thus, activation of BDNF release and its high affinity receptor, tropomyosin receptor kinase B (TrkB) are necessary

for ketamine to exert its antidepressant-like activity. Furthermore, a low dose of ketamine (3 mg/kg) did not produce antidepressant-like effects as measured 30 min and 24 h after administration to homozygous BDNF knockout mice (rapid and sustained effects, respectively) (Autry et al., 2011). This latter group focusing on the hippocampus, proposed another synaptic plasticity process in C57BL/6 mice: the fast antidepressant effects of NMDA-R antagonists would depend on deactivation of eukaryotic elongation factor 2 (eEF2) kinase (also called CaMKIII), thus reducing eEF2 phosphorylation and leading to de-suppression of translation of BDNF. Monteggia's group used extracellular field potential recordings and hippocampal slices dissected from mice to describe changes in glutamate neurotransmission and signaling cascades induced by ketamine following NMDA-R blockade (Gideons et al., 2014; Nosyreva et al., 2013). Ketamine applied to these slices potentiated within 30min AMPA-R-mediated neurotransmission in the CA1 region of the hippocampus. Ketamine-mediated synaptic potentiation required a direct NMDA-R blockade, an increased expression of both GluA1 and GluA2 subunits of postsynaptic AMPA-R, protein synthesis, BDNF expression, and a tonic activation of eEF2 kinase. This cascade of events would lead to ketamine's antidepressant response (Nosyreva et al., 2013).

However, contrasting results appeared in the literature regarding the role of BDNF in this cascade of events. For example, unlike monoamine drugs (i.e., SSRI, SNRI), in heterozygous BDNF$^{+/-}$ C57 mice (with up to 50% reduction of central BDNF), ketamine administered at a higher dose than that of Monteggia's group (50 vs 3 mg/kg, i.p.) still produced a characteristic antidepressant-like response without activating BDNF signaling in the hippocampus (Lindholm et al., 2012). Perhaps more pronounced reductions in BDNF levels are required to block the behavioral effects of ketamine. Taken together, these data suggest that the weakened antidepressant response to ketamine typically seen in approximately 30% of patients might be at least partially related to the Val66Met polymorphism (Laje et al., 2012). However, new evidence suggests that the occurrence of the Met allele does not block the ketamine response in an Asian population (Su et al., 2017).

Converging findings suggest that ketamine-induced fast antidepressant-like activity is related, at least in part, to neuroplasticity changes in the frontocortical/hippocampal networks via activation of AMPA-R-dependent glutamate transmission. However, ketamine effects could also be mediated by one or several ketamine metabolites and activation of other neurotransmitters (GABA, 5-HT) and brain circuits (mPFC/DRN). It is even more difficult to clarify the mechanism of action of an acute sub-anesthetic dose of ketamine knowing that the time of observation is an important parameter to analyze its rapid (30min), sustained (24h post-injection) or long-term (one week) antidepressant-like activity in adult rodents. Stereotypies limit the ability to analyze the antidepressant-like activity of ketamine in the FST shortly after its systemic administration, for example, and to compare the results across studies. The behavioral response of rodents in the FST has strong predictive validity for antidepressant drug activity in patients (Nestler et al., 2002).

Still, it is unclear whether specific brain regions, cell types or circuits are selectively more sensitive to ketamine (Huang & Liston, 2017) and to what extent glutamatergic and monoaminergic systems (mainly 5-HT) play a role in ketamine's antidepressant-like activity. Ketamine binding parameters to glutamatergic NMDA-R (Ki = 0.25 μM in rat cortical and hippocampal preparation: (Morris et al., 2017)) suggest that glutamate, the major excitatory neurotransmitter in the brain, could play an important role for guiding future therapeutic strategies. In addition, there is currently a debate to compare binding affinities of ketamine enantiomers and metabolites to NMDA-R or AMPA-R and their pharmacological properties (i.e., putative antidepressant-like activity in the FST in rodents): (R)-ketamine vs (S)-ketamine, or vs. numerous ketamine metabolites: norketamine, HNKs and others (Shirayama & Hashimoto, 2017; C. Yang, Han, et al., 2016; Yang, Qu, et al., 2015; Zhang, Li, & Hashimoto, 2014).

In summary, the current knowledge regarding different steps involved in the mechanism of action of a single, sub-anesthetic dose of ketamine (leading to its *fast antidepressant-like activity*) can be summarized as follows (Fig. 2):

1- Ketamine binds to NMDA-R located on GABAergic interneurons
2- Bursts of glutamate neurons (LTP) induce glutamate release from pyramidal cells located in the mPFC
3- Stimulation of post-synaptic AMPA-R
4- Increases in BDNF synthesis and release, activation of TrkB/Akt
5- Activation of the mTORC1 signaling pathway (Li et al., 2010) in the mPFC (Duman et al., 2016), but deactivation of the eEF2 kinase in the ventral hippocampus (Autry et al., 2011)
6- Synapse maturation and synaptogenesis, plasticity
7- Fast, long-lasting antidepressant-like activity

In our research, we have been interested to know whether GABA and 5-HT release participate in this pathway (Fig. 3) and contribute to the fast antidepressant-like activity in rodents (naïve vs. animal models of anxiety/depression). Indeed, alterations in these neurotransmitter systems may contribute to the pathophysiology of MDD (Krystal et al., 2002).

4. Acute-administration of ketamine & molecular alterations

4.1. Serotonin (5-HT)

This part of the review focuses on the knowledge that links ketamine to the brain serotonergic system. However, we have chosen not to focus on the molecular proteins/events that specifically occur in 5-HT neurons such as tryptophan hydroxylase 2 - TPH2, Pet1 and DRN signaling cascade behind 5-HT receptors, because there are many recent publications detailing these points (i.e., du Jardin et al., 2016; Hamon & Blier, 2013).

Serotonergic neurons of the mammalian brain comprise the most extensive and complex neurochemical network in the CNS after that of glutamate, which makes up the basic wiring of the brain (Artigas, 2013; Martin et al., 2014). It has been estimated that the human brain contains about 250,000 5-HT neurons of a total of hundred billion neurons (Jacobs & Azmitia, 1992). 5-HT in the central nervous system (CNS) modulates numerous physiological functions (stress, food intake, sleep-wakefulness, pain, etc.) (Sodhi & Sanders-Bush, 2004), and therefore is implicated in the etiology of many mental illnesses such as MDD (Hamon & Blier, 2013). Indeed, many effective antidepressants share the ability to enhance brain 5-HT neurotransmission, which appears to be, at least in part, necessary for their therapeutic effects (Delgado et al., 1994). There are various 5-HT receptor types, with the three main families: 5-HT$_1$, 5-HT$_2$ and 5-HT$_3$, and four smaller ones: 5-HT$_4$, 5-HT$_5$, 5-HT$_6$ and 5-HT$_7$ (see the official IUPHAR classification of receptors). 5-HT$_{1A}$ and 5-HT$_{1B}$ receptor subtypes are located both pre- and post-synaptically in the CNS. Interestingly, in the hippocampus and mPFC, most 5-HT receptor subtypes are found on both pyramidal cells and interneurons (Artigas, 2013; du Jardin et al., 2016; Pehrson & Sanchez, 2014). For example, 5-HT$_{1A}$ receptors direct the orientation of plasticity in layer V pyramidal neurons of the mouse mPFC (Meunier, Amar, Lanfumey, Hamon, & Fossier, 2013). Thus, the observation that 5-HT receptors are located on interneurons and pyramidal neurons suggests a complex role to maintain a balance between excitatory and inhibitory neurotransmission. In addition, to understand how discrete raphe cell subpopulations account for the heterogeneous activities of the midbrain serotonergic system, recent findings defined anatomical and physiological identities of 5-HT raphe neurons (e.g., dorsal and median raphe 5-HT neurons project to the medial mPFC, amygdala and dorsal hippocampus). 5-HT neurons projecting to these brain regions form largely non-overlapping populations and have characteristic excitability and membrane properties (Fernandez et al., 2016).
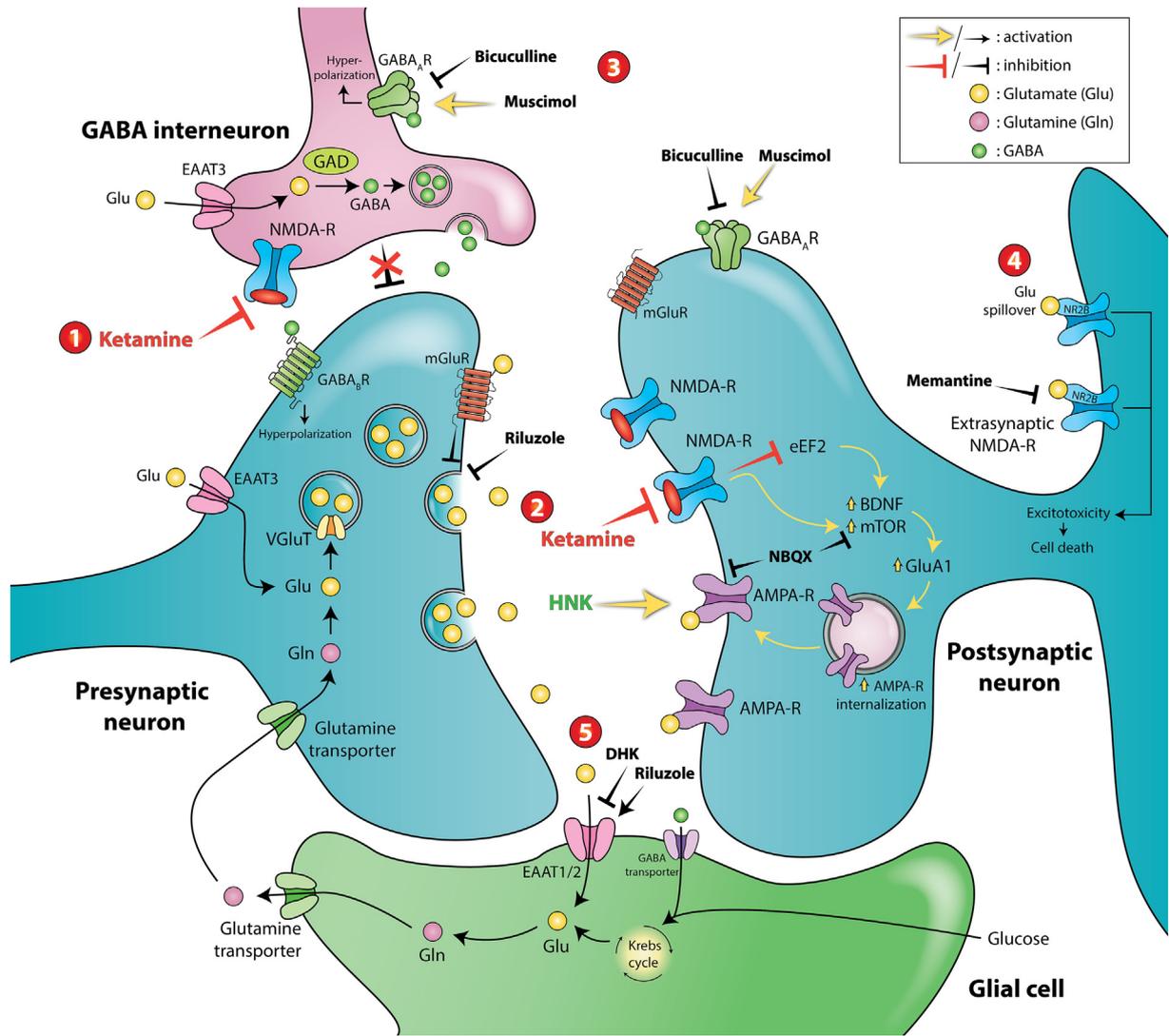
Fig. 2. Potential mechanisms of action of ketamine rapid antidepressant-like activity involved glutamatergic neurons (pyramidal cells), GABAergic interneurons and astrocytes in the medial prefrontal cortex. (1) These putative mechanisms are described following a single sub-anesthetic dose of ketamine (*e.g., under our experimental conditions, 30min after its administration at 10 mg/kg, i.p., plasma level of ketamine was 250 ng/ml in BALB/Cj mice, and undetectable at 24h: see Fig. 1E in Pham* et al., *2018*). Ketamine may first block pre-synaptic NMDA receptor (NMDA-R) located on GABAergic interneurons in the mPFC, which induces a disinhibition of these inhibitory GABAergic interneurons on glutamatergic pyramidal neurons. This disinhibition increases the firing activity in these pyramidal cells, leading to an increase in glutamate release. As a result, extracellular levels of glutamate increase and consequently activates the post-synaptic AMPA receptor (AMPA-R), prolonging the excitatory effects to other neurons and triggering other neurotransmitters' release (e.g., 5-HT, dopamine). (2) Ketamine could also block post-synaptic NMDA-R located on glutamatergic neurons. Consequently, a decreased eukaryotic elongation factor 2 (eEF2) phosphorylation occurs and leads to de-suppression of BDNF translation in the hippocampus (Autry et al., 2011). Ketamine effects also require activation of the mammalian target of rapamycin (mTOR) pathway in the mPFC in an AMPA-R-dependent manner, as NBQX, an AMPA-R antagonist, blocks this pathway and ketamine's antidepressant-like activity in the mPFC (N. Li et al., 2010). The activation of mTOR pathway and de-suppression of BDNF increase translation of various synaptic proteins, including GluA1, which reinforces the AMPA-R internalization for more AMPA-R trafficking to synapses and increases synapse spine numbers and stabilization, a process called synaptogenesis (Duman & Aghajanian, 2012). (2R,6R)-hydroxy-norketamine (HNK), one of the main brain metabolites of ketamine, has gained a lot of interest lately because it could display an antidepressant-like activity *via* a direct activation of post-synaptic AMPA-R, which involves an increase in extracellular glutamate and GABA levels in the mPFC (Pham et al., 2018). (3) GABA_ARs are found on both GABAergic and glutamatergic neurons. The combination of a low ketamine dose (≤10 mg/kg) with muscimol, a GABA_AR agonist, induces a fast antidepressant-like activity in mice (P. B. Rosa et al., 2016). GABA is synthesized from glutamate by glutamic acid decarboxylase (GAD), which is found in neurons, but not in glial cells. The role of GABA_B receptor (GABA_BR) in ketamine actions is still unknown, This receptor is activated by GABA to induce neuronal hyperpolarization, thus limiting glutamate release. This could participate in the control of GABAergic interneurons to limit glutamatergic neuronal firing activity. Glutamate metabotropic receptors (mGluR) are G protein-coupled receptors found both on pre- and post-synaptic nerve terminals. Activation of this receptor family blocks glutamate release. Antagonists of this receptor (e.g., LY341495) also display antidepressant-like activity (Fukumoto et al., 2014; Koike & Chaki, 2014). (4) The excessive increase in extracellular glutamate levels could lead to neuronal excito-toxicity; this could be reduced by glial cells. Indeed, the glutamate spillover could bind to extrasynaptic NMDA-Rs, which are rich in GluN2B subunits. Consequently, the activation of the apoptotic pathway can lead to neuronal death. Memantine, an NMDA-R channel blocker, would target predominantly this receptor subtype (Johnson et al., 2015). (5) The excessive levels of glutamate could be reuptaken by excitatory amino acid transporters (EAATs), located on glial cells (EAAT 1/2) and on presynaptic neurons (EAAT3). In glial cells, glutamate is transformed into glutamine, which is stocked until necessary. Herein, GABA could also be transformed into glutamate from glucose and the Krebs cycle. The utility of glucose is increased after ketamine administration (Milak et al., 2016). Glutamine stocked inside glial cells could be transported back into presynaptic neurons by glutamine transporters to allow glutamate synthesis. Glutamate will be stocked inside synaptic vesicles by vesicular glutamate transporters (VGluT) and then released to the extracellular compartment when depolarization. Dihydrokainic acid (DHK), a selective inhibitor of EAAT2, displays antidepressant-like activity in rats (Gasull-Camos et al., 2017) associated with a huge increase in extracellular glutamate in the PFC. Meanwhile, ketamine failed to reduce EAATs function (Pham et al., 2018). In addition, riluzole, a glutamate positive allosteric modulator (PAM) of EAAT2, has shown neuroprotective properties by facilitating the function of this transporter and prevent glutamate release by presynaptic neurons. The use of riluzole as an 'add-on therapy' to ketamine treatment in treatment-resistant depression is still under debate.
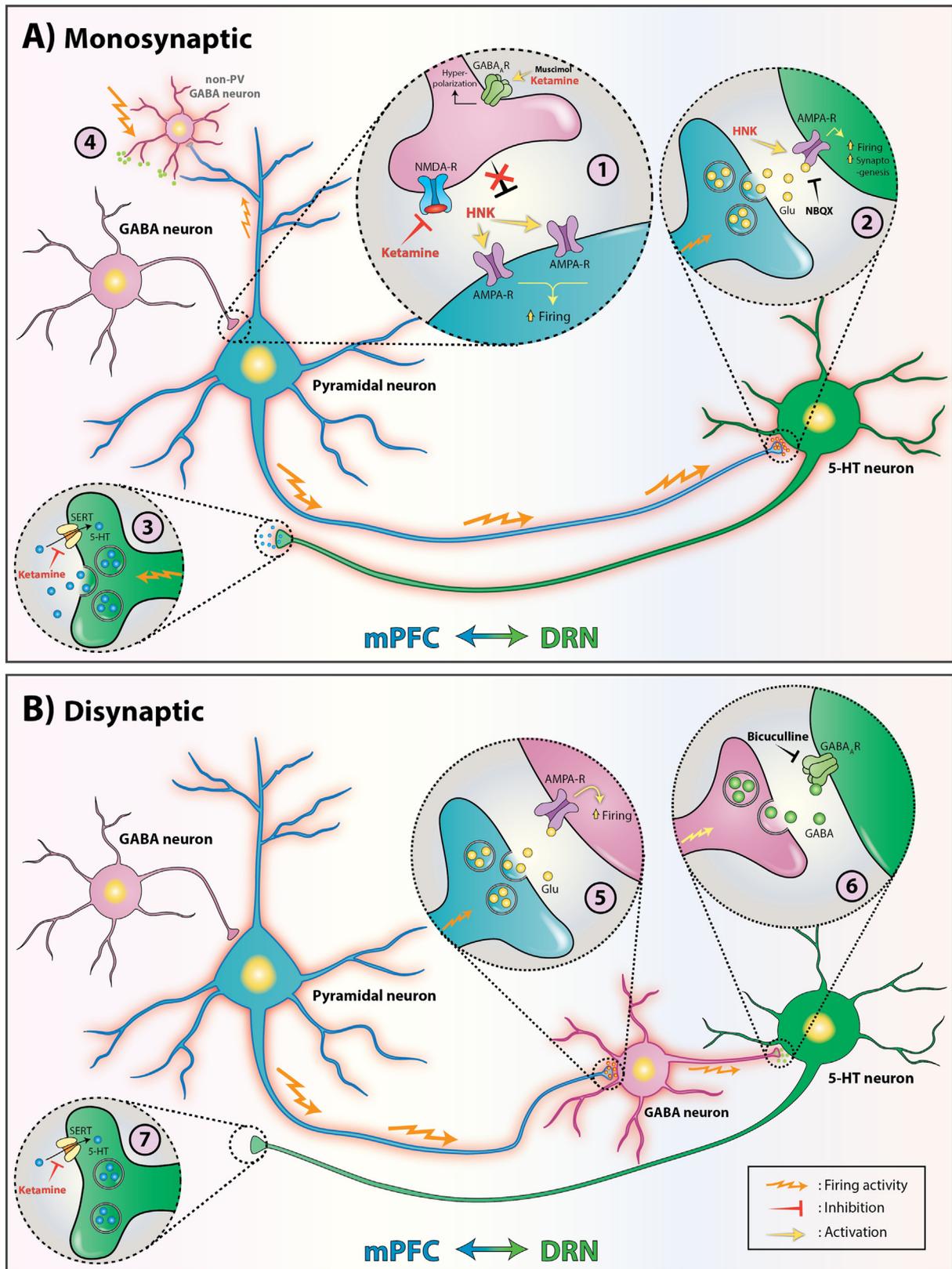
Fig. 3. Hypotheses of ketamine and (2R,6R)-hyrdoxynorketamine (HNK) antidepressant-like activity based on the direct (monosynapse) and indirect (disynapses via GABA neuron) pathways of medial prefrontal cortex – dorsal raphe nucleus (mPFC-DRN) circuit (according to Miller et al., 2016): involvement of glutamatergic, GABAergic and serotonergic neurotransmissions. A) Monosynaptic pathway: mPFC pyramidal cells are controlled by GABA interneurons (mostly parvalbumin (PV)-positive cells) located on the cell bodies. These glutamatergic neurons have projections toward 5-HT neurons located in the DRN, while their dendrites synapse with other non-PV-positive GABA neurons in the mPFC. (1) Ketamine blocks NMDA-R located on GABA neurons that control the action potential of pyramidal cells, thus leading to a disinhibition of these neurons and subsequently facilitating their action potential – firing activity. This induces bursts of glutamate release by presynaptic neurons to activate postsynaptic receptors, such as AMPA receptors (AMPA-R), to initiate further neurotransmission enhancement. Ketamine-induced disinhibition would be indirect via its metabolite HNK, which can release glutamate in the mPFC (Pham et al., 2017). (2) The excitatory signal is transferred to the DRN, where glutamatergic pyramidal cells synapses with 5-HT cell bodies. This stimulates postsynaptic AMPA-R on 5-HT neurons and facilitates

4.1.1. Serotonergic system dysfunction in depression

Clinical studies have shown that a deficit in serotonin is a putative biomarker for MDD. Indeed, clinical studies found reduced cerebrospinal fluid (CSF) and plasma concentrations of the 5-HT major metabolite – 5-hydroxyindoleacetic acid (5-HIAA) – in drug-free depressed patients that was associated with higher suicidal attempts (Placidi et al., 2001; Roy, De Jong, & Linnoila, 1989; Saldanha, Kumar, Ryali, Srivastava, & Pawar, 2009), suggesting an altered 5-HT turnover rate in MDD. Consistent with this evidence, treatment with para-chlorophenylalanine (pCPA), a tryptophan hydroxylase inhibitor, that depleted central 5-HT system, caused a rapid relapse in depressed patients who had responded to the antidepressant drug medication (Stockmeier, 1997). Therefore, drugs targeting the serotonin transporter (SERT) – namely, SSRIs and SNRIs – have been used for the treatment of MDD, although with limitations already mentioned above (Cipriani et al., 2018; Delgado et al., 1994). Thus, a therapeutic response can be achieved via this approach. This efficacy suggests that the underlying biological basis for depression is a deficiency of central serotonergic system (Hirschfeld, 2000). However, data showing brain 5-HT deficits in MDD are sparse: there are many negative studies that do not support the monoamine hypothesis of depression. Other factors, e.g., genetic, environmental, immunologic, endocrine factors and neurogenesis, have been identified as mechanisms involved the pathophysiology of depression (Liu, Liu, Wang, Zhang, & Li, 2017). The concentration of synaptic 5-HT is controlled by its reuptake into the pre-synaptic terminal by SERT, and by 5-HT$_{1A}$ and 5-HT$_{1B}$ autoreceptors (Hagan, McDevitt, Liu, Furay, & Neumaier, 2012); Saldanha et al., 2009). Reduced post-mortem SERT availability in depressed patients reinforced these findings (Kambeitz & Howes, 2015). However, a long-delay onset of action (from 4 to 6 weeks) and a high rate of non-response/resistance have limited the efficacy of these classical antidepressant drugs.

At clinically relevant doses, SSRIs increase extracellular 5-HT levels (5-HT$_{ext}$) in the midbrain raphe nuclei, thereby activating inhibitory somatodendritic 5-HT$_{1A}$ autoreceptors in pre-clinical studies. Consequently, the firing activity of 5-HT neurons is reduced and the enhancement of 5-HT$_{ext}$ in forebrain is dampened. Blocking this negative feedback control by using 5-HT$_{1A}$ autoreceptor antagonists (such as WAY 100635) permits SSRIs to produce a marked increase in 5-HT$_{ext}$ in the forebrain (Romero, Hervas, & Artigas, 1996). These results provided a neurobiological basis for the potentiation of certain antidepressant drugs by pindolol, a 5-HT$_{1A}$/beta-adrenoceptor antagonist, in MDD. The treatment of these patients using an SSRI and pindolol markedly reduced the latency of the antidepressant response in previously untreated patients and induced a rapid improvement in TRD (Artigas, Adell, & Celada, 2006; Artigas, Romero, de Montigny, & Blier, 1996; Fabre et al., 2000; Gardier, 2013; Guilloux et al., 2006; Le Poul et al., 2000; Malagie et al., 2001; Riad et al., 2004). Overall, as most of commercialized antidepressant drugs share the ability to enhance brain 5-HT neurotransmission, understanding the interaction between ketamine and the serotonergic system will bring more insights into their molecular and cellular mechanisms of action.

4.1.2. Ketamine and 5-HT levels

The most used technique to access the level of 5-HT in rodents' brains is in vivo microdialysis in rodents. By far, the mPFC has been the most well-studied brain region for ketamine's influence on 5-HT neurotransmission (e.g., infralimbic vs pre-limbic cortex in rats (Gasull-Camos, Tarres-Gatius, Artigas, & Castane, 2017)). At sub-anesthetic doses, ketamine increased mPFC 5-HT$_{ext}$ in rats. Indeed, using systemic (25 mg/kg, s.c.) and intra-mPFC (3 mM) routes of administration, an increase in 5-HT$_{ext}$ was described in the mPFC (Lopez-Gil et al., 2012). Interestingly, a bilateral, but not local, injection of ketamine intra-mPFC altered 5-HT$_{ext}$ levels, suggesting that a bilateral activation of the mPFC is required to induce an effect of ketamine on 5-HT efflux. Moreover, only systemic, but not local, injection of ketamine provoked hyperlocomotion and stereotypies, thus indicating a role of other brain regions in these behavioral effects. Several teams confirmed that a dose-dependent effect of ketamine occurred on mPFC 5-HT$_{ext}$ in naïve, non-stressed rats (Amargos-Bosch, Lopez-Gil, Artigas, & Adell, 2006; Lorrain et al., 2003; Nishitani et al., 2014), except in rodents subjected to cortical depletion of 5-HT levels by a tryptophan hydroxylase inhibitor (in rats: (Gigliucci et al., 2013); in mice: (Pham et al., 2017)) or following a combination of 5-HT depletion and a restraint stress (Gigliucci et al., 2013). Acute low doses of ketamine (3 and 10 mg/kg, i.p.) also increased 5-HT levels in ex vivo brain tissue homogenates from the mPFC, hippocampus and striatum, which correlated with an increase in the number of head movements in the head-twitch-response (a serotonin-dependent test) in rats (Rivera-Garcia, Lopez-Rubalcava, & Cruz, 2015).

These observations are consistent with a role for cortical 5-HT in mediating neurochemical effects of ketamine as measured 1 or 24 h prior to test. This time point was chosen to avoid the acute schizophrenia-like effects of ketamine. However, it underlines the importance of the experimental models used in these studies. In addition, the interaction between ketamine and the serotonergic system is mostly described after an acute ketamine injection. We have therefore recently reported changes in 5-HT$_{ext}$ at 24 h post-injection of ketamine (10 mg/kg, i.p. (Pham et al., 2017; Pham et al., 2018)). At this time point, when compared to fluoxetine (an SSRI), we found a significant increase in 5-HT$_{ext}$ that correlated positively with increases in the swimming duration in the FST (i.e., a serotonin-dependent parameter) in male BALB/cJ mice. Our data brought up interesting findings supporting a link between neurochemical and behavioral changes that could contribute to the mechanism of ketamine's antidepressant-like actions. Studying the sustained-t24h effect of ketamine in vivo offers several advantages: it can be analyzed in various preclinical behavioral tests in rodents because its adverse effects (i.e., psychotomimetic, stereotypies) are no longer observed at this time point (Lindholm et al., 2012). The range of ketamine doses is also very important. Only low sub-anesthetic doses (less than 25 mg/kg, i.p.) would be relevant to measure ketamine antidepressant-like activity in rodents since higher doses were used to develop a model of schizophrenia (25 mg/kg: (Razoux, Garcia, & Lena, 2007)).

4.1.3. Implication of the mPFC-DRN circuit

Given that the mPFC is one of the few forebrain areas projecting densely to the DRN, where the majority of 5-HT cell bodies are located, the circuit mPFC-DRN has been largely studied to confirm its implication in depression (Aghajanian & Marek, 1997; Hajos, Richards, Szekely, & Sharp, 1998; Peyron, Petit, Rampon, Jouvet, & Luppi, 1998). Indeed, using an optogenetic circuit dissection approach, Warden et al. (2012) were the first to demonstrate that the selective stimulation of

the release of 5-HT at nerve terminals (mPFC). This hypothesis is reinforced by a loss of ketamine antidepressant-like activity in rodent's behaviors as well as on 5-HT levels by intra-DRN injection of an AMPA-R antagonist NBQX (Pham et al., 2017). (3) Extracellular levels of 5-HT are increased, possibly due to 5-HT release or an indirect blockade of serotonin transporters (SERT) by ketamine. (4) mPFC pyramidal cells could also transfer excitatory signals locally to non-PV-positive GABA neurons to induce GABA bursts, as observed in many clinical and preclinical studies (see 4.3.2). B) Disynaptic pathway: mPFC pyramidal cells are also known to synapse onto GABA-rich area of the DRN (Soiza-Reilly & Commons, 2011; Weissbourd et al., 2014). Thus, GABA interneurons would control 5-HT neurons in the DRN. (5) After being stimulated by the ketamine-induced disinhibition (or HNK-induced activation), glutamatergic pyramidal cells would send excitatory signals to DRN GABA neurons, which induce local GABA bursts. (6) GABA bursts subsequently activate postsynaptic GABA$_A$R located on 5-HT neurons to inhibit their neuronal activity. This could explain for an unchanged or even decreased DRN 5-HT neuronal firing following ketamine injection. An intra-DRN injection of bicuculline, GABA$_A$R antagonist, blocks this inhibition and facilitates the neuronal response (Carreno et al., 2016). (7) 5-HT release in the mPFC might not be accelerated, but ketamine could still weaken 5-HT reuptake by SERT indirectly to maintain the 5-HT level.

mPFC cells projections to the DRN induced potent antidepressant-like effects in rats (Warden et al., 2012). However, these glutamatergic inputs from the mPFC to DRN serotonergic neurons could be direct (monosynaptic) or indirect through DRN GABAergic interneurons, thus leading to different outcomes of 5-HT neurotransmission. For example, using electron microscopy, it was found that the mPFC projections to the DRN preferentially targets local GABAergic neurons (Varga, Szekely, Csillag, Sharp, & Hajos, 2001), which are well known to synapse with 5-HT neurons (Harandi et al., 1987; Wang, Ochiai, & Nakai, 1992), whereas others project directly to 5-HT neurons (Soiza-Reilly & Commons, 2011; Weissbourd et al., 2014).

Microcircuits implicated in top-down control of 5-HT neurons in the DRN by excitatory inputs from the mPFC have been also identified. Thus, a combination of c-Fos mapping (a marker of neuronal activation) with *in vivo* optogenetic stimulation of mPFC terminals expressing channelrhodopsin (ChR2) was used to determine DRN neuronal activation. It was demonstrated for the first time that excitatory mPFC axons project to GABA-rich areas of the DRN, and drive the synaptic activity of these DRN GABA neurons via an AMPA receptor-dependent mechanism (Challis, Beck, & Berton, 2014). These data agree with a study demonstrating that the control of dorsal raphe serotonergic neurons by the mPFC involves 5-HT$_{1A}$ and GABA receptors (Celada, Puig, Casanovas, Guillazo, & Artigas, 2001). It is also consistent with mPFC projections to the DRN preferentially targeting local-circuit GABAergic neurons (Jankowski & Sesack, 2004; Varga, Kocsis, & Sharp, 2003; Wang et al., 1992). In addition, identification of monosynaptic glutamatergic inputs from the PFC to serotonergic neurons in the DRN was reported (Pollak Dorocic et al., 2014), indicating that a direct mPFC-DRN pathway that exerts excitatory control over serotonergic neurons in the DRN also exists.

Up to now, there have been two major studies using optogenetic to investigate the pathways involved in ketamine actions: the mPFC (Fuchikami et al., 2015) and the mPFC-vHipp circuit (Carreno et al., 2016). To identify the precise cellular mechanisms underlying ketamine's rapid and sustained antidepressant-like activity, Fuchikami et al. (2015) (Fuchikami et al., 2015) used an optogenetic stimulation of IL-PFC, a sub-region of the mPFC involved in emotional processes in rats. Neuronal inactivation of the IL-PFC by muscimol completely blocked the antidepressant and anxiolytic effects of systemic ketamine (10 mg/kg). By contrast, optogenetic stimulation of glutamatergic neurons in the IL-PFC produced rapid and sustained antidepressant-like effects, which were associated with increased number and function of spine synapses of layer V pyramidal neurons (as in Li et al. (2010)). Thus, local intra-IL-PFC ketamine infusions or optogenetic stimulation of IL-PFC produced behavioral and synaptic responses similar to the effects of systemic ketamine administration. These *in vivo* optogenetic results support a role for cortical neuronal activity in the mPFC in the antidepressant-like activity of ketamine. Although, while this was the first study using optogenetics to investigate the mechanism of ketamine's actions, there are some limitations, e.g., this study was not performed in an animal model of anxiety-depression. In addition, the authors indicated that ketamine (80 mg/kg) was used as an anesthetic before the surgery, which could compromise the results.

The second study by Carreno et al. (2016) (Carreno et al., 2016) was published one year later and brought new insights into ketamine action. Using two different viruses (ChR2 for activation and halorhodopsin for inhibition) to activate and inactivate the neuronal circuit mPFC-vHipp in rats, they confirmed that this circuit is essential for ketamine's antidepressant-like activity in the FST. The vHipp is connected to the limbic system with afferents to the mPFC and NAcc in rats (Ishikawa & Nakamura, 2006). Furthermore, the hippocampus is implicated in the effects of stress, depression and antidepressant drug response (Russo & Nestler, 2013). In this optogenetic study, the FST was performed in rats 30min or one week following a single administration of ketamine (10 mg/kg, i.p.). Both optogenetic and pharmacogenetic specific activation of the vHipp-mPFC pathway using Designer Receptors Exclusively

Activated by Designer Drugs (DREADDs) mimicked the antidepressant-like response to ketamine (10 mg/kg, i.p.). Interestingly, this activation could only took place when the feedback response in the DRN was blocked by bicuculline, to inhibit the control of GABA interneurons on 5-HT neurons, thus underlining an involvement of the disynaptic pathway, via GABA interneurons, in the mPFC-DRN circuit. However, this study would have benefited from using several behavioral tests, instead of one (the FST) to verify this "DRN feedback inhibition" hypothesis. The vHipp-mPFC circuit is specific because its activation of the vHipp/NAcc circuit did not reproduce this response. Furthermore, optogenetic inactivation of the vHipp/mPFC pathway (using the halorhodopsin virus) at the time of FST reversed ketamine's antidepressant-like response. In this experiment, only one ketamine dose was administered, and the test was performed immediately one week after. Thus, these data demonstrate that activity within the vHipp-mPFC pathway and early transient vHipp BDNF/TrkB activation are essential for the sustained antidepressant-like response to ketamine. Indeed, it was suggested that a low ketamine dose could induce a molecular cascade, including BDNF release and TrkB receptor activation underlying the rapid antidepressant activity of ketamine (Li et al., 2010). Another point raised by these authors is that activity-dependent BDNF signaling in the vHipp initiated a unique cellular cascade leading to plasticity, which had occurred one week following ketamine administration.

To know whether 5-HT synthesis is involved in the antidepressant-like effects of ketamine, a pre-treatment with pCPA was performed. Ketamine response in the FST was blocked by pCPA at 24 h post-treatment, thus implicating 5-HT synthesis in the antidepressant mechanism of ketamine (Gigliucci et al., 2013; Pham et al., 2017). Meanwhile, paroxetine, a classic antidepressant drug that acts mainly by blocking SERT, failed to induce a sustained effect similar to ketamine, suggesting that the role of the serotonergic system is different between these two antidepressant drugs (Fukumoto et al., 2016). Interestingly, microinjection of ketamine intra-mPFC also had no antidepressant-like effects in the FST after pCPA pretreatment, emphasizing a particular modulation of mPFC in ketamine action. Furthermore, in this latter study, systemic administration of ketamine also increased c-Fos immunoreactivity in DRN 5-HT neurons, which were blocked by microinjection of NBQX into the mPFC. Collectively, these findings suggest that activation of a subset of DRN 5-HT neurons modulated by mPFC projections may have an important role in the antidepressant effects of ketamine. Thus, the serotonergic systems selectively modulated by the mPFC-DRN projections may be involved in the antidepressant effects. This hypothesis was underpinned by the finding that deep brain stimulation (DBS) of the mPFC exerted an antidepressant effect in animal models of depression, which was abolished by 5-HT depletion (Hamani & Nobrega, 2010). These studies also demonstrate the functional complexity of mPFC circuitry in depression and antidepressant drug responses. An important caveat of all these preclinical findings is that many used unstressed animals. More studies using chronic stress or performed in rodent models of aspects of anxiety/depression (social defeat, CORT model, or BALB/cJ mice) before ketamine administration are needed.

4.1.4. Activation of DRN neurons itself does not induce antidepressant effects

In contrast to the effects of intra-mPFC ketamine injections, local intra-DRN injection had no effect on 5-HT release (Nishitani et al., 2014). However, acute application of high doses of ketamine (100 μM) on raphe slices decreased the 5-HT$_{ext}$ (Nishitani et al., 2014) and reduced basal 5-HT neuronal firing rate (McCardle & Gartside, 2012). In rat DRN slices, application of the same dose of ketamine (100 μM) increased both 5-HT release (up to 80%) and reuptake (up to 200%) (Tso, Blatchford, Callado, McLaughlin, & Stamford, 2004). According to this study, the stimulation of 5-HT reuptake, which overcame the increase in electrical stimulation inducing 5-HT efflux, could explain the decrease in 5-HT levels. We have also reported a similar decrease

in 5-HT neuronal activity using electrophysiology in anesthetized mice, 24 h after a 10 mg/kg dose of ketamine, i.p. (Pham et al., 2017). At this dose, no alteration of 5-HT neurons firing activity in rat DRN was observed, whereas significant changes were found on firing activity of noradrenaline, dopamine neurons (El Iskandrani, Oosterhof, El Mansari, & Blier, 2015). Ketamine modulation of 5-HT neuronal firing occurred via AMPA and NMDA receptors, since applications of AMPA and NMDA (10–100 μM) in rat brain slices dose-dependently increased 5-HT firing activity that was enhanced by GABA$_A$-R antagonist bicuculline, suggesting that both AMPA and NMDA evoked local release of GABA (Gartside, Cole, Williams, McQuade, & Judge, 2007). Interestingly, in this study, only the direct effect of NMDA on 5-HT neurons was blocked by AMPA-R antagonist DNQX, indicating that NMDA evoked local release of glutamate, which subsequently activated AMPA-R located on 5-HT neurons. The indirect implication of NMDA in 5-HT neuronal firing is intriguing, since ketamine is an NMDA-R antagonist. Further studies are needed to elucidating this mechanism of action.

Remarkably, subsequent preclinical studies using microdialysis *in vivo* have demonstrated that NMDA has a dose-dependent effect that varied according to the brain region. Infusion of low doses of NMDA (25 μM) into the rat raphe nucleus decreased 5-HT$_{ext}$ locally and increased 5-HT$_{ext}$ in the frontal cortex. Conversely, infusion of 100 μM NMDA into the rat raphe increased local 5-HT$_{ext}$ and decreased cortical release of 5-HT (Pallotta, Segieth, Sadideen, & Whitton, 2001; Pallotta, Segieth, & Whitton, 1998; Smith & Whitton, 2000). Interestingly, while the 5-HT$_{1A}$ receptor antagonist WAY100635 had no influence on NMDA (100 μM)-induced changes in 5-HT$_{ext}$ in these experiments, an NMDA-R antagonist reversed the increase and decrease in 5-HT$_{ext}$ in the DRN and PFC, respectively (Pallotta et al., 1998). This observation is similar to the data we obtained with ketamine (Pham et al., 2017), underlining complex interactions between NMDA-R, AMPA-R and GABA$_A$-R to modulate 5-HT neurotransmission, as well as a profound involvement of mPFC-DRN pathway in these alterations.

4.1.5. Ketamine and the serotonin transporter (SERT)

The intriguing increases in 5-HT levels induced by ketamine raise the question as to whether this is due to a blockade of the selective 5-HT transporter (SERT), similar to classical SSRIs antidepressant drugs. It was suggested that ketamine can bind to SERT with a weak affinity (Martin, Introna, & Aronstam, 1990). Evidence in support of this theory comes from studies showing that a downregulation of SERT binding was demonstrated in a positron emission tomography (PET) study in non-human primates following an acute ketamine i.v. injection (Yamanaka et al., 2014), indicating an interaction between SERT and ketamine that might be involved in its antidepressant action. However, the affinity of ketamine for SERT occurred at a much higher dose than treatment-relevant doses (Roth et al., 2013; Zhao & Sun, 2008). Thus, such doses or concentrations have little relevance for its antidepressant effects.

4.2. Ketamine and serotonergic receptors

We are going to focus this part of the review mainly on some 5-HT receptor subtypes that have been evaluated in pre-clinical ketamine studies. 5-HT can either inhibit or facilitate neurotransmission depending on the 5-HT receptor subtype activated. Activation of 5-HT$_1$ receptor induced neuronal hyperpolarization, while that of 5-HT$_3$ and 5-HT$_7$ receptors produced depolarization of neurons in rodent brain.

4.2.1. Ketamine and 5-HT1 receptor

At least five 5-HT$_1$ receptor subtypes have been identified: 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1D}$, 5-HT$_{1E}$ and 5-HT$_{1F}$. All are seven transmembrane G-protein coupled receptors (GPCRs) (via Gi or Go) and negatively coupled to adenylyl cyclase (see the official classification of receptors from the International Union of Basic and Clinical Pharmacology (IUPHAR)). So far, the interaction between ketamine and two receptor

subtypes has been described: 5-HT$_{1A}$ and 5-HT$_{1B}$. Each subtype divided into auto-receptors (presynaptic) and heteroreceptors (postsynaptic). The inhibitory 5-HT$_{1A}$ receptor exists in two separated populations with distinct effects on serotonergic signaling: (i)- 5-HT$_{1A}$ autoreceptor is localized on the soma and dendrites of serotonergic neurons in the DRN and its activation by endogenous 5-HT or receptor agonists limit 5-HT release at 5-HT nerve terminals throughout the brain and (ii)- 5-HT$_{1A}$ heteroreceptors located on the membrane of non-serotonergic neurons and mediating an inhibitory response (Gardier, 2013).

The gap in timing between the immediate blockade of SERT *in vitro* (Owens, Knight, & Nemeroff, 2001), increases in the synaptic 5-HT levels in the brain mediated by SSRIs (David et al., 2003; Gardier, Malagie, Trillat, Jacquot, & Artigas, 1996; Nguyen et al., 2013) and the long delay to observe an antidepressant activity *in vivo* in clinical studies (Stassen, Angst, & Delini-Stula, 1997) and in animal models (David et al., 2009) has not been completely explained yet. It is well known that the activation of 5-HT$_{1A/1B}$ autoreceptors limits the effects of SSRIs at serotonergic nerve terminals (Malagie et al., 2001). Thus, the functional desensitization of the presynaptic DRN 5-HT$_{1A}$ receptor sub-type induced by a chronic SSRI treatment partially explains this phenomenon (Artigas et al., 1996; Le Poul et al., 2000). Somatodendritic 5-HT$_{1A}$ autoreceptors activated by SSRI-induced increases in endogenous 5-HT levels in raphe nuclei that limits 5-HT release at nerve endings (i.e., in the mPFC) are gradually desensitized after 4 to 6 weeks of SSRI treatment ((Gardier et al., 1996); see the pindolol story in "Serotonergic system dysfunction in depression" section). For example, WAY100635 (0.5 or 1 mg/kg), a selective somatodendritic 5-HT$_{1A}$ antagonist, potentiated fluoxetine-induced increases in 5-HT$_{ext}$ in rat v-Hipp or mPFC (Guiard et al., 2007; Trillat et al., 1998). This functional adaptation of 5-HT$_{1A}$ autoreceptors that occur after a chronic SSRI treatment would be related to a decrease in the transcription of the gene coding for 5-HT$_{1A}$ receptors, decoupling of G-alpha (i3) subunit protein isoforms in the anterior raphe, and/or internalization into DRN 5-HT neurons (Mannoury la Cour, El Mestikawy, Hanoun, Hamon, & Lanfumey, 2006; Riad, Watkins, Doucet, Hamon, & Descarries, 2001). Such molecular events do not occur in postsynaptic brain regions, such as the hippocampus, because 5-HT$_{1A}$ receptors are likely coupled to different G proteins compared to the DRN (Mongeau, Welner, Quirion, & Suranyi-Cadotte, 1992).

WAY100635 (3 mg/kg, s.c.) blocked ketamine (30 mg/kg, i.p.) effects in the NSF in mice (Fukumoto, Iijima, & Chaki, 2014). However, at such a high dose, WAY100635 is non-selective for 5-HT$_{1A}$ because it also blocked dopamine D4 and 5-HT$_7$ receptors (Forster et al., 1995; Martel et al., 2007). Rivera-Garcia et al. (2015) (Rivera-Garcia et al., 2015) has therefore reported no effect of WAY100635 (1 mg/kg, i.p.) on ketamine (3 and 10 mg/kg, i.p.) positive effects in the head-twitch response (a serotonin-dependent test) and 5-HT levels in post-mortem rat brain tissue homogenates, indicating that 5-HT$_{1A}$ autoreceptors unlikely play a significant role in ketamine-induced increases in 5-HT neurotransmission.

Presynaptic 5-HT$_{1B}$ autoreceptors located at serotonergic nerve terminals are involved in a negative feedback control of 5-HT release (Gothert, Schlicker, Fink, & Classen, 1987; Hoyer & Middlemiss, 1989). In contrast, 5-HT$_{1B}$ heteroreceptors are involved in the regulation of the release of various neurotransmitters, e.g., inhibitory activity on glutamatergic, GABAergic, dopaminergic, noradrenergic and cholinergic neurons (Langlois et al., 1995). Microdialysis data obtained in knockout 5-HT$_{1B}$ mice brought additional information by suggesting that 5-HT$_{1B}$ autoreceptors limit the effects of SSRIs on dialysate 5-HT levels at serotonergic nerve terminals in the mPFC (Guilloux et al., 2011). In the PET study described above with macaques (Yamanaka et al., 2014), ketamine increased 5-HT$_{1B}$ receptor binding in the nucleus accumbens and ventral pallidum, and a pretreatment with NBQX blocked this effect. It suggests that AMPA-R activation exerts a critical role in ketamine-induced upregulation of postsynaptic 5-HT$_{1B}$ receptors in these brain regions, which may be involved in the antidepressant action of ketamine.

4.2.2. Ketamine and 5-HT₂ receptor

Adverse effects of ketamine: psychotomimetic activity (addiction) and long term impairment of cognitive function:

Ketamine (10 and 20 mg/kg, i.p.) enhanced the head-twitch response, in mice, which was blocked by cyproheptadine, a 5-HT₂ receptor antagonist, and NMDA (H. S. Kim, Park, Lim, & Choi, 1999). It suggests an interaction between NMDA-R blockade and post-synaptic 5-HT₂ receptor activation in ketamine increases in serotonergic pathway. In agreement with these findings, electrophysiological studies in rat brain slices have shown that the activation of 5-HT$_{2A}$ receptors in the cerebral cortex, a region where these receptors are enriched, produced a dramatic increase in glutamatergic excitatory postsynaptic potentials in the apical dendritic region of layer V pyramidal cells (Aghajanian & Marek, 1997). Co-application of 5-HT$_{2A/2C}$ receptor antagonists with ketamine diminished its schizophrenic-like effects. Indeed, 5-HT$_{2A/2C}$ receptor antagonists blocked ketamine-induced increases in dialysate 5-HT$_{ext}$ levels (at schizophrenic-relevant dose: 25 mg/kg, s.c.) (Amargos-Bosch et al., 2006). Disruption of pre-pulse inhibition (PPI), a phenomenon linked to abnormalities found in rodent models of schizophrenia that caused impaired cognition, was induced by ketamine (10 mg/kg, s.c, 15 min prior to testing) and was attenuated by ziprasidone, a novel clozapine-like antipsychotic 5-HT$_{2A}$ receptor antagonist (Mansbach, Carver, & Zorn, 2001). Discriminative stimulus in rats induced by ketamine (5 and 30 mg/kg, i.p.) was also blocked by ketanserin, a 5-HT₂ receptor antagonist, and clozapine (Yoshizawa et al., 2013). Together, these data suggest that the combination of ketamine with atypical antipsychotics could limit its psychotomimetic effects that occur shortly after its administration. Interestingly, another 5-HT$_{2A}$ receptor antagonist, ritanserin (0.5 mg/kg, i.p.) did not impede ketamine antidepressant-like effect in mice (Fukumoto et al., 2014). Therefore, finding a range of ketamine dose in which 5-HT₂ receptor antagonists could help to reduce its adverse effects, without affecting its antidepressant-like activity is a necessary good research direction that might bring promising results.

4.2.3. Ketamine and the 5-HT3 receptor

5-HT₃ receptors are unique among the 5-HT receptor family as they are non-selective Na$^+$/K$^+$ ion channel receptors (Maricq, Peterson, Brake, Myers, & Julius, 1991). They modulate fast neuronal excitation. Its strongest expression in the mouse brain was found in the cortex, hippocampus and amygdala, while the thalamus, hypothalamus and midbrain exhibited a few 5-HT₃-expressing cells. In addition, 5-HT$_{3A}$ receptor is expressed in a sub-population of GABAergic interneurons containing somatostatin or calretinin (Koyama, Kondo, & Shimada, 2017). Interestingly, Kos et al. (2006) found that a 5-HT₃ receptor antagonist, MDL72222, co-administered with a high dose of ketamine (40 mg/kg, given i.p. immediately prior to testing) failed to reverse ketamine-induced behavioral deficits in rats (i.e., discriminative stimulus, pre-pulse inhibition - PPI - and cognitive disruption), but potentiated ketamine antidepressant-like effects in the TST (12.5 mg/kg, i.p.) (Kos et al., 2006). Taken together, the blockade of the ionotropic excitatory 5-HT₃ receptor may contribute to the action of antidepressant drugs.

4.2.4. Ketamine and 5-HT7 receptor

5-HT₇ receptors is a GPCR also positively coupled to adenylyl cyclase and the distributions of 5-HT₇ receptor mRNA and radioligand binding exhibit strong similarities with the highest receptor densities present in the thalamus and hypothalamus and significant densities in the hippocampus and cortex (Hedlund & Sutcliffe, 2004; Naughton, Mulrooney, & Leonard, 2000). Within the mouse brain, the 5-HT₇ receptor is located in both dendrites and axon terminals of GABAergic neurons (Belenky & Pickard, 2001). Some studies have evaluated the effects of selective 5-HT₇ receptor antagonists on ketamine-induced deficits in recognition tasks in rats. SB-269970, the most used 5-HT₇ receptor antagonist, can block ketamine (30 mg/kg, s.c.)-induced hyperlocomotion in mice (Galici, Boggs, Miller, Bonaventure, & Atack, 2008), and cognition deficits and disruption of social interactions at a lower dose in rats (20 mg/kg, i.p., (Holuj, Popik, & Nikiforuk, 2015; Nikiforuk et al., 2013)). Remarkably, 5-HT₇ receptor agonists abolished the reversed ketamine-induced social withdrawal of 5-HT₇ receptor antagonist, suggesting an important participation of this receptor in this effect. In addition, 5-HT₇ receptor antagonists, unlike 5-HT₂ receptor antagonists, did not reverse ketamine-induced PPI deficits, thus underlining the selective involvement of the 5-HT₂ receptor in this behavioral task.

Overall, the brain serotonergic system appears to interact fully with different aspects of ketamine's pharmacological properties and adverse effects. First, ketamine increases 5-HT levels in various brain regions in rodents, which is positively correlated with its antidepressant-like activity (Pham et al., 2017). This observation was demonstrated mostly in the mPFC, a key region in ketamine's effects, yet not in the DRN, where a high density of 5-HT neuronal cell bodies are located. Moreover, to the best of our knowledge, the 5-HT$_{1A}$ autoreceptor does not seem to take part in ketamine antidepressant-like activity, which is an interesting difference with classical antidepressant drugs such as SSRIs. This appears intriguing, but could be explained by an involvement of a complex communication between different neurotransmitters that modulate the outcome of 5-HT levels in the DRN. Indeed, an interaction between glutamatergic-GABAergic-serotonergic systems are strongly implicated in ketamine's actions because: (i)- the majority of mPFC neuronal projections to the DRN are mostly indirect through GABAergic interneurons, which are well-known to synapse with local DRN 5-HT neurons; (ii)- modulation of 5-HT neurons firing activity in the DRN involves both glutamatergic and GABAergic receptors. In addition, further investigation of ketamine effects on the excitatory/inhibitory balance in the mPFC and hippocampus would give more information than just analyzing changes in one neurotransmitter. Furthermore, ketamine requires activation of the brain serotonergic neurotransmission to exert its antidepressant-like effects, as depletion of this system decreased changes in its antidepressant-like activity as well as in mPFC 5-HT$_{ext}$ levels. An indirect involvement of SERT might be necessary to ketamine-induced increases in mPFC 5-HT$_{ext}$ levels. A knockout SERT study in mice could bring more insights into this interaction. In addition, behavioral and neurochemical responses to acute ketamine administration in animal models of anxiety/depression are needed, and if possible, to test for the antidepressant response. Finally, except for 5-HT₁ receptors, the other classes of serotonergic receptors seem to take part in regulating ketamine-induced adverse effects, especially the 5-HT$_{2A}$ antagonists. Combination of these agents with ketamine is a promising direction to limit its undesirable schizophrenic symptoms, but also to enhance its antidepressant-like effects at lower and safer doses. These effects of ketamine involved serotonergic system in preclinical studies are summarized in Table 1.

4.3. Glutamate neurotransmission

Modern stereological methods have estimated that approximately 60% of neurons in the human brain use glutamate as primary excitatory neurotransmitter (Douglas & Martin, 2007). Glutamate exerts its actions via its binding to three different ionotropic receptor subtypes, which are classified as NMDA-R, AMPA-R and kainate receptor, and through metabotropic receptors (mGluR) (Lodge, 2009). Ionotropic receptors are post-synaptic, while mGluR are located on the membrane of both post- and pre-synaptic neurons. Initial studies on glutamate were focused on the neurotoxic effects of glutamate following calcium influx (Choi, Maulucci-Gedde, & Kriegstein, 1987). However, subsequent studies have reported that, while excessive stimulation is neurotoxic, physiological stimulation of glutamate receptors is involved in cell growth and neuronal plasticity (Balazs, 2006).

Under normal conditions, glutamate plays a key role in regulating neuroplasticity, learning and memory. Indeed, the balance between

Table 1
Ketamine antidepressant-like activity involved 5-HTergic neurotransmission in preclinical studies (rats and mice).

References	Species (rats or mice) and strain	Ketamine dose and route of administration	Microdialysis and 5-HT content in brain extracts	Behavioral changes	Molecular/cellular, neuronal firing acitivity changes
I) Ketamine altered 5-HT levels in the mPFC, the DRN and the ventral hippocampus measured by microdialysis					
Lorrain, Schaffhauser, et al., 2003	Sprague–Dawley rats	Ketamine 25 mg/kg, s.c. (acutely)	- Increased 5-HT$_{ext}$ (ventral hippocampus)		
Amargos-Bosch et al., 2006	Wistar rats	Ketamine 25 mg/kg, s.c. (acutely)	- Increased 5-HT$_{ext}$ (mPFC)		
		Ketamine 100, 300 and 1000 µM perfusion intra-mPFC	- No changes was seen on 5-HT$_{ext}$ (mPFC)		
Lopez-Gil et al., 2012	Wistar rats	Ketamine 25 mg/kg, s.c. (acutely)	- Increased 5-HT$_{ext}$ (mPFC), blocked by tetrotodoxin intra-mPFC perfusion (1 µM)	- Only systemic injection increased hyperlocomotion and stereotypies, not blocked by TTX	
		Ketamine 3 mM intra-mPFC perfusion (acutely)	- Only bilateral (but not monolateral perfusion) increased 5-HT$_{ext}$ (mPFC)		
Nishitani et al., 2014	Wistar rats	Ketamine 5 and 25 mg/kg, s. c. (acutely) + NBQX 30 nmol intra-DRN (10 min prior to ketamine injection)	- Ketamine dose-dependently increased 5-HT$_{ext}$ (mPFC and DRN). - The increase of 5-HT$_{ext}$ in the DRN was blocked by NBQX		
		Ketamine 36.5 nmol intra-DRN (acutely)	- No change was seen on 5-HT$_{ext}$ (DRN)		
	Rat organotypic DRN slice	Ketamine 100 µM	- Decreased 5-HT$_{ext}$		
Pham et al., 2017	BALBc/J mice	Ketamine 10 mg/kg, i.p. (24h prior testing) Ketamine 2 nmol intra-mPFC (24h prior testing) + NBQX 0.1 µg intra-DRN (30 min prior to ketamine injection)	- Increased 5-HT$_{ext}$ (only in the mPFC, not in the DRN) - Increased 5-HT$_{ext}$ (mPFC), blocked by NBQX	- Increased swimming duration (FST) - Blocked by pretreatment of pCPA - Increased swimming duration (FST) in the same mice (correlated positively with mPFC 5-HT$_{ext}$), blocked by NBQX	- Reduced 5-HT neuronal firing (DRN)
Pham et al., 2017	BALBc/J mice	Ketamine 10 mg/kg, i.p. (24h prior testing) Ketamine 2 nmol intra-mPFC (24h prior testing)	- Increased 5-HT$_{ext}$ (mPFC) - Increased 5-HT$_{ext}$ (mPFC)	- Increased swimming duration (FST) in the same mice	
II) Ketamine altered 5-HT contents in brain extracts					
Kari et al., 1978	Sprague-Dawley rats	Ketamine 50 mg/kg, i.p. (acutely)	- Increased 5-HT level (last for 12 hours)		
Chatterjee et al., 2012	Swiss albino mice	Ketamine 100 mg/kg, i.p. (acutely)	- No change in 5-HT level (cortex, striatum and hippocampus) - Increased 5-HIAA level (striatum)		
		Ketamine 100 mg/kg, i.p. x 10 days (sacrificed on the 11th day)	- Increased 5-HT level (only striatum) - Increased 5-HIAA level (cortex, striatum and hippocampus)		
		Ketamine 100 mg/kg, i.p. x 10 days (sacrificed on the 21th day for withdrawal protocol)	- Increased 5-HT level (only cortex) - No change in 5-HIAA level		
Gigliucci et al., 2013	Sprague-Dawley rats	Ketamine 25 mg/kg, i.p. (1h or 24h prior testing) + pCPA pretreatment	- pCPA depleted cortical 5-HT content	- Ketamine reduced immobility duration (FST) - pCPA blocked ketamine (24h prior FST) effect, but not the 1h one.	
Rivera-Garcia et al., 2015	Wistar rats	Ketamine 3 and 10 mg/kg, i. p. (acutely)	- Ketamine (only at 10 mg/kg) increased 5-HT tissue content (hippocampus, striatum and PFC)		
III) Ketamine altered only behavioral and molecular/cellular, neuronal firing activity changes					
Tso et al., 2004	Wistar rats forebrain slices	(S)- and (R)-Ketamine 100 µM (20 min prior testing)			- Increased 5-HT efflux (up to 80%) and 5-HT uptake (up to 200%)
McCardle & Gartside, 2012	Rats DRN slices	Ketamine 100 and 300 µM (acutely)			- Decreased 5-HT neuronal firing rate and enhanced responses to 5-HT (DRN)

Table 1 (continued)

References	Species (rats or mice) and strain	Ketamine dose and route of administration	Microdialysis and 5-HT content in brain extracts	Behavioral changes	Molecular/cellular, neuronal firing acitivity changes
Fukumoto et al., 2014	C57BL/6J mice	Ketamine 30 mg/kg, i.p. (30 min prior testing) + pCPA pretreatment		- pCPA blocked ketamine effects in the NSF	
El Iskandrani et al., 2015	Sprague–Dawley rats	Acute: Ketamine 10 and 25 mg/kg i.p. (30min prior to electrophysiology) Chronic: Ketamine 10 mg/kg/day x 3 days			- No change in 5-HT neuronal firing rate (DRN)
Fukumoto et al., 2016	C57BL/6J mice	Ketamine 3, 10 and 30 mg/kg, i.p. or 0.3 and 3 nmol/side intra-mPFC (30min or 24h prior testing) + pCPA pretreatment. Mice were sacrificed at 90 min post-injection of ketamine for the c-Fos colocalization		- Ketamine (only at 30 mg/kg or 0.3 nmol intra-mPFC, at both time points) decreased immobility (FST), blocked by pCPA	- Ketamine (only at 30 mg/kg or 0.3 nmol intra-mPFC) increased c-Fos expression on 5-HT neurons (DRN)
IV) Ketamine interacted with 5-HT receptors					
Kim et al., 1999	ICR mice	Ketamine 10 and 20 mg/kg, i.p. Cyproheptadine 1 and 3 mg/kg, i.p. (30 min prior to ketamine)		- Ketamine increased head-movements number (HTR test), while cyproheptadine decreased this parameter	
Mansbach et al., 2001	Wistar rats	Ketamine 10 mg/kg, s.c. (15 min prior testing) + Ziprasidone 17.8 mg/kg orally (3h prior testing) Clozapine 3.2 and 5.6 mg/kg, s.c. (30 min prior testing)			- Ketamine disrupted PPI (startle response session), blocked by ziprasidone and clozapine
Amargos-Bosch et al., 2006	Wistar rats	Ketamine 25 mg/kg, s.c. (acutely) + Ritanserin 5.0 mg/kg, i.p. Clozapine 1.0 mg/kg, s.c. Olanzapine 1.0 mg/kg, s.c. (15 min prior to ketamine injection)	- Ketamine alone increased 5-HT$_{ext}$ (mPFC) - Only Olanzapine and Clozapine, but not Ritanserin, blocked this effect of ketamine		
Kos et al., 2006	Sprague–Dawley rats	Ketamine 15 mg/kg, i.p. (acutely) + MDL72222 0.3, 1 and 3 mg/kg, s.c. (30 min prior testing)		- MDL72222 did not alter ketamine-induced deficit in PPI or ketamine's discriminative effects	
	C57BL/6J mice	Ketamine alone 12.5 – 66 mg/kg, i.p. (30 min prior testing) OR Combination of: Ketamine 12.5 mg/kg, i.p. (5 min prior testing) + MDL72222 1 mg/kg, s.c. (25 min before ketamine)		- Ketamine alone (at 50 and 66 mg/kg) induced decrease of immobility (TST) - MDL72222 potentiated ketamine's effect in this test from 12.5 mg/kg of ketamine.	
Galici et al., 2008	C57BL6/J mice	Ketamine 30 mg/kg, s.c. + SB-269970 3, 10 and 30 mg/kg, i.p. (30 min prior to ketamine injection)		- SB-269970 reversed ketamine-induced hyperactivity but not the PPI deficit	
Nikiforuk, Fijal, et al., 2013	Sprague–Dawley rats	EMD 386088 2.5 and 5 mg/kg, i.p.		- EMD 386088 reversed ketamine-induced cognition and memory deficit, but not the deficit in PPI	
Nikiforuk, Kos, et al., 2013	Sprague–Dawley rats	Ketamine 20 mg/kg, i.p. (30 min prior testing) + SB-269970 1 mg/kg, i.p. (30 min prior ketamine injection)		- SB-269970 ameliorated ketamine-induced cognition and memory deficit, but not the deficit of PPI	
Yoshizawa et al., 2013	Fischer rats	Ketamine 1.25-5 mg/kg, i.p. (10 min prior testing) + Clozapine 1 mg/kg, s.c. Ketanserin 0.3 mg/kg, s.c. (30 min prior testing)		- Ketamine induced discriminative stimulus effect, blocked by clozapine and ketanserin	
Fukumoto et al., 2014	C57BL/6J mice	Ketamine 30 mg/kg, i.p. (30 min prior testing) + WAY100635 0.3, 1 and 3 mg/kg, s.c. (60 min prior testing)		- WAY100635 (only at 3 mg/kg) blocked ketamine effects in the NSF	
		Ketamine 30 mg/kg, i.p.		- Ritanserin blocked ketamine effects in	

Table 1 (*continued*)

References	Species (rats or mice) and strain	Ketamine dose and route of administration	Microdialysis and 5-HT content in brain extracts	Behavioral changes	Molecular/cellular, neuronal firing acitivity changes
		(30 min prior testing) + Ritanserin 0.5 mg/kg, i.p. (60 min prior testing)		the NSF	
Yamanaka et al., 2014	Rhesus monkeys	Ketamine 30 mg/kg, i.v. bolus (100 min prior to PET scan) + 7.5 mg/kg/h i.v. continuous + NBQX 1 mg/kg, i.v. (15 min prior to PET scan)			- Increased 5-HT$_{1B}$ binding and decreased SERT binding (nucleus accumbens and ventral pallidum), blocked by NBQX
Holuj et al., 2015	Sprague–Dawley rats	Ketamine 20 mg/kg, i.p. (30 min prior testing) + SB-269970 1 mg/kg, i.p. (30 min prior ketamine injection)		- SB-269970 reversed ketamine-induced social withdrawal	
Rivera-Garcia et al., 2015	Wistar rats	Ketamine 3, 10 and 20 mg/kg, i.p. (20 min prior testing) + WAY100635 1 mg/kg, i.p. (20 min prior to ketamine injection)		- Ketamine alone induced increases on head-movements number (a 5-HT-dependent parameter). WAY100635 does not affect this effect	

5-HT$_{ext}$: extracellular level of glutamate, measured by microdialysis. FST: forced swim test. NSF: novelty suppressed feeding. HTR: head-twitch response. mPFC: medial prefrontal cortex. PFC: prefrontal cortex. DRN: dorsal raphe nucleus. i.p.: intraperitoneal injection. s.c.: sub-cutaneous injection. pCPA: para-chlorophenylalanine. TTX: tetrodotoxin. PPI: prepulse inhibition.

glutamate and GABA, the primary inhibitory neurotransmitter in the brain is essential for the physiological homeostasis in the CNS (Petroff, 2002). Abnormalities in this excitatory/inhibitory neurotransmitter systems may lead to aberrant functional connectivity and altered synaptic levels of both neurotransmitters mainly in the cortex, thus playing a critical role in anxiety and depression (Hartmann et al., 2017; Lener et al., 2017; Ren et al., 2016). Glutamatergic neurons and synapses by far outnumber all other neurotransmitter systems in the brain with the only exception of the GABAergic system (Sanacora, Treccani, & Popoli, 2012). As an example, it has been estimated that, in the whole human brain, there are roughly two hundred thousand serotonergic neurons out of ninety billion total neurons (Baker et al., 1991; Herculano-Houzel, 2009). In mouse brain, there are only twenty six thousand serotonergic neurons out of seventy million total neurons, of which sixteen thousand cells were found in the raphe system (Heresco-Levy et al., 2013; Ishimura et al., 1988). Therefore, excessive increases in glutamatergic neurotransmission are known as a potent neuronal neurotoxicity (Hardingham & Bading, 2010).

In the brain, glutamatergic neurotransmission and metabolism are united by the conceptualization of the tripartite synapse (Fig. 2), which consists of a presynaptic neuron, a postsynaptic neuron, and an astrocyte (glial cell). Glial cells have all of the necessary components for synthesis, release, and reuptake of glutamate (Magistretti, 2006; Perez-Alvarez & Araque, 2013). Glutamate released from neurons is taken up by glial cells *via* excitatory amino-acid transporters (EAAT 1&2) to be converted into glutamine. When necessary, glutamine is then transported out of the glia and taken up by neurons where it is converted back to glutamate, thereby complete the glutamate-glutamine cycling (Gunduz-Bruce, 2009). This neuronal-glial cycling serves as a reservoir to limit an excess of synaptic glutamate levels, which could lead to excitotoxicity (Rothstein et al., 1996; Zheng, Scimemi, & Rusakov, 2008). Thus, it has been suggested that astroglial dysfunction may have a considerable role in neuropsychiatric diseases such as MDD (Verkhratsky, Rodriguez, & Steardo, 2014).

4.3.1. The glutamatergic deficit hypothesis of depression

The hypothesis of glutamate abnormalities in MDD has become more and more widely accepted in the literature. However, the evidence for or against altered levels of glutamate in depression are mixed. Indeed, when glutamate was measured in the blood and CSF, higher levels were found in patients with MDD (Altamura et al., 1993; J. S. Kim, et al. 1982; Levine et al., 2000; Mauri et al., 1998; Mitani

et al., 2006). In addition, there is a positive correlation between plasma glutamate levels and severity of depressive symptoms in patients with MDD (Mitani et al., 2006). Interestingly, a five-week treatment with antidepressant drugs (SSRIs) significantly decreased the levels of glutamate in serum in depressed patients (Kucukibrahimoglu et al., 2009; Maes, Verkerk, Vandoolaeghe, Lin, & Scharpe, 1998), suggesting the possible role of glutamate in the action of antidepressants.

The dosage of glutamate levels *in vivo* in the human brain was also performed using the non-invasive magnetic resonance spectroscopy (MRS). This method quantifies glutamate and glutamine together as a composite measurement of the glutamate-glutamine cycling (Glx). In depressed patients, decreased Glx levels have been found in the anterior cingulate (Auer et al., 2000; Mirza et al., 2004; Pfleiderer et al., 2003) or PFC (Hasler et al., 2007; Michael et al., 2003). Thus, altered Glx in MDD was reversed by antidepressant drug treatment (Hashimoto, 2011; Krystal et al., 2002). Unipolar depressed patients treated with antidepressant drugs or electroconvulsive therapy (ECT) showed increases in cortical Glx to levels no longer different from those of age-matched controls (Bhagwagar et al., 2007; Michael et al., 2003).

Comparison of quantitative data between rodent and human brains are difficult due to the lack of refined *in vivo* assays measuring brain glutamate levels, thus limiting the understanding of the pathophysiology of the glutamatergic activity and effects of drug treatment. The hypothalamic–pituitary–adrenal axis (HPA axis) has been shown to be associated with stress. Long-term exposure to high level of glucocorticoids (hyperactivities of HPA) involved the activation of forebrain glutamate neurotransmission, e.g., by four-fold in the hippocampus (Hartmann et al., 2017; Sapolsky, 2000). Indeed, both stress and glucocorticoids (often elevated in depressed patients) increase glutamate release in the rat mPFC (Moghaddam, 1993; Musazzi et al., 2010).

Studies in animals also described a glutamate hypothesis of depression (Popoli, Yan, McEwen, & Sanacora, 2011; Sanacora et al., 2012) and have confirmed these alterations in glutamate neurotransmission. Acute stress is associated with increased glutamatergic neurotransmission mainly in the mPFC, hippocampus and amygdala as measured by *in vivo* microdialysis (Bagley & Moghaddam, 1997; Lowy, Wittenberg, & Yamamoto, 1995; Reznikov et al., 2007), while treatment with antidepressants attenuated stimulation-evoked glutamate release (Bonanno et al., 2005; Michael-Titus, Bains, Jeetle, & Whelpton, 2000; Tokarski, Bobula, Wabno, & Hess, 2008).

Chronic stress has been developed in different animal models of anxiety/depression such as chronic unpredictable stress (CUS) or chronic

unpredictable mild stress (UCMS) and social defeat. Using *ex vivo* ^{1}H-MRS in a chronic stress model of depression in rats, a decrease in both glutamate and Glx in the mPFC and hippocampus was measured in a depression-like rat model of chronic forced swimming stress (C. X. Li et al., 2008). Similarly, *ex vivo* liquid chromatography tandem-mass spectrometry detected a decreased glutamate in the mPFC in the chronic social defeat stress mice model of depression (W. Wang et al., 2016). Interestingly, CUS is associated with dendritic atrophy and decreased glutamate receptor expression in the mPFC (Jett, Bulin, Hatherall, McCartney, & Morilak, 2017). UCMS mice display an increase in glutamate and a decrease in glutamine contents in the hippocampus, which were reversed by a chronic fluoxetine treatment (Ding et al., 2017). Noteworthy, in animals and depressed individuals, there are regional differences in glutamatergic neurotransmission with a hypofunction in the mPFC and a hyperfunction in the hippocampus, amygdala, locus coeruleus (Rubio-Casillas & Fernandez-Guasti, 2016). These regions are interconnected (e.g., mPFC-vHipp pathway: Jett et al. (2015)) and influence each other via direct and indirect neural activities in the control of stress response. Therefore, chronic stress is associated with more complex neuronal changes, different from normal, physiological response to acute stress. Indeed, by modifying glutamate release and reuptake, chronic stress affects the cortex by reducing synaptic AMPA-R and NMDA-R availability, synapse density and diameter and dendritic arborization and length, thus consistently leading to neuronal atrophy in the PFC and hippocampus and to a decrease in synaptic functioning (see review Murrough, Abdallah, & Mathew (2017)). Stress induced by UCMS in mice caused a hypofunction of the PFC, which could initiate an increased glutamatergic neurotransmission from amygdala onto prefrontal parvalbumin interneurons that contributed to their behavioral impairment following UCMS (Shepard & Coutellier, 2018).

There has been increasing interest in the role of glutamate in mood disorders, especially considering the effects of ketamine in improving depressive symptoms in patients with TRD. One hypothesis which underpins glutamatergic dysfunction in mood disorders is via neuroinflammation; several studies have elucidated potential innate and adaptive immunopathological mechanisms (Barnes, Mondelli, & Pariante, 2017; Miller & Raison, 2016). Increased inflammation has been observed in a significant subgroup of patients with mood disorders, and inflammatory cytokines have been shown to influence glutamate metabolism through effects on astrocytes and microglia (Haroon & Miller, 2017). In addition, the administration of the inflammatory cytokine interferon-alpha has been shown to increase brain glutamate levels in the basal ganglia and dorsal anterior cingulate cortex as measured by MRS in patients with MDD (Haroon et al., 2016). Thus, it was proposed that an exaggerated release of glutamate by glial cells during an immune activation promotes aberrant signaling through stimulation of extrasynaptic glutamate receptors, ultimately resulting in synaptic dysfunction and loss (Haroon, Miller, & Sanacora, 2017).

Overall, normalization of glutamate neurotransmission is likely a common effect of antidepressant drugs. In addition, a decreased number of glia cells may contribute to depression, due to the crucial role of glutamate uptake by glial cells in removing glutamate from synapses.

4.3.2. Ketamine and glutamate content

Ketamine, as blocker of NMDA-R, induces an immediate increase in glutamate release, and stimulates neuronal cortical excitability after an acute administration in MDD patients (Cornwell et al., 2012). Various tools and experimental protocols have been used to analyze these changes, some of them being used in both human and rodents. For example, a rapid and transient increase in mPFC Glx in response to a single dose of ketamine (0.5 mg/kg, intravenous - i.v.) was demonstrated in *ex vivo* studies using ^{1}H-[^{13}C]-nuclear MRS in depressed patients with MDD (Milak et al., 2016). At such a low ketamine dose, ten of eleven patients remitted having a 50% reduction in the Hamilton score of depression, HAMD-24 scale. In addition, using pharmaco-metabolomics in

human, an increase in plasma glutamate levels was found two hours after ketamine i.v. administration (Rotroff et al., 2016).

Preclinical evidence also using *ex vivo* ^{1}H-MRS, confirmed these data, i.e., a rapid and transient increase in glutamate, glutamine and GABA levels in the mPFC was found in rats immediately after ketamine injection (3, 10 and 30 mg/kg, i.p.) (Chowdhury et al., 2017). Performance in the FST 24 h after ketamine administration at 30 mg/kg (but not at 3 and 80 mg/kg) partially mirrors the dose-dependent effects on rat glutamate/GABA-glutamine cycling. Using a neurochemical assay in dissected brain regions of stressed CUS rats, Melo et al. (2015) found a significant decrease in post-mortem brain tissue homogenates levels of glutamate in the nucleus accumbens, a brain region involved in anhedonia), but not in the PFC, and a combination treatment of ketamine (10 mg/kg for 3 days) and fluoxetine or imipramine (10 mg/kg for 14 days) reversed this effect.

To access the extracellular levels of glutamate (Glu$_{ext}$), *in vivo* microdialysis is the most relevant tool when performed in freely moving rodents because a correlation can be drawn between changes in neurotransmitter levels in dialysates and responses to a behavioral test (e.g., the FST). The Glu$_{ext}$ monitored by *in vivo* microdialysis reflects the balance between neuronal release and reuptake into the surrounding nerve terminals and glial elements (Gardier, 2013). Moghaddam et al. (1997) have first tested a range of ketamine doses (from 10 to 200 mg/kg, i.p.) and found that only low subanesthetic doses (less than 30 mg/kg) increased Glu$_{ext}$ in rat mPFC. This effect was confirmed by Lorrain, Baccei, Bristow, Anderson, & Varney (2003) using also a low ketamine dose (18 mg/kg, i.p.) in rats. Interestingly, this study found that only a systemic, but not a local intra-mPFC dose of ketamine, increased local Glu$_{ext}$, indicating that ketamine might also act outside of the mPFC to enhance glutamate release.

In the dorsal hippocampus, ketamine decreased Glu$_{ext}$ in UCMS rats, at doses 10, 25 and 50 mg/kg, i.p., together with a decrease in depressive-like behavior (Zhu, Ye, Wang, Luo, & Hao, 2017). These results reinforce the concept of regional differences in glutamatergic neurotransmission: a hypofunction in the PFC and a hyperfunction in the hippocampus, amygdala, locus coeruleus in mood-related disorders in animals and depressed individuals (Rubio-Casillas & Fernandez-Guasti, 2016).

4.3.3. Glutamate receptors and ketamine's antidepressant-like activity

4.3.3.1. NMDA-R

4.3.3.1.1. Physiology. NMDA-Rs are tetrameric ionotropic glutamate receptors. They exert a critical role in glutamate-mediated excitatory signaling, being involved in synaptic transmission and plasticity (Lord et al., 2013). NMDA-R dysfunction has been implicated in neurologic and psychiatric disorders, including Alzheimer's disease, Huntington's disease, depression, schizophrenia, chronic and neuropathic pain, epilepsy, and neuron death following stroke (Gladding & Raymond, 2011). NMDA-Rs are composed of a combination of GluN1 subunits with GluN2 and/or GluN3 subunits. Most NMDA-Rs are composed of two GluN1 subunits together with either two GluN2 subunits or a combination of GluN2 and GluN3 subunits. NMDA-Rs activation requires simultaneous binding of both glutamate (binding to GluN2 subunits) and glycine (binding to GluN1 and GluN3 subunits) (see a review Traynelis et al. (2010)). The biophysical properties of the NMDA-R channel that determine its specific involvement in physiological synaptic processes are: (i) a high permeability for Ca^{2+} ions and (ii) a voltage-dependent blockade by Mg^{2+} ions. Only a significant depolarization (for instance, induced by activation of AMPA-type receptors) leads to release of Mg^{2+} and allows Ca^{2+} entry through NMDA-R channels. In turn, Ca^{2+} influx can trigger numerous physiological and pathological intracellular processes (Nikolaev, Magazanik, & Tikhonov, 2012).

4.3.3.2. Pathophysiology of NMDA-R in depression. To test for the role of glutamate neurotransmission in specific neurons *in vivo*, genetic

manipulations using conditional knockout mice and cell type-specific promoters have been set up. Regarding gene deletion of NMDA-R or its GluN1 subunit: mice lacking NMDA-R in parvalbumin GABAergic interneurons, (Pozzi, Pollak Dorocic, Wang, Carlen, & Meletis, 2014) did not observe altered behavioral responses in the FST and in a sucrose prefernce test in mutant mice. By contrast, developmental, selective genetic deletion of the NMDA-R GluN2B subunit only from forebrain parvalbumin interneurons revealed a critical role of this receptor in ketamine's antidepressant-like activity (O. H. Miller et al., 2014).

Mood disorders could be underlined by an increased inhibition (the GABAergic system) or a decreased excitation (the glutamatergic system). The impact of stress and glucocorticoids on glutamate neurotransmission involved a sustained activation of ionotropic NMDA-R (Boyer, Skolnick, & Fossom, 1998; Popoli et al., 2011; Sanacora et al., 2012). Indeed, chronic stress could enhance glutamate release (Zhu et al., 2017), which over-activated NMDA-R and consequently impaired AMPA-R activity. Chronic stress also decreased expression of GluN1, GluN2A and GluN2B subunits of NMDA-R in rat PFC (Lee & Goto, 2011). Such changes of NMDA-R and AMPA-R function can exert two opposite effects depending on the synaptic or extrasynaptic receptor concentration (Sanacora et al., 2012). Recent evidence suggests that the extrasynaptic glutamatergic receptor signaling pathway mainly contributes to the detrimental effects of TRD (Kim & Na, 2016).

4.3.3.3. Drug treatment. The disinhibition hypothesis of the glutamatergic transmission is based on the efficacy of NMDA-R antagonists in TRD and led to conceptualization of potential cellular and molecular mechanisms underlying the fast-acting antidepressant effects of drugs such as ketamine (see below; (Miller et al., 2016)). Chronic antidepressant drug treatment can regulate glutamate receptors via reducing NMDA-R function by producing region-specific decreases in the expression of transcripts for GluN1 subunits in the cortex, but not in the hippocampus in rodents (Boyer et al., 1998; Pittaluga et al., 2007), and conversely by potentiating AMPA-R-mediated transmission both in the PFC and hippocampus (Barbon et al., 2011). Various studies have shown that treatment with antidepressant drugs decreases plasma glutamate levels in MDD patients and reduced NMDA-R function by decreasing the expression of its subunits and by potentiating AMPA-R-mediated transmission (Rubio-Casillas & Fernandez-Guasti, 2016). In addition, defects in GABAergic synaptic transmission can have an impact on glutamatergic transmission. Indeed, GABA$_A$ receptor (GABA$_A$-R) γ2 subunit heterozygous (γ2$^{+/-}$) mice displayed a homeostatic-like reduction in the cell surface expression of NMDA-R and AMPA-R, and functional impairment of glutamatergic synapses in the hippocampus and mPFC. A single subanesthetic dose of ketamine normalized these deficits mainly in the mPFC (Ren et al., 2016).

Recent evidence indicates that the major determinant of ketamine effects is the location of NMDA-R rather than the degree of calcium influx (Kim & Na, 2016). The complexity of NMDA-R modulation has escalated with the knowledge that receptors can traffic between synaptic and extrasynaptic sites, and its location on the plasma membrane profoundly affects the physiological function of NMDA-Rs (Groc, Bard, & Choquet, 2009). The balance between synaptic and extrasynaptic NMDA-R activity is crucial as the two receptor populations can differentially signal to cell survival and apoptotic pathways, respectively (Hardingham & Bading, 2010) (Fig. 2). In fact, extrasynaptic NMDA-Rs are activated when an excess of Glu$_{ext}$ causes overstimulation of NMDA-Rs. This leads to an increased calcium influx into neuronal cells and an elevation of intracellular calcium levels, which activate toxic metabolic processes and trigger cell death (Deutschenbaur et al., 2015). Typically, NMDA-Rs are found at postsynaptic sites. In the adult forebrain, synaptic NMDA-Rs are predominantly di-heteromeric GluN1/GluN2A and tri-heteromeric GluN1/GluN2A/GluN2B receptors, although their ratios may vary between inputs. By contrast, peri- and extrasynaptic sites are enriched in GluN2B-containing receptors, while normal (non-pathological) parvalbumin-positive interneurons are enriched in GluN2A subunits (for more details, see below on GABA; (Paoletti, Bellone, & Zhou, 2013). NMDA-Rs are mobile (at least in cultured neurons), particularly the GluN2B-containing ones, and probably exchange through lateral diffusion between synaptic and extrasynaptic sites (Paoletti et al., 2013). Therefore, GluN2B subunit receptor antagonists preferentially target extrasynaptic receptors composed of GluN1/GluN2B subunits, which constitute a major hub for signaling pathways that lead to neuronal death (Paoletti et al., 2013).

Studies of glutamatergic transporters dysfunction have demonstrated that chronic stress may impair the effective clearance of glutamate from synapses by glial EAATs, thus leading to excessive extrasynaptic NMDA-R function (Marsden, 2011; Popoli et al., 2011). The physiological function of extrasynaptic NMDA-Rs is not fully understood, but their activation by glutamate spillover may contribute to long-term depression (LTD) (Hardingham & Bading, 2010). Extrasynaptic NMDA-Rs are involved in excitotoxicity because a selective activation of these receptors in hippocampal neurons triggers the same amount of cell death as activation of all NMDA-Rs (Stanika et al., 2009). Thus, it is plausible to consider that changes in the balance between synaptic and extrasynaptic NMDA-R activity contribute to the effects of NMDA-R-mediated glutamatergic neurotransmission, which influence neuronal survival and synaptogenesis (Hardingham & Bading, 2010).

NMDA-R antagonists (e.g., MK-801, CGP37849 and CGP39551) can potentiate the effects of antidepressant drugs (see Pilc, Wieronska, & Skolnick (2013), Skolnick, Popik, & Trullas (2009) for a review). Moreover, evidence suggests a role for NMDA-Rs containing GluN2B, the subunit usually found in extra-synapses, in the rapid antidepressant actions of ketamine. Indeed, some studies have supported the antidepressant-like effects of GluN2B selective blockers in rodents such as Ro25-6981 (Kiselycznyk et al., 2015) and eliprodil (Layer, Popik, Olds, & Skolnick, 1995) or in human (CP-101,606 Li et al. (2011)). *In vivo* deletion of GluN2B, only in cortical pyramidal neurons, mimics and occludes ketamine's actions in depression-like behavior and excitatory synaptic transmission, despite the hyperlocomotion measured in these knockout mice under basal conditions (Miller et al., 2014). To support this theory, it was shown that chronic stress might also enhance GluN2B-containing NMDA-Rs in the hippocampus and suppress synaptic plasticity (Bagot et al., 2012). However, another study suggested that memantine, also an NMDA-R antagonist as ketamine, predominantly targets extrasynaptic NMDA-Rs, whereas synaptic NMDA-Rs would be mainly inhibited by ketamine (Johnson, Glasgow, & Povysheva, 2015). Moreover, both ketamine and memantine antagonize the NMDA-R at rest when Mg^{2+} is absent, but only ketamine blocks the NMDA-R at rest when physiological concentrations of Mg^{2+} are present (Gideons et al., 2014). In most clinical studies, memantine was not effective in the treatment of MDD (Lenze et al., 2012; Zarate Jr. et al., 2006). There have been many questions about this failure: was the number of patients high enough? Did differences in exclusion criteria (co-morbidity of anxiety disorders with MDD; history of negative/positive response to treatment with monoaminergic antidepressant drugs; ratio of female gender in the population of patients) influence the results? Was the dose of memantine used high enough? For example, memantine was effective at 5–20 mg/day for 8 weeks (in 8 MDD, a low sample of patients) (Ferguson & Shingleton, 2007), but ineffective at the same dose schedule in 32 MDD patients (Zarate Jr., Singh, Quiroz, et al., 2006). In preclinical studies, there is some evidence that high doses of memantine (20 mg/kg) disrupt spatial memory in rats (see (Amidfar, Reus, Quevedo, & Kim, 2018) for a review). It is likely that memantine and ketamine display different mechanisms of action due to their binding either to extrasynaptic or synaptic NMDA-Rs.

An interesting study (Jimenez-Sanchez, Campa, Auberson, & Adell, 2014) testing selective antagonists of GluN2A (NVP-AAM077) and GluN2B (Ro25-6981) subunits of NMDA-R for their antidepressant-like activities and stereotypies in rats have shown that antagonism of both subunits concomitantly induced psychotomimetic symptoms,

while antagonism of only one subunit (GluN2A or GluN2B) induced an antidepressant-like effect in the FST. Moreover, NVP-AAM077 and the non-selective channel blocker MK-801, but not Ro25-6981, were capable of increasing Glu_{ext} and/or $5\text{-}HT_{ext}$ in the mPFC (*in vivo* microdialysis) (Jimenez-Sanchez et al., 2014). By contrast, Chowdhury et al. (2017) showed that by measuring glutamate cycling in rats with *ex vivo* ^{13}C-nuclear MRS, Ro25-6981 increased the percentage of ^{13}C enrichments of glutamate and glutamine in rat mPFC (Chowdhury et al., 2017). However, behavioral results in this study are difficult to analyze because a pre-test was performed in the FST; thus, cognitive adaptation may have influenced the results in the second test. These data suggest that increasing neurotransmitters efflux is not the key element for antidepressant effects of GluN2B selective antagonists. One important remark is that in this study, these antagonisms targeted predominantly pyramidal cells. In addition to this finding, micro-injection of Ro25-6981 intra-mPFC was sufficient to induce antidepressant effect, but selective genetic removal of GluN2B subunit on interneurons did not occlude this response (Kiselycznyk et al., 2015). These data suggest that the consequences of GluN2B blockade are different depending on where they are located, i.e., either on glutamatergic pyramidal cells or on GABAergic interneurons, thus underlining the importance of neuronal types (glutamatergic *vs* GABAergic ones) in studying ketamine responses.

In addition, restricted deletion of GluN1 in forebrain interneurons did not significantly affect FST behavior (Pozzi et al., 2014), meaning that these animals retained their antidepressant-like behavioral response to ketamine despite lacking the putative target responsible for its NMDA-R antagonism. This argues against the hypothesis that antidepressant-like effects are produced by loss of interneuron NMDA-R activity, leading to a transient disinhibition of pyramidal neuronal firing. A transient effect is critical because a sustained glutamate release may produce excitotoxicity (Voleti et al., 2013). However, this conclusion is tempered by the fact that GluN1 is only deleted on a subset of (primarily parvalbumin-expressing) interneurons – leaving open the possibility that the remaining interneuron receptors were sufficient to maintain normal FST behavior in these mutants.

Whether or not NMDA-R antagonism is essential for ketamine antidepressant activity is still a matter of debate, i.e., NMDA-R antagonism leading to a local decreased in Ca^{2+} flux via extrasynaptic NMDA-R containing GluN2B subunit (Miller et al., 2016; Miller et al., 2014). Ketamine has a higher potency for NMDA-R expressing GluN1/GluN2C subunits (Kotermanski & Johnson, 2009; Zorumski, Izumi, & Mennerick, 2016), a combination preferentially expressed on GABAergic interneurons. The GluN2B subunit was shown to contribute to the rapid antidepressant-like activity of ketamine and its effects on cortical signaling pathways in mice (Miller et al., 2014). Interesting clinical results from Cornwell et al. (2012) showed an increase in cortical excitability at 6.5 h after ketamine infusion in a group of depressed patients responding to ketamine, but not in non-responders. Since this time point occurs much later than psychotomimetic effects associated with the drug, these data are consistent with the hypothesis that the direct NMDA-R antagonism is not sufficient to explain therapeutic effects of ketamine, but rather enhanced non-NMDA receptor-mediated glutamatergic neurotransmission via synaptic potentiation is crucial to ketamine's antidepressant effects (see below for AMPA-R). Such residual effects were also observed in rodents 24h after ketamine administration (N. Li et al., 2010; Pham et al., 2018; Pham et al., 2017).

4.3.3.4. AMPA-R

4.3.3.4.1. Physiology. AMPA-R, together with kainate receptors, play a major role in excitatory synaptic transmission and plasticity by mediating fast postsynaptic potentials (Deutschenbaur et al., 2015). AMPA-R channel properties are largely determined by subunit composition of the tetrameric receptor, assembled from GluA1-4 subunits (Barbon et al., 2006). In synapses of hippocampal principal neurons, most AMPA-R are heteromers of GluA1 and GluA2 (80%) and the remaining

20% are assembled from GluA2 and GluA3 subunits (Lu et al., 2009). The GluA4 subunit is only expressed in interneurons and in juvenile principal neurons (Jensen et al., 2003). Binding of endogenous glutamate to at least two of the receptor subunits is required to trigger rapid channel opening, allowing depolarizing current carried mostly by Na^+ ions to enter into the cell (Murrough et al., 2017). AMPA-R interacts with a variety of signal transduction events to induce synaptic changes (Hayashi, Umemori, Mishina, & Yamamoto, 1999). Interestingly, the number of AMPA-R at synapses is dependent on relative rates of exocytosis and endocytosis at the post-synaptic membrane: this process is called "AMPA-R trafficking" (Anggono & Huganir, 2012). AMPA-R can be trafficked into and out of synapses to increase or decrease synaptic transmission, in order to induce LTP or LTD, respectively (Hayashi et al., 2000; Shi, Hayashi, Esteban, & Malinow, 2001).

4.3.3.4.2. Pathophysiology of AMPA-R in depression. Changes to synaptic plasticity are further coordinated with those to structural plasticity within the tripartite synapse. On pyramidal neurons, LTP and LTD induce dendritic spine growth and retraction respectively, whilst AMPA-R expression is positively related to the size of the spine head (Kasai, Fukuda, Watanabe, Hayashi-Takagi, & Noguchi, 2010). In depression, subregions of the PFC and hippocampus structural and synapse-related findings seem consistent with a deficit in LTP and facilitation of LTD, particularly at excitatory pyramidal synapses (Marsden, 2013). Among all subunits, the GluA1 seems to be of particular importance in LTP as GluA1/A2 heteromers are trafficked to synapses during LTP (Shi et al., 2001). Especially, using GluA1-knockout mice, Zamanillo et al. (1999) reported the essential role of this subunit in LTP establishment, most likely due to a selective loss of extrasynaptic AMPA-R reserve pools, thus preventing activity-dependent synaptic insertion of AMPA-Rs (Andrasfalvy, Smith, Borchardt, Sprengel, & Magee, 2003; Zamanillo et al., 1999). Interestingly, the duration of stress exposure seems to modify GluA1 differently: short-term exposure to stress increased GluA1 (Rosa, Guimaraes, Pearson, & Del Bel, 2002; Schwendt & Jezova, 2000), while long-term (28 days) exposure decreased its expression in hippocampal neurons (Duric et al., 2013; Kallarackal et al., 2013; Toth et al., 2008). AMPA-R is strongly involved in synaptic plasticity, in particular those containing GluA1-subunit. Using *in situ* hybridization studies (Naylor, Stewart, Wright, Pearson, & Reid, 1996; Wong et al., 1993), it was shown that repeated electroconvulsive shock (ECS) in rats increased GluA1 mRNA expression in hippocampus areas that are connected to the LTP and consequently increased synaptic efficacy. Compelling evidence suggests that classical antidepressant drugs up-regulate AMPA-R function, which in turn may lead to changes in synaptic strength and plasticity. Indeed, chronic fluoxetine (SSRI) or reboxetine (SNRI) treatment increased the expression of all AMPA-R subunits both in the PFC and hippocampus in a time-dependent manner that was consistent with their antidepressant-like efficacy in rats (Ampuero et al., 2010; Barbon et al., 2011).

In patients with MDD, the results of recent studies on the involvement of AMPA receptors in post-mortem brain tissue (cortex, hippocampus) are equivocal: increase in radio-ligand binding (Gibbons, Brooks, Scarr, & Dean, 2012) or decrease in mRNA expression levels of AMPA receptor subunits (Duric et al., 2013). Clearly, additional studies are required to solve these inconsistencies (Freudenberg, Celikel, & Reif, 2015).

Interestingly, AMPA-R activation is capable of promoting neuronal survival (i.e., protects cells from apoptosis). This process involves a powerful activation of BDNF synthesis and release, which activates dendritic spine development (Rubio-Casillas & Fernandez-Guasti, 2016). Antidepressant drugs induced marked increases of AMPA-R subunits expression in rat hippocampus, suggesting the targeting of AMPA-R as a therapeutic approach for the treatment of depression (Barbon et al., 2011; Martinez-Turrillas, Frechilla, & Del Rio, 2002).

The role of AMPA-R in depression is accompanied by the regulation of NMDA-R. A model of GluA1-knockout mice displayed increased learned helplessness, decreased hippocampus 5-HT and norepinephrine levels,

and disturbed glutamate homeostasis with increased glutamate tissue levels and increased NMDA-R GluN1 subunit expression (Chourbaji et al., 2008), thus indicating a particular interaction between GluA1 and several neurotransmitter systems in provoking depression-like behaviors. The up-regulation of glutamate levels in this study is possibly due to a compensatory mechanism in response to the lack of GluA1-containing AMPA-Rs. Furthermore, the increased expression of GluN1 subunit agrees with downregulation of this subunit by SSRI and SNRI treatment in mouse brain (Boyer et al., 1998; Pittaluga et al., 2007). These data support the notion that physiological and pharmacological properties of NMDA-R play a critical role in the therapeutic actions of structurally diverse antidepressants.

In the absence of GluN2B subunit, the synaptic levels of AMPA-R are increased and accompanied by a decreased constitutive endocytosis of GluA1-containing AMPA-R (Ferreira et al., 2015), which is in accordance with findings regarding the concomitant role of GluN2B in mood disorders and the antidepressant effects of GluN2B-selective antagonism (see the NMDA-R section).

4.3.3.4.3. Treatment (ketamine and other AMPA-R agonists). Recent results have confirmed that ketamine requires an activation of AMPA-R to exert its antidepressant-like activity. NBQX, an AMPA-R antagonist, blocked the antidepressant-like effects of ketamine in rodents (Koike & Chaki, 2014; Koike, Iijima, & Chaki, 2011; Li et al., 2010; Li et al., 2011; Maeng et al., 2008; Pham et al., 2017). AMPA-R-mediated excitatory synaptic function in the frontal cortex and hippocampus is enhanced by ketamine (Autry et al., 2011; Li et al., 2010). This has led to the glutamate hypothesis of depression and its treatment, e.g., an enhanced glutamate release in the mPFC following ketamine administration results in an activation of AMPA-R, which is necessary for the antidepressant-like activity of NMDA-R antagonists (Maeng et al., 2008; Pham et al., 2018). An up-regulation of AMPA-R GluA1 subunit expression was observed in stressed rodents after an acute ketamine treatment (Beurel, Grieco, Amadei, Downey, & Jope, 2016; Zhang et al., 2015). Interestingly, this upregulation of the hippocampal cell-surface AMPA-R expression is selective to this GluA1 subunit since ketamine did not alter the localization of GluA2, GluA3 or GluA4 subunits (Beurel et al., 2016), indicating that sub-anesthetic doses of ketamine affected a very precise cell-surface AMPA-R GluA1 subunit in the hippocampus.

It is important to remember here the previous findings on classical SSRI antidepressant drugs. For instance, GYKI52466, an AMPA-R antagonist, blocked the antidepressant-like effects of fluoxetine (Farley, Apazoglou, Witkin, Giros, & Tzavara, 2010) in stressed mice. Up-regulation of GluA1, GluA2/A3 subunits was found in rats PFC and hippocampus (Ampuero et al., 2010; Barbon et al., 2011; Martinez-Turrillas et al., 2002; Martinez-Turrillas, Del Rio, & Frechilla, 2005) and in mice (Tan, He, Yang, & Ong, 2006) after chronic treatment with classical antidepressants. Meanwhile, the observation of increased GluA1 following antidepressant drug treatment is more consistent as it was still elevated at 72 h post-treatment, while upregulated effects on the GluA2/3 subunits was transient (Martinez-Turrillas et al., 2002; Martinez-Turrillas et al., 2005). Moreover, the increase was found on the membrane fraction, not the total extract, suggesting a facilitation of AMPA-R trafficking from intracellular pools to synaptic sites following antidepressant drug treatment. An upregulation of AMPA-R surface expression (Li et al., 2010; Maeng et al., 2008; Ren et al., 2016) is therefore a strong candidate mechanism underlying the antidepressant-like effects of ketamine. The drug could trigger critical synaptic changes at excitatory synapses that mediate the relatively long-lasting increases in cortical excitability (Cornwell et al., 2012).

Whether or not ketamine exerts its antidepressant-like effects *via* a direct activation of AMPA-R remains uncertain (via BDNF/TrkB receptor activation in the frontal cortex or the hippocampus). An increase in population activity was observed in AMPA-R located in the dorsal hippocampus of anesthetized rats immediately, but not two days after, an i.p. administration of ketamine (10 mg/kg) indicating that this may

contribute to ketamine immediate therapeutic effects, but not to its sustained effects (El Iskandrani et al., 2015). Interestingly, this study found that this low dose of ketamine significantly increased the AMPA-, but not NMDA-, evoked firing at 30 min post-injection. The lack of blockade of NMDA-R-evoked firing of glutamatergic pyramidal neurons by ketamine may appear puzzling since ketamine is an NMDA-R antagonist, but it could stem from the fact that ketamine exerts its effect via GABA interneuron disinhibition. Indeed, ketamine and MK-801, the most potent NMDA-R antagonist, selectively target NMDA-R located on GABA neurons and lead to decreased inhibition (disinhibition) following a surge in glutamate, thus resulting in an enhancement of AMPA-R activation (Abdallah, Sanacora, Duman, & Krystal, 2015; Homayoun & Moghaddam, 2007).

In summary, AMPA-R is essential for inducing LTP and LTD, through its trafficking process in and out of post-synaptic membranes. Targeting GluA1 subunit has brought new insights into the function of AMPA-R in depression. Importantly, the antagonism of AMPA-R has become a popular approach in highlighting the necessary stimulation of AMPA-R in fast antidepressant drugs' action, especially ketamine. Here, we underline the importance of distinguishing between the acute, 30 min post-injection and the sustained, 24 h post-administration, of ketamine.

The acute effect of ketamine seems to potentiate AMPA-R and glutamate release. However, the choice of the single dose administered to rodents and subsequently its responses to behavioral tests are highly questionable when performed 30min post-treatment because of the acute hyperactivity and dissociative effects of ketamine. Understanding how AMPA-R impacts other receptor subtypes and other neurotransmitter system might be the key to understand how ketamine expresses its sustained antidepressant-like activities.

There are potential toxicological concerns associated with chronic activation of AMPA-R (e.g., neurotoxicity, seizures) that could either limit the therapeutic range or preclude the long-term use of such agonists (Pilc et al., 2013). However, using drugs acting as positive allosteric modulators (PAMs) could offer several advantages, which include no intrinsic agonist activity and no synaptic activation (Bretin et al., 2017). For example, LY392098, an AMPA-R PAM, would act downstream of the NMDA-R/GABAergic interneuron/glutamatergic axis engaged by ketamine. LY392098 potentiated AMPA-R-mediated currents of PFC neurons (Baumbarger, Muhlhauser, Yang, & Nisenbaum, 2001) and also possessed an antidepressant-like activity in the FST and TST, which required AMPA-R activation, unlike imipramine (X. Li et al., 2001). Surprisingly, it exerted little influence on extracellular NA and 5-HT levels in mPFC dialysates in rats at doses that were active in the FST (X. Li, Witkin, Need, & Skolnick, 2003), indicating a different mechanism involved in AMPA-R PAMs that is not commonly seen in SSRI.

4.3.4. Glutamate transporters and ketamine's antidepressant-like activity

Glutamate transporters play an important role in regulating Glu_{ext} to maintain dynamic synaptic signaling processes. There are a number of transporter families for glutamate, including the plasma membrane EAATs, the vesicular glutamate transporters (VGLUTs), and the glutamate-cysteine exchanger (reviewed by Vandenberg & Ryan (2013)). Excessive glutamate receptor stimulation is toxic to neurons, and glutamate transporters rapidly clear glutamate from the synapse to avoid deleterious consequences. An appropriate reuptake of glutamate by astrocytes is thus crucial for preventing 'spill-over' of synaptic glutamate concentrations and binding to the extrasynaptic NMDA-R (Kim & Na, 2016).

There are three classes of VGLUTs: VGLUT1, VGLUT2 and VGLUT3, ensuring the vesicular uptake of glutamate in the brain. VGLUTs can be found on many types of neurons such as glutamatergic, GABAergic and serotonergic ones (reviewed by El Mestikawy, Wallen-Mackenzie, Fortin, Descarries, & Trudeau (2011)). VGLUT1 and VGLUT2 are often used as markers of presynaptic glutamatergic transmission since glutamate is released into the synapse via these vesicular glutamate transporters in the forebrain (Montana, Ni, Sunjara, Hua, & Parpura, 2004;

Wojcik et al., 2004). Recent clinical studies reported decreased levels of VGLUT1 in the entorhinal cortex of depressed patients (Uezato, Meador-Woodruff, & McCullumsmith, 2009). In addition, the number of synapses containing VGLUT1 and VGLUT2 was decreased in stressed mice (Brancato et al., 2017).

EAATs divide into five subtypes: EAAT1 (or GLAST1), EAAT2 (or GLT-1), EAAT3, 4 and 5. EAAT1 is highly abundant and is the major glutamate transporter in the cerebellum, being about 6-fold more abundant than EAAT2. Moreover, EAAT1 is responsible for 90-95% of glutamate uptake in the forebrain. EAAT1 and EAAT2 are both predominantly localized on astrocytes and abundant in the hippocampus and cerebral cortex (Gegelashvili, Dehnes, Danbolt, & Schousboe, 2000). In contrast, EAAT3 is a neuronal transporter and also abundant in the cerebral cortex. Meanwhile expression of EAAT4 and EAAT5 is restricted to the cerebellum and retina, respectively (Gegelashvili & Schousboe, 1998).

Using a microarray analysis, a down-regulation of glutamate transporters in glial cells (EAAT-1 & EAAT-2/GLT-1) was found in post-mortem cerebral cortex of patients who had suffered from MDD (Choudary et al., 2005). Deficits in these glutamate transporters could impair glutamate reuptake from synaptic cleft by astrocytes, thus prolonging activation of postsynaptic receptors by the endogenous glutamate. Increases in Glu_{ext} could then perturb the balance of excitation/inhibition and the average firing rates of neurons (Cryan & Kaupmann, 2005). Moreover, the reduced levels of glial cell number and density in the brain of patients with mood disorders are one of the most consistent pathological findings in psychiatric research, suggesting that a decrease in glial-cell function could help to explain the altered glutamate content observed in several brain regions of these patients (Sanacora et al., 2008). In addition, the blockade of astrocytic glutamate uptake (EAAT2/GLT-1) in rat mPFC followed by an increase in Glu_{ext} and neuronal activity is sufficient to produce anhedonia, a core symptom of depression (John et al., 2012), indicating a critical involvement of prefrontal glial dysfunction in anhedonia-like outcomes.

In rats receiving a different regimen of UCMS, the expression of EAAT2 and EAAT3 was downregulated. In addition, the stress-induced increase in Glu_{ext} in the hippocampus was reversed by the three doses of ketamine (10, 25, and 50 mg/kg/day for 5 days), which also upregulated the expression of glutamate transporters EAAT2 and EAAT3 (Zhu et al., 2017). Similarly, EAAT2 level in this brain region was downregulated in CUS-exposed rats, which is reversed by an acute dose of ketamine (10 mg/kg, i.p.) at 24h post-treatment (Liu et al., 2016). These data suggest that the antidepressant-like effect of ketamine would link to the regulation of EAATs expression and the enhancement of glutamate uptake in the hippocampus of depressive-like rats.

Recently, dihydrokainic acid, a selective inhibitor of EAAT2 (GLT-1) displayed antidepressant-like effects in rats (Gasull-Camos et al., 2017). Micro-infusion of DHK into the infralimbic cortex (IL-PFC) decreased the immobility duration in the FST and the latency to feed in the NSF, and increased Glu_{ext} and $5-HT_{ext}$ in the IL-PFC. These effects were reproduced by s-AMPA, a synthetic agonist of AMPA-R, and blocked by the pretreatment with pCPA that blocked 5-HT synthesis. DHK seems to share the same pharmacological properties as ketamine in mice, since an increase in Glu_{ext} and $GABA_{ext}$ in the mPFC together with an increase in swimming duration in the FST were observed during DHK perfusion intra-mPFC (Pham et al., 2018, in preparation) (Fig. 2). However, ketamine failed to reduce the function of EAATs in the zero-net-flux experiment, a method of quantitative microdialysis that allows verifying the reuptake function of neurotransmitter transporters (Pham et al., 2018). These results indicate that the increase in Glu_{ext} observed at 24 h post-injection of ketamine is likely due to an increase in glutamate release in the mPFC. A combination of ketamine with VGLUTs inhibitors would bring interesting results to complete this observation.

In addition, riluzole, a glutamate PAM, GLT-1, an FDA-approved medication for the treatment of amyotrophic lateral sclerosis, has been shown to potently and rapidly inhibit glutamate release in both *in vitro* and *in vivo* studies (Doble, 1996). It has both neuroprotective

and anticonvulsant properties due to its ability to inhibit glutamate release and enhance both glutamate reuptake and AMPA-R trafficking (Frizzo, Dall'Onder, Dalcin, & Souza, 2004), thus protecting glial cells against glutamate excitotoxicity (Fig. 2). Results from several, mostly open label and observational clinical trials, has suggested efficacy of riluzole as an 'add-on therapy' in treatment-resistant major depression (see the review of Zarate Jr. et al. (2010), even though riluzole alone was insufficient for clinical response in these patients (Mathew, Gueorguieva, Brandt, Fava, & Sanacora, 2017). However, using riluzole with ketamine treatment in TRD patients did not significantly alter the course of antidepressant response to ketamine alone (Ibrahim et al., 2012).

Together, these data point out that rapid enhancement of glutamate transporters following an inhibition of glutamate release may not contribute to ketamine's therapeutic action. It seems more likely that the blockade of glutamate transporters increases Glu_{ext} as ketamine does. The brain regions (e.g., mPFC or hippocampus) plays an important role in defining specific roles of EAATs that interact with ketamine. Meanwhile, VGLUTs should be studied more to have a better understanding of the link between glutamate release and reuptake in the antidepressant-like activities of ketamine. These effects of ketamine involved glutamatergic system in preclinical studies are summarized in Table 2.

4.4. GABA

GABA is the principal neurotransmitter mediating neural inhibition in the brain. GABAergic neurons represent between 20 and 40% of all neurons depending on brain regions and are known to balance and fine-tune excitatory neurotransmission of various neuronal systems, including the monoaminergic projections to the forebrain.

There are two major classes of GABA receptors: ionotropic $GABA_A$ and metabotropic $GABA_B$. $GABA_A$-Rs are known as key control elements of anxiety states based on the potent anxiolytic activity of benzodiazepines, which act as positive allosteric modulators of this receptor (Luscher, Shen, & Sahir, 2011). Structurally, $GABA_A$-Rs represent heteropentameric GABA-gated chloride channels, and can be found at synapses, extra-synapses, or at axon terminals.

The $GABA_B$ receptor ($GABA_B$-R) is a heterodimeric, metabotropic, class C of G protein-coupled site, which represents a more complex structure than other G protein-coupled receptors (GPCRs) (Pinard, Seddik, & Bettler, 2010). $GABA_B$-R is involved in affective disorders based on altered anxiety- and depression-related behaviors observed in mice following pharmacological or genetic manipulations of this receptor (see the review by Luscher et al. (2011)). In the CNS, $GABA_B$-Rs are presynaptic receptors (auto- and heteroreceptors), inhibiting the release of neurotransmitters from nerve terminals, as well as postsynaptic receptors, which are stimulated by GABA release to hyperpolarize pyramidal cells. Activation of $GABA_B$-R causes downstream changes in K^+ and Ca^{2+} channels, mainly through an inhibition of the cAMP synthesis (Bowery et al., 2002).

A systematic classification of cortical GABAergic interneurons was recently published (DeFelipe et al., 2013). Three groups of interneurons account for nearly all cortical GABAergic interneurons (Rudy, Fishell, Lee, & Hjerling-Leffler, 2011). The three markers are the Ca^{2+}-binding protein parvalbumin (PV), the neuropeptide somatostatin (SST), and the ionotropic $5-HT_{3A}$ receptor. Each group includes several types of interneurons that differ in morphological and electrophysiological properties, thus having different functions in the cortical circuit. PV interneurons, the main group, account for ~40% of GABAergic neurons, which include fast spiking cells. These fast-spiking interneurons regulate the activity of cortical pyramidal neurons and provide the inhibitory postsynaptic potential to these neurons (Povysheva et al., 2006). The other two groups represent ~30% of GABAergic interneurons (Rudy et al., 2011). All these interneurons are modulated by 5-HT and acetylcholine via ionotropic receptors (Demars & Morishita, 2014).

4.4.1. The GABAergic deficit hypothesis of depression

4.4.1.1. In patients with MDD and patients with TRD.
The GABAergic deficit hypothesis of MDD has been identified as one of the four causes of depression, together with altered monoaminergic neurotransmission, altered HPA axis function, and glutamatergic hypofunction. This hypothesis is reinforced by reports of decreased GABA levels in the plasma (Petty & Schlesser, 1981; Petty & Sherman, 1984) and CSF (Gerner & Hare, 1981) in depressed patients. More recently, brain imaging approaches using ^{1}H-MRS show dramatic reductions of GABA in the PFC region of MDD patients (Hasler et al., 2007; Sanacora et al., 1999; Sanacora et al., 2004). Interestingly, GABA deficits are more pronounced and severe in TRD patients (Price et al., 2009).

The GABAergic deficit hypothesis in depression also includes diminution in the number of PFC GABA neurons in patients with MDD. (post-mortem studies: Maciag et al., 2010; Rajkowska, O'Dwyer, Teleki, Stockmeier, & Miguel-Hidalgo, 2007). These data suggest GABAergic neurons vulnerability to pathological factors, thus their dysfunction may be the primary changes for the pathogenesis and prognosis of MDD (Luscher et al., 2011; Xu, Cui, and Wang, 2016). Together with down-regulation of glutamate transporters found in glial cells in MDD patients, these data highlight the tight coupling of the GABA synthesis with glutamate cycling, which involves glutamate decarboxylase-67 the isoform (GAD67). A recent proteomic approach in post-mortem cingulate cortex found persistent decreases in proteins such as GAD67 and EAAT3 across current MDD episodes or remission (Scifo et al., 2018).

Together, these data point out the fact that abnormal GABAergic signals of neurotransmission play a role in MDD. Thus, the elucidation of the molecular mechanisms underlying GABAergic neurons involvement is critically important to develop an efficient strategy for the treatment of MDD (K. Ma et al., 2016).

4.4.1.2. In animal models of anxiety/depression.
Studies in rodents are in line with these clinical results, i.e., depressive-like phenotypes of GABA$_A$-R mutant mice can be reversed by treatment with conventional antidepressant drugs, as well as with ketamine. Thus, GABAergic deficits may causally affect anxiety/depression-like phenotypes in mice (Fuchs et al., 2017). In addition, a sub-anesthetic dose of ketamine displays an antidepressant-like activity and enhance GABAergic synaptic transmission in the mPFC in BALB/cJ mice, known to have an anxious phenotype (Pham et al., 2018). A selective inactivation of the γ2 subunit gene of GABA$_A$-Rs in SST-positive GABAergic interneurons increased excitability of SST-positive interneurons, and in turn, increased the frequency of spontaneous inhibitory postsynaptic currents of targeted pyramidal cells (Fuchs et al., 2017). In another animal model, a chronic stress in rats induced a decrease in the frequency, but not the amplitude, of GABAergic inhibitory synaptic currents recorded from PV-positive GABAergic interneurons, suggesting presynaptic deficits in GABA release in this animal model of depression (Verkuyl, Hemby, & Joels, 2004).

4.4.1.3. Role of GABA$_A$ and GABA$_B$ receptors in anxiety/depression.
Strong evidence implicates the GABA$_A$-R in MDD or in co-morbidity of anxiety and depressive disorders. First, the phenotype of forebrain-specific GABA$_A$-R γ2 subunit (γ2$^{+/-}$) heterozygous mice includes anxious- and depressive-like emotional behaviors in seven different tests (Earnheart et al., 2007; Shen et al., 2010). These behavioral deficits involve a reduction in adult hippocampal neurogenesis as well as an elevation in plasma corticosterone levels. In addition, the modest reductions in GABA$_A$-Rs function and GABAergic synaptic transmission in γ2$^{+/-}$ mice resulted in a decreased expression of NMDA-R and AMPA-R, and impaired glutamatergic synapses in the mPFC and hippocampus (Ren et al., 2016). A single sub-anesthetic dose of ketamine fully restored synaptic function of pyramidal cells in γ2$^{+/-}$ mice along with antidepressant-like behavior. In parallel, GABAergic synapses of γ2$^{+/-}$ mice were potentiated by ketamine, but only in the mPFC (Ren et al.,

2016). Second, it seems that the distribution of GABA$_A$-R links glial cells to the pathophysiology of depression. Indeed, post-mortem cerebral cortex from MDD patients who died by suicide displayed up-regulation of GABA$_A$-R subunit gene expression in glial cells (Choudary et al., 2005). Third, antidepressant-like effects of MK-016, a negative allosteric modulator of GABA$_A$-R containing the α5 subunit, were also observed in rodents (Fischell, Van Dyke, Kvarta, LeGates, & Thompson, 2015; Zanos et al., 2017). These data suggest that benefits of antidepressant drug treatment can impact the GABAergic inhibitory neurotransmission, mainly in the mPFC (see Luscher et al., 2011).

GABA$_B$-Rs have also been studied as a target of antidepressant drugs. Indeed, preclinical studies showed that mice lacking functional GABA$_B$-Rs exhibit an antidepressant-like phenotype (Mombereau et al., 2004; Mombereau et al., 2005). A chronic pharmacological blockade of GABA$_B$-Rs increases adult hippocampal neurogenesis and induced an antidepressant-like response in BALB/Cj mice (Felice, O'Leary, Pizzo, & Cryan, 2012; Mombereau et al., 2004; Nowak et al., 2006).

In summary, data dealing with the role of GABAergic system in mechanisms involved in antidepressant-like activity point to the activation of GABA$_A$-Rs and a selective blockade of GABA$_B$-Rs in the brain.

4.4.1.4. GABAergic synaptic transmission in acute vs chronic stress.
While acute stress enhanced GABAergic synaptic transmission in the hippocampus, chronic stress reduced GABAergic synaptic currents and altered the integrity of hippocampal PV-positive interneurons (Hu, Zhang, Czeh, Flugge, & Zhang, 2010). In a UCMS model of depression in mice, GABA release by presynaptic terminals, and genes and proteins related to GABA synthesis and uptake (i.e., GAD67 and GABA transporters) decreased specifically in the mPFC (Ma et al., 2016). Moreover, this latter study showed decreased innervations from GABAergic axons to glutamatergic neurons. The stress-induced changes in GABAergic and glutamatergic neurons lead to imbalanced neural networks in the mPFC, which may be the pathological basis of MDD (Ma et al., 2016; Xu, Cui, and Wang, 2016).

4.4.2. The GABAergic system and ketamine's antidepressant-like activity

4.4.2.1. Ketamine-induced changes in GABA levels.
Recent clinical studies have demonstrated that fast antidepressant-like activity of ketamine impacted the GABAergic system. Using ^{1}H-MRS method in patients with MDD, Milak et al. (2016) (Milak et al., 2016) reported a rapid and robust ex vivo increases in both mPFC Glx and GABA in response to a single subanesthetic dose of ketamine intravenously. This up to 40% increase in cortical Glx and GABA concentrations may be explained by changes in brain glucose utilization. Virtually all the glucose entering into the brain is metabolized through glutamate because one molecule of glucose gives rise to two molecules of acetyl-CoA, which enter the tricarboxylic acid cycle to become α-ketoglutarate and then glutamate. In GABAergic neurons, this same process feeds GABA synthesis because glutamate is the precursor of GABA. Thus, the robust correlation between increases in Glx and GABA concentrations in this study supports the hypothesis that glucose utilization drives the glutamate/GABA neurotransmitter balance. These effects of ketamine support the GABAergic deficit hypothesis in depression (Luscher et al., 2011). Clinical reports also showed lower CSF, blood or in vivo brain imaging measurements of GABA levels in MDD patients, and monoaminergic antidepressant drugs reversed these effects. Indeed, depressive patients had lower serum GABA levels compared with healthy individuals, and one ECT increased baseline GABA levels (Esel et al., 2008). Using ^{1}H-MRS in patients with MDD, the decreased cortical GABA concentration was reversed either after treatment with repetitive transcranial magnetic stimulation (Dubin et al., 2016), or following SSRI treatment and ECT (Bhagwagar et al., 2004; Sanacora et al., 2003; Sanacora, Mason, Rothman, & Krystal, 2002).

Similarly in preclinical studies, microinjection of bicuculline (a GABA$_A$-R antagonist) increased local cerebral glucose utilization in

Table 2
Ketamine antidepressant-like activity involved glutamatergic neurotransmission in preclinical studies (rats and mice).

References	Species (rats or mice) and strain	Ketamine dose and route of administration	Behavioral and neurochemical changes	Molecular/cellular changes, brain region studied
I) Ketamine increases glutamate content				
Moghaddam et al., 1997	Rats	Ketamine 10, 20 and 30 mg/kg, i.p. (acutely)	- Increased Glu_{ext} level (PFC)	
Lorrain, Baccei, et al., 2003	Sprague–Dawley rats	Ketamine 18 mg/kg, s.c. (acutely)	- Increased Glu_{ext} level (mPFC)	
Melo et al., 2015	Wistar rats, UCMS model	Ketamine alone or combined: ketamine (4 days) + fluoxetine or imipramine (14 days), all at dose 10 mg/kg, i.p.	- Ketamine alone or in combination: reversed UCMS-induced anhedonia in the FST, sucrose preference, EPM. - UCMS-induced decrease Glu levels in the NAc, but not the PFC, and the combination reversed these effects	
Chowdhury et al., 2017	Sprague–Dawley rats	Ketamine 3, 10 and 30 mg/kg, i.p. (30 min and 24h prior testing)	- Increased Glu, GABA and Gln contents only at 30 min post-injection, not at 24h (mPFC) - Reduced immobility duration (FST, only at dose 30 mg/kg, 24h post-injection)	
Zhu et al., 2017	Sprague–Dawley rats, UCMS model	Ketamine 10, 25 and 50 mg/kg, i.p. (5 days)	- UCMS induced an increase of Glu_{ext} (hippocampus), reversed by ketamine	
Pham et al., 2017	BALBc/J mice	Ketamine 10 mg/kg, i.p., (24h prior testing)	- Increased Glu_{ext} (mPFC) - Increased swimming duration (FST)	
II) Ketamine alters NMDA- and AMPA-R function				
Moghaddam et al., 1997	Rats	Ketamine 10, 20 and 30 mg/kg, i.p. (acutely) + CNQX 50 µM infused intra-PFC (acutely)	- CNQX blocked ketamine-induced increase in $dopamine_{ext}$ level (PFC)	
Wakasugi et al., 1999	Rat hippocampal slices	Ketamine 10 mM (acutely)		- Reduced NMDA-R-mediated responses and enhances $GABA_A$-receptor-mediated responses
Maeng et al., 2008	Mice	Ketamine 2.5 mg/kg, i.p. (24h or 2 weeks prior testing) + NBQX (10 mg/kg, i.p., 10 min prior to ketamine)	- NBQX blocked ketamine effects in the FST	- Ketamine reduced p-GluA1 (hippocampus), blocked by NBQX
		Ro 25-6981 (selective NR2B antagonist) 3 mg/kg, i.p. (30 min prior testing) + NBQX (10 mg/kg, i.p.)	- NBQX blocked Ro 25-6981 effects in the FST	
Li et al., 2010, Li et al., 2011	Rats	Ketamine 10 mg/kg, i.p. (24h prior testing) + NBQX 10 mg/kg, i.p. (10 min prior to ketamine)	- Ketamine decreased immobility in the FST, latency to feed in the NSF and number of escaspe failure (LH paradigm)	- Ketamine rapidly increase synaptic proteins and spine number (PFC) - NBQX blocked ketamine-induced increase in p-mTOR, p4E-BP1 and pp70S6K expression (PFC)
		Ro 25-6981 (selective NR2B antagonist) 10 mg/kg, i.p. (24h prior testing)	- Produced rapamycin-sensitive behavioral response (FST and NSF)	- Activated mTOR
Autry et al., 2011	C57Bl6 mice	Ketamine 3 mg/kg, i.p. (30 min prior testing) + NBQX 10 mg/kg, i.p. (30 min prior testing)	- NBQX blocked ketamine effects in the FST	
		Ketamine 1, 5, 20 and 50 µM in hippocampal cultures (acutely)		- blocked NMDA-R spontaneous activity (from 1 µM) - increased AMPA-R-mediated synaptic responses (at 20 µM)
Koike et al., 2011	ICR mice (for TST) Sprague-Dawley rats (LH paradigm)	Ketamine 10 mg/kg, i.p. (30 min prior testing) + NBQX 10 mg/kg, s.c. (5 min prior to ketamine)	- NBQX blocked ketamine effects in reducing the number of escape failure (LH paradigm) and immobility duration in the TST	
		Ketamine 30 mg/kg, i.p. : 72h prior testing) + NBQX 10 mg/kg, s.c. (72h prior testing)	- NBQX blocked ketamine effects in the TST	
Koike & Chaki, 2014	Sprague-Dawley rats	Ketamine 10 mg/kg, i.p. (24h prior testing) + NBQX 1, 3 & 10 mg/kg, s.c. (30 min prior testing)	- NBQX (10 mg/kg) blocked ketamine effects in the FST	
Miller et al., 2014	NR2B KO mice	Ketamine 50 mg/kg, i.p. (30 min prior to TST and 24h prior to electrophysiology)	- NR2B KO in mice increased immobility duration in the TST, similar to ketamine	- NR2B KO occluded ketamine-induced increase in excitatory synaptic transmission (PFC) - NR2B KO occluded ketamine-induced increase in BDNF, SAP-102, GluA1, p-mTOR expression
Nishitani et al., 2014	Wistar rats	Ketamine 5 and 25 mg/kg, s.c. (acutely) + NBQX 30 nmol intra-DRN (10 min prior to ketamine)	- Increased $5\text{-}HT_{ext}$ (mPFC and DRN), blocked by NBQX	
Björkholm et al., 2015	Sprague–Dawley rats	Ketamine 10 mg/kg, i.p. (24 prior testing)		- Increased AMPA- and NMDA-induced current activation

Table 2 (continued)

References	Species (rats or mice) and strain	Ketamine dose and route of administration	Behavioral and neurochemical changes	Molecular/cellular changes, brain region studied
El Iskandrani et al., 2015	Sprague–Dawley rats	Ketamine 10 and 25 mg/kg, i.p. (30 min prior testing) + NBQX 3 mg/kg. i.p. (10 min prior to ketamine)		- Increased AMPA-evoked (from 10 mg/kg) firing and decreased NMDA-evoked firing (only at 25 mg/kg) (hippocampus) - NBQX blocked ketamine-induced increases in population activity of VTA dopamine neurons and firing rate of LC norepinephrine neurons
Zhang et al., 2015	C57BL/6J mice, Social defeat model	Ketamine 10 mg/kg, i.p. (3h prior testing)	- Decreased immobility (FST and TST) - Long-lasting effects (up to 7 days) on sucrose preference test	- Decreased proBDNF (PFC), increased BDNF, PSD-95 and GluA1 (PFC, hippocampus), at 4 and 8 days post-treatment
Beurel et al., 2016	Mice knock-in GSK3 alpha/beta homozygous	Ketamine 10 mg/kg, i.p. (24h prior testing)		- GSK3 knockin blocked ketamine-induced up-regulation of BDNF. mTOR and GluA1 expression (hippocampus)
Fukumoto et al., 2016	C57BL/6J mice	Ketamine 30 mg/kg, i.p. (30 min prior testing) + NBQX 1, 3 and 10 mg/kg, s.c. OR + NBQX 0.01 and 0.03 nmol/side intra-mPFC (35 min prior testing)	- NBQX (only at 3 and 10 mg/kg or 0.03 nmol intra-mPFC) blocked ketamine effects in the FST	- NBQX (0.03 nmol intra-mPFC) blocked ketamine-induced increase of c-Fos expression on 5-HT neurons (DRN)
Ren et al., 2016	GABA$_A$R subunit gamma2$^{+/-}$ mice (129X1/SvJ) cell cultures	Ketamine 10 μM (3-6h prior testing)		- Reversed NR1, AMPA-R cell surface expression and glutamatergic synapses density deficit
	GABA$_A$R subunit gamma2$^{+/-}$ mice (C57BL/6J)	Ketamine 3 mg/kg, i.p. (8h prior testing) Ketamine 10 mg/kg, i.p. (24h prior testing)	- Increased time and entries in open arm (EPM) - Increased swimming time (FST)	- Increased NMDA-R (NR2B subunit) surface expression (PFC, hippocampus) - Increased AMPA-R surface and total expression (only hippocampus) - Reversed the deficit of functional glutamatergic synapses
Pham et al., 2017	BALBc/J mice	Ketamine 2 nmol (intra-mPFC, 24h prior testing) + NBQX 0.1 μg (intra-DRN, 30min prior to ketamine)	- NBQX blocked ketamine-induced decrease in immobility duration (FST) and increase in 5-HT$_{ext}$ level (mPFC)	

Glu: glutamate. Gln: glutamine. Glu$_{ext}$: extracellular level of glutamate, measured by microdialysis. 5-HT$_{ext}$: extracellular level of glutamate, measured by microdialysis. LH: learned helplessness. TST: tail suspension test. FST: forced swim test. NSF: novelty suppressed feeding. EPM: elevated plus maze. i.p.: intraperitoneal injection. s.c.: sub-cutaneous injection. KO: knock-out. mPFC: medial prefrontal cortex. PFC: prefrontal cortex. DRN: dorsal raphe nucleus. VTA: ventral tegmental area. NAc: nucleus accumbens. NMDA-R: NMDA receptor. AMPA-R: AMPA receptor. UCMS: unpredictable chronic mild stress. BDNF: brain-derived neurotrophic factor.

rats, while muscimol (a GABA$_A$-R agonist) did the opposite (Feger & Robledo, 1991). This pharmacological study suggests that the brain GABAergic system could limit ketamine-mediated glutamate release and reduce excessive spread of glutamatergic excitation. To our knowledge, increases in GABA levels in rodents after ketamine administration has also been reported: using *ex vivo* ^{1}H-MRS, Chowdhury et al. (2017) reported a rapid and transient increase in GABA levels in post-mortem mPFC homogenates after a single i.p. ketamine injection in rats. Using a 4.7-T magnetic resonance system in anesthetized rats, two doses of ketamine (10 and 25 mg/kg) increased BOLD image contrast in the mPFC and hippocampus, but not in the ventral pallidum (Littlewood et al., 2006). Using *in vivo* microdialysis in freely moving BALB/Cj mice, ketamine also increased extracellular GABA levels (GABA$_{ext}$) in the mPFC at 24 h post-administration (Pham et al., 2018). Thus, these results suggest that ketamine produced a dose-dependent cortical GABA release, which could correct the deficit in the GABAergic system found in MDD, most effectively in the mPFC, a region highly implicated in MDD, underlining an important role of GABAergic interneurons in this brain region in the fast/sustained antidepressant activity of ketamine. However, opposite results regarding changes in cortical GABA levels as measured *ex vivo* in post-mortem brain homogenates by ^{1}H-MRS have been reported in the CUS model in Sprague Dawley rats: Indeed, when CUS model lasted for 35 days, Banasr et al. (2010) found decreases in GABA levels from the prelimbic cortex (Banasr et al., 2010). By contrast, CUS model for 11 days increased GABA levels in the anterior cingulate cortex, and a sub-anesthetic dose of ketamine (40 mg/kg, i.p.) normalized this effect (Perrine et al., 2014). Differences in experimental protocols may explain these

opposite effects. Taken together, these data emphasize the effects of ketamine on the GABAergic system, depending on different techniques applied and brain regions studied in rodents.

4.4.2.2. Ketamine effects in combination with GABA modulators. More studies are digging into the role of GABA$_A$ and GABA$_B$ receptors. Recently, a combination of low doses of ketamine (0.1 mg/kg, i.p.) and muscimol (0.1 mg/kg, i.p.) was sufficient to induce an early antidepressant-like effect in the TST 30min after drug administration (Rosa, Neis, Ribeiro, Moretti, & Rodrigues, 2016). There was no alteration in spontaneous locomotion when it was assessed 10 min after the TST. However, measurement of ketamine antidepressant-like activity at these early time points is problematic because of its acute dissociative effect.

Similarly, a sub-anesthetic (15 mg/kg, i.p.) dose of ketamine antagonized the seizure induced by bicuculline (a GABA$_A$-R antagonist) (Irifune et al., 2000). In rat cortical neurons in culture, muscimol opened GABA-Cl(-)-channel, permitted inward Cl$^-$ fluxes and increased basal glutamate release by potentiating intracellular Ca^{2+}, an effect reversed by bicuculline (Herrero, Oset-Gasque, Lopez, Vicente, & Gonzalez, 1999), suggesting a role of GABA$_A$-R activation in inducing neuronal excitation. Similar to muscimol and baclofen (a GABA$_B$-R agonist), ketamine also reduced bicuculline influence on spontaneous proximal discharges on rat cortical slices (Horne, Harrison, Turner, & Simmonds, 1986), indicating that ketamine also would possess a GABA$_B$-R agonistic property. Activation of GABA$_A$-R in the rat mPFC has been recently demonstrated to produce an anxiolytic-like response in the elevated plus maze test (EPM), while antagonism of this receptor by bicuculline produced anxiogenic-like behavior (Solati, Hajikhani, & Golub, 2013).

Indeed, bicuculline-induced convulsive symptoms in rats at 7.5 mg/kg was prevented by pre-treatment with ketamine (40 mg/kg) (Schneider & Rodriguez de Lores Arnaiz, 2013). It is important to note that, if a receptor antagonist induces a cellular response when administered alone (as bicuculline 8 mg/kg i.p.: Irifune et al., 2000), it suggests that GABA$_A$-Rs are tonically activated by endogenous GABA levels.

Ketamine reduced NMDA-R-mediated responses and enhanced GABA$_A$-R-mediated responses on rat hippocampal slices, indicating specific actions on inhibitory synapses and changes in the balance between glutamate (excitatory) and GABA (inhibitory) synaptic transmission in vitro (Wakasugi, Hirota, Roth, & Ito, 1999). Thus, agonism of GABA$_A$-R, even indirectly, could possibly contribute to ketamine mechanism of antidepressant-like activity (Nakao et al., 2003). Combining GABA$_A$ or GABA$_B$ receptors pharmacological activation with ketamine also produced intriguing results, e.g., muscimol and baclofen can cause impaired memory acquisition and aggravate the negative effects of ketamine (Farahmandfar, Akbarabadi, Bakhtazad, & Zarrindast, 2017; Khanegheini, Nasehi, & Zarrindast, 2015).

Ketamine may have different influences on GABAergic system depending on the brain regions. By increasing γ power in the rat hippocampus, low dose of ketamine (3 mg/kg, s.c.) increased local pyramidal cell firing possibly by disinhibition of local inhibitory interneuron, which are the causes of psychosis-relevant behaviors (Ma & Leung, 2018). This effect is blocked effectively by local injection of muscimol into this region, indicating that agonism of GABA$_A$-R in brain regions other than mPFC is conversely necessary to limit ketamine's psychosis effect.

4.4.2.3. Role of PV interneurons in ketamine's effects. Ketamine as an NMDA-R antagonist is attracted predominantly to this target located on GABAergic interneurons according to the disinhibition hypothesis proposed by the literature (Homayoun & Moghaddam, 2007). PV interneurons receive the largest glutamatergic input among all GABA-releasing neurons in the cortex. This class of interneurons is highly sensitive to NMDA-R antagonists and enriched with GluN2A subunits (Behrens et al., 2007; Paoletti et al., 2013), which could be the primary target of ketamine. However, several selective subunit NMDA-R antagonists did not demonstrate efficacy in TRD (Abbasi, 2017). Alterations of PV-positive cells by ketamine have been well established in schizophrenia (Brown et al., 2015; Jeevakumar et al., 2015; Sabbagh et al., 2013), but the role of PV in ketamine-induced antidepressant-like activity needs to be further investigated. Recently, Wang et al. (2014) reported that ketamine down-regulated the activity of PV interneurons by reducing the levels of PV and GAD67, thus down-regulating the GABA levels and up-regulating glutamate levels in the rat hippocampus and PFC, suggesting that PV interneurons may be involved in ketamine's antidepressant-like activity. Moreover, Zhou et al. (2015) confirmed that an acute dose ketamine (10 and 30 mg/kg) displayed an antidepressant-like activity in the FST at 30min and 2hr post-treatment and reduced PV and GAD67 tissue levels at 30min in the mPFC of 'naïve', non-stressed rats. It also increased glutamate levels and decreased GABA levels in the mPFC. In addition, only the higher dose of ketamine (30 mg/kg) at repeated administration (5 days) reduced PV and GAD67 cortical tissue levels at 2hr post-treatment, but this regime elicited stereotyped behaviors and hyperlocomotion, and a longer duration of PV and GAD67 loss, higher glutamate levels and lower GABA levels in the mPFC, which may mediate a disinhibition of glutamatergic neurotransmission in 'naïve' rat PFC. In support of these findings, stress induced by UCMS in mice increased mPFC PV expression, which could originate from activation of glutamatergic circuit from amygdala onto frontal PV neurons (Shepard & Coutellier, 2018). Indeed, glutamatergic afferents from the amygdala to the PFC drive robust inhibition through monosynaptic activation of PV interneurons (McGarry & Carter, 2016). Unfortunately, Shepard et al. (2017) (Shepard & Coutellier, 2018) did not use any antidepressant drugs, i.e., ketamine or SSRI, to reverse these observed alterations of PV in

UCMS mice, which could bring interesting insights to the subject. Intriguingly, Yang et al. (2015) (Yang et al., 2015) has reported that (S)-ketamine, but not (R)-ketamine, induced PV-positive cells loss in a social defeat stress model of mice, which displayed a lack of antidepressant-like effects compared to the (R)- enantiomer.

Remarkably, a study used genetically modified C57Bl/6 mice lacking NMDA-R specifically in PV cells to probe directly the connection between NMDA-R-dependent function of PV interneurons and depression-like behavior. The mutation itself did not provoke a depression-like behavior, and ketamine still produced an antidepressant-like effect in the FST of mutant PV-Cre+/NR1f/f mice (Pozzi et al., 2014). This study used constitutive adult knockout mice, thus compensatory events may have occurred during the development. These results suggest that NMDA-Rs located on PV interneurons are not responsible for the antidepressant-like activity of ketamine. However, these effects were observed immediately after administration of a very low ketamine dose (3 mg/kg). Interestingly, the same decrease in PV and GAD67 was observed with the GluN2A-, but not the GluN2B-subunit selective NMDA-R antagonist in cortical PV interneuron in culture (Kinney et al., 2006), suggesting that the activity of GluN2A-containing NMDA-Rs plays a pivotal role in the maintenance of the GABAergic function of PV interneurons and subsidizes ketamine effects. Furthermore, alteration of PV interneurons before ketamine administration (10 mg/kg, i.p.) diminished its long-term antidepressant-like activity in rats (Donegan & Lodge, 2017), indicating that ketamine requires these interneurons to observe these effects. Taken together, these data suggest that upregulation of PV interneurons are implicated in anxiety/depression-like symptoms and are regulated by ketamine in rodents. Even though the alteration of PV precisely in depression still remains unclear, these studies indicate that loss of PV interneurons contributes to the antidepressant-like activity of ketamine. Meanwhile, there has been little to no information about how other classes of interneurons (SST and 5-HT$_{3A}$) would be involved in ketamine's action. Their locations as well as their functions in controlling neuronal activities are distinct from that of PV interneurons. More studies targeting individual class of interneurons could bring more insights into how ketamine functions as a fast-acting antidepressant drug as well as how to improve its safety profile in regard of psychotomimetic and addictive effects. It also underlines the key role of the balance between glutamate/GABA systems in its mechanism of action.

4.4.2.4. Ketamine increases GABA synaptic transmission. NMDA-R blockade is known to acutely increase spontaneous γ oscillations activity (Carlen et al., 2012), including ketamine (Hong et al., 2010; Lazarewicz et al., 2010; Pinault, 2008). Computational modeling supports the hypothesis that ketamine directly reduces NMDA-R-mediated inputs to fast-spiking PV-positive GABAergic interneurons, thus leading to enhanced cortical excitability in TRD (Cornwell et al., 2012). In this study, the NMDA-R antagonists-induced increase in spontaneous γ activity was limited to the period just after drug intake, when psychotomimetic symptoms were most prominent. Thus, ketamine-related increases in spontaneous γ cortical activity might be more relevant to the acute, dissociative than the antidepressant effects. Moreover, NMDA-R activation exerts a control on inhibitory GABAergic neurotransmission, e.g., in CA1 pyramidal neurons: NMDA increased firing of GABAergic interneurons, thereby leading to GABA release from GABAergic axons in mouse hippocampal slices (Xue et al., 2011). In addition, the NMDA-R antagonist MK-801 suppressed NMDA-induced increase in spontaneous inhibitory post-synaptic currents (IPSC). Thus, ketamine may have a similar mechanism of action.

Taken together, these studies confirm the implication of the GABAergic system in ketamine induced fast-antidepressant-like activity. There is a consensus in the literature for a decrease in the inhibitory role of cortical PV interneurons elicited by ketamine. It is now clear that ketamine is efficient in enhancing glutamatergic transmission, but its influence on GABAergic transmission still diverges between non-stress

and stress models in rodents. These effects of ketamine involved GABAergic system in preclinical studies are summarized in Table 3.

5. Conclusions

In this review, we have analyzed current data on ketamine antidepressant-like activity that involved the glutamatergic, GABAergic and serotonergic neurotransmissions.

The current indirect cortical disinhibition hypothesis regarding the cascade of cellular and molecular events leading to a fast antidepressant-like activity of an acute ketamine dose can be summarized as follows: ketamine binds to NMDA-R located on GABAergic interneurons, and induces a selective blockade of inhibitory GABA interneurons, thus increasing glutamate bursts (LTP) and glutamate release from pyramidal cells located in the mPFC. The subsequent activation of a ligand-dependent Na^+/Ca^{2+} channel, i.e., AMPA-R signaling located on post-synaptic glutamatergic neurons has described by many authors (see Duman et al., 2016; Miller et al., 2016; Rantamaki & Yalcin, 2016). It increases BDNF synthesis and release, which activates TrkB/Akt, then the mTORC1 signaling pathway in the mPFC (Duman's group: Li et al. (2010)), but deactivation of the eEF2 kinase in the ventral hippocampus (Monteggia's group: Autry et al. (2011)). These cascade ultimately led to synapse maturation and synaptogenesis, plasticity and a *fast antidepressant-like activity*.

However, several points need to be clarified. One of them is whether, in addition to glutamate, GABA and 5-HT release participate to this pathway. Ketamine is likely to enhance these three neurotransmitters, at least in the mPFC, but several specific brain circuits could contribute to its antidepressant-like activity. Using microdialysis technique in awake, freely moving mice, we found a concomitant increase in the Glu_{ext}, $GABA_{ext}$ and $5-HT_{ext}$ in the mPFC, while several authors reported increases in one of them. Thus, the question of which neurotransmitter was first modified and lead to further alteration of the others is also pending.

5.1. Glutamate release

In microdialysis studies, the increase in Glu_{ext} after administration of a single sub-anesthetic dose of ketamine, was observed in the mPFC either immediately after administration (in rats: Lopez-Gil et al., 2007; Lorrain, Schaffhauser, et al., 2003; Moghaddam et al., 1997) or 24 h after (in mice: Pham et al., 2017; Pham et al., 2018). So, ketamine rapid antidepressant-like effect may induce quick bursts of glutamate and glutamate release that set off a cascade of subsequent events involving GABA and 5-HT neurotransmission stimulation. Since ketamine binds to glutamate NMDA-R, glutamate release within the mPFC/hippocampus/DRN circuit is likely the first neurotransmitter initiating the cellular cascade leading to plasticity, then fast antidepressant-like activity. Cortical pyramidal neurons belong to two groups: single spiking cells (few) and repetitive bursting cells (present in most cortical areas). Both cell types also differ morphologically. Glutamate-induced bursts require activation of NMDA-R (by contrast, application of AMPA evoked single spikes) (Shi & Zhang, 2003). Thus, if bursts of glutamate are necessary for pyramidal neurons to activate GABA interneurons as suggested by Duman et al. (2016), ketamine, as an NMDA-R antagonist, may weaken the connections between pyramidal cells and GABA interneurons. Whether or not this mechanism is involved only in the fast antidepressant-like effects of ketamine, but also in its effects against stress (Brachman et al., 2016), pain relief (analgesic) (Zhao, Wang, & Wang, 2018), or psychotomimetic effects is currently unknown. Brain regions, circuits (amygdala and emotion), and neurotransmitters involved in these various properties must be different.

5.2. BDNF release/TrkB activation

Activity of the mPFC-hippocampus pathway suggests that an early transient activation of BDNF release and its binding to high affinity TrkB receptors in the hippocampus is essential for the sustained

antidepressant-like response to ketamine (Carreno et al., 2016). However, the hypothesis was questioned in heterozygous $BDNF^{+/-}$ mice. They found that neither ketamine nor the AMPA-R PAM LY451656 activated BDNF signaling, but produced a characteristic antidepressant-like response in these mice. Thus, unlike monoaminergic antidepressants, BDNF signaling would play a minor role in the antidepressant effects of glutamate-based compounds (Lindholm et al., 2012).

5.3. GABA release

Results regarding changes in $GABA_{ext}$ after ketamine have shown either no effect in several rat brain regions (Lindefors, Barati, & O'Connor, 1997; Littlewood et al., 2006), or an increase in the mPFC in BALB/cJ mice (Pham et al., 2018). This latter ketamine response in stressed mice is difficult to reconcile with the GABA deficit hypothesis in depression. The new multimodal antidepressant, vortioxetine also inhibits GABAergic neurotransmission in some brain regions (mPFC, vHipp) via a $5-HT_3$ receptor antagonism-dependent mechanism and thereby disinhibit pyramidal neurons and enhance glutamatergic signaling (Dale et al., 2018; Riga, Sanchez, Celada, & Artigas, 2016). However, it was shown that UCMS in mice impaired GABA release and reuptake by upregulating miRNAs and downregulating GAD67 in mouse cortex (Ma et al., 2016). It would be interesting to identify the family of GABA interneurons inhibited by ketamine (PV, SST, receptor $5-HT_{3A}$). For example, the cellular vulnerability to stress is exacerbated in SST-positive GABAergic interneurons (Fuchs et al., 2017; Lin & Sibille, 2015). In addition, the balance of excitation/inhibition is disrupted in various psychiatric disorders including MDD in which a selective vulnerability of GABAergic interneurons that co-express SST was recently suggested in cortical microcircuits (Fee, Banasr, & Sibille, 2017).

A functional potentiation of inhibitory GABAergic transmission from SST-positive GABAergic interneurons to pyramidal cells result in reductions in the synaptic excitation/inhibition ratio and was sufficient to elicit an antidepressant-like phenotype (Fuchs et al., 2017). Thus, glutamate/GABA balance, i.e., excitation/inhibition ratio of microdialysate levels reinforced this assertion (Pham et al., 2018). These data are consistent with the GABAergic deficit hypothesis of MDD and with an enhancement of GABAergic synaptic transmission by antidepressant therapies. Increases in dialysate levels of both glutamate and GABA could help balancing the brain's neurochemistry since neuronal atrophy and decreases in hippocampal volume are regularly reported in patients with MDD (Duman, 2009). A sustained activation of glutamate neurotransmission in the cortex and/or hippocampus can induce large increases in dialysate glutamate levels, and a subsequent retrograde excitotoxicity, neuronal degeneration or seizure susceptibility (Morales, Sabate, & Rodriguez, 2013). Studying the contribution of synaptic *versus* extrasynaptic NMDA-R in ketamine responses may help to address this question. In our study (Pham et al., 2018), ketamine enhanced Glu_{ext} (+100% *vs* control group, in pmol/sample) to a greater extent than $GABA_{ext}$ (+50% *vs* control group, in fmol/sample). Thus, this range of concentration could translate into distinct pharmacological (antidepressant-like activity) or pathological (neuronal death) role for extracellular glutamate (Moussawi, Riegel, Nair, & Kalivas, 2011).

The GABAergic alteration in ketamine's action depends on the type of stress. A chronic stress decreased GABA neurotransmission, and repeated antidepressant therapy (e.g., antidepressant drugs, ECT or ketamine) corrected this deficit. However, the increase in GABA levels seems unusual since GABA is the principal neurotransmitter regulating neural inhibition of the brain. This could be explained as a consequence of glutamate bursts, which induce fast-spiking GABAergic interneurons, then activates GABA release by GABAergic vesicular (Fig. 2). It might not be an enhancement of GABA synthesis, at least in the PFC and hippocampus, because ketamine downregulated the expression of GAD67 in these brain regions (Wang et al., 2014; Zhou et al., 2015). GAD67 is the enzyme endorsing the degradation process from glutamate to GABA in the glutamine-glutamate-GABA tripartite-synapse cycle. The

downregulation of GAD67 expression suggests that GABA synthesis is not the cause of GABA$_{ext}$ increases that we observed in the mPFC. However, this could be only selective to PV-positive (fast-spiking), but not other classes of interneurons (e.g., SST), since PV expression is also reduced in these studies. Downregulation of PV expression facilitated synaptic current in mice (Caillard et al., 2000), thus accelerated glutamatergic neurotransmission. In addition, this increase in GABA$_{ext}$ could also be explained by an increase in glucose utilization, which metabolized glutamate – the precursor of GABA or even a blockade of GABA reuptake by transporters located on pre-synaptic neurons or on glial cells.

5.4. Glutamatergic/GABAergic balance

The modification of ketamine on glutamatergic and GABAergic neurotransmission, together with the glutamate and GABA deficit hypothesis of depression, underline the importance of excitatory:inhibitory (E:I) balance of MDD. Modifying this balance seems to be the key of antidepressant therapies, as shown in a recent study (Fuchs et al., 2017). Here, our review resumes that ketamine is capable of enhancing both glutamate and GABA levels in the brains. The increase in excitability allows the brain to boost its function by increasing neurotransmission and reinforcing connections between brain regions. Increases in GABA levels elevation may limit the excessive increases in glutamate and to maintain the homeostasis of the brain. However, how ketamine induces such an increase still remains unclear. PV-positive interneurons target the proximal regions of pyramidal cells, whereas SST-positive interneurons are dendrite-preferring interneurons (Kuki et al., 2015) (Fig. 3). A downregulation of PV, the calcium-binding protein that control greatly the generation and timing of pyramidal cells' action potentials, was observed after treatment of ketamine. However, there has been little information of how ketamine interacts with SST-positive interneurons in the brain. Ketamine-induced downregulation of this protein was already described, but only at anesthetic dose (Pongdhana et al., 1987). We could imagine that the downregulation of PV expression will facilitate the action potential of pyramidal cells to occur, leading to an increase in glutamate release. However, how SST-positive interneurons control the dendrites of these cells to transfer the signals further in subcortical regions still require more investigations. Understanding how ketamine modifies particular subtypes of GABA interneurons is an important puzzle pieces to resolve the E:I balance implication in ketamine-induced antidepressant-like actions.

5.5. Serotonin release

It is likely that impaired cortical glutamate/GABA balance induced by NMDA-R antagonists lead to downstream changes in other neurotransmitters. Thus, several groups described increases in swimming duration in the FST, a serotonergic parameter (Cryan, Markou, & Lucki, 2002), and in mPFC 5-HT$_{ext}$ following systemic ketamine administration. However, the mechanism underlining ketamine-induced increases in 5-HT neurotransmission is intriguing, since it involved a decrease, but not an increase, in DRN firing rate (Pham et al., 2017), an effect similar to what was described following an acute SSRI treatment (Blier, Chaput, & de Montigny, 1988; Le Poul et al., 1995). The firing activity of 5-HT neurons returned to baseline after a chronic SSRI treatment because DRN 5-HT$_{1A}$ autoreceptors gradually desensitized (Chaput, de Montigny, & Blier, 1986; Hanoun, Mocaer, Boyer, Hamon, & Lanfumey, 2004). Activation of AMPA-R located on 5-HT neurons in the in the DRN might have facilitate 5-HT release in the mPFC, since pre-clinical studies found that selective AMPA-R antagonists blocked ketamine antidepressant-like activity together with the 5-HT$_{ext}$ increase in the mPFC. The mPFC projects densely towards the DRN either directly or indirectly via GABA interneurons (Fig. 3). When examining glutamate receptor mediated excitatory effects on DRN 5-HT neuronal activity in rat brain slices, Gartside et al. (2007) (Gartside et al., 2007) found that the selective

blockade of somatodendritic 5-HT$_{1A}$ receptors failed to enhance the excitatory response of DRN 5-HT neurons to AMPA and NMDA. Taken together, these data suggest that 5-HT could be subsequently modified by ketamine-induced glutamate bursts in the mPFC, without a high degree of tonic activation of 5-HT$_{1A}$ autoreceptors in the DRN.

5.6. Complex neurotransmission between NMDA, AMPA, GABA$_A$ and 5-HT receptors

The mechanism of ketamine antidepressant-like activity involves many receptor subtypes, and such a complicated network can not be analyzed separately. Herein, we point to the role of NMDA, AMPA, GABA$_A$ and 5-HT receptors. Ketamine is a NMDA-R channel blocker and the role of GluN1 sub-unit is still a matter of debate. The importance of GluN2A and GluN2B sub-units in ketamine's antidepressant-like activity needs to be further investigated. Ketamine blocks GluN2A- and GluN2B-containing NMDA-Rs equally (Kotermanski & Johnson, 2009), thus the implication of both subunits should be studied in parallel in ketamine antidepressant-like activity. The disinhibition theory of ketamine antidepressant-like activity suggests a selective blockade of NMDA-R located on GABAergic interneurons, which therefore disinhibits pyramidal cells to enhance their electrical activities. This pathway is considered as indirect. Since the PV-positive interneurons are enriched with GluN2A subunit of NMDA-R, and the downregulation of PV activity are strongly implicated in ketamine actions, it is possible that ketamine is attracted more to this subunit of NMDA-R to induce the disinhibition effect. The GluN2B subunit could be involved in the direct pathway of ketamine antidepressant-like activity. This direct pathway, according to Hall's team (Miller et al., 2016), takes place at pyramidal cells' dendrites, which, unlike the indirect pathway, might not involve an increase in Glu$_{ext}$ and 5-HT$_{ext}$. The selective blockade or removal of this subunit on pyramidal neurons engaged in a rapid increase in excitatory synaptic input onto these neurons to induce antidepressant effects. This is an interesting hypothesis since GluN2B selective antagonists have shown inconsistent results in clinical trials. More studies targeting GluN2B subunits on pyramidal cells will help to better understand this point.

Meanwhile, numerous results pointed out that the activation of AMPA-R is essential for ketamine antidepressant activity. Whether ketamine exerts these effects directly on AMPA-R or indirectly by blocking NMDA-R located on GABAergic interneurons remains unclear. AMPA-R activation might be required for the fast ketamine effect (i.e., when administration occurred 30min prior testing) to set off the glutamate bursts, while NMDA-R blockade might be involved in its sustained effects. The trafficking process of AMPA-R is demonstrated to be essential for ketamine's sustained effects, since it enhanced synaptogenesis and functional connectivity between brain regions (Duman & Aghajanian, 2012). Moreover, alteration of NMDA-R subunits expression in GluA1-knockout mice and alteration of AMPA-R subunits expression in GluN2B-knockout mice have confirmed an interaction between these two glutamatergic receptor subtypes in regulating depression. These two receptors also modulate 5-HT neuronal firing and local GABA release in the DRN.

It is still unclear to what extent the monosynaptic connection and the disynaptic connection – via GABA interneurons between the mPFC and DRN are involved in ketamine actions. The monosynaptic glutamatergic inputs from the PFC to serotonergic neurons in the DRN could modulate directly the increase in presynaptic 5-HT release. By contrast, the disynaptic pathway via GABA interneurons could involve a more complex pathway in which AMPA-R, NMDA-R and GABA$_A$-Rs interact concomitantly to induce an increase in cortical GABA levels. This could implicate the interneurons in both regions, the mPFC and DRN, since ketamine corrected the deficit of GABAergic neurotransmission most effectively in the mPFC, the region known to project densely towards the GABA-rich zone of the DRN (Fig. 3).

Optogenetic techniques could help to effectively differentiate these two distinct pathways. This innovative approach is used extensively

Table 3
Ketamine antidepressant-like activity involved GABAergic neurotransmission in preclinical studies (rats and mice).

References	Species (rats or mice) and strain	Ketamine dose and route of administration	Behavioral and neurochemical changes	Molecular/cellular changes, brain region studied
Horne et al., 1986	Slices of rat cerebral cortex	Ketamine 100 μM (acutely)		- Reduced spontaneous paroxysmal discharges, similar to muscimol 2μM and baclofen 10 μM
Wakasugi et al., 1999	Rat hippocampal slices	Ketamine 10 mM (acutely)		- Reduced NMDA-R-mediated responses and enhances $GABA_A$-receptor-mediated responses
Irifune et al., 2000	ddY mice	Ketamine 15 mg/kg, i.p. (acutely) + Bicuculline 8 mg/kg, i.p. (5 min after ketamine injection)	- Bicuculline induced tonic seizures, which was blocked by ketamine	
Nakao et al., 2003	Wistar rats	Ketamine 100 mg/kg, i.p. (2h prior to sacrificing) + Propofol 2 mg/kg, i.v. and bicuculline 0.5 mg/kg, i.v., bolus		- Increased c-Fos expression in the posterior cingulate and retrosplenial cortices, inhibited by propofol and disinhibited by bicuculline
Kinney et al., 2006	Cultured cortical PV interneurons of Swiss mice	Ketamine 0.5 μM (exposed during 24h)		- Decreased GAD67 expression specifically on PV+ neurons, similar to NR2A-selective antagonist NVP-AAM077.
Littlewood et al., 2006	Sprague–Dawley rats	Ketamine 10 and 25 mg/kg, s.c.(acutely)	- No alteration in $GABA_{ext}$ (ventral pallidum) was found acutely after ketamine injection	
Pinault, 2008	Wistar rats	Ketamine 2.5 - 10 mg/kg, s.c. (acutely)		- Dose-dependently increased the power (200%–400%) of wake-related gamma oscillations in the neocortex, similar to MK-801
Lazarewicz et al., 2010	CA3 region of mouse hippocampus			- Attenuated theta frequency band and enhanced gamma frequency range in both background and evoked power
Schneider and Rodriguez de Lores Arnaiz, 2013	Wistar rats	Ketamine 40 mg/kg, i.p. (acutely) + Bicuculline 5 mg/kg, i.p. (30 min after ketamine injection)		- Ketamine alone decreased [³H]-QNB binding (a parameter correlated with convulsant seizures), and blocked bicuculline-induced seizures
Perrine et al., 2014	Sprague–Dawley rats (CUS model)	Ketamine 40 mg/kg, i.p. (24h prior testing)	- Decreased immobility (FST) - CUS rats showed increase GABA level (ex vivo ¹H-MRS, mPFC), reversed by ketamine	
Pozzi et al., 2014	C57BL/6N mice lacking NMDA-R specifically in PV interneurons	Ketamine 3 mg/kg, i.p. (24h et 1 week prior testing)	- Ketamine alone reduced immobility (FST) - The mutation alone didn't induce depression-like behavior but attenuated ketamine's acitiviy in the FST	
Wang et al., 2014	Wistar rats	Ketamine 10 mg/kg, i.p. (30 min prior testing)	- Decreased immobility (FST) and latency to feed (NSF) - Decreased GABA level and increased glutamate level (PFC and hippocampus), detected by ELISA kits	- Decreased NRG1and p-ErbB4 genes expression (marker for pyramidal cells-PV+ interneurons activation) (PFC and hippocampus) - Decreased PV and GAD67 expression (PFC and hippocampus)
Zhou et al., 2015	Wistar rats	Ketamine 10 and 30 mg/kg, i.p. (30 min and 2h prior testing) The dose 30 mg/kg was administered repeatedly for 3 days consecutive	- Decreased immobility (FST) - Ketamine 30 mg/kg induced hyperactivity (Open Field test) - Increased glutamate level (PFC) - Decreased GABA level (PFC): acutely at 30 min for ketamine 10 mg/kg and persistently for ketamine 30 mg/kg	- Reduced PV and GAD67 expression (PFC): acutely at 30 min for ketamine 10 mg/kg and persistently for ketamine 30 mg/kg
Yang et al., 2015	C57Bl6/J social defeat model	(R)- or (S)-ketamine 10 mg/kg, i.p. (24h or 7 days before testing)	- Both induced antidepressant responses in the succrose preference test, TST and FST: (R)-ketamine is more potent in these tests - (S)-ketamine induced hyperlocomotion and PPI	- Increased synaptogenesis, BDNF-TrkB signaling (PFC and hippocampus) - (S)-Ketamine induced loss of PV+ cells (PFC and hippocampus)
Ren et al., 2016	$GABA_AR$ subunit gamma2$^{+/-}$ mice (C57BL/6J)	Ketamine 3 mg/kg, i.p. (8h prior behavioral tests) Ketamine 10 mg/kg, i.p. (24h prior molecular/cellular analysis)	- Gamma2$^{+/-}$ mice responded better to ketamine than wild-type mice in the FST, EPM	- Increased GABAergic synapses number and vesicular GABA transporters expression (only in mPFC) - Increased glutmatergic synaptic function (mPFC and hippocampus) - Down-regulation of NR1, NR2B, GluA2/3 surface expression by gamma2$^{+/-}$ were reversed by ketamine (mPFC, hippocampus)
Rosa et al., 2016	Female Swiss mice	Ketamine 0.1 mg/kg, i.p. (1h prior testing) + Muscimol 0.1 mg/kg, i.p. (30 min after ketamine injection)	- Decreased immobility (TST)	
		Ketamine 1 mg/kg, i.p. (30 min prior testing) + Baclofen 1 mg/kg, i.p. (30 min before ketamine injection)	- Ketamine 1 mg/kg alone was sufficient to decrease immobility (TST), which was blocked by Baclofen	

Table 3 (continued)

References	Species (rats or mice) and strain	Ketamine dose and route of administration	Behavioral and neurochemical changes	Molecular/cellular changes, brain region studied
Chowdhury et al., 2017	Sprague–Dawley rats	Ketamine 3, 10 and 30 mg/kg, i.p. (30 min and 24h prior testing)	- Increased GABA content only at 30 min post-injection, not at 24h (mPFC) - Reduced immobility duration (FST, only at dose 30 mg/kg)	
Donegan & Lodge, 2017	Sprague–Dawley rats treated with chondroitinase to degrade PV+ neurons	Ketamine 10 mg/kg, i.p. (30 min and 1 week prior testing)	- Ketamine alone decreased immobility (FST), blocked by PV+ neurons degradation	
Pham et al., 2017a	BALBc/J mice	Ketamine 10 mg/kg, i.p., (24h prior testing)	- Increased GABA$_{ext}$ (mPFC) - Increased swimming duration (FST)	
Ma & Leung, 2018	Long-Evans hooded rats	Ketamine 3 mg/kg, s.c. (acutely) + muscimol 0.5 µg/ 0.5 µL/side (intra-hippocampus, 15 min prior to ketamine)		- Ketamine alone induced gamma wave increase (posterior cingulate cortex (PCC) and hippocampus), blocked by muscimol intra-hippocampus (only in hippocampus)
		Ketamine 0.4 µg/ 0.4µL/side (intra-PCC, acutely) + Muscimol at same dose (15 min prior to ketamine)	- Ketamine induced hyperlocomotion, normalized by muscimol	- Ketamine disrupted prepulse inhibition, blocked by muscimol

GABA$_{ext}$: extracellular level of GABA. PV+: parvalbumin positive. FST: forced swim test. EPM: elevated plus maze. TST: tail suspension test. NSF: novelty suppressed feeding. i.p.: intraperitoneal injection. s.c.: sub-cutaneous injection. mPFC: medial prefrontal cortex. PFC: prefrontal cortex. PCC: posterior cingulate cortex. ^{1}H-MRS: proton magnetic resonance spectroscopy. CUS: chronic unpredictable stress.

today to study brain circuits. Using photosensitive receptors, this technique allows neurobiologists to access specific neuronal pathways with a high selectivity targeting neuronal types. Further studies using an optogenetic approach, in combination with conventional techniques (e.g., microdialysis, electrophysiology) should be conducted to examine the specific role of each neuronal type (glutamate, GABA, 5-HT) in some potential circuits such as mPFC-DRN and mPFC-vHipp to understand more deeply the connections between these neurons and the order in which they are altered in ketamine's actions.

5.7. Ketamine response rate in TRD

Defining ketamine responders and non-responders in rodent models of anxiety/depression could bring relevant information in line with the clinical interest of ketamine in TRD. Protein expression represents a combination of markers associated with the maintenance of animals in a refractory state, or associated with behavioral improvement (Mekiri, et al. November 2015; Mendez-David et al., 2017). Future preclinical studies will be required to validate whether proteomic changes observed in responders and non-responders ketamine-treated mice mirror biological and imaging changes (e.g., ex vivo nuclear magnetic resonance spectroscopy, PET scan, magnetic resonance imaging studies) observed in TRD patients.

In conclusion, the mechanism of ketamine requires complex interactions between different neurotransmitters, receptors, and brain regions. Indirect and direct pathways, as well as the monosynaptic and disynaptic connections, have been suggested to understand ketamine antidepressant mechanism of action. Identifying how all these factors connect together to induce such a rapid and sustained antidepressant-like activity of ketamine, esketamine, their metabolites and AMPA-R agonists require more studies combining several techniques, e.g., the coupling of optogenetic and in vivo microdialysis analysis realized during behavioral tests in rodents (Tritschler et al., 2018). The glutamatergic/GABAergic balance must be in the center of these investigations. We need to get more information about the pharmacological properties of NMDA-R and AMPA-R subunit-specific ligands (e.g., GluN2A, GluN2B, GluA1) at particular location (pyramidal cells, PV- versus SST-GABA interneurons, 5-HT neurons), in particular neuronal circuits (e.g., mPFC-DRN, mPFC-hippocampus). These preclinical discoveries will pave the way for the clinical development of the next generation of antidepressant drugs being fast-acting, more effective, and better tolerated.

Conflict of interest

The authors declare no conflict of interest.

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