Trends in Neurosciences

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REVIEWS

Review

Lateral Habenular Burst Firing as a Target of the Rapid Antidepressant Effects of Ketamine

Yihui Cui,[1,3] Shaohua Hu,[1,4] and Hailan Hu [1,2,3,*]

The revolutionary discovery of the rapid antidepressant ketamine has been a milestone in psychiatry field in the last half century. Unlike conventional antidepressants that often take weeks to months to show efficacy, ketamine causes rapid antidepressant effects, emerging as early as within 1 h after administration. However, how ketamine improves mood symptoms so quickly has remained elusive. Here, we first introduce the historical background of ketamine as a rapid antidepressant. We then discuss current hypotheses underlying ketamine's rapid antidepressant effects, with a focus on our latest discovery that ketamine silences NMDAR-dependent burst firing in the 'anti-reward center', the lateral habenula. While ketamine may act on many brain regions, we argue that its rapid antidepressant effects are critically dependent on ketamine's action in the lateral habenula, with this brain region acting as a primary site of action (or one among a few primary nodes). This molecular-, cellular-, and circuit-based mechanism advances our understanding of the etiology of depression and suggests a new conceptual framework for the rapid antidepressant effects of ketamine.

Highlights

Ketamine, as a blocker of N-methyl D-aspartate (NMDA) receptors, has been shown to cause rapid antidepressant effects, sometimes as early as within 1 h after administration.

While ketamine may act on many brain regions, recent findings from animal models indicate that its rapid antidepressant action is likely mediated by one or a limited number of regions. In particular, the lateral habenula (LHb) seems to act as a primary site of ketamine's rapid antidepressant action.

As an 'anti-reward center', the LHb is known to mediate negative emotions and inhibit dopaminergic and serotonergic neurons in the brain's aminergic reward centers. During depression, LHb neurons display significant increase in burst firing and theta-band synchronization, which are reversed by ketamine.

Since LHb bursts critically depend on NMDARs, ketamine can rapidly silence LHb bursts, thereby disinhibiting downstream reward centers to cause rapid improvement of depressive symptoms.

Background of Ketamine as a Rapid Antidepressant

Ketamine is a psychoactive drug that was discovered in the 1960s. It was characterized as an NMDAR blocker [1] and initially used as a safe, tolerable, and commonly used anesthetic [2]. Unexpectedly, Dr John Krystal's team uncovered a strikingly rapid antidepressant effect of ketamine (starting within 4 h and lasting for at least 3 days) elicited by only a single subanesthetic dose (0.5 mg/kg) in major depressive disorder (MDD) patients, when initially attempting to investigate the link between NMDAR hypofunction and schizophrenia [3]. Later, in an exciting clinical trial reported by Dr Carlos Zarate's team, a single dose of ketamine in patients with treatment-resistant depression rapidly (starting within 40 min and peaking at 1 day) elicited significant antidepressant effects that lasted for about 1 week [4]. Further evidence showed that ketamine is also effective in treating major depressive episodes of treatment-resistant bipolar disorder [5,6], rapidly decreasing suicidal ideation [7,8] and reducing anhedonia [9]. Afterwards, the rapid antidepressant effects of ketamine were reported extensively both in human patients [10–12] and in animal models of depression [13–17].

Indeed, a little over a decade before the above-mentioned discoveries, Dr Skolnick and colleagues identified the importance of NMDAR in animal models of depression when they evaluated NMDAR blockers in the forced swim test (FST) and tail suspension test (TST), both of which are paradigms commonly used for testing antidepressant effect of drugs. Intriguingly, they found that dizocilpine (MK801, an NMDAR open channel blocker), AP7 (2-amino-

[1]Center for Neuroscience and Department of Psychiatry of First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310000, China
[2]Interdisciplinary Institute of Neuroscience and Technology, Qiushi Academy for Advanced Studies, Zhejiang University, Hangzhou 310058, China
[3]NHC and CAMS Key Laboratory of Medical Neurobiology, Mental Health

7-phosphonoheptanoic acid, an NMDA competitive antagonist), and ACPC (1-aminocyclopropanecarboxylic acid, an NMDAR glycine-site partial agonist, acting as a competitive antagonist in presence of a full agonist) all rapidly (within 15 min) alleviated depression-like phenotypes [18]. These data suggest that NMDAR may be involved in the pathophysiology of depression.

However, despite the knowledge that ketamine blocks NMDARs, the conundrum is that NMDARs are expressed throughout the brain. While ketamine may act on many brain regions, it seems quite possible, in fact, that its rapid antidepressant action is mediated by only a limited number of critical nodes, or perhaps even primarily by a single brain region [19–21]. If so, which brain region(s) or cell group(s) is the prime target of ketamine to mediate its rapid antidepressant action (Figure 1A)? There were a few clues toward this 'million-dollar question'. First, ketamine is a phencyclidine (PCP)-like, use-dependent, open channel blocker of NMDAR [22] (Figure 1B). Apart from its rapid action, ketamine also has a fast metabolic turnover rate, with a half-life of 3 h in humans [23]. This rapid 'hit-and-go' temporal profile and the use-dependent blocking nature suggest that the suspect target region of ketamine is intrinsically active and has NMDAR channels open. Second, ketamine is known to quickly elevate the level of several neurotransmitters related to mood and motivation including dopamine, serotonin, norepinephrine, and glutamate [24,25], suggesting that the target region of ketamine may suppress the aminergic reward centers [including the dopaminergic ventral tegmental area (VTA) and the serotonergic dorsal raphe nucleus (DRN)], the source of these transmitters.

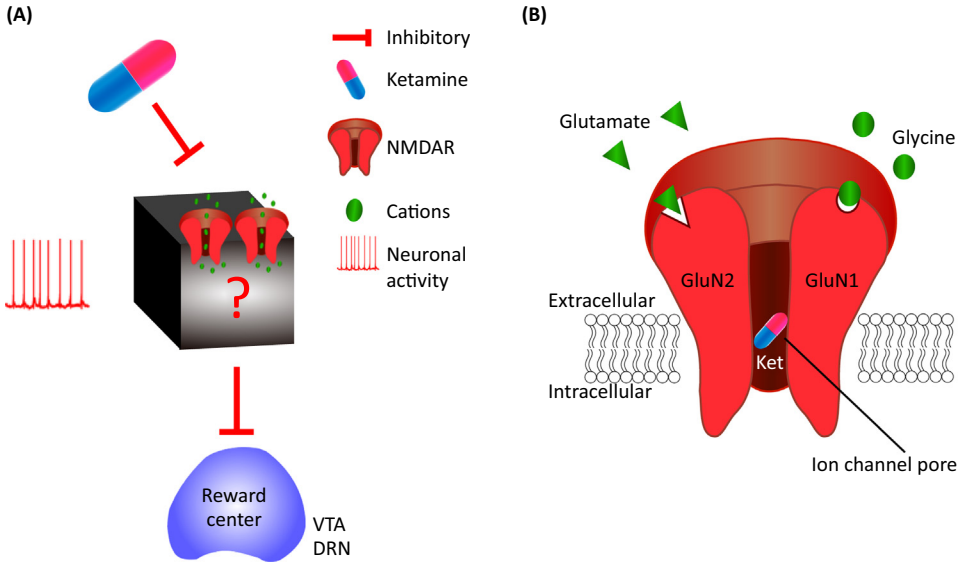

Figure 1. A Circuit-Based Disinhibition Model of Ketamine's Antidepressant Mechanisms. (A) Ketamine is likely to act on a system (the black box with a question mark) that is intrinsically active and has NMDAR channels in the open state. This system should also likely suppress the reward-related aminergic centers so that ketamine application may lead to a disinhibition of the reward centers and a quick increase of the level of neurotransmitters related to mood, including dopamine, serotonin and glutamate. (B) Schematic of the NMDAR complex. The NMDAR is a complex comprising four subunits that form a pore that is permeable to calcium. The schematic shows location of the orthosteric site in GluN1 (bound to glycine) and GluN2 (bound to glutamate) and of the ion channel pore site in the transmembrane domain. At resting state, the pore is blocked by Mg^{2+}. Mg^{2+} is removed, however, by depolarization during neuronal activity, allowing entry of calcium. Ketamine is an activity-dependent blocker that blocks calcium influx of NMDAR at open state [38]. Abbreviations: DRN, dorsal raphe nucleus; Ket, ketamine; VTA, ventral tegmental area.

Center, Zhejiang University, Hangzhou 310058, China
[4]The Key Laboratory of Mental Disorder Management in Zhejiang Province, Brain Research Institute of Zhejiang University, Hangzhou 310003, China

*Correspondence.
huhailan@zju.edu.cn (H. Hu).

With regard to the first clue, much attention was placed on fast-spiking γ-aminobutyric-acid (GABA)-ergic inhibitory neurons, in particular parvalbumin (PV)-expressing interneurons, which have high intrinsic activity. In a few prevalent models, ketamine was proposed to block presynaptic NMDARs on the cortical or hippocampal inhibitory interneurons [26–28], resulting in the release of a tonic inhibition onto the pyramidal neurons. The disinhibition of the pyramidal neurons then triggers a cascade of changes that alter synaptic communication including potentiated AMPAR signaling [13,16,29,30], stimulated translation and release of brain-derived neurotrophic factor (BDNF) [19,31], and increased mammalian target of rapamycin (mTOR)-dependent synaptogenesis [19,32,33] (see Box 1 for current hypotheses regarding ketamine's rapid antidepressant effects). The brain region of interest in these models is the prefrontal cortex (PFC) or hippocampus, areas negatively impacted in depression. But the link of these areas to the aminergic centers is indirect, and it is not clear then how this fits with the expectation that the target region of ketamine's action suppresses the aminergic reward centers. Furthermore, the proposed signaling processes typically operate on relatively long timescales and may not fully explain why ketamine acts so quickly.

In this review article, we focus on an alternative new model involving the brain's 'anti-reward' center, the lateral habenula (LHb). As described below, the LHb fits the profile of a prime suspect target of ketamine's rapid antidepressant actions: it is intrinsically active, becomes hyperactive in depression, and can inhibit aminergic neurons through a GABAergic relay nucleus. We propose that by silencing NMDAR-dependent burst firing of LHb neurons, ketamine can exert its antidepressant effects through disinhibition of the aminergic reward

Box 1. Current Models of the Rapid Antidepressant Mechanism of Ketamine

Currently, there are several hypotheses regarding the rapid antidepressant mechanism of ketamine in various brain regions:

(i) Disinhibition via blocking presynaptic NMDARs of GABAergic interneuron in the PFC and hippocampus. Some interneurons (particularly PV-expressing neurons) fire tonically with a high frequency, allowing the removal of the Mg^{2+} from the NMDAR pore region. These neurons dominantly express the NMDAR NR2D subunit that shows higher affinity for ketamine binding than other subunits. Therefore, ketamine may preferentially block the presynaptic NMDARs of spontaneously active GABAergic interneurons, resulting in the release of a tonic inhibition that subsequently leads to increased firing of pyramidal neurons [28–30].

(ii) Direct inhibition of extra-synaptic NMDARs of pyramidal neurons in the cortex. The extra-synaptic NMDARs are comprised primarily of NR2B-containing heterotetramers and are not typically activated by excitatory synaptic inputs but instead by ambient glutamate [34]. Under basal conditions, activation of extra-synaptic NMDARs suppresses protein synthesis to mediate synaptic homeostasis [35]. Previous studies suggested that ketamine may de-suppress protein synthesis and induce rapid antidepressant actions via an extrasynaptic NR2B-dependent mechanism [36,37].

(iii) Inhibition of spontaneous NMDAR-mediated neurotransmission in the PFC and hippocampus. Ketamine is also suggested to exert its antidepressant effects by blocking NMDAR-mediated miniature excitatory postsynaptic current (NMDAR-mEPSCs) at rest, leading to decreased phosphorylation of eukaryotic elongation factor 2 and a subsequent de-suppression of BDNF protein translation [14,15].

(iv) An NMDAR-independent mechanism via the ketamine metabolite hydroxynorketamine (HNK) in the hippocampus. HNK is proposed to cause rapid antidepression through an early and sustained activation of AMPAR [16], although whether it blocks NMDAR or not remains controversial [38,39].

The above-mentioned four hypotheses involve a consequent increase of downstream BDNF and mTOR and enhanced AMPAR-dependent synaptic transmission or synaptogenesis [13,20,21,31,32].

(v) More recently, we proposed a new model in which ketamine blocks NMDAR-dependent burst firing of neurons in the LHb, the anti-reward center, to rapidly relieve symptoms of depression [17,40].

centers to rapidly improve depressive symptoms. In the 'Concluding Remarks and Future Perspectives', we also speculate on how the proposed mechanism could relate to the more persistent actions of ketamine.

The Lateral Habenula: An Anti-reward Center Showing Increased Burst Firing in Depression

The LHb has recently emerged as an essential brain region in mediating the pathophysiology of major depression [41–45]. It is activated by aversive emotional stimuli or negative reward prediction error [46–48]. In animal models of depression or depressed patients, the LHb is metabolically hyperactive [49–51] and shows increased synaptic transmission [52–54] or excitability [55].

Circuitry-wise, the LHb acts as a gateway that interconnects the limbic forebrain with the midbrain monoaminergic nucleus [42] (Box 2). Although the majority of neurons in the LHb are glutamatergic [56], the LHb can inhibit dopaminergic neurons in the VTA and serotonergic neurons in the DRN through a GABAergic rostromedial tegmental nucleus (RMTg) as well as through feedforward inhibition within the aminergic nuclei [57–59]. Indeed, electrical stimulation of the LHb in primates elicits strong instant inhibition of VTA dopamine (DA) neurons [46]. Consistently, inhibition of the LHb in behaving animals transiently increased dopamine release in the PFC and striatum [60].

We stumbled upon the role of the LHb in mediating ketamine's effects when we were attempting a local drug infusion in the LHb. The LHb is a small nucleus located below the third ventricle, with a diameter of around 1 mm in rats. It contains dense fibers that make accurate local drug infusion even more challenging. When we first set up the dual guide cannulae system in the LHb, we decided to test a putative positive control, the AMPAR blocker NBQX [1,2,3,4-tetrahydro-6-nitro-2,3-dioxo-benzo(*f*)quinoxaline-7-sulfonamide]. We reasoned that since LHb is hyperactive in depression, blocking the majority of its excitatory inputs using an AMPAR blocker should theoretically cause antidepressant effects. Out of curiosity, we tested the NMDAR blocker AP5 (2-amino-5-phosphonopentanoic acid) in a parallel experiment. Surprisingly, AP5, but not NBQX, produced a strong antidepressant effect in the FST when locally infused into the LHb [17].

Since ketamine is also a blocker of NMDAR, this serendipitous discovery led us to test the behavioral effects caused by local infusion of ketamine into the LHb. In both the FST and the sucrose preference test (SPT), tests that model two aspects of depression, behavioral despair and anhedonia, respectively, ketamine rapidly alleviates depressive-like symptoms within 1 h after local bilateral infusion into the LHb [17]. This is achieved at a treatment-relevant dosage (~5 μM), as demonstrated by liquid chromatography-tandem mass spectrometry. To our

Box 2. Interaction of LHb with Heterogeneous VTA Dopaminergic Neurons

VTA dopamine (DA) neurons play a pivotal role in reward processing and are also activated by stress [61–70]. Recent work has attempted to map the two populations of DA neurons of opposite valence [64,69]. According to the current view, the reward-activated and stress-activated DA neurons are segregated in the VTA based on their cell body location and input/output pathways [47,64,71–74]. Evidence so far suggests that LHb may inhibit reward-coding DA neurons and excite aversion-coding DA neurons [46,59,75,76]. Recordings of DA neurons in the VTA of rhesus monkeys showed that excitation of the LHb inhibits reward-coding DA neurons [46]. This inhibition is mediated by the RMTg nucleus that relays the negative reward-prediction errors in the LHb into the positive reward-prediction errors of DA neurons [59]. By contrast, optogenetic or pharmacological activation of the LHb is shown to excite aversion-coding DA neurons, which locate at the medial VTA and project to the mPFC [75,76]. In summary, current data suggest the LHb inhibits reward-coding DA neurons and excites aversion-coding DA neurons.

knowledge, this may be the first evidence that ketamine can cause antidepressant effects from within just one brain area at this rapid timescale.

The following question arises: What does ketamine do to LHb neurons? LHb neurons were previously shown to be divided into silent, tonic firing, and burst firing types [77,78]. Bursting neurons fire clusters of high-frequency action potentials. They constitute a small percentage of the LHb neuron population in healthy animals [77,78]. Strikingly, we found that the percentage of bursting neurons, as well as the spikes in bursting mode, show more than 100% increase in animal models of depression, including congenitally learned helpless (cLH) rats and mice after chronic restraint stress [17]. Notably, systemic injection of ketamine reverses these changes, as shown by both *in vitro* and *in vivo* electrophysiology [17].

To test the behavioral significance of LHb bursts, we devised an eNpHR3.0-dependent optogenetic rebound burst protocol based on the mechanism of LHb bursts (see 'Mechanism of LHb Burst: Role of NMDAR, T-VSCCs, and Membrane Potential'). We found that bursting activity in the LHb is sufficient to cause real-time aversion and depressive-like behaviors [17]. In contrast, driving tonic firing with the same number of overall spikes fails to cause similar effects. Thus, it is the mode of burst firing, but not a general increase in firing rate *per se*, that is important for the induction of depressive-like behaviors. Furthermore, pharmacological or molecular genetic manipulations that specifically block LHb bursting are sufficient to prevent depressive-like symptoms [17,40]. These results provide direct evidence that bursting activity of a particular brain region is both sufficient and necessary to encode a psychiatric, depressive-like behavioral state.

Why is bursting so important? In fact, patterns of spike activity are crucial for neural computation. While a single action potential sometimes fails to reach downstream synaptic targets, bursts can decrease synaptic failure, enhance the signal-to-noise ratio, trigger release of neuropeptides, and entrain network synchronization (we indeed observed enhanced theta-band synchronization in the LHb of depressive-like mice [17]), therefore providing a robust form of information coding [79–84]. Bursting activities have been associated with physiological information coding such as reward prediction error in DA neurons [85] or with pathophysiological conditions such as epilepsy [86]. A well-characterized case of burst function in information coding is exemplified in DA neurons, which fire bursts of spikes specifically when reward exceeds expectation (positive reward prediction error) [85]. Consistently, only burst-type, but not tonic-type, optogenetic stimulation of DA neurons causes rewarding and antidepressant effects [87,88]. Intriguingly, recordings in monkeys revealed that LHb neurons provide negative reward signal input to DA neurons and fire high-frequency burst-like spikes toward aversive stimuli [46]. We speculate that burst firing mode in the LHb may carry specific, negative emotion-related information that is qualitatively different from that conveyed by spikes fired tonically. One possible circuit mechanism for this differential effect is that burst firing may provide a stronger input than tonic firing into the downstream GABAergic RMTg or GABAergic interneurons within the VTA or DRN. Another possibility is that burst firing may specifically stimulate the release of certain neuropeptides, given that the LHb nucleus has enriched expression of many neuropeptides [56,78].

Mechanism of LHb Burst: Role of NMDAR, T-VSCCs, and Membrane Potential

Given that LHb burst firing is critical to depression as discussed above, blockade of LHb bursts may be a prominent mechanism mediating the fast antidepressant actions of ketamine. The question then becomes as follows: Does ketamine act directly to block LHb bursts, or does it

act via intermediate steps? In LHb brain slices, we found that ketamine eliminates burst firing within minutes after perfusion into the recording solution, again, at a behaviorally relevant concentration (~1–10 μM) [17]. This effect is mimicked by a more specific NMDAR blocker, AP5. Interestingly, consistent with the behavioral effects in the cannular experiment, blockade of AMPAR with NBQX reduces bursting activity by only ~20% [17], suggesting that LHb bursting is mostly driven by the neurons' intrinsic properties and is only moderately modified by synaptic inputs mediated by AMPAR (Box 2). Notably, the classical selective serotonin reuptake inhibitor (SSRI)-type antidepressant fluoxetine does not instantly block LHb bursts but reduces bursts after chronic treatment (Cui *et al.*, unpublished). While requiring further validation, these emerging findings could suggest that reduced burst firing of LHb neurons may be a common endpoint for antidepressant drugs to exert their efficacy.

When it comes to roles of the NMDAR in synaptic and circuit functions, much of the classical work has focused on synaptic plasticity, and specifically the role of NMDAR as a coincidence detector for the generation of long-term potentiation or long-term depression during learning and memory [89–91]. But in fact, NMDAR-mediated calcium influx also plays a pivotal role in burst generation in various neural systems. Earlier work on NMDAR-dependent bursting activity has mostly focused on rhythmic motor behaviors, as exemplified in the motor neurons of lamprey [92] and rodents [93–95] as well as neurons of mammalian brainstem [96,97]. Further studies revealed however that NMDAR-dependent bursts exist in more diverse brain areas (sensorimotor cortex [98], hypothalamus [99], hippocampus [100], VTA [101], subthalamic nucleus [102], frontal cortex [103]). Because of its relatively slow decay kinetics, calcium entry through NMDAR may summate with calcium entry through voltage-gated calcium channels, producing locally a supralinear calcium signal [104]. In this way, NMDARs may integrate inputs over a longer duration and over farther distances to support burst generation.

Apart from NMDAR, LHb bursts also require low-voltage-sensitive T-type calcium channels (T-VSCCs) [17]. *In vitro* electrophysiology and modeling experiments unraveled that the ionic mechanism of bursting in the LHb bears resemblance to several well-characterized bursting systems in other brain regions. The characteristics of the burst firing pattern (including intra-burst frequency, inter-burst frequency, and number of spikes per burst) in the LHb are reminiscent of that of thalamic relay neurons, where T-VSCCs and HCNs interact to generate bursts during sleep or anesthesia [105–107]. T-VSCC currents recorded in the LHb are much smaller though than those in the thalamus (~50 versus 400 pA at −60 mV) [17,105]. This may explain why NMDARs are required to further augment the driving force to power the bursts in the LHb (Figure 2; Box 3). Such joint actions of T-VSCCs and NMDARs in burst generation have also been reported in the substantia nigra pars compacta [108], the hypothalamic magnocellular dorsal nucleus [109], and nucleus basalis [110].

Because of the rebound nature of LHb bursts (Figure 2, Box 3), membrane potential also plays an important role in burst generation in the LHb. Tonic-firing neurons can be quickly converted to burst-firing with a hyperpolarizing current injection or by reducing extracellular potassium [17]; vice versa, bursting neurons can be converted to tonic firing with a depolarizing current injection [17], or by blocking an astroglial potassium channel, Kir4.1, that regulates extracellular potassium level $K_{[out]}$ and hence resting membrane potential (RMP) of neurons [40]. Indeed, in an unbiased proteomic screen, Kir4.1 was identified to be upregulated in the LHb of cLH rats [53]. The excessive potassium buffering mediated by upregulated Kir4.1 is shown to be responsible for increased burst firing of LHb neurons in several animal models of depression [40].

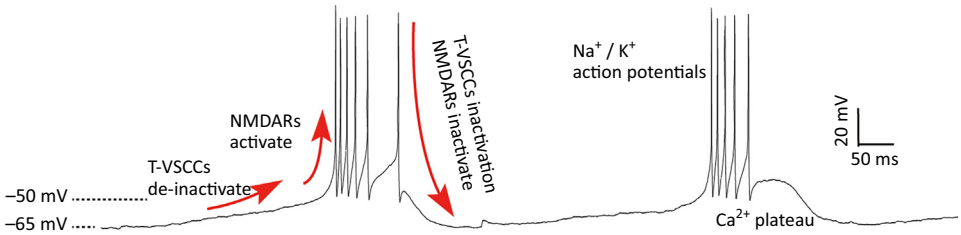

Figure 2. An Example of an Electrophysiological Recording Trace Summarizing the Ionic Components and Channel Mechanisms Involved in LHb Bursting. Activation of voltage-sensitive T-type calcium channels (T-VSCCs) removes the Mg blockade of NMDARs. The opening of these two channels synergistically drives membrane potential toward the threshold for a burst of action potentials. As resting membrane potential (RMP) falls back to below −55 mV, it de-inactivates T-VSCCs and results in the intrinsic propensity of lateral habenula (LHb) neurons to initiate another cycle of burst. Modified with permission from Yang *et al*. [17].

LHb Bursts as a Novel Target for the Rapid Antidepressant Ketamine

Based on the above-mentioned evidence, we put forward a new and simple model to explain the rapid antidepressant mechanism of ketamine: By blocking NMDAR-dependent bursting of LHb neurons, which normally inhibit the brain's reward centers, ketamine can disinhibit the aminergic reward centers and rapidly improve depressive symptoms (Figure 3, Key Figure). Consistently, a previous positron emission tomography imaging study in MDD patients showed that habenular metabolism decreased significantly following ketamine infusion [111].

Compared with previous models on ketamine action, this disinhibition model has fewer direct steps to reach the core of the reward centers. Notably, activation or disinhibition of aminergic centers has a greater impact than mere increase of the level of monoamines themselves. Monoaminergic neurons often co-release monoamines together with other neurotransmitters such as glutamate [112,113]. Indeed, it has been recently shown that the glutamate

Box 3. The Ionic Mechanism of LHb Burst Firing and Its Possible Modulators

Burst generation, in general, relies on either intrinsic cellular properties, network synaptic inputs, or the interaction of both [85,86]. In the LHb, burst generation depends critically on the synergistic activation of T-VSCC (IT) and NMDAR (INMDA). According to a model of LHb neurons [17], hyperpolarization of neurons to membrane potentials negative to −55 mV slowly de-inactivates T-VSCC. IT continues to grow as the de-inactivated T-VSCCs increase, leading to a transient Ca plateau potential. The Ca plateau helps remove the magnesium blockade of NMDARs, while T-VSCC inactivates rapidly during the depolarization. After the Ca^{2+} plateau reaches approximately −45 mV, INMDA dominates the driving force to further depolarize RMP to the threshold for Na spike generation. The falling phase of a burst is associated with the inactivation of IT and INMDA. The falling back of RMP below −55 mV again de-inactivates IT and results in the intrinsic propensity of LHb neurons to generate the next cycle of burst.

According to this bursting mechanism, regulation of RMP is an effective way to affect burst generation. Indeed, the astroglial potassium channel Kir4.1 can regulate the level of LHb bursts by altering K[out] and RMP [40].

Besides these intrinsic features mediated by T-VSCC, NMDAR, and Kir4.1, synaptic inputs from AMPARs and GABARs can also potentially modulate LHb burst generation. Although AMPAR blocker in the LHb only slightly reduces burst probability and does not cause significant antidepressant effects [17], enhancing LHb AMPAR signaling may still be able to promote bursting activity during the emergence of depression. Indeed, a puff of AMPA onto the LHb neurons in electrophysiological recordings or doubling AMPAR currents in modeling experiments both increase burst frequency [17]. During bursts, the Ca^{2+} entry through T-VSCCs and NMDARs may help phosphorylate the β form of calcium/calmodulin-dependent protein kinase II and potentiate AMPAR transmission [53], which may further enhance bursts. Overall, we propose that LHb bursts *in vivo* are generated through refined interaction between the intrinsic membrane properties and network inputs transmitting negative emotional information.

Key Figure

A Conceptual Model of How Depressive State and Ketamine Bidirectionally Regulate LHb Burst Firing

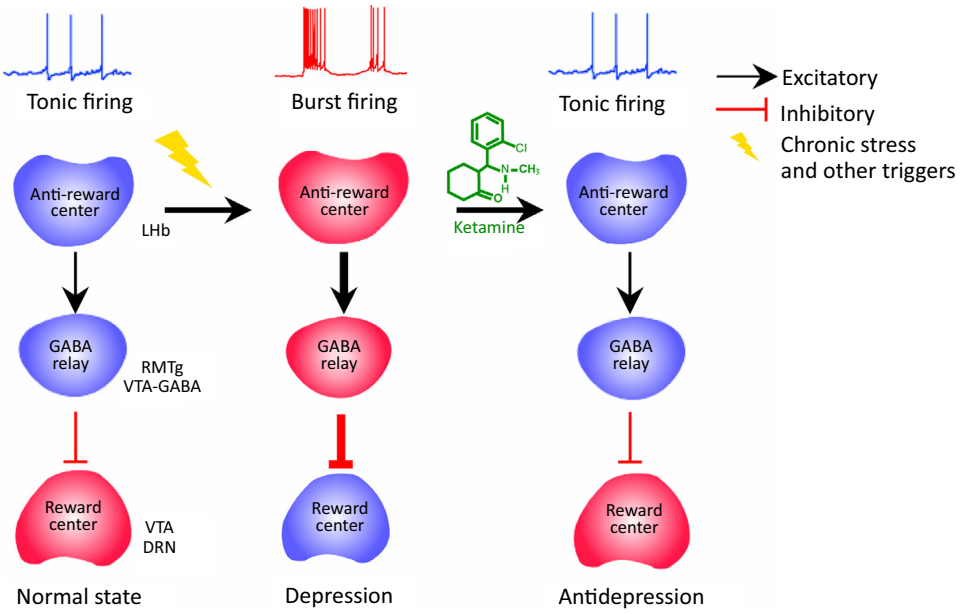

Figure 3. As an anti-reward center, lateral habenula (LHb) inhibits the aminergic reward centers (including VTA and DRN) through the GABAergic RMTg nucleus, as well as through feedforward inhibition within these nuclei [57–59]. Under depression state, burst firing of LHb neurons is significantly enhanced, which leads to stronger suppression of downstream reward centers. Thicker arrows represent stronger innervations. Since LHb bursts depend on NMDAR, ketamine blocks LHb bursts, resulting in a disinhibition of the reward centers, thereby rapidly alleviating the depressive symptoms. Blue color indicates low activity; red color indicates high activity. Abbreviations: DRN: dorsal raphe nucleus; RMTg, rostromedial tegmental nucleus; VTA, ventral tegmental area.

co-released from 5-hydroxytryptamine (5-HT) neurons, as well as the glutamatergic neurons within the DRN, mediates acute rewarding effects [112,114,115]. Hence, we propose that the co-released neurotransmitters from aminergic neurons, or disinhibition of other neuron types in the aminergic centers, may contribute to the fast antidepressant effects of ketamine downstream of LHb. This hypothesis may explain why ketamine works faster than classical antidepressants (e.g., SSRI inhibitors such as fluoxetine), which also quickly increase DA and 5-HT levels within hours in the brain [116].

A previous study showed that PCP-like drugs, including MK801, increase the bursting of VTA-DA neurons when systematically administered [117]. It will be interesting to tease out whether such effect is mediated directly through the VTA local circuit or by the disinhibition from the LHb. Of interest, local infusion of ketamine directly into the VTA region did not significantly change immobility of cLH rats in FST (Yang *et al.*, unpublished), suggesting that it is unlikely that ketamine acts directly on the VTA to cause rapid antidepressant responses.

Concluding Remarks and Future Perspectives

In this review article, we have proposed that by silencing NMDAR-dependent burst firing of LHb neurons, ketamine can exert its antidepressant effects through disinhibition of the aminergic reward centers to rapidly improve depressive symptoms. Below, we speculate on how the proposed mechanism could relate to the more persistent actions of ketamine and consider subsequent areas of interest (see Outstanding Questions).

Sustained Effects of Ketamine

Ketamine's antidepressant effects are not only rapid but also long-lasting, sustaining for 3–10 days after a single shot [11,13,14,118–121]. In many clinical studies, the 24-h time point is often used to measure the primary outcome of ketamine's sustained antidepressant effects, because early studies suggested the optimal response to be at 24 h [122]. Whether this sustained effect of ketamine still depends on NMDAR, and whether it is mediated by BDNF-mTOR signaling [14,15,32,33], hydroxynorketamine [16,123], synaptogenesis [32], neurogenesis [124], LHb bursts [125] or brain network connectivity [126], remain fascinating open questions. It will be relevant to test the behavioral effects of local ketamine infusion into LHb at 24 h or a later time point. The extent to which LHb bursts are inhibited should also be measured at different time points after systemic injection of ketamine.

Possible Involvement of Other Brain Regions in Ketamine's Antidepressant Effects

Several earlier studies have tried local infusion of ketamine in different brain areas (e.g., PFC or hippocampus) and indicated antidepressant effects in different paradigms (e.g., learned helpless, uncontrollable tail shock) and at several time points (e.g., 24 h or 4 days after infusion) [119,121,127]. It is possible that ketamine's effects at different time points (e.g., 1 versus 24 h or days) may be mediated by different nodes and involve different signaling mechanisms. However, to determine whether this is the case, or whether there is a common pathway mediating the various effects, it will be necessary to compare notes and aim for more consistency in the experimental protocols, that is, perform the tests in the same brain region(s), at the same time point(s), and using the same paradigm(s).

T-VSCC and Kir4.1 as New Targets for Rapid Antidepressants

The dependency of LHb bursts on T-VSCCs suggests that T-VSCCs may also be a potent target of new antidepressants [17]. Indeed, systemic injection of the T-VSCC blocker ethosuximide, which can cross the blood–brain barrier, or local LHb infusion of a more specific T-VSCC blocker, mibefradil, both caused rapid antidepressant responses in rodents within 1 h [17]. Ethosuximide is a classical treatment for absence seizures that depend on thalamic T-VSCCs [128]. In animal models of epilepsy, ethosuximide was reported to ameliorate the depressive-like symptoms accompanying epilepsy [129]. Considering that depression is a common comorbidity of epilepsy [130], and in light of our finding that LHb bursts require T-VSCC activity, it will be very interesting to explore the effects of additional epilepsy drugs on depression, especially those targeting on T-VSCCs.

As discussed above, Kir4.1 is also a potent regulator of LHb bursts and thus a potential target for rapid antidepressants [40]. Specific inhibitors for Kir4.1 are currently not available but worth exploring. Treatment with a cocktail of blockers targeting on different ion channels involved in LHb bursts (e.g., NMDAR, T-VSCCs, and Kir4.1) may reduce the dosage and side effects of each drug alone and may thus offer a promising new avenue for therapeutic intervention.

During the preparation of this review article, a new study showed that ethosuximide did not improve depressive-like phenotypes in the FST, TST, and SPT assays in a chronic social defeat

Outstanding Questions

What accounts for the long-term antidepressant effects of ketamine? Does ketamine cause sustained inhibition of bursting activity in the LHb?

What is the role of different brain regions, for example, prefrontal cortex, hippocampus, and LHb, in mediating the rapid and sustained antidepressant effects of ketamine? Could they kick in at different time points to mediate antidepressant responses?

What kind of emotional stimuli and upstream inputs can acutely elicit burst firing in the LHb? What signaling mechanism underlies the upregulation of Kir4.1 and increased LHb burst firing during depression?

What is the consequence of LHb burst firing at the downstream neural circuits? How does it alter the phasic response of dopaminergic neurons? Are there any neuropeptides, released by bursting LHb neurons, that are involved in the manifestation of depression?

Can other clinically available drugs targeting LHb bursting, such as T-VSCC blockers, also cause rapid antidepressant effect? If so, could cocktail treatments combining ketamine with these drugs be more effective than ketamine alone, and have reduced side effects?

Apart from depression, does NMDAR-dependent burst firing in other brain regions serve as a critical neural substrate for other psychiatric diseases (e.g., schizophrenia) as well?

stress mouse model [131]. Somewhat unfortunately, the time points chosen for phenotype evaluation in the study may be too late: There were 4-, 24-, or 48-h delays for TST, FST, and SPT, respectively, after ethosuximide intraperitoneal injection. However, the half-life of ethosuximide is about 1 h in mice [132] and 54 h in humans [133]. Another recent study from the same group used these same time points to test inhibitors of Kir4.1 (sertraline and quinacrine) and may cause the same concern [134]. In addition, sertraline has >2000 times higher affinity for serotonin transporter (SERT) than for kir4.1 (IC_{50} for SERT, 2.8 nM; for Kir4.1, 7 μM) [135,136]. We deem it crucial to consider a drug's specificity and pharmacokinetics, including half-life and off-rate, in both rodents and humans, when designing new antidepressant drugs and testing their behavioral effects.

Upstream and Downstream of LHb Bursts

LHb receives inputs from various limbic and basal ganglion structures that convey different components of positive or negative emotional states to regulate LHb activity. Tonic (~20–40 Hz), optogenetic stimulation of different afferent inputs [basal ganglia, lateral preoptic, ventral pallidum, VTA, lateral hypothalamus, medial prefrontal cortex (mPFC)] to LHb have been reported to elicit aversive or depressive-like response [42,43]. It will be fascinating to figure out how these inputs and emotional stimuli alter the burst versus tonic firing patterns in the LHb.

On the output side, it will also be important to determine downstream changes triggered by the LHb bursts. Tonic patterns (in the range of ~15–60 Hz) of optogenetic stimulation have been used to stimulate the LHb output to RMTg, VTA, or DR pathways and elicit aversive, anti-reward responses [42,43]. It will be interesting to revisit these pathway-specific stimulation experiments using burst-like patterns and test whether burst stimulation differentially recruits the GABAergic RMTg or GABAergic interneurons within the aminergic centers, or perhaps stimulates release of certain neuropeptides, to cause depression.

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