Cell and Tissue Research (2019) 377:59–71
https://doi.org/10.1007/s00441-019-03007-9

REVIEW

Alterations and adaptation of ventral tegmental area dopaminergic neurons in animal models of depression

Jennifer Kaufling[1]

Received: 19 November 2018 / Accepted: 11 February 2019 / Published online: 8 March 2019

Abstract

Depression is one of the most prevalent psychiatric diseases, affecting the quality of life of millions of people. Ventral tegmental area (VTA) dopaminergic (DA) neurons are notably involved in evaluating the emotional and motivational value of a stimulus, in detecting reward prediction errors, in motivated learning, or in the propensity to initiate or withhold an action. DA neurons are thus involved in psychopathologies associated with perturbations of emotional and motivational states, such as depression. In this review, we focus on adaptations/alterations of the VTA, particularly of the VTA DA neurons, in the three most frequently used animal models of depression: learned helplessness, chronic mild stress and chronic social defeat.

Keywords Ventral tegmental area · Dopamine · Depression · Social stress · Environmental stress

Introduction

Major depressive disorder (MDD, also referred to as "depression" in this review) is one of the most disabling neuropsychiatric diseases, with devastating consequences for both the patients and for their families. Nowadays, depression affects more than 300 million people worldwide and is a leading cause of disability and a major contributor to the overall global burden of diseases (Ferrari et al. 2013; WHO 2013). It is underpinned by a complex physiopathology and etiology. This is particularly reflected by the list of symptoms described in the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association 2013) where MDD is defined by a period of at least 2 weeks during which the patient expresses depressed mood and/or loss of interest or pleasure associated with four other symptoms in a list of seven including fatigue, feelings of worthlessness and psychomotor agitation or retardation.

In addition to variability in the expression of the disease, another significant contribution to the burden of depression is the difficulty to effectively treat and cure patients. Indeed, classic antidepressant treatments usually take weeks to show efficacy, often have side effects and are not always effective, with 1/3 of patients still failing to be cured after 4-treatment trials (Rush et al. 2006).

For these reasons, over the last few decades, research has made a substantial effort to better understand this pathology (Chaudhury et al. 2015; Nestler et al. 2002; Willner et al. 2013). Thus, animal models attempting to recapitulate some of the cardinal symptoms of depression, such as loss of pleasure or motivation, despair, or social avoidance, have been developed. In line with the complexity of the disease, those models are numerous and reflect the various etiologies and symptomatic heterogeneity of depression (Willner and Belzung 2015; Yin et al. 2016).

Two of the main symptoms of depression, easily replicable in laboratory animals, are the loss of interest or motivation and the inability to feel pleasure (anhedonia). These two phenomena are well-studied and known to involve dopaminergic (DA) neurons and more specifically, ventral tegmental area (VTA) DA neurons. Indeed, among other functions, VTA DA neurons and their projections to the nucleus accumbens (NAc) encode for the response to unexpected reward and more importantly, for reward prediction error (the discrepancy between the reward and its prediction) (Bromberg-Martin et al. 2010; Lammel et al. 2014; Schultz 2013, 2016). It, therefore, seems almost implicit that DA systems might be disturbed in animal models of depression.

It is difficult to decipher the roles of VTA DA neurons in depressive-like phenotypes without investigating their electrophysiological activity. VTA DA neurons have complex

✉ Jennifer Kaufling
kaufling@inci-cnrs.unistra.fr

[1] Centre National de la Recherche Scientifique, Institut des Neurosciences Cellulaires et Intégratives, 8 Allée du Générale Rouvillois, 67000 Strasbourg, France

electrophysiological patterns including tonic and phasic activities that are both regulated at several levels (for reviews, see Morikawa and Paladini 2011; Paladini and Roeper 2014; White et al. 2006). Intrinsic regulations, like those involving hyperpolarization-activated cation current (Ih), contribute to the pacemaker activity of VTA DA neurons. Local intra-VTA regulations contribute to their tonic activity, notably via the inhibitory controls exerted by D2 autoreceptors or by local GABAergic interneurons (Johnson and North 1992). Finally, in a broader perspective of neural networks, extrinsic regulations from VTA afferents are also critical (Watabe-Uchida et al. 2012). These afferents include GABAergic inputs from the ventral pallidum (VP) (Mahler et al. 2014) or the tail of the VTA (tVTA) (Kaufling et al. 2010) and glutamatergic afferents from the medial prefrontal cortex (mPFC) (Geisler et al. 2007), the bed nucleus of the stria terminalis (BNST) (Kaufling et al. 2017), or the pedunculopontine nucleus (PPN) (Dautan et al. 2016). They are complimented by cholinergic afferents from the laterodorsal tegmentum nucleus (LDTg) (Fernandez et al. 2018) and noradrenergic inputs from the locus coeruleus (LC) (Isingrini et al. 2016; Zhang et al. 2018). These different levels of regulation represent an important excitatory/inhibitory balance controlling the electrical activity of the VTA DA neurons and their homoeostasis and are fundamental for the physiological roles of DA systems. Although many structures and circuits underlie a pathology as complex as depression, we chose, in this review, to summarize the current state of knowledge regarding VTA DA neurons in three classic animal models of depression, including learned helplessness, chronic mild stress and social defeat models (Fig. 1). We will focus on alterations/adaptations of the VTA DA neuron activity involving these different levels of regulation.

VTA DA neurons in the learned helplessness model

The learned helplessness model is a robust model of stress-induced depression (Czéh et al. 2016; Vollmayr and Gass 2013) developed by Seligman and his colleagues in the 1970s, first in dogs and later in rats (Drugan et al. 1997; Seligman 1972; Maier and Seligman 1976). In the first of two phases, the animal receives repeated footshocks in a closed, inescapable environment. Later, in a second phase, when the animal is introduced to a similar context but with a clear possibility to escape, it shows an impairment to do so. This deficit to escape is interpreted as "helplessness" or the inability to defend or act effectively to protect itself (Willner 1986; Willner and Belzung 2015).

Even if the behavioral deficit induced by this procedure is often effective only for a short time period (about a week but it could be longer depending on the protocol), this model has been extensively used to address the antidepressant potential of drugs. Most of these investigations concern the most classic and efficient classes of drugs acting on serotonin and norepinephrine systems but some studies also investigated DA receptor modulators. For instance, agonists of D1 and D2 DA receptors reversed the active avoidance deficit of helpless rats (Bertaina-Anglade et al. 2006; Takamori et al. 2001) and mice (Duterte-Boucher et al. 1988). However, this effect was mediated by systemic injection, so although these pharmacologic studies surely involved DA action, they did not provide information on the role of the VTA DA neurons per se. Indeed, only a few studies specifically explored either the impact of learned helplessness on DA neurons or how DA neuron manipulations impact learned helplessness behavior.

Investigating depressive-like behaviors associated to Parkinson's disease, Winter et al. (2007) observed that partial or complete hemi-VTA and/or substantia nigra (SNC) lesion by the 6-hydroxydopamine (6-OHDA) that targets DA neurons exacerbated depressive-like phenotypes. Here, a slightly modified paradigm of learned helplessness was used to demonstrate that lesioned animals showed an increase in the latency to press a lever to stop a series of footshocks (Winter et al. 2007). In a more recent study investigating the fast antidepressant-like effect of the non-competitive NMDA receptor antagonist ketamine, Belujon and Grace (2014a) highlighted a direct effect of the learned helplessness procedure on the activity of VTA DA neurons in vivo. In helpless

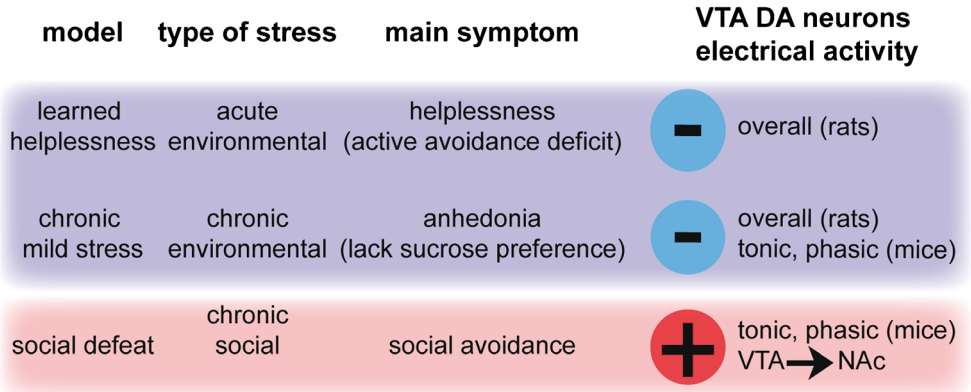

Fig. 1 Summary of the consequences of the three models of depression described in this review

rats, the overall activity of the VTA DA neuron population was decreased (number of active cells *per* recording track), with no significant difference in the average firing rate or burst firing. Ketamine restored both the escape behavior and VTA DA activity as well as long-term potentiation in the hippocampus-NAc pathway, via, in part, activation of D1 receptors (Belujon and Grace 2014a). Morphine has also been shown, by Besson and collaborators, to display an antidepressant-like effect in the learned helplessness test (Besson et al. 1998). Morphine, via mu-opioid receptors, inhibits the activity of VTA and tVTA GABAergic neurons, cells known to tonically inhibit VTA DA neurons (Bourdy and Barrot 2012). It may therefore be hypothesized that, in helpless rats, acute morphine, via its ability to activate VTA DA neurons by disinhibition, might reverse the decreased VTA DA activity cited above (Belujon and Grace 2014a), which could contribute to its observed antidepressant-like effect in this test (Besson et al. 1998).

Another mechanism may involve the pathway between the lateral habenula (LHb), a region that has been implicated in depression and VTA DA neurons (Knowland and Lim 2018; Proulx et al. 2014). Li et al. (2011) showed that, in rats subjected to a learned helplessness protocol, excitatory synapses onto LHb neurons projecting to the VTA were potentiated due to an enhanced presynaptic release probability. As LHb deep brain stimulation (DBS) has been successfully used to alleviate the major depressive state of a treatment-resistant patient (Sartorius et al. 2010), the authors used a similar DBS protocol in helpless rats (Li et al. 2011). They recapitulated the DBS antidepressant-like effect and linked this to a reduction in excitatory synaptic transmission on VTA-projecting LHb neurons. Therefore, in contrast to Belujon and Grace (2014a), this study (Li et al. 2011) suggested that the learned helplessness procedure might favor VTA DA neurons' activity. In fact, the anatomical link between LHb and VTA may reconcile the two observations: in addition to a direct LHb-VTA minor connection, there is a major indirect pathway through the GABAergic neurons of the tVTA (Hong et al. 2011). Thus, in helpless rats, increased activity of LHb neurons could directly lead to an increased activity of some VTA DA neurons (excitatory direct pathway) but also to a decreased activity of other VTA DA neurons via the tVTA (inhibitory indirect pathway). It is yet to be shown whether subpopulations of VTA DA neurons are selectively activated/inhibited in response to learned helplessness but such a selective enhancement of activity in specific subgroups of VTA DA neurons could potentially explain the limited efficacy of current antidepressant treatments that would target all DA neurons equally.

VTA DA neurons in chronic mild stress models

In the learned helplessness model, animals usually receive a single series of footshocks and the procedure could therefore be considered as an "acute" stress model where depressive-like behavioral consequences are usually expressed over a short period of time only (about a week). Indeed, the learned helplessness model, although robust, is limited and does not, for instance, recapitulate the chronicity of the symptoms observed in depressed patients. Furthermore, in many studies, it is even considered as a model of post-traumatic stress disorder (PTSD) rather than depression (Hammack et al. 2012; Schöner et al. 2017).

Chronic mild stress (CMS), a more valid model with regard to human depression symptomatology, was developed in the 1980s in rats (Katz 1982; Willner et al. 1987) and later adapted to mice (Schweizer et al. 2009). This model repeats a succession of minor stressors during a period of several weeks, progressively leading to different symptoms, including anhedonia. The stressors are imposed daily, in an unpredictable way; usually, they include food and water deprivation and a set of other mild stressors such as cage tilting, inversion of light-dark cycle, or group/single housing alternation. This exposure leads to an impairment in the response to rewarding stimuli, which in rodents is generally assessed by the loss of preference for a sweet sucrose solution over water. Other depressive-like symptoms are also associated with CMS, such as decreases in sexual behavior and self-care and weight loss. These symptoms persist for several weeks after the removal of stressors, supporting the validity of the model (Wiborg 2013; Willner 2017; Willner and Belzung 2015).

Despite CMS being more complex and time-consuming to implement than learned helplessness, the literature investigating the CMS effect on midbrain DA neurons is more abundant. In 2014, Chang and Grace (2014) used in vivo single neuron recording in anesthetized rats and reported a decrease in VTA DA neuron activity in animals subjected to CMS. These data have been subsequently replicated in three other publications from the same group (Moreines et al. 2017a, b; Rincón-Cortés and Grace 2017). In CMS-exposed rats, they observed a reduction of up to 50% of VTA DA active neurons (spontaneously firing) encountered *per* electrode track. Importantly, this effect was not associated with impairment in the two classic firing modes, tonic (basal activity) and phasic (burst firing), of the remaining spontaneously active VTA DA neurons (Chang and Grace 2014; Moreines et al. 2017a; Rincón-Cortés and Grace 2017). This reduction in the spontaneous activity of DA neuronal population in rats appears to be specific to the medial and central parts of the VTA (Moreines et al. 2017b) and the reduction is even greater in female rats that underwent CMS (Rincón-Cortés and Grace 2017).

This same research group also highlighted that VTA afferents could contribute to this pathological decrease in DA activity. They found that the activity of DA neurons in the VTA of animals submitted to CMS returned to control levels after local inactivation of the infralimbic prefrontal cortex

(ILPFC) (Moreines et al. 2017b), the basolateral amygdala (BLA) (Chang and Grace 2014), or the ventral pallidum (VP) (Chang and Grace 2014). Intriguingly, this recovery was not observed after LHb inactivation (Moreines et al. 2017b).

The effects of antidepressant drugs on CMS have also highlighted DA mechanisms underlying this action. In line with the antidepressant effect of ketamine in the learned helplessness model (Belujon and Grace 2014b), Rincón-Cortés and Grace (2017) observed that an acute systemic administration of ketamine restored VTA DA activity for up to 7 days in both male and female rats exposed to CMS. Another interesting molecule, quetiapine, a new-generation D2 antagonist recently used to treat patients resistant to classic antidepressant drugs, has also been tested in the CMS model (Moreines et al. 2017a). When administered acutely, this drug increases the population activity of VTA DA neurons in non-stressed rats but not in CMS-exposed rats. On the contrary, chronic quetiapine administration rescued the population activity of tVTA DA neurons in CMS-exposed rats. Interestingly, as mentioned by the authors, these data highlight a distinct effect of the molecule on the same neuronal population, in "normal" and depressed-like pathological state (Moreines et al. 2017a). Finally, the effect of morphine on CMS-exposed rats is in agreement with data obtained in the learned helplessness model (Besson et al. 1998). Indeed, intra-VTA infusion of morphine hydrochloride markedly elevated the firing rates of VTA DA neurons in CMS mice but not in naive animals. Accordingly, acute intra-VTA morphine infusion relieved depressive-like behaviors (despair and anhedonia) induced by CMS in mice both 4 h and 1 day after the infusion (Liu et al. 2018).

The reduced activity of VTA DA neurons observed in rats subjected to CMS seems to be largely conserved in mice and is perhaps even exacerbated with CMS in mice, decreasing not only the proportion of active DA neurons (cells *per* track), as in rats but also the tonic (mean firing rate) and phasic (burst duration and mean spike *per* burst) activities of DA neurons (Liu et al. 2018; Tye et al. 2013; Zhong et al. 2018). Importantly, the localization within the VTA of DA neurons affected by CMS seems to differ between mice and rats. In rats, reduced DA activity affects the medial part of the VTA (Moreines et al. 2017b), whereas in mice, it affects the lateral VTA (Zhong et al. 2018), more specifically a VTA subregion called the parabrachial pigmentosum (PBP), which contains DA neurons projecting to the lateral portion of the nucleus accumbens shell (latNAcSh) involved in reward processing (Lammel et al. 2012). Using ex vivo recording, Zhong et al. showed that CMS exposure led to decreased hyperpolarization-activated currents (Ih) in LatNAcSh-projecting VTA DA neurons. This effect could contribute to the CMS-induced decreased firing rate activity of VTA DA neurons (Zhong et al. 2018). However, there is no consensus concerning the projection target of DA neurons affected by CMS in mice. Indeed, Liu et al. (2018), using patch clamp recording, reported a dampening of the VTA DA neurons activity in CMS-exposed animals affecting DA neurons projecting specifically to the mPFC but not the NAc.

Finally, a key study revealed a causal role of the VTA DA neurons in both the induction of depressive-like symptoms in non-stressed mice and in the alleviation of these symptoms in animals submitted to CMS (Tye et al. 2013). To link DA neuronal activity to the induction of a depressive-like phenotype, the authors inhibited VTA DA neurons optogenetically to induce despair-like behavior in mice. This core depressive-like symptom was assessed through a reduction of escape-related behaviors in two classic tests: the tail suspension test and the forced swim test. In a separate set of experiments, following detection of a reduction in the activity of VTA DA neurons in CMS-exposed mice, the authors used optogenetic stimulation in order to restore DA neuron activity, which attenuated depressive-like behaviors. Finally, further experiments allowed them to conclude that this rescue of the depressive-like phenotype induced by CMS required phasic activation of VTA DA neurons and of DA receptors in the NAc (Tye et al. 2013).

VTA DA neurons in chronic social defeat models

Learned helplessness and CMS are essential paradigms to understand the link between chronic stress and depressive-like behaviors. However, they mainly use physical stressors that may not be representative of the social nature of stressful events encountered by human beings in everyday life. Thus, a different paradigm, called social defeat (SD), which focuses on social stressors, has been developed. SD models were developed in the late 1970s (Miczek 1979) but their optimization to efficiently recapitulate depressive-like behaviors in rodents was mostly achieved in the early 2000s. Such models are also called subordination models and are based on a resident-intruder paradigm, implemented in rats and mice. Classically, an adult animal (the intruder) is introduced in the home cage of an older, bigger, more aggressive dominant male of the same species (the resident). Hostile interactions and fights rapidly occur, until the intruder adopts a submissive posture. This physically stressful interaction is brief (max, 5 min) and generally followed by a physical separation of the two animals by a transparent plastic plate pierced with holes, which is placed in the middle of the resident cage. This device allows adding an emotional or psychogenic stress to the brief physical stress since the intruder will be able to see the resident. This second phase can last from 20 min to 24 h depending on the protocol. In the case of chronic models, the intruder is subjected to the assault of a new resident every day or intermittently according to the protocol.

Links between SD and depressive-like symptoms

The impact of SD on depressive-like behaviors has been extensively studied (for review, see Han and Nestler 2017) and the continuous 10-day paradigm initially developed in mice (Berton et al. 2006) is the most widely used SD model of depression-like phenotypes (called SD10 paradigm in the following sections). Animals that underwent this procedure normally expressed classical behavioral depressive-like symptoms, such as weight loss or anhedonia (see Krishnan et al. 2007 for complete behavioral characterization). However, the face validity of this paradigm is mostly based on the occurrence of one symptom easily observable in rodents and stable for at least 4 weeks after the SD procedure: social avoidance (Berton et al. 2006; Han and Nestler 2017; Krishnan et al. 2007). Another feature of this model is that it allows separation of mice into two groups: susceptible vs resilient (or unsusceptible) (Krishnan et al. 2007). Indeed, 40 to 50% of the mice subjected to this paradigm will not develop depressive-like states (Krishnan et al. 2007). This SD model, by recapitulating the resilience phenomenon also observed in humans, is a remarkable tool to investigate structural, molecular and even genetic mechanisms that underlie inter-individual variability in response to SD. Due to its extensive use in the field, this model has provided valuable insight into SD-induced alterations in various brain structures, including the NAc and the amygdala and also the VTA DA neurons and some of their afferents.

VTA DA electrophysiological alterations (intrinsic and local)

In 2007, the first observation of an increased activity of VTA DA neurons in susceptible mice was reported (Krishnan et al. 2007). Indeed, the authors observed a 35% increase of the VTA DA neuron firing rate in susceptible mice compared to resilient mice. The electrophysiological activity of non-DA VTA neurons was unchanged. Interestingly, using DNA microarrays, the authors observed that more genes were regulated in the VTA of resilient mice than in the VTA of susceptible ones, suggesting that resilience could be an active phenomenon. Additionally, several voltage-gated potassium K^+ channels were overexpressed in resilient mice (Krishnan et al. 2007). As these channels are known to reduce intrinsic neuronal excitability (Shah and Aizenman 2014), the authors hypothesized that their overexpression could contribute to the development of the resilient phenotype. Accordingly, a reversion of the social avoidance (after a SD10 procedure) was seen after using a viral approach to overexpress the inward rectifier K^+ channel (Kir2.1) in the VTA of susceptible mice. This effect was associated with a reduction of BDNF protein levels in the NAc (see below for more detail on BDNF regulation of DA neurons) and a regulation of VTA DA neuron electrophysiological activity to levels similar to those observed in naive and resilient animals (Krishnan et al. 2007). On the other hand, the inactivation of a K^+ channel (Kcnab2) in naïve mice increased the firing rate of VTA DA neurons and promoted the development of a susceptible phenotype after a sub-maximal exposure to social stress (three defeats within 1 day) (Krishnan et al. 2007). Together, these results illustrated that maintaining the VTA DA neuron electrophysiological activity to levels observed in naïve animals, notably via an increase in K^+ channels, could promote resilience to SD (Krishnan et al. 2007). However, resilience and susceptibility to SD are considerably more complex and involve several mechanisms, as discussed further in the following sections.

Another interesting DA neuron parameter promoting resilience is the Ih current (Cao et al. 2010), which is considered as a potential key component in the mechanisms underlying increased VTA DA activity associated with SD, due to both its presence in a large population of VTA DA neurons and because of its involvement in their tonic pacemaker activity (Morikawa and Paladini 2011; Paladini and Roeper 2014). Cao and collaborators indeed observed an increased Ih activity in VTA DA neurons of susceptible mice. This effect was normalized by chronic use of the classic antidepressant drug fluoxetine, a selective serotonin reuptake inhibitor, or by local infusion of Ih inhibitors (Cao et al. 2010). Combining in vivo and ex vivo electrophysiology, the authors further investigated the role of the VTA DA neurons in susceptible mice exposed to SD and observed that the VTA DA neurons' firing rate and bursting rate were negatively correlated to social avoidance (Cao et al. 2010).

More recently, optogenetic manipulations of VTA DA neuronal activity have highlighted new mechanisms supporting the link between the VTA DA neurons and depression. Consistent with previous data, the group of Dr. Ming-Hu Han in collaboration with the groups of Pr. Nestler and Pr. Deisseroth showed that a subthreshold SD paradigm combined with optogenetic stimulation of the VTA DA neurons promoted susceptibility. Similarly, optogenetic stimulation of the VTA DA neurons induced a susceptible phenotype in previously resilient mice that underwent the classic SD10 procedure (Chaudhury et al. 2013). Here, the use of optogenetic approaches expanded previous studies by allowing two surprising observations: (1) only chronic high-frequency phasic optogenetic stimulation (20 Hz) but not low-frequency tonic stimulation (0.5 Hz), was able to promote susceptibility and (2) phasic activation of VTA DA neurons projecting to the NAc but not to the mPFC promoted susceptibility. Conversely, optogenetic inhibition of the DA VTA-NAc pathway induced resilience, whereas inhibition of the DA VTA-mPFC projections promoted susceptibility (Chaudhury et al. 2013). A follow-on study from the same group further deciphered the complexity of the activity of VTA DA neurons projecting to the NAc in the development of susceptibility to

SD. They first observed that "further" (more days) chronic optogenetic activation of the VTA DA neurons in susceptible mice (20 Hz, 40 ms stimulation; 20 min/day; 5 days) normalized the firing rate of VTA DA neurons to naïve levels and reversed social avoidance behaviors and thus reverted mice from susceptible to resilient (Friedman et al. 2014). Interestingly, they showed that the increased Ih current in VTA DA neurons of susceptible mice and the associated increase in K^+ channel current (also in VTA DA neurons) (Cao et al. 2010) were further exacerbated in resilient mice. They also observed that pharmacological increases in Ih current in the VTA completely reversed depression-related behaviors induced by a SD10 paradigm (Friedman et al. 2014). This suggests that increased Ih current in response to SD may be important for mediating the resilience to depressive symptoms and the authors hypothesized that both VTA DA manipulations (optogenetic stimulation or exacerbated Ih current) would "trigger self-tuning compensation of K^+ currents and functionally normalize the firing of these hyperactive DA neurons in susceptible animals, a homeostatic plasticity seen in VTA-NAc projection, but not in VTA-mPFC pathway" (Friedman et al. 2014). Specifically, a feedback loop was observed in resilient mice that comprised the following: (1) increased Ih current, (2) enhanced phasic activity of the VTA DA neurons, (3) K^+ current upregulation and (4) reduced VTA DA neuronal activity to control levels. In susceptible mice, this homeostatic mechanism fails to be triggered, due to an insufficient increase of the Ih current in the first step (Fig. 2). This homeostatic mechanism was recently confirmed in a study where overexpression of specific K^+ channel families (KCNQ channels) in the VTA and also chronic treatment with retigabine (a KCNQ-type K(+) channel opener), normalized the neuronal hyperactivity and the depressive-like phenotype induced by chronic SD (Friedman et al. 2016). Together, these results highlight the potential of molecules promoting these active resilience mechanisms, such as retigabine, to perhaps become new antidepressant drugs (Friedman et al. 2016).

VTA DA electrophysiological alterations (afferents)

Noradrenergic (NA) modulations

In addition to the intrinsic alterations/adaptations of the VTA DA neurons described in the previous section, some upstream structures regulating the VTA DA neurons seem to be involved in depressive-like phenotypes observed in mice subjected to SD. Among VTA afferents, noradrenergic (NA) projections have been of particular interest. Two different publications (Isingrini et al. 2016; Zhang et al. 2018) have recently examined the role of NA LC-VTA projections in the neural adaptations to SD. Both studies carried out complementary experiments to demonstrate the pro-resilient effect of LC NA projections to the VTA via an inhibitory control of DA neurons. Following the SD10 paradigm, Isingrini and colleagues observed, in susceptible mice, decreased NA levels in the VTA and reduced cFos expression in LC neurons projecting to VTA DA neurons. These VTA DA neurons, in turn, project to the NAc but not to the mPFC (Isingrini et al. 2016). Additionally, Zhang et al. (2018), using in vivo electrophysiological recordings, observed increased tonic (firing rate) and phasic (bursting rate) activities in LC NA neurons of resilient mice. Using transgenic strategies to knockout (KO) the vesicular monoamine transporter-2 (VMAT2) in NA neurons, Isingrini et al. (2016) also observed that NA transmission promoted resilience. Indeed, KO VMAT2 mice showed a higher risk of becoming susceptible than wild-type animals. Conversely, both research groups observed, in susceptible mice, that chronic (5 to 10 days) phasic optogenetic stimulation of LC NA fibers projecting to the VTA reversed susceptibility (Isingrini et al. 2016; Zhang et al. 2018). Furthermore, Zhang et al. (2018) showed that this phenomenon was associated with a normalization of the pathological increase in the activity of the VTA DA neurons that was observed in susceptible mice and also with the expression of the homeostatic plasticity observed in the VTA DA neurons of resilient mice

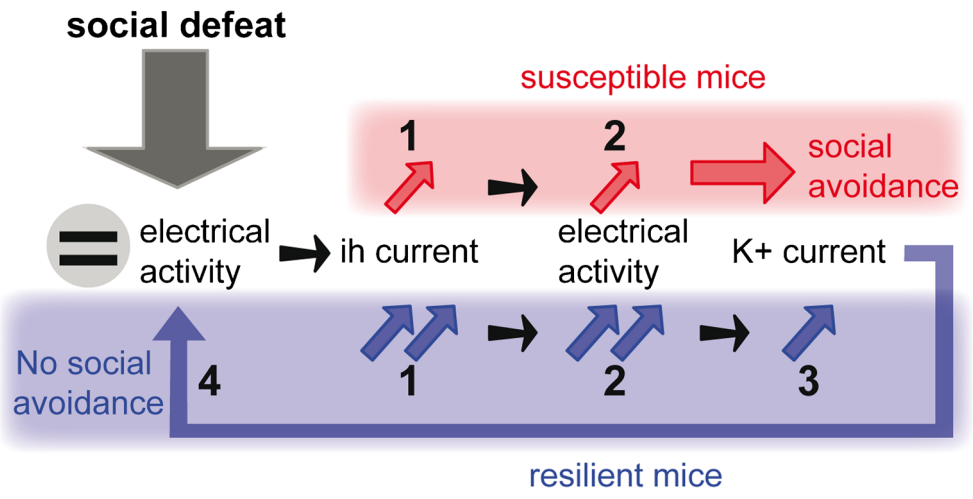

Fig 2 Mechanism observed in VTA DA neurons projecting to NAc, in susceptible vs resilient mice subjected to social defeat. In blue: feedback loop observed in resilient mice; (1) increased Ih current, (2) enhanced phasic activity of the VTA DA neurons, (3) K^+ current upregulation, (4) reduced VTA DA neuronal activity to control levels. In red: in susceptible mice, this homeostatic mechanism fails to be triggered due to an insufficient increase of the Ih current in the first step

(increased Ih and K^+ current). Finally, both groups, using pharmacological approaches, confirmed that increased local VTA NA is sufficient to promote resilience to stress. Dr. Bruno Giros' group used chronic administration of α2 NA receptor antagonists or NA reuptake inhibitors to increase extra-synaptic NA levels and found, as with optogenetic stimulation, reduced social aversion in susceptible mice (Isingrini et al. 2016). Using molecular profiling, the group of Dr. Ming-Hu Han highlighted that the adrenergic receptors α1 and β3 were the most highly expressed in the VTA DA neurons projecting to the NAc and showed that chronic activation of these receptors induced a pro-resilient effect by reversing susceptible behavioral and molecular phenotypes (Zhang et al. 2018). Together, these data demonstrate that NA neurotransmission from the LC to the VTA is both necessary and sufficient to promote resilience to social defeat.

Cholinergic (Ach) modulations (nicotinic receptors)

Acetylcholine (Ach) is another neurotransmitter involved in both the regulation of VTA DA neurons and social stress. Morel et al. (2018) focused on the link between nicotinic acetylcholine receptors (nAChRs) and chronic SD consequences, notably because of the strong comorbidity between nicotine addiction and depression. Indeed, depression is frequently associated with other chronic psychiatric disorders such as schizophrenia (Kim et al. 2018) or drug addiction (Ng et al. 2017; Tolliver and Anton 2015), neurodegenerative diseases such as Parkinson's disease (Faivre et al. 2018), or maladaptive disorders such as chronic pain (Cahill and Taylor 2017; Taylor et al. 2015; Yalcin et al. 2014; Yalcin and Barrot 2014). For these reasons, deciphering interconnected mechanisms between depression and their comorbid pathologies is fundamental to better understand depression itself. Morel and colleagues observed that SD10 procedures blunted the known VTA DA neuronal excitation mediated by acute nicotine (Faure et al. 2014) and were associated with an enhanced cholinergic tone in the VTA (Morel et al. 2018). Nicotine effects are predominantly mediated by nAChR subtypes containing α7 or β2 subunits and via these receptors (located on both GABA and DA neurons in the VTA), acute nicotine excites VTA DA neurons in naive animals (Faure et al. 2014). Pharmacological approaches have shown that β2 nAChR antagonists block the development of social avoidance, while α7 nAChR antagonists block its expression (Morel et al. 2018). After illustrating the alteration of social stress on the nicotinic system, it was then critical to understand whether nicotine alters the effect of social stress. They found that nicotine administration before mice underwent a classic subthreshold SD paradigm (Chaudhury et al. 2013) promoted social avoidance and increased both tonic and phasic VTA DA neuron activities (Morel et al. 2018), illustrating that nicotine (via α7 nAChRs) increases social stress sensitivity and could therefore constitute a risk factor in the mechanism underlying depressive-like phenotypes.

Establishing VTA ACh signaling as critical for some of the alterations induced by chronic social stress raises another question: which ACh afferents are critical for this effect? One possibility is the laterodorsal tegmental nucleus (LDTg) (Morel et al. 2018; Fernandez et al. 2018) as this tegmental structure is known to control the electrophysiological pattern of VTA DA neuron activity, most notably their bursting mode, via both ACh and glutamatergic (Glu) projections (Chen and Lodge 2013; Wang and Morales 2009). Using different conditional transgenic mouse lines (cre-mice) and chemogenetic approaches, the authors demonstrated that the SD10 paradigm increased LDTg Glu and ACh neuronal excitability. Furthermore, the inhibition of LDT ACh neurons before each social stress episode of a SD10 procedure prevented SD-induced exacerbation of VTA DA neurons and social avoidance. In addition, they demonstrated that selective activation of the LDTg neurons projecting to the VTA increased susceptibility to social stress, as indicated by the expression of social avoidance after such activation during a subthreshold SD paradigm (Chaudhury et al. 2013). Surprisingly, inhibition of the Glu neurons in the LDTg did not prevent SD-induced dysregulation of the VTA DA neurons and depressive-like behaviors (Fernandez et al. 2018). The authors thus revealed a specific role for exacerbated activity in LDT ACh neurons projecting to the VTA in the development of dopaminergic-related behavioral and cellular aspects of the depressive-like phenotype induced by chronic SD. Finally, the authors also identified CRF (through CRF-R1 on LDTg ACh neurons) as the upstream molecular determinant responsible for the exacerbated ACh neuronal activity induced by chronic stress in the LDTg (Fernandez et al. 2018).

Morphological modifications

While many studies have focused on alterations induced by SD10 in given brain areas, others have investigated broader morphological and structural changes in several brain regions. Among these, two studies mentioned structural VTA alterations that may contribute to resilience versus susceptibility in defeated mice. Using Golgi staining, an increase in dendritic spines in the NAc and the VTA of susceptible mice relative to resilient and control animals has been observed, whereas the density of dendritic spines in the prelimbic cortex (PrL), the hippocampal CA3 (CA3) and the dentate gyrus (DG) of susceptible mice was lower than in resilient and control mice (Qu et al. 2018). Using structural magnetic resonance imaging and diffusion tensor imaging (Anacker et al. 2016), it has been reported that the social avoidance observed in mice subjected to the SD10 paradigm positively correlated with the volumes of the VTA, LHb, periaqueductal gray (PAG), cerebellum, hypothalamus and CA3, while it negatively correlated with

volumes of the cingulate cortex (Cg), NAc, thalamus, raphe nuclei and BNST. Finally, the authors also observed synchronized anatomic differences notably between the VTA and Cg and the hippocampus and VTA (Anacker et al. 2016).

Brain-derived neurotrophic factor

BDNF is a member of the neurotrophin family of growth factors produced by VTA DA neurons and released in the VTA itself and in both the ventral and dorsal striata. BDNF has been involved in the synaptic plasticity observed on VTA DA neurons in response to various types of stress and considered as a pro-depressive factor in the mesolimbic pathway (for review, see Nestler and Carlezon 2006). Accordingly, chronic SD has been shown to recruit VTA DA neurons and to increase BDNF levels in the NAc (Berton et al. 2006). In a series of three publications, the groups of Pr. Eric Nestler and Dr. Ming-Hu Han studied the pro-depressant effect of BDNF in the VTA-NAc pathway (Berton et al. 2006; Krishnan et al. 2007; Wook Koo et al. 2016). In the first study, the authors showed that BDNF is required for the expression of social aversion induced by chronic SD (Berton et al. 2006). They observed that animals exposed to the SD10 paradigm had increased BDNF protein levels in the NAc. As the main source of BDNF proteins in this region is the VTA (indicated by the high levels of mRNA expression in the VTA compared to the NAc; Conner et al. 1997; Seroogy et al. 1994), the authors used a viral approach to knock down VTA BDNF expression in mice that were subsequently subjected to the SD10 procedure. This VTA BDNF deletion had an antidepressant-like effect by reducing social avoidance behavior in defeated mice (Berton et al. 2006). In their next study, the authors showed that only susceptible mice displayed this increased BDNF protein levels in the NAc. Accordingly, VTA BDNF gene deletion reduced susceptibility to chronic SD, suggesting that BDNF transported from the VTA to the NAc contributes to behavioral susceptibility (Krishnan et al. 2007). Finally, their most recent study provided an understanding of the link between alterations in BDNF signaling in the NAc and increased VTA DA neuronal activity, two factors concomitantly observed in mice susceptible to chronic SD (Wook Koo et al. 2016).

Indeed, several articles reported that the SD10 paradigm increased the phasic firing rate of VTA DA neurons projecting to the NAc in susceptible mice (Cao et al. 2010; Krishnan et al. 2007, 2008). Consistent with the finding that chronic optogenetic phasic stimulation of VTA DA neurons during SD procedures exacerbated social avoidance symptoms (Chaudhury et al. 2013; Friedman et al. 2014), phasic stimulation of the VTA-NAc pathway was shown to facilitate the release of BDNF and DA from VTA DA terminals (Bass et al. 2013; Tsai et al. 2009). Building on these data, Wook Koo et al. (2016) showed that pharmacological inactivation of NAc BDNF-TrkB signaling but not NAc DA signaling, prevented the development of SD10-induced social avoidance. In addition, chronic optogenetic phasic stimulation of VTA DA neurons increased NAc BDNF levels and exacerbated social avoidance induced by the SD10 paradigm. Finally, BDNF-TrkB blockade in the NAc and VTA BDNF knockdown prevented aggravation of social avoidance. Thus, the authors demonstrated that BDNF signaling but not DA signaling, in the VTA-NAc pathway is required for the development of the susceptible phenotype induced by chronic social stress (Wook Koo et al. 2016).

- Mu opioid receptors

VTA DA neurons are known to be tonically inhibited by the VTA GABAergic interneurons and GABAergic inputs from an adjacent structure named the tVTA (also known as RMTg or rostromedial tegmental nucleus) (Bourdy and Barrot 2012). Mu opioid receptors (MORs) expressed on these neurons mediate the disinhibition of VTA DA neurons induced by (Jalabert et al. 2011; Kaufling and Aston-Jones 2015; Matsui et al. 2014) opiates and, interestingly, SD seems to have a strong impact on VTA MOR. Studies from the group of Dr. Nikulina and Dr. Hammer showed increased VTA MOR mRNA expression 30 min to 6 days after a single SD experience in mice, using in situ hybridization (ISH) (Nikulina et al. 1998). This increase was also present in rats after a chronic SD paradigm (5 continuous days), could be detected 2 h after the last SD exposure (Nikulina et al. 2008) and was still present 7 (Nikulina et al. 2005) and 21 days later (Nikulina et al. 2008). Knocking-down VTA MOR using a lentiviral approach prevented social avoidance and attenuated weight gain normally observed after SD. Interestingly, VTA MOR knockdown prevented stress-induced expression of VTA BDNF (Johnston et al. 2015), highlighting a potential therapeutic target for preventing the pro-depressive effects of increased BDNF signaling following SD described above.

Phosphorylated thymoma viral proto-oncogene

Pr. E.J. Nestler and its collaborators highlighted the implication, within the VTA, of a specific proto-oncogene in the development of susceptibility to chronic social defeat in mice: the phosphorylated (active) form of the thymoma viral proto-oncogene (pAKT) (Krishnan et al. 2008). Combining pharmacological, viral and electrophysiological approaches, they demonstrated that a diminution of pAKT was necessary and sufficient for the expression of depressive-like phenotypes (social avoidance) and was associated with susceptibility to the SD10 paradigm in mice (Krishnan et al. 2008). Their results showed that (i) pharmacological local reduction of AKT level within the VTA increased the firing rate of VTA DA neurons, which is classically observed in susceptible mice

(as discussed above); this exacerbated electrophysiological activity has been shown to be mediated by a GABAA receptor–dependent mechanism, as indicated by a reduced amplitude and frequency of GABAA inhibitory post-synaptic currents (IPSCs); (ii) rapid and transient local VTA suppression of AKT using a herpes simplex (HSV) viral approach promotes susceptibly to social stress, a subthreshold SD paradigm, not typically shown to induce depressive-like phenotypes in naïve animals, becoming sufficient to induce social avoidance in mice that underwent this AKT reduction; and (iii) conversely, virally induced increases in VTA AKT levels in susceptible animals 11 days after the end of the SD10 protocol were sufficient to promote resilience, as illustrated by a reduction of the social avoidance behavior 13 days after the end of the SD10 procedure (Krishnan et al. 2008). This illustrates that susceptibility, similar to resilience, could be an active mechanism (Krishnan et al. 2008).

Therapeutic potential in targeting DA system and final considerations

Considering the studies described in this review and the fact that more than a third of depressed patients treated with selective serotonin reuptake inhibitors do not obtain remission, the prospective of new treatments targeting the DA system may be appealing. However, the fact that animal models of environmental and social stress leading to same depressive symptoms are linked to opposite dysregulation of the VTA DA neurons' electrical activity (respectively inhibition and exacerbation) may question this strategy. Nevertheless, based on recent therapeutic advances in the pharmacological treatment of depression, drugs acting on the activity of DA neurons showed some effectiveness. As an example, ketamine has been used successfully in patients with treatment-resistant depression (Schwartz et al. 2016). As described earlier, the rapid and durable effect of this non-competitive glutamatergic *N*-methyl-D-aspartate receptor antagonist seems to be at least partially mediated by a normalization of VTA DA neuron activity in an animal model of depression induced by environmental stress (Belujon and Grace 2014c; Rincón-Cortés and Grace 2017). In the same line of evidence, the use of second-generation dopamine D2 receptor antagonists in association to more classic selective serotonin reuptake inhibitors has been successfully used in patients (Belujon and Grace 2017). On the other hand, when depressed states have been hypothetized to be mediated by an increased activity of VTA DA neurons projecting to the NAc, related pharmacological treatments have not been already used in patients; however, some of the animal studies discussed in this review highlighted targets of interest. We can notably cite drugs promoting the intrinsic homoeostasis plasticity of VTA DA neurons observed in resilient mice, such as the KCNQ-type K(+) channel opener retigabine (Friedman et al. 2016).

This review highlights the many functional roles of VTA and more particularly of VTA DA neurons, both in the development of maladaptation leading to depressive-like phenotypes and in the adaptations leading to resilience. However, it is not yet understood how the diversity of VTA DA neurons participates in depression; it is likely that DA neurons with different localizations within the VTA, different projection targets and/or molecular and neurochemical profiles uniquely contribute to depressive states. The mechanism underlying the higher prevalence of depression among women than men is another important aspect that is now becoming the focus of investigations and it is interesting to hypothesize that a differential regulation of DA neurons may underlie this phenomenon. Finally, an interesting question arises from the different electrophysiological adaptations of VTA DA neurons in animals subjected to these different models. For example, CMS induces reduced VTA DA activity associated with depressive-like behaviors, while the opposite is true in mice susceptible to SD, where increased activity of VTA DA neurons is linked to the depressive-like behaviors. Furthermore, phasic activation of VTA DA neurons rescues depression-like behavior induced by CMS but promotes susceptibility in SD. Here, we highlight research showing that these three models implicate VTA DA neurons with different projection targets (i.e., NAc or mPFC projecting) and/or distinct afferent modulatory pathways. These results suggest that two different origins (environmental or social stress), which lead to similar symptoms (anhedonia, despair), are the result of different underlying DA mechanisms. This raises the question: could shared mechanism(s) supporting similar symptoms of depression but arising from different etiologies exist? This important question can likely be addressed by investigating and comparing the electrophysiological activities of VTA DA neurons in animals subjected to other models of depression such as early life stress or comorbid models such as chronic pain of protracted morphine withdrawal.

Acknowledgments We thank Dr. Barrot, Dr. Yalcin and Dr. Massotte (INCI CNRS UPR 2312) for critical comments on the manuscript.

Funding information This work was supported by the CNRS (contract UPR3212), Université de Strasbourg and Strasbourg Neuropôle.

References

American Psychiatric Association., American Psychiatric Association. DSM-5 Task Force (2013) Diagnostic and statistical manual of mental disorders: DSM-5. American Psychiatric Association

Anacker C, Scholz J, O'Donnell KJ, Allemang-Grand R, Diorio J, Bagot RC, Nestler EJ, Hen R, Lerch JP, Meaney MJ (2016) Neuroanatomic differences associated with stress susceptibility and resilience. Biol Psychiatry 79:840–849. https://doi.org/10.1016/J.BIOPSYCH.2015.08.009

Bass CE, Grinevich VP, Gioia D, Day-Brown JD, Bonin KD, Stuber GD, Weiner JL, Budygin EA (2013) Optogenetic stimulation of VTA dopamine neurons reveals that tonic but not phasic patterns of dopamine transmission reduce ethanol self-administration. Front Behav Neurosci 7:173. https://doi.org/10.3389/fnbeh.2013.00173

Belujon P, Grace AA (2014a) Restoring mood balance in depression: ketamine reverses deficit in dopamine-dependent synaptic plasticity. Biol Psychiatry 76:927–936. https://doi.org/10.1016/j.biopsych.2014.04.014

Belujon P, Grace AA (2014b) Restoring mood balance in depression: ketamine reverses deficit in dopamine-dependent synaptic plasticity. Biol Psychiatry 76:927–936. https://doi.org/10.1016/j.biopsych.2014.04.014

Belujon P, Grace AA (2014c) Restoring mood balance in depression: ketamine reverses deficit in dopamine-dependent synaptic plasticity. Biol Psychiatry 76:927–936. https://doi.org/10.1016/J.BIOPSYCH.2014.04.014

Belujon P, Grace AA (2017) Dopamine system dysregulation in major depressive disorders. Int J Neuropsychopharmacol 20:1036–1046. https://doi.org/10.1093/ijnp/pyx056

Bertaina-Anglade V, La Rochelle CD, Scheller DKA (2006) Antidepressant properties of rotigotine in experimental models of depression. Eur J Pharmacol 548:106–114. https://doi.org/10.1016/j.ejphar.2006.07.022

Berton O, McClung CA, Dileone RJ, Krishnan V, Renthal W, Russo SJ, Graham D, Tsankova NM, Bolanos CA, Rios M, Monteggia LM, Self DW, Nestler EJ (2006) Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress. Science 311:864–868. https://doi.org/10.1126/science.1120972

Besson A, Privat AM, Eschalier A, Fialip J (1998) Reversal of learned helplessness by morphine in rats: involvement of a dopamine mediation. Pharmacol Biochem Behav 60:519–525

Bourdy R, Barrot M (2012) A new control center for dopaminergic systems: pulling the VTA by the tail. Trends Neurosci 35:681–690. https://doi.org/10.1016/J.TINS.2012.06.007

Bromberg-Martin ES, Matsumoto M, Hikosaka O (2010) Dopamine in motivational control: rewarding, aversive, and alerting. Neuron 68:815–834. https://doi.org/10.1016/j.neuron.2010.11.022

Cahill CM, Taylor AM (2017) Neuroinflammation-a co-occurring phenomenon linking chronic pain and opioid dependence. Curr Opin Behav Sci 13:171–177. https://doi.org/10.1016/j.cobeha.2016.12.003

Cao J-L, Covington HE, Friedman AK, Wilkinson MB, Walsh JJ, Cooper DC, Nestler EJ, Han M-H, Han M-H (2010) Mesolimbic dopamine neurons in the brain reward circuit mediate susceptibility to social defeat and antidepressant action. J Neurosci 30:16453–16458. https://doi.org/10.1523/JNEUROSCI.3177-10.2010

Chang C-H, Grace AA (2014) Amygdala-ventral pallidum pathway decreases dopamine activity after chronic mild stress in rats. Biol Psychiatry 76:223–230. https://doi.org/10.1016/j.biopsych.2013.09.020

Chaudhury D, Walsh JJ, Friedman AK, Juarez B, Ku SM, Koo JW, Ferguson D, Tsai H-C, Pomeranz L, Christoffel DJ, Nectow AR, Ekstrand M, Domingos A, Mazei-Robison MS, Mouzon E, Lobo MK, Neve RL, Friedman JM, Russo SJ, Deisseroth K, Nestler EJ, Han M-H (2013) Rapid regulation of depression-related behaviours by control of midbrain dopamine neurons. Nature 493:532–536. https://doi.org/10.1038/nature11713

Chaudhury D, Liu H, Han M-H (2015) Neuronal correlates of depression. Cell Mol Life Sci 72:4825–4848. https://doi.org/10.1007/s00018-015-2044-6

Chen L, Lodge DJ (2013) The lateral mesopontine tegmentum regulates both tonic and phasic activity of VTA dopamine neurons. J Neurophysiol 110:2287–2294. https://doi.org/10.1152/jn.00307.2013

Conner JM, Lauterborn JC, Yan Q, Gall CM, Varon S (1997) Distribution of brain-derived neurotrophic factor (BDNF) protein and mRNA in the normal adult rat CNS: evidence for anterograde axonal transport. J Neurosci 17:2295–2313. https://doi.org/10.1523/JNEUROSCI.17-07-02295.1997

Czéh B, Fuchs E, Wiborg O, Simon M (2016) Animal models of major depression and their clinical implications. Prog Neuro-Psychopharmacol Biol Psychiatry 64:293–310. https://doi.org/10.1016/J.PNPBP.2015.04.004

Dautan D, Souza AS, Huerta-Ocampo I, Valencia M, Assous M, Witten IB, Deisseroth K, Tepper JM, Bolam JP, Gerdjikov TV, Mena-Segovia J (2016) Segregated cholinergic transmission modulates dopamine neurons integrated in distinct functional circuits. Nat Neurosci 19:1025–1033. https://doi.org/10.1038/nn.4335

Drugan RC, Basile AS, Ha JH, Healy D, Ferland RJ (1997) Analysis of the importance of controllable versus uncontrollable stress on subsequent behavioral and physiological functioning. Brain Res Brain Res Protoc 2:69–74

Duterte-Boucher D, Leclère JF, Panissaud C, Costentin J (1988) Acute effects of direct dopamine agonists in the mouse behavioral despair test. Eur J Pharmacol 154:185–190

Faivre F, Joshi A, Bezard E, Barrot M (2018) The hidden side of Parkinson's disease: studying pain, anxiety and depression in animal models. Neurosci Biobehav Rev. https://doi.org/10.1016/j.neubiorev.2018.10.004

Faure P, Tolu S, Valverde S, Naudé J (2014) Role of nicotinic acetylcholine receptors in regulating dopamine neuron activity. Neuroscience 282:86–100. https://doi.org/10.1016/J.NEUROSCIENCE.2014.05.040

Fernandez SP, Broussot L, Marti F, Contesse T, Mouska X, Soiza-Reilly M, Marie H, Faure P, Barik J (2018) Mesopontine cholinergic inputs to midbrain dopamine neurons drive stress-induced depressive-like behaviors. Nat Commun 9:4449. https://doi.org/10.1038/s41467-018-06809-7

Ferrari AJ, Somerville AJ, Baxter AJ, Norman R, Patten SB, Vos T, Whiteford HA (2013) Global variation in the prevalence and incidence of major depressive disorder: a systematic review of the epidemiological literature. Psychol Med 43:471–481. https://doi.org/10.1017/S0033291712001511

Friedman AK, Walsh JJ, Juarez B, Ku SM, Chaudhury D, Wang J, Li X, Dietz DM, Pan N, Vialou VF, Neve RL, Yue Z, Han M-H (2014) Enhancing depression mechanisms in midbrain dopamine neurons achieves homeostatic resilience. Science 344:313–319. https://doi.org/10.1126/science.1249240

Friedman AK, Juarez B, Ku SM, Zhang H, Calizo RC, Walsh JJ, Chaudhury D, Zhang S, Hawkins A, Dietz DM, Murrough JW, Ribadeneira M, Wong EH, Neve RL, Han M-H (2016) KCNQ channel openers reverse depressive symptoms via an active resilience mechanism. Nat Commun 7:11671. https://doi.org/10.1038/ncomms11671

Geisler S, Derst C, Veh RW, Zahm DS (2007) Glutamatergic afferents of the ventral tegmental area in the rat. J Neurosci 27:5730–5743. https://doi.org/10.1523/JNEUROSCI.0012-07.2007

Hammack SE, Cooper MA, Lezak KR (2012) Overlapping neurobiology of learned helplessness and conditioned defeat: implications for PTSD and mood disorders. Neuropharmacology 62:565–575. https://doi.org/10.1016/j.neuropharm.2011.02.024

Han M-H, Nestler EJ (2017) Neural substrates of depression and resilience. Neurotherapeutics 14:677–686. https://doi.org/10.1007/s13311-017-0527-x

Hong S, Jhou TC, Smith M, Saleem KS, Hikosaka O (2011) Negative reward signals from the lateral habenula to dopamine neurons are mediated by rostromedial tegmental nucleus in primates. J Neurosci 31:11457–11471. https://doi.org/10.1523/JNEUROSCI.1384-11.2011

Isingrini E, Perret L, Rainer Q, Amilhon B, Guma E, Tanti A, Martin G, Robinson J, Moquin L, Marti F, Mechawar N, Williams S, Gratton A, Giros B (2016) Resilience to chronic stress is mediated by noradrenergic regulation of dopamine neurons. Nat Neurosci 19:560–563. https://doi.org/10.1038/nn.4245

Jalabert M, Bourdy R, Courtin J, Veinante P, Manzoni OJ, Barrot M, Georges F (2011) Neuronal circuits underlying acute morphine action on dopamine neurons. Proc Natl Acad Sci U S A 108:16446–16450. https://doi.org/10.1073/pnas.1105418108

Johnson SW, North RA (1992) Two types of neurone in the rat ventral tegmental area and their synaptic inputs. J Physiol 450:455–468

Johnston CE, Herschel DJ, Lasek AW, Hammer RP, Nikulina EM, Nikulina EM (2015) Knockdown of ventral tegmental area mu-opioid receptors in rats prevents effects of social defeat stress: implications for amphetamine cross-sensitization, social avoidance, weight regulation and expression of brain-derived neurotrophic factor. Neuropharmacology 89:325–334. https://doi.org/10.1016/j.neuropharm.2014.10.010

Katz RJ (1982) Animal model of depression: pharmacological sensitivity of a hedonic deficit. Pharmacol Biochem Behav 16:965–968

Kaufling J, Aston-Jones G (2015) Persistent adaptations in afferents to ventral tegmental dopamine neurons after opiate withdrawal. J Neurosci 35:10290–10303. https://doi.org/10.1523/JNEUROSCI.0715-15.2015

Kaufling J, Veinante P, Pawlowski SA, Freund-Mercier MJ, Barrot M (2010) gamma-Aminobutyric acid cells with cocaine-induced DeltaFosB in the ventral tegmental area innervate mesolimbic neurons. Biol Psychiatry 67:88–92. https://doi.org/10.1016/j.biopsych.2009.08.001

Kaufling J, Girard D, Maitre M, Leste-Lasserre T, Georges F (2017) Species-specific diversity in the anatomical and physiological organisation of the BNST-VTA pathway. Eur J Neurosci 45:1230–1240. https://doi.org/10.1111/ejn.13554

Kim EJ, Bahk Y-C, Oh H, Lee W-H, Lee J-S, Choi K-H (2018) Current status of cognitive remediation for psychiatric disorders: a review. Front Psychiatry 9:461. https://doi.org/10.3389/fpsyt.2018.00461

Knowland D, Lim BK (2018) Circuit-based frameworks of depressive behaviors: the role of reward circuitry and beyond. Pharmacol Biochem Behav 174:42–52. https://doi.org/10.1016/j.pbb.2017.12.010

Krishnan V, Han M-H, Graham DL, Berton O, Renthal W, Russo SJ, LaPlant Q, Graham A, Lutter M, Lagace DC, Ghose S, Reister R, Tannous P, Green TA, Neve RL, Chakravarty S, Kumar A, Eisch AJ, Self DW, Lee FS, Tamminga CA, Cooper DC, Gershenfeld HK, Nestler EJ (2007) Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions. Cell 131:391–404. https://doi.org/10.1016/J.CELL.2007.09.018

Krishnan V, Han M-H, Mazei-Robison M, Iñiguez SD, Ables JL, Vialou V, Berton O, Ghose S, Covington HE, Wiley MD, Henderson RP, Neve RL, Eisch AJ, Tamminga CA, Russo SJ, Bolaños CA, Nestler EJ, Nestler EJ (2008) AKT signaling within the ventral tegmental area regulates cellular and behavioral responses to stressful stimuli. Biol Psychiatry 64:691–700. https://doi.org/10.1016/j.biopsych.2008.06.003

Lammel S, Lim BK, Ran C, Huang KW, Betley MJ, Tye KM, Deisseroth K, Malenka RC (2012) Input-specific control of reward and aversion in the ventral tegmental area. Nature 491:212–217. https://doi.org/10.1038/nature11527

Lammel S, Lim BK, Malenka RC (2014) Reward and aversion in a heterogeneous midbrain dopamine system. Neuropharmacology 76 Pt B:351–359. https://doi.org/10.1016/j.neuropharm.2013.03.019

Li B, Piriz J, Mirrione M, Chung C, Proulx CD, Schulz D, Henn F, Malinow R (2011) Synaptic potentiation onto habenula neurons in the learned helplessness model of depression. Nature 470:535–539. https://doi.org/10.1038/nature09742

Liu D, Tang Q-Q, Yin C, Song Y, Liu Y, Yang J-X, Liu H, Zhang Y-M, Wu S-Y, Song Y, Juarez B, Ding H-L, Han M-H, Zhang H, Cao J-L (2018) Brain-derived neurotrophic factor-mediated projection-specific regulation of depressive-like and nociceptive behaviors in the mesolimbic reward circuitry. Pain 159:175. https://doi.org/10.1097/j.pain.0000000000001083

Mahler SV, Vazey EM, Beckley JT, Keistler CR, McGlinchey EM, Kaufling J, Wilson SP, Deisseroth K, Woodward JJ, Aston-Jones G (2014) Designer receptors show role for ventral pallidum input to ventral tegmental area in cocaine seeking. Nat Neurosci 17:577–585. https://doi.org/10.1038/nn.3664

Maier SF, Seligman MEP (1976) Learned helplessness: theory and evidence. J Exp Psychol Gen 1:3–46

Matsui A, Jarvie BC, Robinson BG, Hentges ST, Williams JT (2014) Separate GABA afferents to dopamine neurons mediate acute action of opioids, development of tolerance, and expression of withdrawal. Neuron 82:1346–1356. https://doi.org/10.1016/j.neuron.2014.04.030

Miczek KA (1979) A new test for aggression in rats without aversive stimulation: differential effects of d-amphetamine and cocaine. Psychopharmacology 60:253–259. https://doi.org/10.1007/BF00426664

Moreines JL, Owrutsky ZL, Gagnon KG, Grace AA (2017a) Divergent effects of acute and repeated quetiapine treatment on dopamine neuron activity in normal vs. chronic mild stress induced hypodopaminergic states. Transl Psychiatry 7:1275. https://doi.org/10.1038/s41398-017-0039-9

Moreines JL, Owrutsky ZL, Grace AA (2017b) Involvement of Infralimbic prefrontal cortex but not lateral habenula in dopamine attenuation after chronic mild stress. Neuropsychopharmacology 42:904–913. https://doi.org/10.1038/npp.2016.249

Morel C, Fernandez SP, Pantouli F, Meye FJ, Marti F, Tolu S, Parnaudeau S, Marie H, Tronche F, Maskos U, Moretti M, Gotti C, Han M-H, Bailey A, Mameli M, Barik J, Faure P (2018) Nicotinic receptors mediate stress-nicotine detrimental interplay via dopamine cells' activity. Mol Psychiatry 23:1597–1605. https://doi.org/10.1038/mp.2017.145

Morikawa H, Paladini CA (2011) Dynamic regulation of midbrain dopamine neuron activity: intrinsic, synaptic, and plasticity mechanisms. Neuroscience 198:95–111. https://doi.org/10.1016/J.NEUROSCIENCE.2011.08.023

Nestler EJ, Carlezon WA (2006) The mesolimbic dopamine reward circuit in depression. Biol Psychiatry 59:1151–1159. https://doi.org/10.1016/J.BIOPSYCH.2005.09.018

Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM (2002) Neurobiology of depression. Neuron 34:13–25. https://doi.org/10.1016/S0896-6273(02)00653-0

Ng E, Browne CJ, Samsom JN, Wong AHC (2017) Depression and substance use comorbidity: what we have learned from animal studies. Am J Drug Alcohol Abuse 43:456–474. https://doi.org/10.1080/00952990.2016.1183020

Nikulina EM, Marchand JE, Kream RM, Miczek KA (1998) Behavioral sensitization to cocaine after a brief social stress is accompanied by changes in Fos expression in the murine brainstem. Brain Res 810:200–210. https://doi.org/10.1016/S0006-8993(98)00925-1

Nikulina EM, Miczek KA, Hammer RP (2005) Prolonged effects of repeated social defeat stress on mRNA expression and function of mu-opioid receptors in the ventral tegmental area of rats. Neuropsychopharmacology 30:1096–1103. https://doi.org/10.1038/sj.npp.1300658

Nikulina EM, Arrillaga-Romany I, Miczek KA, Hammer RP Jr (2008) Long-lasting alteration in mesocorticolimbic structures after repeated social defeat stress in rats: time course of mu-opioid receptor mRNA and FosB/DeltaFosB immunoreactivity. Eur J Neurosci 27:2272–2284. https://doi.org/10.1111/j.1460-9568.2008.06176.x

Paladini CA, Roeper J (2014) Generating bursts (and pauses) in the dopamine midbrain neurons. Neuroscience 282:109–121. https://doi.org/10.1016/J.NEUROSCIENCE.2014.07.032

Proulx CD, Hikosaka O, Malinow R (2014) Reward processing by the lateral habenula in normal and depressive behaviors. Nat Neurosci 17:1146–1152. https://doi.org/10.1038/nn.3779

Qu Y, Yang C, Ren Q, Ma M, Dong C, Hashimoto K (2018) Regional differences in dendritic spine density confer resilience to chronic social defeat stress. Acta Neuropsychiatr 30:117–122. https://doi.org/10.1017/neu.2017.16

Rincón-Cortés M, Grace AA (2017) Sex-dependent effects of stress on immobility behavior and VTA dopamine neuron activity: modulation by ketamine. Int J Neuropsychopharmacol 20:823–832. https://doi.org/10.1093/ijnp/pyx048

Rush AJ, Kraemer HC, Sackeim HA, Fava M, Trivedi MH, Frank E, Ninan PT, Thase ME, Gelenberg AJ, Kupfer DJ, Regier DA, Rosenbaum JF, Ray O, Schatzberg AF (2006) Report by the ACNP task force on response and remission in major depressive disorder. Neuropsychopharmacology 31:1841–1853. https://doi.org/10.1038/sj.npp.1301131

Sartorius A, Kiening KL, Kirsch P, von Gall CC, Haberkorn U, Unterberg AW, Henn FA, Meyer-Lindenberg A (2010) Remission of major depression under deep brain stimulation of the lateral habenula in a therapy-refractory patient. Biol Psychiatry 67:e9–e11. https://doi.org/10.1016/J.BIOPSYCH.2009.08.027

Schöner J, Heinz A, Endres M, Gertz K, Kronenberg G (2017) Post-traumatic stress disorder and beyond: an overview of rodent stress models. J Cell Mol Med 21:2248–2256. https://doi.org/10.1111/jcmm.13161

Schultz W (2013) Updating dopamine reward signals. Curr Opin Neurobiol 23:229–238. https://doi.org/10.1016/j.conb.2012.11.012

Schultz W (2016) Dopamine reward prediction-error signalling: a two-component response. Nat Rev Neurosci 17:183–195. https://doi.org/10.1038/nrn.2015.26

Schwartz J, Murrough JW, Iosifescu DV (2016) Ketamine for treatment-resistant depression: recent developments and clinical applications: table 1. Evid Based Ment Heal 19:35–38. https://doi.org/10.1136/eb-2016-102355

Schweizer MC, Henniger MSH, Sillaber I (2009) Chronic mild stress (CMS) in mice: of anhedonia, "anomalous anxiolysis" and activity. PLoS One 4:e4326. https://doi.org/10.1371/journal.pone.0004326

Seligman MEP (1972) Learned helplessness. Annu Rev Med 23:407–412. https://doi.org/10.1146/annurev.me.23.020172.002203

Seroogy KB, Lundgren KH, Tran TMD, Guthrie KM, Isackson PJ, Gall CM (1994) Dopaminergic neurons in rat ventral midbrain express brain-derived neurotrophic factor and neurotrophin-3 mRNAs. J Comp Neurol 342:321–334. https://doi.org/10.1002/cne.903420302

Shah NH, Aizenman E (2014) Voltage-gated potassium channels at the crossroads of neuronal function, ischemic tolerance, and neurodegeneration. Transl Stroke Res 5:38–58. https://doi.org/10.1007/s12975-013-0297-7

Takamori K, Yoshida S, Okuyama S (2001) Repeated treatment with imipramine, fluvoxamine and tranylcypromine decreases the number of escape failures by activating dopaminergic systems in a rat learned helplessness test. Life Sci 69:1919–1926

Taylor AMW, Castonguay A, Taylor AJ, Murphy NP, Ghogha A, Cook C, Xue L, Olmstead MC, De Koninck Y, Evans CJ, Cahill CM (2015) Microglia disrupt mesolimbic reward circuitry in chronic pain. J Neurosci 35:8442–8450. https://doi.org/10.1523/JNEUROSCI.4036-14.2015

Tolliver BK, Anton RF (2015) Assessment and treatment of mood disorders in the context of substance abuse. Dialogues Clin Neurosci 17:181–190

Tsai H-C, Zhang F, Adamantidis A, Stuber GD, Bonci A, de Lecea L, Deisseroth K (2009) Phasic firing in dopaminergic neurons is sufficient for behavioral conditioning. Science 324:1080–1084. https://doi.org/10.1126/science.1168878

Tye KM, Mirzabekov JJ, Warden MR, Ferenczi EA, Tsai H-C, Finkelstein J, Kim S-Y, Adhikari A, Thompson KR, Andalman AS, Gunaydin LA, Witten IB, Deisseroth K (2013) Dopamine neurons modulate neural encoding and expression of depression-related behaviour. Nature 493:537–541. https://doi.org/10.1038/nature11740

Vollmayr B, Gass P (2013) Learned helplessness: unique features and translational value of a cognitive depression model. Cell Tissue Res 354:171–178. https://doi.org/10.1007/s00441-013-1654-2

Wang H-L, Morales M (2009) Pedunculopontine and laterodorsal tegmental nuclei contain distinct populations of cholinergic, glutamatergic and GABAergic neurons in the rat. Eur J Neurosci 29:340–358. https://doi.org/10.1111/j.1460-9568.2008.06576.x

Watabe-Uchida M, Zhu L, Ogawa SK, Vamanrao A, Uchida N (2012) Whole-brain mapping of direct inputs to midbrain dopamine neurons. Neuron 74:858–873. https://doi.org/10.1016/J.NEURON.2012.03.017

White F, Hu X, Marinelli M, Rudick C (2006) Excitability of dopamine neurons: modulation and physiological consequences. CNS Neurol Disord Drug Targets 5:79–97. https://doi.org/10.2174/187152706784111542

WHO(2013) | The World Health Report 2008 - primary health care (now more than ever). WHO

Wiborg O (2013) Chronic mild stress for modeling anhedonia. Cell Tissue Res 354:155–169. https://doi.org/10.1007/s00441-013-1664-0

Willner P (1986) Validating criteria for animal models of human mental disorders: learned helplessness as a paradigm case. Prog Neuropsychopharmacol Biol Psychiatry 10:677–690

Willner P (2017) The chronic mild stress (CMS) model of depression: history, evaluation and usage. Neurobiol Stress 6:78–93. https://doi.org/10.1016/j.ynstr.2016.08.002

Willner P, Belzung C (2015) Treatment-resistant depression: are animal models of depression fit for purpose? Psychopharmacology 232:3473–3495. https://doi.org/10.1007/s00213-015-4034-7

Willner P, Towell A, Sampson D, Sophokleous S, Muscat R (1987) Reduction of sucrose preference by chronic unpredictable mild stress, and its restoration by a tricyclic antidepressant. Psychopharmacology 93:358–364

Willner P, Scheel-Krüger J, Belzung C (2013) The neurobiology of depression and antidepressant action. Neurosci Biobehav Rev 37:2331–2371. https://doi.org/10.1016/J.NEUBIOREV.2012.12.007

Winter C, von Rumohr A, Mundt A, Petrus D, Klein J, Lee T, Morgenstern R, Kupsch A, Juckel G (2007) Lesions of dopaminergic neurons in the substantia nigra pars compacta and in the ventral tegmental area enhance depressive-like behavior in rats. Behav Brain Res 184:133–141. https://doi.org/10.1016/j.bbr.2007.07.002

Wook Koo J, Labonté B, Engmann O, Calipari ES, Juarez B, Lorsch Z, Walsh JJ, Friedman AK, Yorgason JT, Han MH, Nestler EJ (2016) Essential role of mesolimbic brain-derived neurotrophic factor in chronic social stress–induced depressive behaviors. Biol Psychiatry 80:469–478. https://doi.org/10.1016/j.biopsych.2015.12.009

Yalcin I, Barrot M (2014) The anxiodepressive comorbidity in chronic pain. Curr Opin Anaesthesiol 27:520–527. https://doi.org/10.1097/ACO.0000000000000116

Yalcin I, Barthas F, Barrot M (2014) Emotional consequences of neuropathic pain: insight from preclinical studies. Neurosci Biobehav Rev 47:154–164. https://doi.org/10.1016/j.neubiorev.2014.08.002

Yin X, Guven N, Dietis N (2016) Stress-based animal models of depression: do we actually know what we are doing? Brain Res 1652:30–42. https://doi.org/10.1016/j.brainres.2016.09.027

Zhang H, Chaudhury D, Nectow AR, Friedman AK, Zhang S, Juarez B, Liu H, Pfau ML, Aleyasin H, Jiang C, Crumiller M, Calipari ES, Ku SM, Morel C, Tzavaras N, Montgomery SE, He M, Salton SR, Russo SJ, Nestler EJ, Friedman JM, Cao J-L, Han M-H (2018) α1- and β3-adrenergic receptor–mediated mesolimbic homeostatic plasticity confers resilience to social stress in susceptible mice. Biol Psychiatry. https://doi.org/10.1016/J.BIOPSYCH.2018.08.020

Zhong, P., Vickstrom, C.R., Liu, X., Hu, Y., Yu, L., Yu, H.-G., Liu, Q.-S., 2018. HCN2 channels in the ventral tegmental area regulate behavioral responses to chronic stress. Elife 7. doi https://doi.org/10.7554/eLife.32420