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Depression and schizophrenia viewed from the perspective of amino acidergic neurotransmission: Antipodes of psychiatric disorders

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ABSTRACT

Depression and schizophrenia are burdensome, costly serious and disabling mental disorders. Moreover the existing treatments are not satisfactory. As amino-acidergic (AA) neurotransmitters built a vast majority of brain neurons, in this article we plan to focus on drugs influencing AA neurotransmission in both diseases: we will discuss several facts concerning glutamatergic and GABA-ergic neurotransmission in these diseases, based mainly on preclinical experiments that used stimulators and/or blockers of both neurotransmitter systems. In general a picture emerges showing, that treatments that increase excitatory effects (with either antagonists or agonists) tend to evoke antidepressant effects, while treatments that increase inhibitory effects tend to display antipsychotic properties. Moreover, it seems that the antidepressant activity of a given compound excludes it as a potential antipsychotic and vice versa.

Contents

1. Introduction

It is estimated that each year, 38.2% of the European Union (EU) population (or 164.8 million people) suffer from a mental disorder: 7.8% suffer from depression and 1.2% from psychotic diseases (Wittchen et al., 2011). In terms of disability measured in DALYs (disability adjusted life years), depression has already become by far the most burdensome disorder of all diseases in the EU as well as the most costly brain disease (Andlin-Sobocki, Jonsson, Wittchen, & Olesen, 2005). On the other hand, schizophrenia is considered to be among the most serious mental diseases and one of the most individually disabling of the mental disorders (Ormel et al., 2008), (Rossler, Salize, van Os, & Riecher-Rossler, 2005).

The serendipitous discovery of antidepressant and antipsychotic drugs at the beginning of the 1950s (Laborit, Huguenard, & Alluaume, 1952) (Kuhn, 1958) led to the development of monoaminergic theories of both depression (Schildkraut, 1965); (Lapin & Oxenkrug, 1969) and schizophrenia (Carlsson & Lindqvist, 1963) (Horn & Snyder, 1971), which dominated the field for next 40 years and, to a large extent, are still dominant. The problem arises when it comes to the treatment of both diseases. Despite the fact that monoaminergic drugs to treat both

Abbreviations: AAR, amino acidergic receptors; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AMN082, N,N′-dibenzhydrylethane-1,2-diamine dihydrochloride; CNS, central nervous system; DALYs, disability-adjusted life years; GABA, γ- aminobutyric acid; Glu, Glutamate; iGlu, Ionotropic glutamate receptors; KO, knockout; mGlu, metabotropic glutamate receptor; NAM, negative allosteric modulator; NMDA, *N*-methyl-D-aspartate acid; PAM, positive allosteric modulator.

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depression and schizophrenia have been on the market for over 60 years, neither their efficacy nor the adverse effect profiles are satisfactory; moreover, long-term treatment is necessary to achieve a positive clinical outcome (Rosenzweig-Lipson et al., 2007); (Leucht, Wahlbeck, Hamann, & Kissling, 2003).

Drug discovery in neuroscience involves behavioral testing of new compounds at the preclinical level. Analyzing the results, one can observe that the compounds active in animal models of depression are, in most cases, not active as antipsychotics and vice versa. What the mechanism of this phenomenon is, remains an area of speculation at present. Are depression and schizophrenia two poles of brain disability, and is their treatment mutually exclusive? In this article, we will discuss these questions.

2. Glutamate and GABA as promising targets for new psychotropic drugs

Cells that produce γ-aminobutyric acid (GABA) or glutamate (Glu) comprise the vast majority of brain neurons; it is presumed that up to 99.9% of neurons (0.1% = 100 million neurons) are either GABAergic or glutamatergic (van der Zeyden, Denziel, Rea, Cremers, & Westerink, 2008). Moreover, both systems stay in physiological balance by being inhibitory and excitatory forces, respectively (Schoepp, 2001). All of the other neurotransmitters and neuromodulators play supporting roles and are under the control of the two biggest players. An important factor is that the receptors that are able to receive and process the signals from glutamate or GABA are present on all cells in the brain, including neurons and glia. Therefore, it is highly probable that disturbances in glutamatergic or GABAergic neurotransmission may underlie many CNS disorders and that manipulation of GABA- or glutamate-dependent pathways will have a great impact on brain functioning. As such, these receptors may prove to be excellent drug targets.

Is the functioning of the brain dependent on the physiological balance between excitation and inhibition? In the nervous system, we have examples showing that whole networks can operate on such a basis. An obvious example is the autonomic nervous system (ANS). Here, the functioning of almost all of the internal organs depends on the balance between two transmitter systems: the cholinergic (parasympathetic) system and the adrenergic (sympathetic) system. For example, the stimulation of the cholinergic system slows down the heart rate, while the stimulation of the adrenergic system does the opposite. The bronchi can be dilated either by blocking the parasympathetic system or by stimulating the sympathetic system (Lundberg, 1996). Such examples can be given for virtually all internal organs. Can this rather simplistic mechanism be functioning in such an immensely complicated structure as the central nervous system (CNS)?

3. Ionotropic glutamate receptors

The activity of glutamate is controlled by the number of ionotropic and metabotropic receptors that are expressed in almost all neurons in the CNS. The ionotropic (iGlu) receptors are ligand-gated cation channels which are named after the agonists that they were originally identified. Three major types of iGlu are *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate receptors, (Kew & Kemp, 2005; Parsons, Danysz, & Quack, 1998).

3.1. NMDA receptors – the first examples of dichotomy

The observations concerning NMDA receptor ligands are important to consider. The NMDA receptors that mediate the rise in postsynaptic Ca2+ are cationic ion channels involved in physiological and pathological processes in the brain (Lau & Zukin, 2007). The first preclinical data showing that NMDA receptor antagonists produce antidepressant-like effects were published by Trullas and Skolnick in 1990 (Trullas & Skolnick, 1990). These findings were reproduced by a number of researchers for a number of compounds [for review, see (Pilc, Wieronska, & Skolnick, 2013)]. This research indicated that treatments that inhibited or attenuated NMDA-receptor mediated neurotransmission had antidepressant activity. It was confirmed later in clinical trials that the blockade of NMDA receptors ameliorates symptoms in severely depressed patients (Berman et al., 2000); (Zarate et al., 2006) reviewed in (Machado-Vieira, Henter, & Zarate, 2016). It is postulated that the antagonistic action of ketamine on NMDA receptors located on GABA-ergic neurons (Fig. 1 A) results in the loss of inhibitory control over glutamatergic neurons and produces a subsequent glutamate efflux in the

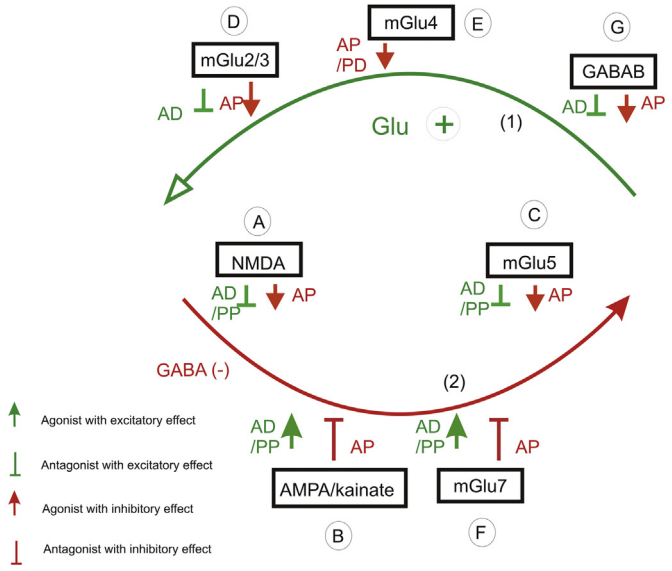

Fig. 1. The basic excitatory-inhibitory loop on the level of the whole brain with the placement of receptors for amino acidergic agents to explain their preclinical effectiveness as antidepressant or antipsychotic substances. (1) Excitatory glutamatergic neuron (green - go), (2) inhibitory GABA-ergic neuron (red - stop). AD: antidepressant, PD: pro-depressant, AP: antipsychotic, PP: pro-psychotic.

A) The NMDA receptors are placed postsynaptically at the GABA-ergic neuron. The inhibition of NMDA receptors leads to antidepressant (AD) effects that may be accompanied by pro-psychotic (PP) activity. These effects are perhaps due to disinhibition of GABA neurons and the increase in glutamate influx. This is an example of action of an antagonist with excitatory effects (green bars -⊥). The co-agonists of NMDA receptors show antipsychotic (AP) efficacy, perhaps due to inhibitory effects on glutamate influx. This is an example of an action of an agonist with inhibitory effects (red arrows-↑).

B) Stimulation of AMPA receptors produces antidepressant, while inhibition antipsychotic-like effects.

C) As mGlu5 and NMDA receptors are closely related, mGlu5 receptors are placed on GABA-ergic neurons together with NMDA receptors. Antagonists and/or NAMs of mGlu5 receptors produce AD effects that may be accompanied by PP activity. Agonists and PAMs of mGlu5 receptors have AP activity in animal models.

D) The mGlu2/3 receptors are placed presynaptically and are negatively coupled to AC. Inhibition of these receptors is connected with AD activity. Stimulation of mGlu2/3 receptors mediates the inhibitory effects of glutamatergic transmission and displays AP efficacy.

E) The mGlu4 receptors share presynaptic placement and second messenger coupling with mGlu2/3 receptors. Stimulation of mGlu4 receptors produces AP effects (the PD activity was also documented). The effects of mGlu4 antagonists have not yet been determined.

F) Stimulation of mGlu7 receptors mediates the inhibitory effects of glutamatergic transmission. Stimulation of mGlu7 receptors placed on GABA-ergic neurons leads to inhibition of GABA release, hence to increases in glutamate release. This results in AD efficacy, hence the term agonist with excitatory effects (green arrows-↑). The blockade of these receptors, termed an antagonist with inhibitory effects (red bars-⊥) – tends to produce AP activity.

G) The GABA B receptors here are placed presynaptically on glutamatergic neurons. Inhibition of these receptors is connected with AD efficacy. Stimulation of GABA B receptors mediates inhibitory effects of GABA-ergic transmission and produces AP effects.

prefrontal cortex (Moghaddam, Adams, Verma, & Daly, 1997) (hence, the term antagonist with excitatory effects) and thus produces antidepressant effects (Fig. 1 A) [for review, see (Palucha-Poniewiera & Pilc, 2016)].

However, the antidepressant efficacy of NMDA receptor antagonists is accompanied by a number of adverse effects, including psychotomimetic activity and abuse potential described first in 1959 for phencyclidine (angel dust) in humans taking it illegally (Luby, Cohen, Rosenbaum, Gottlieb, & Kelley, 1959). Ketamine is also a drug of abuse.

On the other hand, administration of such agents as Glycine, D-serine, D-alanine (the endogenous co-agonists of the glycine modulatory site of NMDA receptors) as well as D-Cycloserine and GLYX-13 (which are partial agonists of the glycine modulatory site) can be used in schizophrenia as add-on treatments (Hashimoto, Malchow, Falkai, & Schmitt, 2013), (Balu & Coyle, 2015) and can significantly improve the predominantly treatment-resistant negative and cognitive symptoms of the disease (Tsai & Lin, 2010). If, as discussed above, the NMDA receptors are located on GABA-ergic neurons, their stimulation should lead to the release of GABA, hence the term agonists with inhibitory effects (Fig. 1A). Generally, no antidepressant-like activity is observed after administration of these ligands, except for GLYX-13 (rapastinel), which produces rapid antidepressant effects (Liu et al., 2017); however, its partial agonist properties may explain its possible dual antipsychotic and/or antidepressant activity.

Therefore, NMDA receptor studies reveal that a pharmacological dichotomy exists. On the one hand, antagonists/negative modulators of NMDA receptors may act as antidepressants [with psychotomimetic activity (Domino & Luby, 2012)], and on the other hand, enhancers of NMDA-related neurotransmission tend to exert antipsychotic effects (Fig. 1A). This profile of action resembles and follows the ideas put forward by Emil Kraepelin, the father of the theory of dichotomy between schizophrenia and affective disorders (Craddock & Owen, 2010); (Moller, 2008). This division was presented in his textbook "*Compendium der Psychiatrie zum Gebrauche für Studierende und Ärzte*," published in 1899 (Angst & Sellaro, 2000). This book has been highly influential on modern psychiatric classification systems, including the DSM-IV-TR and ICD-10, and its influence is reflected in the taxonomic separation of schizophrenia from affective psychosis. Below are further examples that support this dichotomy perspective.

3.2. AMPA/kainate receptors

Compounds which augment signaling through AMPA receptors (AMPA receptor potentiators) exhibit antidepressant-like behavioral effects in animal models for review see: (Bleakman, Alt, & Witkin, 2007) (Pilc et al., 2013). Pre-treatment with 1,2,3,4-Tetrahydro-6-nitro-2,3-dioxo-benzo[*f*]quinoxaline-7-sulfonamide (NBQX), an AMPA receptor antagonist, attenuated ketamine-induced antidepressant-like behavior (Maeng et al., 2008), the authors suggested that NMDA antagonists might exert rapid antidepressant-like effects by enhancing AMPA relative to NMDA throughput in critical neuronal circuits. The inhibition of GABA release after stimulation of AMPA receptors has been described (Satake, Saitow, Rusakov, & Konishi, 2004) and may lead, similarly as in the case of mGlu7 receptor agonists (see 4.3.2 below) to increases in the function of glutamatergic neurons.

The early studies demonstrated that the MK-801 evoked hyperlocomotion and dopamine release in the nucleus accumbens was antagonized by 6-Cyano-7-nitroquinoxaline-2,3-dione (CNQX) perfusion of the ventral tegmental area (VTA) in a concentration-dependent manner (Mathe, Nomikos, Schilstrom, & Svensson, 1998). Systemic administration of the calcium permeable (CP-AMPA) receptor-selective antagonist, IEM 1460 (*N*,*N*,*N*-trimethyl-5- [(tricyclo [3.3.1.13,7]dec-1-ylmethyl)amino]-1-pentanaminium bromide hydrobromide), inhibited MK-801/PCP-induced hyperactivity in mice (Umino, Umino, & Nishikawa, 2018). Moreover the preferential kainite/AMPA antagonist CNQX – but not the preferential AMPA/kainate antagonist NBQX which displays 30-fold selective for AMPA over kainate receptors, countered the disruption of medial prefrontal cortex (mPFC) low frequency oscillations (LFO) evoked by phencyclidine (Lladó-Pelfort et al., 2016).

Therefore, AMPA/kainate receptor studies reveal that a pharmacological dichotomy exists. On the one hand, agonists/PAMs of AMPA receptors may act as antidepressants and on the other hand, antagonists of AMPA/kainate receptor-related neurotransmission may exert antipsychotic effects (Fig.1B).

4. Metabotropic glutamatergic receptors

The metabotropic glutamatergic (mGlu) receptors constitute a family of at least 8 subtypes, which is divided further into three groups depending on sequence homology, pharmacology, and the second messenger pathways that they activate. Group I mGlu receptors (mGlu1 and mGlu5) are positively coupled to phospholipase C; group II mGlu receptors (mGlu2 and mGlu3) and group III mGlu receptors (mGlu4, mGlu6, mGlu7 and mGlu8) are negatively coupled to adenylyl cyclase (Conn & Pin, 1997).

4.1. The group I metabotropic glutamate receptors

The mGlu1 and mGlu5 receptors are members of the group I mGlu family; they are excitatory in nature as they are positively coupled to phospholipase C, and stimulation of these receptors leads to excitatory responses mediated by activation of the $G_{\alpha q}$ GTP-binding protein subunit (Conn & Pin, 1997). The mGlu5 receptors are closely connected with NMDA receptors at the postsynaptic density via adaptor proteins (Brakeman et al., 1997), (Tu et al., 1999); therefore, in the figure, they are placed on GABA-ergic neurons (Fig. 1C). The connection functions in such a way that stimulation of mGlu5 receptors increases NMDA receptor function, while a decrease in NMDA receptor function is observed after mGlu5 receptor blockade (Attucci, Carla, Mannaioni, & Moroni, 2001), (Awad, Hubert, Smith, Levey, & Conn, 2000), (Pisani, Calabresi, Centonze, & Bernardi, 1997). The response that occurs via the $G_{\alpha q}$ signaling pathway is independent of signaling that occurs through the NMDA receptor complex (Gao & Jacobson, 2013); Rook et al., 2015).

The effects of mGlu5 receptor agonists and antagonists are similar to the effects of NMDA receptor agents. Several preclinical studies show that the blockade of mGlu5 receptors produces antidepressant-like effects (Tatarczynska et al., 2001), (Belozertseva, Kos, Popik, Danysz, & Bespalov, 2007; Hughes et al., 2013) [for review, see (Palucha-Poniewiera & Pilc, 2016)]. Importantly, the recent clinical data tend to support the preclinical studies, showing significant efficacy of basimglurant, the mGlu5 receptor negative allosteric modulator (NAM) as adjunctive therapy to ongoing selective serotonin reuptake inhibitors (SSRI) or selective noradrenaline reuptake inhibitors (SNRI) treatment (Lindemann et al., 2015) (see also (Emmitte, 2017)). The problem of NMDA-like adverse effect (see above) might be solved by the discovery of a biased allosteric mGlu5 receptor modulator, which would not influence NMDA receptors (see below).

The pharmacological dichotomy between depression and schizophrenia is supported by findings that the stimulation of mGlu5 receptors using agonists or positive allosteric modulators (PAMs) such as 3-cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (CDPPB), S-(4-Fluoro-phenyl)-{3-[3-(4-fluoro-phenyl)-[1,2,4]-oxadiazol-5- yl]-piperidin-1-yl}-methanone (ADX47273), 2-(4-(2-(benzyloxy)acetyl) piperazin-1-yl)benzonitrile (VU0364289) or 1-(4-(2,4-difluorophenyl)piperazin-1-yl)-2-((4- fluorobenzyl)oxy)ethanone (DPFE) produced antipsychotic effects in animal studies [for review, see: (Wierońska, Zorn, Doller, & Pilc, 2016)]. However, adverse effects such as epileptiform activity and neuronal death (Parmentier-Batteur et al., 2014) were described. Some researchers believe that mGlu5 agonists or PAMs could be used in humans (Kanuma, Aoki, & Shimazaki, 2010).

Compounds with allosteric agonist activity (e.g., VU0422465) are more likely to induce adverse effects in comparison to pure PAMs (Rook et al., 2013) Importantly, it is possible to obtain biased PAMs of mGlu5 receptors, like VU0409551, with antipsychotic efficacy and which selectively potentiates mGlu5 coupling to $G_{\alpha q}$-mediated signaling but does not affect mGlu5 modulation of NMDAR currents (Rook et al., 2015). This opens up an entirely new possibility of obtaining new mGlu5 receptor ligands that are free of interactions with NMDA receptors and therefore perhaps free of NMDA receptor-related adverse effects. Thus, treatments with mGlu5 receptor antagonists, which have an excitatory effect on glutamatergic neurotransmission (via placement of mGlu5 receptors together with NMDA receptors on GABA-ergic neurons), produce antidepressant (and possibly pro-psychotic) effects, while agonists/PAMs, which exert inhibitory effects, could be antipsychotics (Fig. 1C).

4.2. Group II mGlu receptors: further examples of the opposite action of agonists and antagonists

The mGlu2/3 receptors are members of the group II mGlu receptors which are negatively coupled to adenylate cyclase activity via G_i/G_o proteins and are expressed presynaptically (Conn & Pin, 1997), (Schoepp, 2001) as auto- or heteroreceptors; therefore, in the Fig. 1, they are placed on a glutamatergic neuron (Fig. 1D). Their stimulation leads to inhibition of neurotransmitter release (this is an example of an agonist with inhibitory effects) (Nicoletti et al., 2011). The mGlu2/3 receptor ligands have been widely investigated, and a dual profile of their action has been observed. Thus, the majority of the data show that the orthosteric mGlu2/3 receptor antagonists (1*R*, 2*R*, 3*R*, 5*R*,6*R*)-2-amino-3- (3,4-dichlorobenzyloxy)-6-fluorobicyclo [3.1.0]hexane-2,6-dicarboxylic acid (MGS0039) and (2*S*)-2-amino-2-[(1*S*,2*S*)-2-carboxycycloprop-1-yl]-3-(xanth-9-yl) propanoic acid (LY341495) evoked antidepressant-like effects in animals (Chaki et al., 2004; Palucha-Poniewiera et al., 2010) [for a recent review, see (Chaki, 2017)]. Also, NAMs of mGlu2/3 receptors, such as RO4491533, show antidepressant-like efficacy (Campo et al., 2011). The results of clinical studies on the orthosteric/allosteric group II mGlu receptor antagonists are awaited [for review, see (Chaki, 2017)].

On the other hand, the agonists of group II mGlu receptors and selective mGlu2 receptor PAMs exerted antipsychotic-like activity (Cartmell, Monn, & Schoepp, 2000; Klodzinska, Tokarski, Bijak, & Pilc, 2002; Moghaddam & Adams, 1998; Takamori, Hirota, Chaki, & Tanaka, 2003) [for review, see (Wierońska et al., 2016) (Galici et al., 2006; Hikichi et al., 2015)]. However, the clinical studies that at first demonstrated the antipsychotic effects of mGlu2/3 receptor agonists in humans (Patil et al., 2007) were not reproduced latter (Kinon et al., 2011). The use of mGlu2 PAMs was also not successful [for review, see (Maksymetz, Moran, & Conn, 2017)]. The controversial results of the clinical trials, failure of mGlu2/3 receptor agonists may be explained by the fact that the mGlu2/3 receptors form heterocomplexes with 5-HT2A receptors (Gonzalez-Maeso et al., 2008). The epigenetic modifications induced at the mGlu2 promoter by atypical (but not typical) antipsychotics (Kurita et al., 2012) might be the reason for the lack of efficacy of mGlu2/3 receptor agonists in those patients [for discussion see: (Muguruza, Meana, & Callado, 2016)]. The recent findings indicate that the use of mGlu2 ligands in young patients free from antipsychotic therapy history may produce positive results (Kinon, Millen, Zhang, & McKinzie, 2015).

Thus, antagonists of mGlu2/3 receptors, which have an excitatory effect on glutamatergic neurotransmission by increasing glutamate release, produce antidepressant effects, while agonists, which exert inhibitory effects, are antipsychotics (Fig. 1D). However, in one report the potentiation of mGlu2 receptor activity by *N*-(4-((2-(trifluoromethyl)-3- hydroxy-4(isobutyryl)phenoxy)methyl)benzyl)-1-methyl-1*H*-imidazole-4-carboxamide (THIIC) also evoked antidepressant-like activity (Fell et al., 2011). It is possible that the efficacy of THIIC might represent the single compound effect and might not be representative of a class effect.

4.3. Group III mGlu receptors

The group III mGlu receptors share the presynaptic placement with group II mGlu receptors and are also negatively linked to adenylate cyclase. Their stimulation leads to inhibition of glutamate release as in the case of mGlu2/3 receptors (Schoepp, 2001). The group III mGlu receptors represent the largest group of the metabotropic glutamate receptors, as they consist of four receptor subtypes: mGlu4, mGlu6, mGlu7 and mGlu8 receptors. The difference between the groups is that group II mGlu receptors are placed perisynaptically, whereas group III mGlu receptors are placed presynaptically within the synapse (Vizi, Fekete, Karoly, & Mike, 2010). The paucity of selective and brain-penetrant ligands has slowed down the research on the third group of mGlu receptors; however, some selective compounds have been discovered recently.

4.3.1. The mGlu4 receptors

The activators of mGlu4 receptors have been shown to exert antipsychotic-like effects in animal models, including orthosteric agonists such as [((3*S*)-3-Amino-3-carboxy)propyl][(4-hydroxy-5-methoxy-3-nitrophenyl) hydroxymethyl]phosphinic acid; (LSP1-2111) (Wierońska, Stachowicz, Acher, Lech, & Pilc, 2012) and [((3*S*)-3-Amino-3-carboxy) propyl] [(4-(carboxymethoxy)phenyl) hydroxymethyl]phosphinic acid; (LSP4-2022) (Wozniak et al., 2016), as well as PAMs such as (1*S*,2*R*)-N1-(3,4-dichlorophenyl)-cyclohexane-1,2-dicarboxamide) (LuAF21934) and LuAF32615, which showed positive results in the models of positive, negative and cognitive symptoms of schizophrenia (Sławińska et al., 2013). Antipsychotic-like activity was also described for 5-Methyl-N-(4-methylpyrimidin-2-yl)-4-(1H-pyrazol-4-yl)thiazol-2-amine (ADX88178), another mGlu4 receptor PAM (Kalinichev et al., 2014). The results obtained with mGlu4 receptor agonists and PAMs are in line with those obtained using group II mGlu receptor stimulators (see above), showing that compounds that exert inhibitory effects on glutamate release are antipsychotics at the preclinical level. Simultaneously, the LuAF21934 did not possess antidepressant-like activity (Slawinska et al., 2013) or even a pro-depressive effect of LSP4-2022 was observed (Podkowa et al., 2015), which is also in agreement with the proposed dichotomy (Fig. 1E). However, further studies with the use of mGlu4 receptor antagonists or NAMs, to demonstrate their anticipated antidepressant efficacy, are needed. Moreover, the efficacy of ADX88178 in the forced swim test was also described in one study (Kalinichev et al., 2014).

4.3.2. The mGlu7 receptors

The available positive allosteric modulator of mGlu7 receptors-N,N′-dibenzhydrylethane-1, 2-diamine dihydrochloride (AMN082)-induced clear antidepressant-like activity in animal models of depression (Palucha et al., 2007); (Palucha-Poniewiera, Branski, Lenda, & Pilc, 2010). Supporting the proposed dichotomy (Fig. 1F), the compound induced pro-psychotic activity in the (5*S*,10*R*)-(+)-5-Methyl-10,11-dihydro-5H-dibenzo[a,d] cyclohepten-5,10-imine maleate (MK-801)-induced hyperactivity test and DOI-induced head twitches test (Wierońska et al., 2012).

There are few available mGlu7 antagonists, and their activity in animal models has not been fully investigated yet. The available data indicate that ADX71743, a potent and selective mGlu7 receptor NAM may have some antipsychotic, but not antidepressant-like activity (Kalinichev et al., 2013), again supporting the proposed dichotomy (Fig. 1F). However, clearly more experiments are needed to explore the subject further.

The mGlu7 receptors share the presynaptic placement with group 2/3 receptors and mGlu4 receptors; however, the major dissimilarity lies in the fact that while agonists of mGlu2/3 or mGlu4 receptors exert

antipsychotic-like effects, the agonists of mGlu7 receptors possess antidepressant-like activity.

There are several possible explanations for this. One explanation is that mGlu7 receptors are predominantly placed on GABA-ergic nerve terminals, which create synapses with other GABAergic neurons (Dalezios, Lujan, Shigemoto, Roberts, & Somogyi, 2002; Somogyi et al., 2003), where they control the release of GABA. For example, K^+-evoked [^{3}H]GABA release was inhibited by AMN082 in mouse hippocampal synaptosomes (Summa et al., 2013). Therefore, stimulation of mGlu7 receptors leads to inhibition of GABA release [Fig. 1F] and thus may lead to increases in the function of glutamatergic neurons; this is an example of an agonist with excitatory effects. Hence, the action of mGlu7 receptor agonists may resemble the action of group 2/3 (and possibly mGlu4) receptor antagonists. The second possible explanation is that the affinity of glutamate for mGlu4 is high, while it is very low for mGlu7 receptors [see (Schoepp, Jane, & Monn, 1999) for review], suggesting that mGlu7 receptors are stimulated only when the concentration of glutamate is high. The third possible explanation is that the metabolites of the mGlu7 receptor positive allosteric modulator AMN082, which show physiologically relevant binding affinity at monoaminergic transporters, may act as the monoaminergic agents (Sukoff Rizzo et al., 2011). Clearly, more experiments with the use of selective agonists and antagonists of mGlu7 receptors are necessary to elucidate their function as possible antidepressant and/or antipsychotic substances.

Summarizing: while Figs. 1A and C demonstrate the antidepressant efficacy of antagonists placed on GABA-ergic neurons, displaying excitatory effects, or placed on glutamatergic terminals (Fig. 1 D,) increasing the release of glutamate, in the case of mGlu7 receptors (Fig. 1F), it is an agonist, which, due to the placement of GABA-ergic nerve terminals, inhibits the release of GABA [Fig. 1 (2)], also displaying excitatory effects.

4.3.3. The mGlu6/8 receptors

The mGlu6 receptors are present in the retina, and the existing data are too scarce to discuss the involvement of mGlu8 receptors in depression or psychosis.

5. GABA receptors: more examples of dichotomy

GABA is the inhibitory counterpart of glutamate and is the most abundant inhibitory amino acid (IAA); up to 40% of brain neurons are GABA-ergic (van der Zeyden et al., 2008). GABA acts upon two ionotropic receptors ($GABA_A$ and $GABA_C$) and one metabotropic receptor ($GABA_B$) (Chebib & Johnston, 1999).

5.1. $GABA_A$ receptors: question marks

$GABA_A$ receptors are ligand-gated chloride ion channels that are composed of five protein subunits that can belong to different subunit classes. The promiscuity of subunits raises the possibility that more than 800 distinct $GABA_A$-R subtypes might exist in the brain (Olsen & Sieghart, 2009). Drugs like benzodiazepines that modulate the $GABA_A$-R have been on the market for over 50 years and display anxiolytic, sedative/hypnotic, anesthetic, and antiepileptic profiles. However, little data on the antipsychotic or antidepressant effects of agents acting on $GABA_A$ receptors exist.

The blockade of GABA-ergic transmission in the preforontal cortex (PFC) by bicuculine, an antagonist of $GABA_A$ receptors, induces abnormalities in rats that resemble schizophrenia (Tse, Piantadosi, & Floresco, 2015). Enhancement of GABA-ergic activity by TPA023 (MK-0777), a benzodiazepine-like agent with selective activity at $GABA_A$ receptors containing the α2 or α3 subunits, improved cognitive functioning in patients with schizophrenia (Lewis et al., 2008). The fact that a negative allosteric modulator for α5 subunit-containing GABA receptors exerts a rapid and persistent antidepressant-like action (Zanos et al., 2017) is in agreement with the dichotomy perspective. However, recent studies also indicate that neuroactive steroids (NASs), which function as positive allosteric modulators (PAMs), were effective as antidepressants in animal studies [for review, see (Schüle, Nothdurfter, & Rupprecht, 2014)]. Taking into account that 800 distinct $GABA_A$-R subtypes that might exist in the brain, it is premature to place them on the picture.

5.2. $GABA_B$ receptors: clear examples of the dichotomy

$GABA_B$ receptors are broadly distributed throughout the brain, occurring either as presynaptic (auto- or hetero-) receptors or as postsynaptic receptors. This subtype is negatively coupled to AC and to K+ and Ca^{2+} channel receptors (Chebib & Johnston, 1999). Its stimulation leads to inhibition of the release of neurotransmitters from nerve terminals (Misgeld, Bijak, & Jarolimek, 1995).

$GABA_B$ receptor ligands were proposed as putative and effective compounds in treating several CNS disorders. The antidepressant efficacy of $GABA_B$ receptor antagonists (Nakagawa, Sasaki, & Takashima, 1999), (Slattery, Desrayaud, & Cryan, 2005) (Nowak et al., 2006), (Froestl et al., 2004; Ghose, Winter, McCarson, Tamminga, & Enna, 2011) and NAMs was demonstrated in animal models of depression, such as the forced swim test, olfactory bulbectomy or chronic mild stress model of depression, confirming the $GABA_B$-ergic hypothesis of depression proposed in 1984 (Pilc & Lloyd, 1984), but, as stated in a recent review by Alexander, "definitive testing of $GABA_B$ antagonists in depression, however, still awaits the development of potent, selective and brain-penetrant compounds." (Alexander, 2017). It has to be mentioned that one study the $GABA_B$ receptor positive allosteric modulator CGP 7930 and the GABA B receptor agonists baclofen and SKF 97541 displayed antidepressant effects, although a single test (a modified forced swim test) was used (Frankowska, Filip, & Przegaliński, 2007).

In humans baclofen, which has been used for several years mainly to treat spasticity, was reported not to produce beneficial effects in affective disorder; rather, it increased symptoms of depression in some patients (Post, Ketter, Joffe, & Kramlinger, 1991).

On the other hand, agonists or positive allosteric modulators of this receptor were shown to induce antipsychotic-like activity (Arai et al., 2008; Bortolato et al., 2007; Frau et al., 2014; Mizoguchi & Yamada, 2011; J. Wieronska et al., 2015; J. M. Wieronska et al., 2011). The preclinical data are supported by some clinical evidence (Frederiksen & Badr, 1978), but the picture is far from clear as some patients with schizophrenia got worse when taking baclofen (Garbutt & van Kammen, 1983). Clearly further studies on the action of GABA agonists on negative and cognitive symptoms of schizophrenia are needed (Kantrowitz, Citrome, & Javitt, 2009).

Thus, the majority of findings indicate that the treatments that lead to decreased GABA-ergic transmission ($GABA_B$ antagonists) produce antidepressant effects, while agonists (which increase inhibitory effects) are endowed with antipsychotic efficacy (Fig. 1G). Therefore, in this case, the obvious antidepressant vs. antipsychotic pharmacological dichotomy is observed, and in the picture Fig. 1G is identical to Fig. 1 A, C, D.

6. Conclusions

The analysis of pharmacological data on agonists and PAMs or antagonists and NAMs of amino acidergic receptors (AAR) has revealed a very consistent pattern of their effects. Thus, treatments that increase the excitatory effects (either via blockade (see Fig. 1 A, C, D, G) or stimulation of AAR (Fig. 1 B, F) tend to produce antidepressant effects at the preclinical (and sometimes clinical) level, while treatments that increase the inhibitory effects either via stimulation of AAR (see Fig. 1 A, C, D, E, G) or blockade of AAR (Fig. 1 B, F) tend to produce antipsychotic effects. This indicates that depression and schizophrenia may remain opposite in their pathologies. At the same time, it must be noted that the observations based on animal models of psychiatric diseases may not apply

to human patients. Moreover, depression and schizophrenia are not homogenous diseases, and a variety of symptoms like affective symptoms in schizophrenia or psychotic symptoms in depression occur. Therefore, this dichotomy that can be observed at the preclinical level may not be obvious in patients.

However, the observations described above may show the preclinical avenues available for developing new effective and rapidly acting therapies for both depression and schizophrenia.

Conflict of interest statements

The authors declare that there are no conflicts of interest.

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