Review

Dopamine System Dysregulation in Major Depressive Disorders

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Abstract

Anhedonia is considered a core feature of major depressive disorder, and the dopamine system plays a pivotal role in the hedonic deficits described in this disorder. Dopaminergic activity is complex and under the regulation of multiple brain structures, including the ventral subiculum of the hippocampus and the basolateral amygdala. Whereas basic and clinical studies demonstrate deficits of the dopaminergic system in depression, the origin of these deficits likely lies in dysregulation of its regulatory afferent circuits. This review explores the current information regarding the afferent modulation of the dopaminergic system and its relevance to major depressive disorder, as well as some of the system-level effects of novel antidepressants such as agomelatine and ketamine.

Keywords: dopamine, depression, hippocampus, amygdala, ketamine, animal models

Major Depressive Disorders

Major Depressive Disorder (MDD) is one of the most prevalent mental disorders worldwide. Indeed, the lifetime prevalence rates range for most countries between 8% and 12% (Kessler and Bromet, 2013). According to the World Health Organization (WHO, 2008), MDD also carries the heaviest burden of disability among mental and behavioral disorders (Collins et al., 2011). According to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013), a major depressive episode is defined as a period of 2 weeks or longer during which there is either depressed mood or loss of interest or pleasure (i.e., anhedonia) and at least 4 other symptoms that reflect a change in a person's baseline activity, such as fatigue, suicidality, change in sleep, or change in activity (e.g., psychomotor agitation or retardation). This disorder is complex and likely involves a multitude of unique circuitry, and despite its status as a leading cause of burden of disease as well as decades of research into it, its etiology and pathophysiology remain largely unknown.

At present, the majority of approved antidepressants for MDD act through monoaminergic mechanisms. Thus, the first-generation antidepressants, such as tricyclic antidepressants and monoamine oxidase (MAOs) inhibitors, alter the reuptake, metabolism, or receptor pharmacodynamics of the monoamines serotonin and norepinephrine. MAO inhibitors also inhibit the metabolism of dopamine, enhancing its brain level (Tekes et al., 1988). The next generation of antidepressants, thought to carry less significant side effects than first-generation drugs, targets monoaminergic neurotransmission with molecules such as selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors. Although SSRIs have less severe adverse effects than the first-generation agents, their efficacy is limited. Indeed, when the treatment is effective, it can take weeks to get a therapeutic effect (Katz et al., 2004). This is a particular concern when in some depressed patients, there is an imminent risk of suicide. The last generation of antidepressant

includes serotonin antagonists and reuptake inhibitors (SARIs) such as trazodone, noradrenergic and specific serotonergic antidepressant (NaSSA) such as mirtazapine, catecholamine releaser such as bupropion, and triple reuptake inhibitors, such as venlafaxine. This new generation of antidepressant is suggested to have comparable antidepressant efficacy to other drug classes, but is more tolerable (for review Chang and Fava, 2010). Therefore, MDD is very hard to treat, with 2/3 of patients not achieving remission after one course of treatment and 1/3 who fail to remit after 4 treatments (Rush et al., 2006). As a result, there is a pressing need to develop new, fast-acting, and effective drugs and novel pharmacological approaches to treat depression, in particular in patients who are unresponsive to traditional antidepressants.

MDD is a complex disorder, comprised of many symptoms, each symptom likely involving unique neuronal circuits. To study and treat MDD in the most efficient manner, the DSM, based on clusters of clinical symptoms, is unfortunately limited. The National Institute of Mental Health has launched the Research Domain Criteria approach to create a research classification system based on biologically determined variables, such as genetics, imaging, cognitive science, behavior, or neural circuits. Indeed, it is hypothesized that symptoms, more than diagnostic categories, are linked to specific circuit disruptions, and therefore understanding their biological foundations will facilitate the treatment of disorders that include such symptoms. This approach is consistent with fundamental research using animal models of specific disorders, where neurobiological and behavioral disruptions are assessed. Therefore, following the Research Domain Criteria, the present review will focus on anhedonia, a core symptom and a diagnostic criterion for MDD. In particular, we will focus on circuit-based regulation of the dopaminergic system. It should be noted that molecular deficits as well as disruptions in specific neural circuits underlying different reward-related processes have been reviewed in detail in (Der-Avakian and Markou, 2012) and (Nestler and Carlezon, 2006).

Dopamine Deficits in MDD

Anhedonia is a symptom described in various neurodegenerative and psychiatric disorders such as Parkinson's disease (Isella et al., 2003; Zahodne et al., 2012) and schizophrenia (Strauss and Gold, 2012), respectively. It is also characteristic of withdrawal symptoms described in substance abusers (Gawin and Kleber, 1986) and is suggested to play a central role in the increased risk of relapse (Koob and Le Moal, 2001; Volkow et al., 2002). In MDD, it is 1 of 2 hallmark symptoms of this disorder besides depressed mood, and its presence has been shown to be predictive of poor antidepressant response (Klein, 1974). Indeed, it is suggested that anhedonia contributes to the persistence of MDD treatment resistance (McMakin et al., 2012; Vrieze et al., 2013). The DSM defines anhedonia as diminished interest or pleasure in response to stimuli that were previously perceived as rewarding before the development of the disorder (American Psychiatric Association, 2013). Anhedonia is a particularly difficult symptom to treat, as increasing evidence suggests that second-generation antidepressants, such as SSRIs, are not effective in treating positive affect deficits, such as motivation and reward-related cognitive impairment in depression (Nutt et al., 2007; McCabe et al., 2009). It is therefore critical to determine the possible disrupted regulation of the neuronal circuitry underpinning this symptom. It is important to note that anhedonia is not only defined as a loss of the ability to experience pleasure, but encompasses the complex reward-related deficits observed in MDD or other neuropsychiatric disorders, such as disruption of the anticipation, motivation, and decision-making

processes involved in obtaining a reward (Treadway and Zald, 2011). Anhedonia has been linked to dysfunctions in the reward system, and in particular the dopamine (DA) system (Der-Avakian and Markou, 2012). The DA system plays a role in reward prediction (Schultz, 1998b), motivational arousal, and responsiveness to conditioned incentive stimuli (Wise, 1982; Salamone et al., 2003). It is also suggested that DA is necessary for the attribution of incentive salience to motivational stimuli, transforming the perception of liking a reward into a wanted incentive (Berridge and Robinson, 1998), consistent with disruptions of the motivation to seek out pleasurable experiences described in individuals diagnosed with MDD (Sherdell et al., 2012). Although historically depression has been associated with dysfunctions of the serotonin (5-HT)- and norepinephrine-containing circuits (Bunney and Davis, 1965; Schildkraut et al., 1965; Coppen, 1967), research using neuroimaging, pharmacological, and electrophysiological methods in humans and animal models of depression has provided support for the presence of DA dysfunctions (for review, see Yadid and Friedman, 2008). Depression and anhedonia have been shown to be associated with a reduced striatal response to reward (Forbes et al., 2009). Moreover, in depressed patients with anhedonia, PET imaging studies have shown significantly lower DA transporter (DAT) binding compared with healthy subjects (Meyer et al., 2001; Sarchiapone et al., 2006). This suggests a downregulation secondary to lower DA concentrations, as proposed by previous studies showing a decreased DAT density when DA is chronically depleted (Kilbourn et al., 1992; Ikawa et al., 1994; Gordon et al., 1996). Earlier studies have found that MDD patients showed increased striatal D2 receptor binding (D'Haenen and Bossuyt, 1994) as well as an elevated D2/3 receptor binding in the central and basal nuclei of the amygdala of postmortem depressed patients who committed suicide compared with control subjects (Pare et al., 1969), suggesting a decreased DA turnover. These findings are in accordance with the degree of amphetamine-induced rewarding effects described in MDD patients. Indeed, it has been shown that the severity of MDD correlates with the magnitude of euphoria after administration of amphetamine (Tremblay et al., 2002). Thus, the amphetamine-induced DA release would result in an increased DA signal transduction via compensatory mechanisms such as increased postsynaptic DA receptors expression as well as reduced DAT density.

Animal models of depression also demonstrated altered mesolimbic DA system function. Altered DA receptor expression within limbic structures was observed in different models of depression such as the learned helplessness model (Kram et al., 2002) and the chronic mild stress (CMS) model (Dziedzicka-Wasylewska et al., 1997). These changes reflect a decrease in DA release into the synapse, such as, for example, significantly lower homovanillic acid, a DA metabolite (Reddy et al., 1992), as well as reduced striatal dopaminergic activity (Pruessner et al., 2004) also described in depressed patients compared with controls. This downregulation of the DA system is consistent with studies showing altered dopamine release in the nucleus accumbens in animals exposed to the CMS procedure (Di Chiara and Tanda, 1997). Moreover, lesions of the VTA with 6-OHDA in rats induce depressive-like behavior as measured by the learned helpless paradigm (Winter et al., 2007). It has also been reported that the Flinders sensitive rat line, a genetic animal model of depression (Overstreet, 1993), show reduced "burst" firing of VTA neurons (Friedman et al., 2008). Recently, more evidence implicating the activity of the DA system has emerged using animal models of depression (Belujon and Grace, 2014; Tye and Deisseroth, 2012; Chaudhury et al., 2013; Savitz et al., 2013; Chang and Grace, 2014; Moreines et al., 2016). In particular, Tye and collaborators (Tye et al., 2013) showed in 2013 that selective inhibition of DA neurons

recorded in the VTA induces specific depression-like behaviors and that CMS induces several depression-like phenotypes that are reversed by selective activation of the mesolimbic DA system.

Therefore, the majority of studies highlighting the role of the DA system in depression converge on a downregulation of this system. However, little is known about which afferent circuits may mediate dysfunctions in the regulation of the DA system. Indeed, although disruption of the DA system may form the basis of anhedonia in several psychiatric disorders, including MDD, the symptom and/or the pathology is more likely to originate in regions involved in their afferent control. To understand different pathology states, it is therefore critical to characterize the mechanisms by which these afferents control DA population activity.

Reward-Related Circuity

As previously described in numerous reviews (Grace, 1991, 2016; Grace et al., 2007; Belujon and Grace, 2015), the mesolimbic DA neurons can display multiple activity states. It should be noted that in this review, we will refer to neurons that fit the electrophysiological criteria described in Grace and Bunney in 1983 (Grace and Bunney, 1983) as DA neurons (see also Ungless and Grace, 2012). Dopamine neurons can either be spontaneously firing or non-firing; the proportion of neurons spontaneously active is termed population activity (Floresco et al., 2001b). In anesthetized animals, spontaneously active DA neurons can fire either in a slow irregular pattern (tonic activity) or in bursts of action potentials (phasic activity). These bursts are driven by afferents from regions such as the pedunculopontine tegmental nucleus (PPTg), a glutamatergic/cholinergic structure (Floresco et al., 2003; Lodge and Grace, 2006b), and the laterodorsal tegmentum (Lodge and Grace, 2006a). The PPTg, the most potent activator of DA neuron burst firing, is involved in conditioned stimulus responses in reward tasks (Bortolanza et al., 2010). In awake behaving animals, these bursts of action potentials are also present in response to behaviorally salient stimuli (Schultz, 1998a; Zweifel et al., 2009), since DA neurons display phasic burst when an individual is presented with an unpredictable reward or a stimulus previously associated with a rewarding (Schultz, 1998a) or aversive (Lammel et al., 2011; Zweifel et al., 2011) event. In anesthetized and freely moving animals, one-half of DA neurons are not spontaneously active (Grace and Bunney, 1984) due to a constant hyperpolarized, silent state as a result of activation of GABAergic inputs from the ventral pallidum (VP) (Floresco et al., 2003). Activation of the ventral subiculum of the hippocampus (vSub) induces an increase in the number of spontaneously active DA neurons, without affecting the burst firing (Lodge and Grace, 2006b), via a polysynaptic pathway through the nucleus accumbens (NAc) and the VP (Floresco et al., 2001a). Therefore, inactivation of the VP releases inactive DA neurons from inhibition and enables them to fire spontaneously. This supplies a stable baseline level, that is, a tonic state, of extra-synaptic DA in target structures, such as the prefrontal cortex or the NAc. Phasic activation of burst firing can only occur in spontaneously firing neurons; therefore, the PPTg provides the "signal" and the vSub is the gain of this signal. The vSub is involved in the control of contextual processing (Jarrard, 1995; Maren and Quirk, 2004). Therefore, the change in population activity enables the system to be adjusted depending on the stimulus itself but also the physical context in which the stimuli are presented. This is particularly important in several situations, including survival ones, which involves a stress response. For example, in a benign context, where the organism is not aroused, that is, not in an alert state, the vSub maintains DA neurons in a low tonic activity state. However, in a threatening situation (i.e.,

strong context), the activation of the vSub results in an inhibition of the VP, thereby increasing DA neuron population activity. This will cause a behaviorally salient stimulus to induce phasic burst firing of a large proportion of DA neurons leading to an increase in DA release in afferent structures. This will ultimately cause the organism to react appropriately to the arousing situation. An increase in DA population activity has been shown to be accompanied by DA release in the NAc (Floresco et al., 2003) and an increase in amphetamine-induced hyperlocomotion (White et al., 2006), a behavioral consequence of augmented DA neuronal activity (Lodge and Grace, 2007; Gill and Grace, 2011; Chang and Grace, 2013). Moreover, the context-dependent subiculum control of DA population activity is modulated by the medial prefrontal cortex (mPFC), in particular the infralimbic subregion (ilPFC). Indeed, our group has shown that inactivation of the ilPFC increases DA population activity, an effect that is dependent on the vSub (Patton et al., 2013). The mPFC does not project directly to the vSub (Vertes et al., 2006), and we have shown that this effect was mediated by, at least in part, the nucleus reuniens of the thalamus (Zimmerman and Grace, 2016). Indeed, the nucleus reuniens sends dense projections to as well as drives activity in the vSub (Wouterlood et al., 1990; Bertram and Zhang, 1999) (Figure 1). There are direct projections from the mPFC to the entorhinal cortex as well, which also provides powerful excitatory influence over the vSub (van Groen et al., 2003). This structure could also be a relay between the mPFC and the vSub that could potentially affect DA activity.

On the other hand, the amygdala, in particular the basolateral amygdala (BLA), is responsible for the decrease in tonic dopamine neuron firing, that is, population activity (Chang and Grace, 2013), in response to repeated stressors. This decrease is thought to occur via a polysynaptic pathway, since the BLA does not send direct projection to the VTA (Geisler et al., 2007). The VTA receives GABAergic projections from the rostromedial tegmentum as well as the VP and glutamatergic projections from the lateral habenula, among others (Russo and Nestler, 2013). A subset of neurons from the rostromedial tegmentum receives excitatory projections from the lateral habenula (Stamatakis and Stuber, 2012). The BLA sends dense direct projections to these structures (Kaufling et al., 2009; Lee and Kim, 2011) that could act as relay in negatively modulating DA population activity. We have recently shown that the BLA-induced attenuation of DA population activity is reversed by the blockade of glutamate afferents in the VP (Chang and Grace, 2014), which makes the VP a critical relay in the modulation of VTA DA population activity by the BLA. Indeed, BLA sends potent direct excitatory projections onto VP neurons (Maslowski-Cobuzzi and Napier, 1994). The BLA is a limbic structure that attributes emotional significance to external (contextual) stimuli (Aggleton, 1993), which is of significant importance in the stress response (Roozendaal et al., 2009). As previously shown with the vSub, the BLA-dependent attenuation of DA population activity is under control of the ilPFC, since the decrease in DA population activity by activation of the ilPFC is prevented by removal of the BLA influence (Patton et al., 2013). It should be noted that the VTA is not homogenous, the most medial part of the VTA projecting to the NAc shell, which plays an important role in incentive learning, whereas the most lateral part of the VTA, which projects to the NAc core, is involved in the selection of adaptive responding (Ikemoto, 2007). Interestingly, when activated, the ilPFC inhibits preferentially the medial, reward-related part of the VTA (Moreines et al., 2016).

Hence, the tonic DA activity (population) is under 2 distinct and opposing circuits, one activating circuit involving the vSub of the hippocampus (releasing DA neurons from VP GABAergic
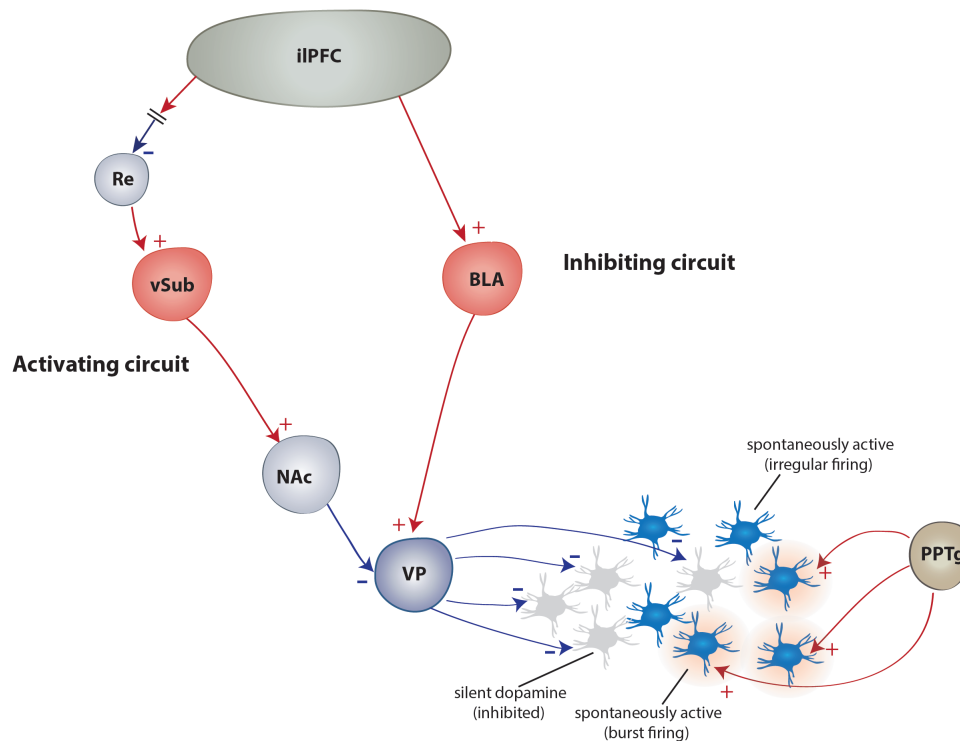
Figure 1. Afferent regulation of the dopamine (DA) system. The DA system is under regulation by an inhibitory circuit including the basolateral amygdala (BLA)-ventral pallidum (VP) pathway that is activated by the infralimbic subregion (ilPFC), as well as an activating circuit. including the Re-ventral subiculum of the hippocampus (vSub)-nucleus accumbens (NAc)-VP pathway that is inhibited by the ilPFC. The result is that at baseline, about one-half of the VTA DA neurons are firing spontaneously. Only DA neurons that fire spontaneously can fire in response to rapid, phasic activation with bursts of action potentials, due to activation of pedunculopontine tegmental nucleus (PPTg) afferents.

inhibition) and one inhibitory circuit involving the BLA (activating VP GABAergic inhibition of DA neurons) (Figure 1). Therefore, in a situation where an individual must respond to intense salient stimuli, large proportions of DA neurons will be activated by the vSub, causing a strong burst firing-dependent DA release allowing the appropriate response to the stimulus. This is downregulated by the amygdala, which will decrease the responsivity of the reward-related DA system.

Dysregulation of the Reward-Related Circuit in MDD

Functional imaging studies have highlighted the critical role of the fronto-limbic circuit in modulating mood states. Dysfunction of activity in one region in particular, the subgenual cingulate (Cg25), has been consistently observed in depressed patients. For example, an increased metabolism is observed in MDD patients (Mayberg et al., 2000; Kumano et al., 2007), remitted MDD patients during depressive relapse (Neumeister et al., 2004), or MDD patients in response to sad face stimuli (Keedwell et al., 2009). Anatomically, MDD is associated with gray matter abnormalities and decreased volume in the mPFC (Price and Drevets, 2010; Kempton et al., 2011) as well as a reduction in the size of neurons and a loss of glia (Drevets et al., 2008). Furthermore, treatments for MDD such as antidepressants (Mayberg et al., 2000), electroconvulsive therapy (Nobler et al., 2001), transcranial magnetic stimulation (George et al., 2010), and vagus nerve stimulation (Nahas et al., 2007) cause a return to normal levels of activity of the PFC that correlate with an improved mood in MDD patients. Stimulation of this region using deep brain stimulation is also used for the treatment of depression (Mayberg et al., 2005). It is,

however, well known that major depression is not the result of selective regional dysfunction but rather involves dysfunction of neural networks that normally modulates mood and emotions (Mayberg, 2003). Indeed, disruption in PFC-amygdala as well as PFC-hippocampus functional connectivity, among others, have been described (Kong et al., 2013; Genzel et al., 2015), suggesting disruption of reciprocal connection between these structures.

The Cg25 in patients is homologous with the infralimbic part of the mPFC in rodents (Heilbronner et al., 2016), and animal models of depression have been important tools for investigating the etiology of depression, the neurocircuitry involved in some symptoms, as well as developing new, effective, and innovative treatment. Most animal models of depression are based on the induction of a depression-like phenotype by stress, which plays a critical role in the onset of depression (Kendler et al., 1999). Among these, CMS, first reported by Willner and colleagues (Willner et al., 1987), is the most extensively validated and widely used model of major depression (Hill et al., 2012). This model is based on clinical and preclinical research suggesting that uncontrollable and prolonged exposure to life stressors is a factor in the development of the disease (Katz, 1982; Kessler et al., 1985; Kendler et al., 1999). This model has high face, construct, and predictive validity. Thus, rodents exposed to this procedure develop a decreased response to reward (i.e., anhedonia), a core symptom of MDD, as well as decreased motivated behavior, weight loss, and sleep disruption (Willner, 1997). There has been extensive research on the anatomical and physiological modifications observed in rodents exposed to the CMS procedure that are similar to the changes observed in MDD patients (Hill et al., 2012) and described in detail in Willner's review in 2017 (Willner, 2017). Comparable with MDD in patients, rats

exposed to CMS show elevated hypothalamo-pituitary-adrenal axis activity (Goshen et al., 2008), decreased dendritic tree of hippocampal (Sousa et al., 2000) and cortical (Liu and Aghajanian, 2008; Li et al., 2011) pyramidal neurons, and increase in the length of dendrites and density of dendritic spines in amygdala neurons (Sharma and Thakur, 2015). CMS in rats causes a prolonged decrease of DA population activity in the VTA (Chang and Grace, 2014; Moreines et al., 2016). This decrease is reversed by inactivation of the ilPFC (Moreines et al., 2016) or the BLA-VP pathway (Chang and Grace, 2014), suggesting that abnormal hyperactivity in the ilPFC leads to hyperactivation of the BLA-VP pathway, responsible for a downregulation of the DA system in depression (Figure 2). This inhibition of the DA system is accompanied by an increased immobility time in the forced swim test, which relates to "behavioral despair" or resignation, and with a decrease in sucrose preference, which is suggested as a hedonic deficit (Katz, 1982), often described in animals exposed to CMS (Willner et al., 1987; Tye et al., 2013). This downregulation of the DA system has also been described in another well-validated model of depression, the learned helplessness model (Belujon and Grace, 2014). In this model, the stress-sensitive Wistar-Kyoto rats are exposed to uncontrollable, unpredictable, and inescapable stress (e.g., shocks). When reexposed to the same shocks while provided with a means to easily escape the shocks, the animals will lose the ability to show escape behavior (failure to escape) or an increased latency to escape (Seligman and Beagley, 1975). Interestingly, approximately one-half of animals exposed to uncontrollable stress developed learned helplessness (helpless animals), that is, a decreased ability to learn how to escape subsequent stressor (Petty et al., 1997). The other one-half, which do not demonstrate learned helplessness (nonhelpless animals), may have undergone alternate adaptations that protected them from the detrimental effects of inescapable stress.

This model has high construct, face, and predictive validity. Indeed, animals exposed to this procedure show weight loss, alterations in sleep patterns, modification of the hypothalamo-pituitary-adrenal axis activity, and a decrease in spine density in the hippocampus and the mPFC (Nestler and Hyman, 2010; Yang et al., 2015). Animals also have symptoms that parallel those of major depression, which are reduced by antidepressant treatment (Takamori et al., 2001). Using this model, altered synaptic plasticity has been described in the activating circuit of the DA system, the vSub-NAc pathway, in helpless rats but not in identically treated rats that are nonhelpless (Belujon and Grace, 2014). In particular, tetanic stimulation of the vSub-NAc pathway induced a long-term depression in NAc neurons in helpless rats, whereas a long-term potentiation is induced in control and non-helpless rats. This suggests a downregulation of the vSub-NAc pathway in helpless rats that could contribute to the decrease in DA neuron activity (Belujon and Grace, 2014). The ilPFC could play a role in the disrupted vSub-NAc plasticity, as described in other psychiatric disorders (Belujon et al., 2014); however, this still needs to be examined in detail.

Although decreased DA activity forms the basis of some symptoms described in MDD, such as anhedonia, its downregulation originates via hyperexcitation of the ilPFC-BLA-VP pathway and possibly via disrupted synaptic plasticity in the vSub-NAc pathway. Therefore, new therapeutics aiming at these regions are more likely to be effective than therapeutics targeting the DA system directly.

Antidepressants and the Reward-Related Circuit in MDD

As previously mentioned, there is now a consensus that the majority of depressed patients treated with SSRIs do not obtain
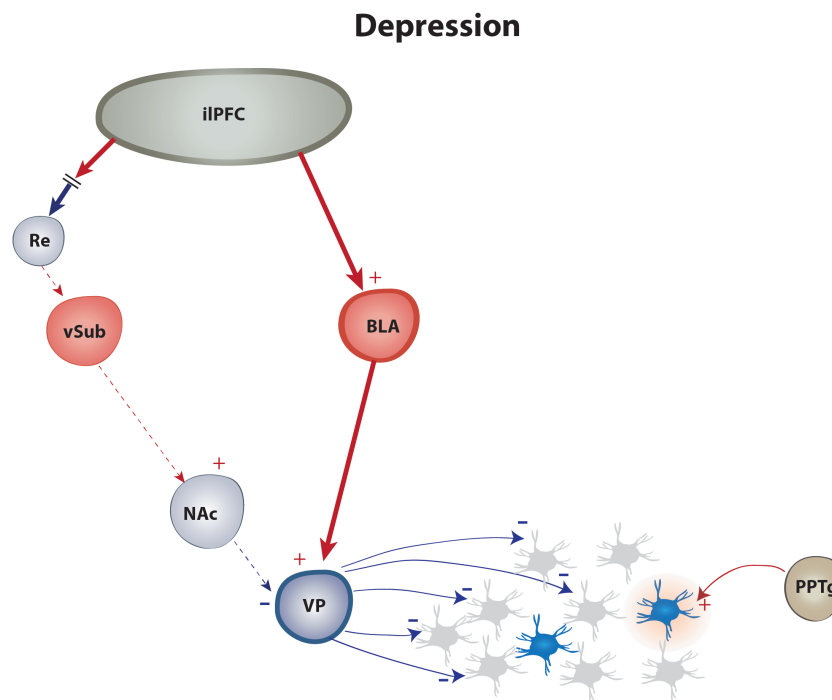

Figure 2. Afferent dysregulation of the dopamine (DA) system in major depressive disorder (MDD). In animal models of depression, the DA system is downregulated, as measured by a decrease in the number of DA neurons that fire spontaneously. This decrease is due to hyperactivity of the infralimbic subregion (ilPFC), driving activity in the inhibitory basolateral amygdala (BLA)-ventral pallidum (VP) pathway while attenuating excitation via the Re-ventral subiculum of the hippocampus (vSub)-nucleus accumbens (NAc)-VP pathway.

remission. The effect of these antidepressants on DA neurons may contribute to their low efficacy. Indeed, it has been shown that the administration of SSRIs such as fluoxetine or escitalopram induced a decrease in DA neuron firing rate in the VTA, whereas citalopram decreased the firing rate and the number of spikes per burst (Prisco and Esposito, 1995; Di Mascio et al., 1998; Dremencov et al., 2009). It is suggested that this class of antidepressant acts through 5-HT2C receptors (Prisco and Esposito, 1995; Dremencov et al., 2009). This is consistent with studies using lesions of the raphe nucleus showing an increase in the firing and bursting of DA neurons in the VTA (Guiard et al., 2008). Considering the critical role of DA in hedonic processes, the decrease in firing as well as the bursting activity by SSRIs might contribute to the resistance to antidepressants in some patients. Therefore, augmentation strategies, involving the addition of a second drug to an existing antidepressant therapy, are often used to optimize treatment, such as the addition of an atypical antipsychotic to an SSRI treatment (Ostroff and Nelson, 1999; Shelton et al., 2001; Thase et al., 2007). The United States Food and Drug Administration has approved several atypical antipsychotics as supplement to ongoing antidepressant treatment for treatment-resistant patients (Thase et al., 2007; Berman et al., 2009; Kato and Chang, 2013). The role of antipsychotics in increasing antidepressant activity has been confirmed by animal models. Thus, aripiprazole, an atypical antipsychotic, has been shown to potentiate the effect of citalopram in the forced swimming test (Bourin et al., 2009) and the effect of fluoxetine in the tail suspension test (Kamei et al., 2008). Interestingly, the combination of aripiprazole with the SSRI escitalopram reversed the inhibitory action of the antidepressant on serotoninergic, dopaminergic, and noradrenergic neuron firing (Chernoloz et al., 2009). The combination of fluoxetine with olanzapine, another atypical antipsychotic, also induces an increase in DA, 5-HT, and norepinephrine extracellular levels in the prefrontal cortex (Zhang et al., 2000). One question would be how would a D2 antagonist improve DA system function in a depressed state? We have found recently that repeated treatment with the second-generation antipsychotic quetiapine to the CMS rat model of depression effectively reversed the decrease in DA neuron population activity (Moreines et al., 2017). We believe this is due to the low-dose quetiapine activating the "silent" DA neurons to restore population activity, whereas the low level D2 blockade can be overcome via homeostatic compensation (e.g., increased D2 receptors, increased tyrosine hydroxylase activity, etc.).

Another augmentation strategy consists of the use of pramipexole, a D2 subfamily receptor agonist in treatment-resistant patients (Cusin et al., 2013). In the CMS model, pramipexole has been shown to increase sucrose intake, a putative indicator of anhedonia in rodents, in stressed animals (Willner et al., 1994). Recently, studies going beyond monoamine transporters and MAOIs highlighted a novel class of promising antidepressant drugs such as agomelatine. Agomelatine is a potent melatonin receptor agonist (Yous et al., 1992) and a selective antagonist of the 5-HT2C receptors (Millan et al., 2003). In the CMS model of depression, agomelatine has been shown to have potent antidepressant activity. Indeed, CMS animals showed decreased sucrose consumption, which is normalized by chronic administration of agomelatine (Papp et al., 2003). In the forced swim test, a predictive model of antidepressant activity, acute and repeated administration of agomelatine, induced an antidepressant-like effect in rats, that is, an increase in swimming, without modification of locomotor activity (Bourin et al., 2004). In patients, both venlafaxine (serotonin and norepinephrine reuptake inhibitor) and agomelatine decreased the score of MDD patients on the Hamilton depression scale as well as the Hamilton anxiety scale (Martinotti et al., 2012). Interestingly, on the Snaith Hamilton pleasure scale for anhedonia, agomelatine induced an improvement in anhedonia scores as early as 1 week after the start of the treatment (Martinotti et al., 2012). The anhedonia score improvement is consistent with animals studies showing that chronic administration of agomelatine increased the number of DA spontaneously active neurons, as well as the bursting activity (Chenu et al., 2013). Although the effect of agomelatine on DA neuron activity in the VTA has yet to be studied in animal models of depression, several studies have highlighted its effect on the PFC, the HPC, and the amygdala (Dagyte et al., 2010; Ladurelle et al., 2012; Grillo et al., 2015), which modulate VTA DA neuron activity. Research on glutamate targets might also hold promise, but it is still at an early stage.

In depressed patients, ketamine, a non-competitive, glutamatergic N-methyl-d-aspartate receptor antagonist, exerts rapid (within hours) and prolonged (up to 1–2 weeks) antidepressant effects after a single dose (Berman et al., 2000; Zarate et al., 2006; Murrough et al., 2013). It is now well-known that ketamine rapidly increases AMPA-dependent glutamate transmission, particularly in the PFC, either via an increased synthesis of synaptic proteins in pyramidal neurons leading to an increase in excitatory synaptic input or via antagonism of N-methyl-d-aspartate receptor on cortical interneurons, leading to disinhibition of pyramidal neurons (for review, see Miller et al., 2016). The cellular and molecular effects of ketamine have been extensively studied in the past years (Wohleb et al., 2016). At the circuit level, we have shown that ketamine restores DA population activity in helpless rats comparable with control and non-helpless animals. We have also shown that ketamine restores long-term potentiation in the vSub-NAc pathway (Belujon and Grace, 2014). It is important to note that this effect is observed in rodent learned helplessness depression models, but not in normal rats in which the vSub-NAc pathway is not abnormally downregulated (Carreno et al., 2016). The effect of ketamine on DA population activity has also been observed following acute amphetamine withdrawal (Belujon et al., 2016). Indeed, a decreased DA population activity after acute withdrawal, suggested to underlie a negative emotional state after withdrawal from psychostimulants, is restored by prior administration of ketamine as well as by inhibition of the BLA (Belujon et al., 2016). Whereas ketamine is known to have potent, rapid, and prolonged antidepressant properties, it also induces short-term dissociative side effects. However, understanding some of ketamine antidepressant properties at a systems level will help in finding new treatment strategies that could induce remission with few side effects in treatment-resistant patients.

Conclusion

Patients diagnosed with MDD exhibit a multitude of symptom clusters, which differ from one patient to another, making it difficult to diagnose and treat effectively. To find new and effective treatments, it is critical to understand some of the complex and unique circuitry underlying these symptoms. Anhedonia, a core symptom of MDD, involves a downregulation of the DA system. It is now clear that the DA system is under intricate regulation via an activating vSub-NAc-VP pathway and via an inhibiting BLA-VP pathway, both under the influence of the ilPFC. It is critical to understand the detailed circuitry modulating the DA system and in particular its disruption underlying anhedonia. Future investigations will facilitate the development of a new, fast-acting, and efficient treatment that will

ultimately reverse depression without inducing severe side effects.

Acknowledgments

Statement of Interest

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