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Rodent ketamine depression-related research: finding patterns in a literature of variability

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Abstract

Discovering that the anesthetic drug ketamine has rapidly acting antidepressant effects in many individuals with major depression is one of the most important findings in clinical psychopharmacology in recent decades. The initial report of these effects in human subjects was based on a foundation of rodent preclinical studies carried out in the 1990s, and subsequent investigation has included both further studies in individuals with depression, as well as reverse translational experiments in animal models, especially rodents. While there is general agreement in the rodent literature that ketamine has rapidly-acting, and generally sustained, antidepressant-like properties, there are also points of contention across studies, including the precise mechanism of action of this drug. In this review, we briefly summarize prominent yet variable findings regarding the mechanism of action. We also discuss a combination of similarities and variances in the rodent literature in the antidepressant-like effects of ketamine as a function of dose, species and strain, test, stressor, and presumably sex of the experimenter. We then present previously unpublished mouse strain comparison data suggesting that subanesthetic ketamine does *not* have robust antidepressant-like properties in *unstressed* animals, and may actually promote depression-like behavior, in contrast to widely reported findings. We conclude that the data best support the notion of ketamine action principally via NMDA receptor antagonism, transiently boosting glutamatergic (and possibly other) signaling in diverse brain circuits. We also suggest that future studies should address in greater detail the extent to which antidepressant-like properties of this drug are stress-sensitive, in an effort to better model major depression present in humans.

INTRODUCTION

Ketamine is currently gaining in clinical use for major depression. Interestingly, many features of ketamine action shown in human patients are also seen in rodents, and many neuroscientists are using rodent models of these effects to study the neurobiological mechanisms of ketamine action on the brain – to better understand both ketamine and depression-related biology itself. In this review we will focus on the rodent literature, with an initial brief background in human clinical findings. Of note, this review is composed of two parts, each relating to major points of variance in the realm of rodent ketamine research.

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The first part deals with variable results regarding the mechanism of action of ketamine in its antidepressant-like action – this point is of import for developing similar compounds in the future as therapeutics. The second part of this review is a meta-analysis of the consistency or variability among antidepressive-like behavioral outcomes published about rodents. This is done with a particular eye toward the role of psychosocial stress, given the importance of that variable in allowing translation. In covering these two major topics we attempt to discuss two major axes of difficulty in the field now. Throughout the rest of the text we will refer to "ketamine" as its typically administered racemic mixture, (*R,S*)-ketamine.

HISTORY, CLINICAL FINDINGS AND LINKAGES

Prior to delving into either major realm of rodent research described above, we will first give some background. Major depressive disorder (depression) is a neuropsychiatric disease often linked to psychological stress and for which pharmacological treatment options are limited (Bonde et al., 2016; Hosang, Shiles, Tansey, McGuffin, & Uher, 2014; Ruhe, Huyser, Swinkels, & Schene, 2006). Commonly used monoaminergic antidepressants, such as the SSRIs, SNRIs, and tricyclics, are not effective in all patients and their timecourse of therapeutic onset is usually slow, often requiring a week or longer for initial effects to become evident (Derivan, 1995; Henkel et al., 2009; Kudlow, Cha, & Mcintyre, 2012). Largely for that reason, there is growing interest in the use of rapidly-acting pharmacological agents with alternate underlying mechanisms to counteract depression, to both help patients who do not respond to other drugs and because these agents work faster. The most prominent of these treatments is the anesthetic (and drug of abuse), (*R,S*)-ketamine (Ebada, 2017; Rosenblat et al., 2019). This drug is already being used clinically worldwide to treat major depression, often being administered intravenously in hospitals and clinics. The recent FDA approval of a nasal spray formulation of its enantiomer (*S*)-ketamine ("esketamine") has added to the feasibility of its widespread use (Targum, Daly, Fedgchin, Cooper, & Singh, 2019). The rapid onset of (*R,S*)-ketamine's antidepressant effects, which occur within 1-4 hours of initial administration, as well as its ability to sustain these favorable effects for days or even weeks in some individuals, has captured the interest of clinicians and translational researchers alike (Berman et al., 2000; Chan et al., 2018; Zarate et al., 2006). Importantly, this rapid temporal profile of treatment effects implies that (*R,S*)-ketamine has a unique mechanism of action compared with conventional monoaminergic antidepressants. This then implies that understanding the effects of (*R,S*)-ketamine may inform us as to new elements of mood-related neurobiology – again provoking great scientific interest. In addition, in a subset of individuals with major depression, (*R,S*)-ketamine may have specific anti-suicidal properties (Machado-Vieira, Salvadore, DiazGranados, & Zarate, 2009).

It should also be noted that (*R,S*)-ketamine remains a popular drug of abuse worldwide, which poses a significant barrier to its use in the clinical treatment of major depression (Liao, Tang, & Hao, 2017). Because of its abuse potential and psychotomimetic properties, there remain some concerns by some in using it as a pharmacological agent for mainstream treatment of depression (Andreae et al., 2016). It indeed must be prescribed with caution to individuals with a history of substance abuse. Also, since it is administered in clinics in the United States, often intravenously over several hours, it is not as convenient to take as most

oral antidepressants. For these reasons, there is great interest in understanding its mechanism of action in order to facilitate development of (*R,S*)-ketamine-like antidepressants that lack this drug's dissociative properties and abuse potential (Duman, 2018).

Berman et al. (2000) provided the initial demonstration of the therapeutic efficacy of (*R,S*)-ketamine in human subjects with major depression (Berman et al., 2000). In that publication, the authors note that a number of rodent depression-related preclinical studies carried out in the 1990s, which used a wide range of NMDA receptor (NMDAR) antagonist drugs, motivated them to investigate whether this drug is an effective treatment of human depression. Zarate et al. (2006) performed another prominent, double-blind placebo-controlled study of (in this case, treatment-resistant) major depression, which generated further interest in (*R,S*)-ketamine as a rapidly acting antidepressant with sustained effects (Zarate et al., 2006). Since then, both preclinical and clinical researchers have focused on (*R,S*)-ketamine, more than other NMDAR antagonists, as a novel treatment for depression, perhaps partly because (*R,S*)-ketamine was and is already being used clinically as a surgical anesthetic, making its repurposing at a lower dose for neuropsychiatric disorders immediately feasible, at least in an off-label manner (Ebada, 2017).

In the rest of this article, we briefly review preclinical studies of (*R,S*)-ketamine as a rapidly acting antidepressant, with a focus on studies in mice and rats. This growing literature is helping us gain a greater understanding of the precise molecular- and circuit-based mechanisms of action of this drug, which aids in using it to more effectively counteract depression, while also driving further innovation in the discovery of the next generation of rapidly acting antidepressants (Gerhard & Duman, 2018). The precise mechanism of action of (*R,S*)-ketamine remains quite controversial, as there is indeed no consensus that it is acting exclusively or even principally as an NMDAR antagonist (Zanos & Gould, 2018; Zanos et al., 2016). There is, in contrast, a large number of rodent studies reporting that (*R,S*)-ketamine has antidepressant-like effects across many dimensions including: dose, specific rodent species and strain, type of depression-related test used, presence of and type of stressor, and presumably sex of the experimenter. The remainder of this review focuses on understanding this variability of both results and approaches in the literature.

MOLECULAR AND RECEPTOR-BASED MECHANISMS OF KETAMINE ACTION – AN AREA OF ACTIVE RESEARCH

While it has long been presumed that the well-documented NMDAR-antagonism is the primary mechanism of action of antidepressant dose (*R,S*)-ketamine given this drug's receptor binding profile, that assumption is now coming into some question. Initial work presented strong evidence that (*R,S*)-ketamine is an antidepressant due to blockade of the NMDAR, ultimately leading to increased brain derived neurotrophic factor (BDNF) production in circuits such as the hippocampus (Autry et al., 2011). Surprisingly, subsequent work suggested that (*R,S*)-ketamine, which is typically administered as a balanced racemic mixture of its (*R*)- and (*S*)-ketamine enantiomers, actually achieves its antidepressant-like effects independently of NMDAR blockade through two of its pharmacologically active metabolites: (*2S,6S*)-hydroxynorketamine and (*.2R,6R*)-hydroxynorketamine (HNK). The

latter of these has been suggested to therapeutically potentiate signaling at glutamatergic AMPA receptors (Zanos et al., 2016). On the other hand, later experiments then demonstrated that (*2R,6R*)-HNK, which had been described as the more behaviorally effective HNK metabolite, also blocks the NMDAR, and may thus produce any antidepressant-like effects through the same NMDAR-dependent pathway as (*R,S*)-ketamine (Suzuki, Nosyreva, Hunt, Kavalali, & Monteggia, 2017). The (*2R,6R*)-HNK hypothesis was further questioned based on the finding that (*S*)-ketamine, which is not metabolized into (*2R,6R*)-HNK *in vivo*, nonetheless has robust antidepressant effects in humans (Collingridge, Lee, Bortolotto, Kang, & Lodge, 2017; Singh et al., 2016). Additionally, numerous preclinical studies carried out (including in the 1990s) in rodents used a wide range of NMDAR antagonist compounds, which are thought to not be metabolized into (*2R, 6R*)-HNK (or (*2S,6S*)-HNK), and nonetheless have robust antidepressant-like properties (Collingridge et al., 2017). Later published discussions (Zanos et al., 2017) countered these assertions by pointing out that the reported superiority of (*R*)-ketamine versus (*S*)-ketamine (C. Yang et al., 2015; J. C. Zhang, Li, & Hashimoto, 2014) is consistent with the (*2R,6R*)-HNK hypothesis, while also pointing out that the various preclinical non-ketamine NMDAR antagonist compounds noted above have only shown inconsistent antidepressant effects, including in humans (Kishimoto et al., 2016; Sanacora et al., 2014; Zarate et al, 2006). This debate over the mechanism of action of (*R,S*)-ketamine continues in more recent publications (Kavalali & Monteggia, 2018; Lumsden et al., 2019; Zanos, Highland, Liu, et al., 2019; Zanos, Highland, Stewart, et al., 2019), including the possibility that (*2R,6R*)-HNK is an open channel blocker of the NMDAR (Thu Ha Pham et al., 2018), or that (*R,S*)-ketamine acts through a non-NMDAR mechanism that is instead dependent on intracellular cAMP signaling (Wray, Schappi, Singh, Senese, & Rasenick, 2018).

Other studies have also weighed in on the (*2R,6R*)-HNK versus NMDAR antagonism question in various rodent publications. It has recently been suggested, for example, that (*2R,6R*)-HNK boosts downstream BDNF signaling, which is then necessary for the antidepressant-like effects of (*R,S*)-ketamine (Fukumoto et al., 2019). Furthermore, a single systemic administration of (*2R,6R*)-HNK itself can rapidly rescue chronic stress-induced depression-like behavior and persist for up to 21 days (Chou et al., 2018). In contrast, recent mouse (Yamaguchi et al., 2018) and rat (Shirayama & Hashimoto, 2018) studies by another group have suggested that whereas (*R*)-ketamine exhibits rapid antidepressant-like properties, its metabolite (*2R,6R*)-HNK does not. These researchers have additionally found that intracerebroventricular infusion of (*2R,6R*)-HNK lacks antidepressant-like effects in a chronic social defeat stress model (CSDS) (Zhang, Fujita, & Hashimoto, 2018). This group has also recently found that (*S*)-norketamine, a principal metabolite of (*S*)-ketamine that can be converted to (*2S,6S*)-HNK, has more favorable effects on prefrontal and hippocampal synaptic plasticity than (*R*)-norketamine, and AMPA receptor antagonists do not block its antidepressant-like effects (Yang et al., 2018). This group has also pointed out that in spite of the recent introduction of the esketamine nasal spray formulation to the market, preclinical data suggest that compared to (*S*)-ketamine, (*R*-ketamine has greater potency and longer duration antidepressant-like effects. In addition, its side effects are more mild than both *S*)-ketamine and (*R,S*)-ketamine (Hashimoto, 2019). That publication also provides a review on the topic of (*R,S*)-ketamine and its enantiomers as antidepressants.

Aside from the above experiments, glutamatergic signaling has long been suggested to play a role in (*R,S*)-ketamine's mechanism of action in depression. A recent review on this topic compared evidence for inhibition of glutamatergic signaling versus its activation, and proposed a synaptic connectivity model of chronic stress pathology and suggested that "transient (prefrontal) glutamate postsynaptic activation" is a primary mechanism of (*R,S*)-ketamine (Abdallah, Sanacora, Duman, & Krystal, 2018). Subanesthetic doses of systemically administered (*R,S*)-ketamine are indeed known to increase medial prefrontal cortex (mPFC) glutamate release, whereas anesthetic doses do the opposite (Moghaddam, Adams, Verma, & Daly, 1997). A human magnetic resonance spectroscopy study found evidence for increased prefrontal glutamatergic signaling after (*R,S*)-ketamine intravenous infusion, which positively correlated with perceptual dissociation (Abdallah, De Feyter, et al., 2018). Regarding the case for glutamatergic inhibition by (*R,S*)-ketamine: it has been shown in rodents that inhibiting NMDARs or glutamate release can block chronic stress-induced dendritic atrophy (McEwen, 1999). It has also been demonstrated that transient exposure to (*R,S*)-ketamine upregulates GluR1 and GluR2 AMPA receptor subunits on human dopamine neurons, which may be involved in a downstream mechanism of action of this drug (Collo, Cavalleri, Chiamulera, & Pich, 2019).

Even if the principal, initial mechanism of action of (*R,S*)-ketamine is glutamatergic, a wide range of neurotransmitter systems and molecular pathways may be modulated by (*R,S*)-ketamine (Zanos & Gould, 2018; Zanos et al., 2018). We will briefly touch upon some of these, beginning with the brain's principal inhibitory neurotransmitter, GABA. Dysfunction in GABAergic interneurons has been implicated in the pathophysiological effects of chronic stress and major depression itself (Fee, Banasr, & Sibille, 2017; Fogaça & Duman, 2019). Some studies have reported decreased brain GABA levels in depression (Hasler et al., 2007; Luscher & Fuchs, 2015), as well as reduced molecular markers of GABA in the default mode network during this disease (Gabbay et al., 2012). These studies and others, coupled with findings of enhanced glutamatergic transmission noted above, have implicated a high excitatory:inhibitory (E:I) ratio in many cases of human major depression (Fee et al., 2017), which (*R,S*)-ketamine may normalize in prefrontal circuits (Fogaça & Duman, 2019). Acute administration of (*R,S*)-ketamine to humans or rodents has been widely reported to enhance the power of electroencephalography (EEG) or local field potential (LFP) gamma oscillations in a number of circuits (Fitzgerald & Watson, 2019; Hakami et al., 2009; Hunt, Garcia, Large, & Kasicki, 2008; Lee, Hudson, O'Brien, Nithianantharajah, & Jones, 2017), and this property may underlie its antidepressant action (Amat-Foraster et al., 2018). There appears to be a relationship between the LFP (including gamma) and the E:I ratio (Watson, Ding, & Buzsaki, 2018), further suggesting a role for (*R,S*)-ketamine in modulating this ratio in depression (Fitzgerald & Watson, 2018).

A recent study found that the opioid receptor antagonist drug, naltrexone, blocked the therapeutic effect of (*R,S*)-ketamine in treatment-resistant depression (Williams et al., 2018). Also, a mu opioid receptor agonist, tramadol, has been found to facilitate the antidepressant-like effect of a sub-effective dose of (*R,S*)-ketamine in the mouse FST (Ostadhadi S et al., 2017). On the other hand, another study reports that blockade, partial agonism and low-affinity agonism of the opioid receptor long-term does not affect the efficacy of (*R,S*)-ketamine for depressive symptoms in human subjects (Marton, Barnes, Wallace, & Woolley,

2019). Moreover, a pilot study in humans with major depression and concurrent alcohol use disorder found that pretreatment with naltrexone did not interfere with the antidepressant effects of (*R,S*)-ketamine (Yoon, Petrakis, & Krystal, 2019). Recent rodent data also found that naltrexone did not block the antidepressant-like effect of (*R,S*)-ketamine in CSDS or lipopolysaccharide models (K. Zhang & Hashimoto, 2019). One reason for differences in results in opioid system-related studies could be that short-term alteration can interfere with the effects of ketamine whereas chronic alteration does not.

Serotonergic signaling may also play a role in (*R,S*)-ketamine action. Such modulation has been demonstrated in rodent models for 5-HT1A, 5-HT3, and 5-HT6 receptors, for example (Fukumoto, Iijima, Funakoshi, & Chaki, 2018; Kordjazy et al., 2016; Suárez-Santiago, Briones-Aranda, Espinosa-Raya, & Picazo, 2017). Also, serotonin depletion with the drug para-chlorophenylalanine (PCPA) can block the antidepressant-like effect of (*R,S*)-ketamine (du Jardin et al., 2016). A recent mouse study, however, found that serotonin depletion with PCPA did not block the antidepressant-like effect of (*R*)-ketamine in a CSDS model (K. Zhang, Dong, Fujita, Fujita, & Hashimoto, 2018).

Noradrenergic signaling is another candidate contributor to the mechanism of action of (*R,S*)-ketamine. In two microdialysis studies in freely moving rats, it was shown that mPFC release of norepinephrine is dose-dependently enhanced by systemic (*R,S*)-ketamine, with an anesthetic dose (100 mg/kg) producing greater synaptic levels than subanesthetic doses (Kubota, Anzawa, et al., 1999; Kubota, Hirota, et al., 1999). It was also demonstrated that this enhanced mPFC level of norepinephrine was counteracted by the drug clonidine, an inhibitor of presynaptic norepinephrine release. This pair of studies may suggest a previously undescribed role for norepinephrine, at high concentrations, in promoting a state of anesthesia rather than alertness or arousal (Fitzgerald & Watson, 2019). A human brain imaging study has demonstrated a decrease in resting state functional connectivity from the noradrenergic locus coeruleus to the thalamus following (*R,S*)-ketamine administration (Liebe et al., 2018). An additional point that may implicate norepinephrine in (*R,S*)-ketamine's mechanism of action: like (*R,S*)-ketamine itself, norepinephrine boosting antidepressants such as reboxetine acutely enhance the power of gamma oscillations (Fitzgerald & Watson, 2018; Hajós, Hoffmann, Robinson, Yu, & Va Hajó S-Korcsok, 2003).

In addition to its effects on neurotransmitter systems, administration of (*R,S*)-ketamine, not surprisingly, modulates a number of downstream intracellular molecular pathways (Duman, Li, Liu, Duric, & Aghajanian, 2012; Zanos & Gould, 2018). For example, systemic (*R,S*)-ketamine has been shown to activate mechanistic target of rapamycin (mTOR) signaling, and prefrontal or intracerebroventricular infusion of rapamycin blocks the antidepressant-like effects of (*R,S*)-ketamine (Abelaira et al., 2017; Li et al., 2011; Thelen et al., 2019). Another group, however, has found that rapamycin blocks the antidepressant-like effect of (*S*)-ketamine but not (*R*)-ketamine in a mouse CSDS model, suggesting mTOR signaling is not necessary for the therapeutic effects of (*R*)-ketamine (Yang, Ren, et al., 2018). Recent data from human subjects suggest that rapamycin actually prolongs, rather than blocks, the antidepressant effect of (*R,S*)-ketamine (Abdallah, Averill, et al., 2018).

As mentioned above, the Monteggia group has implicated BDNF signaling in the therapeutic effects of (*R,S*)-ketamine (Autry et al., 2011), and other groups have also suggested a similar role for this molecule, through both hippocampal and mPFC circuits (Garcia et al., 2008; Lepack, Fuchikami, Dwyer, Banasr, & Duman, 2015). These molecular pathways and others, such as Ras/MAPK, may play a critical role in the downstream synaptic plasticity mechanisms thought to underlie the antidepressant-like effects of (*R,S*)-ketamine (Duman et al., 2012; W. Liu etal., 2017).

Thus clearly a variety of studies by a range of groups have found a remarkable range of correlates with ketamine action. The factors contributing to the variance in these data may range from experimental details to differential outcome measures to use of multiple species to a drug that engages much of the brain. Is a broad brain engagement key to a mechanism of action or a signature of efficacy? As a community we will need to determine which of these effects may be causal – and consistently causal - in the action of ketamine.

BRAIN REGION-BASED MECHANISMS OF ACTION

Regardless of molecular mechanism, changes in neural activity in specific brain regions may be a final common pathway for the behavioral effects of (*R,S*)-ketamine. Yet multiple regions have been implicated in (*R,S*)-ketamine action, including the mPFC, ventral hippocampus and habenula. How these regions cooperate is not clear and each seems to demonstrate at least sufficiency in replicating behavioral depression-related effects in rodents.

The mPFC is a region frequently implicated in mood and emotional regulation, where microinfusion of (*R,S*)-ketamine or optogenetic stimulation of the infralimbic subdivision of mPFC produces antidepressant-like effects similar to systemic administration of (*R,S*)-ketamine in rats (Fuchikami et al., 2015). In rats exposed to chronic unpredictable stress there are decreases in the expression of synaptic proteins and spine numbers in mPFC layer 5 pyramidal cells, and these deficits are rapidly reversed by (*R,S*)-ketamine (Li et al., 2011). A recent study in mice found that chronic exposure to the stress molecule, corticosterone, in the drinking water promotes stress-like behavioral changes and elimination of dendritic spines on mPFC projection neurons, and (*R,S*)-ketamine reverses these synaptic and behavioral effects (Moda-Sava et al., 2019).

The ventral CA3 region of the hippocampus has also been implicated in the therapeutic effects of (*R,S*)-ketamine, particularly its prophylactic effects against social defeat stress in mice, partly mediated by expression of the protein ΔFosB (Mastrodonato et al., 2018). A series of pharmacological, optogenetic, and chemogenetic experiments in rats demonstrated that a ventral hippocampus-mPFC circuit is both necessary and sufficient for the antidepressant-like behavioral effects of (*R,S*)-ketamine (Carreno et al., 2016). Bilateral infusion of the enantiomer (*R*-ketamine into infralimbic (but not prelimbic) cortex, CA3, or dentate gyrus of the hippocampus each produced antidepressant-like effects in a rat learned helplessness model (Shirayama & Hashimoto, 2017).

Other work has suggested that neuronal bursting activity in the lateral habenula (which has been termed the “anti-reward center”) promotes depression-like behavior (Cui et al., 2018; Y. Yang et al., 2018). These papers suggest that (*R,S*)-ketamine blocks this bursting and may disinhibit downstream monoaminergic reward centers, where bursting is bidirectionally modulated by the astroglial potassium channel Kir4.1 (Cui et al., 2018; Y. Yang et al., 2018). Yang et al. (2018) also found that systemic administration of the T-type calcium channel blocker ethosuximide has (*R,S*)-ketamine-like rapid antidepressant-like effects, but this was not replicated in a recent study using the chronic social defeat stress (CSDS) behavioral model of stress (Tian, Dong, Zhang, Chang, & Hashimoto, 2018). Another study by the latter group also found that Kir4.1 channel inhibitors did not produce rapid and sustained antidepressant-like effects in a CSDS model (Xiong et al., 2019).

Perhaps relatedly, (*R,S*)-ketamine and its metabolite (*2R,6R*)-HNK have been shown in mice to impair long-term potentiation in the nucleus accumbens. (*R,S*)-ketamine inhibits phosphorylation of the GluA1 AMPA receptor subunit in this circuit, where these synaptic effects may modulate reward-related behaviors (Yao, Skiteva, Zhang, Svenningsson, & Chergui, 2018).

Moving forward to fully characterize the mechanism of action of ketamine may require a focus on the circuit level effects of (*R,S*)-ketamine – given the clear involvement of many brain regions. One region may drive others, or all may be driven by (*R,S*)-ketamine. Furthermore, their interaction may or may not be crucial, independent of the individual effects in single regions. Targeted multisite recording and stimulation methods may be crucial here to clarify these multiple findings – and again may both help us understand (*R,S*)-ketamine actions and new neurobiology.

In summary, we need still to determine whether (*R,S*)-ketamine has multiple effects simultaneously and at what levels those effects are brought about – action at multiple receptors, multiple downstream intracellular effectors or final common networks. The complexities raised by these pharmacologic studies demonstrate the need for a great deal of further research. In addition, it should be remembered that large-scale effects from any one system can induce changes in other neurotransmitters or other signaling systems. Thus, an important future focus may be on specifically assessing causal relationships in both directions between treatment and effect, as well as at smaller scales – for example examining whether changes in one system are actually induced by (*R,S*)-ketamine versus induction by downstream effects of this drug.

HYPOTHESES ON MECHANISM OF ACTION

While there is much variability in the data as summarized above, which requires further experimentation, other ideas may have sufficiently emerged at this point to allow us to integrate and speculate in ways that may guide future hypothesis testing. A broad range of brain regions, neurotransmitter systems (not limited to glutamatergic signaling) and downstream molecular pathways are recruited and altered by a single, systemic administration of (*R,S*)-ketamine. Regarding the NMDAR antagonism versus AMPA potentiation by (*2R,6R*)-HNK question: we suggest here that NMDAR blockade is more

likely to be the primary initial mechanism of action, if only due to the large number of studies showing this mechanism in ketamine itself and with a variety of drugs that are thought to be NMDAR antagonists (Layer, Popik, Olds, & Skolnick, 1995; Meloni et al., 1993; Moryl, Danysz, & Quack, 1993; Papp & Moryl, 1994, 1996; Przegaliński, Tatarczyńska, Dereń-Wesołek, & Chojnacka-Wójcik, 1997; Trullas & Skolnick, 1990). These drugs are unlikely to all have (*2R,6R*)- or (*2S,6R*)-HNK as metabolites, suggesting the parsimonious hypothesis that (*R,S*)-ketamine and all of these other drugs are acting at least mainly through NMDAR antagonism. If (*2R,6R*-HNK is potentiating AMPAR signaling (i.e., a facilitation of glutamatergic transmission), then this effect could still add to the "glutamatergic burst" that (*R,S*)-ketamine may principally evoke through NMDAR antagonism, where this burst may involve inhibition of GABAergic interneurons bearing NMDA receptors, leading to disinhibition of glutamatergic neurons and increased release of synaptic glutamate (Duman et al., 2012). Additionally, both AMPAR- and NMDAR-based mechanisms will necessarily involve each other due to positive feedback in recurrent mostly-glutamatergic neural networks such as those in the cortex and the hippocampal CA3 region. Further, as noted above, even if the principal, initial mechanism of action of (*R,S*)-ketamine is NMDAR antagonism, a wide range of neurotransmitter systems, molecular pathways, and brain regions may be modulated by (*R,S*)-ketamine due to downstream crosstalk.

We suggest here that the "glutamatergic burst" which follows acute administration of (*R,S*)-ketamine is accompanied by elevated synaptic norepinephrine (Kubota, Anzawa, et al., 1999; Kubota, Hirota, et al., 1999), where the initial release of these two neurotransmitters is interrelated and can be accompanied by the dissociative effects of this drug. In the minutes to hours that follow, both in rodents and humans, compensatory mechanisms are induced to suppress this excessive neural activity (including suppression of noradrenergic and glutamatergic signaling), which decreases the E:I ratio in a number of mood-related circuits and thereby has an antidepressant-like effect that is maintained through many of the molecular and synaptic mechanisms noted above. We draw an analogy here between subanesthetic (*R,S*)-ketamine and electroconvulsive therapy (ECT): both may have an initially "excitatory" mechanism that is followed by suppression of neural activity in diverse circuits (Kheirabadi, Vafaie, Kheirabadi, Mirlouhi, & Hajiannasab, 2019; Kohtala et al., 2018; Mickey et al., 2018; Tadler & Mickey, 2018). Finally, if glutamatergic and noradrenergic signaling are indeed intertwined in the therapeutic effects of (*R,S*)-ketamine, then norepinephrine-lowering drugs may also have rapidly acting antidepressant properties, which has already been demonstrated for the drug guanfacine in rodents (Mineur et al., 2015, 2018).

It is difficult to speculate how the multiple brain regions thus far implicated in the mechanism of action of (*R,S*)-ketamine interact, but mPFC, habenula and hippocampus all have been shown to be of import using causal experimental methodologies. Given that multi-region interactions are frequently observed in many brain phenomena using fMRI and other whole-brain imaging techniques, it is likely that these and possibly other regions interact to enable the effects of (*R,S*)-ketamine. It may actually specifically be the re-balancing of the relative activities of these regions that is the key to (*R,S*)-ketamine function. That said, the sufficiency of manipulation of each region to control ketamine effects suggests that these individual nodes of this potential network are each able to induce relatively full responses

across the network. This is a case where *in vivo* circuit activity measurement - and not just causal experimentation - may shed the most light.

CONSISTENCY OF REPORTED ANTIDEPRESSANT-LIKE BEHAVIORAL EFFECTS

The second half of this paper addresses another intriguing aspect of the (*R,S*)-ketamine literature: the consistent positive reporting of antidepressant-like responses to (*R,S*)-ketamine across dose, mouse or rat species and strain, type of test used, presence or type of stressor, and even the sex of the experimenter. While the similarity of reporting is striking, we specifically analyze the publication record and reporting patterns and ask whether stress does or does not play into various reports and whether it should or should not be considered a major axis of study in the rodent field.

The relatively remarkable reporting of similar antidepressant-like effects across very different tests (tail suspension, sucrose preference, as well as FST) and a wide range of mouse and rat strains (Autry et al., 2011; Cunha et al., 2015; Mishra, Kumar, Behar, & Patel, 2018; Neis et al., 2016) suggests the utility of rodent research for understanding this drug that also appears to help many patients with a variety of clinical depression subtypes. But on the other hand, this finding on animal strain is somewhat surprising, given that the behavior of different strains of mice and rats varies greatly upon exposure to monoaminergic antidepressants (Dulawa, Holick, Gundersen, & Hen, 2004) and in fear-related behavior (Fitzgerald et al., 2014; Hefner et al., 2008), as well as in other tests commonly used in behavioral neuroscience (Fitzpatrick et al., 2013; Gileta et al., 2018; Mozhui et al., 2010). Additionally, while in human populations, (*R,S*)-ketamine is given to individuals with depression, many rodent studies report that (*R,S*)-ketamine has antidepressant-like effects in unstressed animals.

To further investigate this topic, on January 16, 2019 we systematically searched PubMed with the following terms: ketamine AND ("forced swim" OR "forced swimming" OR antidepressant-like OR antidepressant-related OR depression-like OR depression-related). This search of 328 papers yielded 52 that met our criteria to be included in Table 1. This table summarizes all studies from this search that used a single intraperitoneal injection of racemic (*R,S*)-ketamine and measured immobility in the FST 24 hours or more later. Importantly, we chose not to focus on the acute (i.e., minutes to several hours) effects of (*R,S*)-ketamine in this test, which we suggest may be associated with psychotomimetic or dissociative effects of this drug rather than its sustained antidepressant-like qualities that emerge later. Inspection of Table 1 suggests that across a wide range of variables—species and strain, sex, dose, time delay between injection and start of FST, type (or absence) of stressor, and possibly even the sex of the experimenter—(*R,S*)-ketamine displays similar effects in the FST, namely an antidepressant-like decrease in immobility. There are some exceptions to this such as our own recent study (Fitzgerald, Yen, & Watson, 2019), which indicates that stress strongly modulates the effect of (*R,S*)-ketamine.

While the data in Table 1 follow the general trend of demonstrating (*R,S*)-ketamine induced reduction of FST immobility, closer inspection of the table may reveal some more subtle

differences with respect to these variables. For example, C57BL/6 and BALB/cJ mice tend to show stronger antidepressant-like responses to (*R,S*)-ketamine, whereas CD-1 mice show more variable responses. Within several studies, the unstressed groups of rodents did not respond significantly to a certain dose, whereas the stressed animals responded to that same dose, suggesting some degree of stress-sensitivity (Ma et al., 2013; Shepard et al., 2018; Xie et al., 2017). However, a fairly similar proportion of studies that used stress (19/22 = 0.86) versus no stress (28/40 = 0.70) reported a significant decrease in immobility, suggesting a lack of prominent stress sensitivity to (*R,S*)-ketamine in the FST. Mice and rats showed a significant decrease in immobility in a similar proportion of studies (mice: 26/36 = 0.72, rats: 22/30 = 0.73), even though brain-body scaling factors (i.e., larger animals require lower mg/kg ratio dose to receive same effect) would suggest that rats should receive a lower mg/kg dose than mice. For comparison, a dose of 0.5 mg/kg (i.v.) is often used as an efficacious antidepressant dose in humans. The mice and rat studies summarized in Table 1 suggest (*R,S*)-ketamine has antidepressant-like effects in rodents over a wide range of doses (1-30 mg/kg), and the field has apparently settled on 10 mg/kg as the most frequently used dose.

Table 1 includes only a limited number of studies in female animals, so studying sex differences (of the animals used) is an important future direction. These data may nonetheless suggest that female rodents are somewhat more sensitive to (*R,S*)-ketamine than males, considering that all five studies that used groups that were purely female found a significant antidepressant-like effect. These studies include one with both stressed and unstressed experiments whose authors suggest this may be due to hormonal, serotonergic, or glutamatergic sex differences in circuits such as prefrontal cortex and hippocampus (Franceschelli, Sens, Herchick, Thelen, & Pitychoutis, 2015). These authors also suggest that female rodents are more sensitive to earlier (up to 24 hours) effects of this drug, but then these effects wear off sooner than in males (Franceschelli et al., 2015). Although human females are more frequently afflicted with major depression than males, it has been suggested that (*R,S*)-ketamine is similarly effective in both sexes (Williams & Trainor, 2018). Table 1 also illustrates the sustained nature of (*R,S*)-ketamine's antidepressant-like effects: many studies report a sustained and significant decrease in depression-like behavior after 7 days and 14 days, for example. One study even shows a significant decrease in immobility after 28 days (Y. Wang et al., 2018).

KETAMINE ACTION IN UNSTRESSED RODENTS

Figure 1 represents an effort to "meta-analyze" the data from the field gathered in the literature search described above. It shows a funnel plot, summarizing effect size distribution in a subset of the studies listed in Table 1 - specifically the 13 studies for which we were able to obtain immobility data in *unstressed* mice (various strains) at the 24 hour post-injection timepoint, in a moderate subanesthetic dose range between 5-20 mg/kg (for which the highest dose that met our criteria was 17 mg/kg). We chose to plot only unstressed mice in Figure 1 for several reasons: 1) "stressed" animals in the various studies from Table 1 were given a very wide range of stress types across studies, so combining those data in one plot may be confusing; 2) unstressed animals are widely reported to exhibit antidepressant-like responses to (*R,S*)-ketamine in these studies, which may seem surprising since these

animals were presumably not in a depression-like state and this should be investigated further; 3) we sought to compare these various unstressed studies with our own unstressed mouse strain comparison data (Figure 2).

In Figure 1 we also included data from two of our own cohorts that used 10 mg/kg (*R,S*)-ketamine in male C57BL/6J mice (see Legend), obtained from our previous publication (Fitzgerald, Yen, & Watson, 2019). The "meta analysis" data shown in Figure 1 have more points on the right side of the graph, which means that more published studies show a decrease in immobility in the FST under these conditions. One of our two cohorts falls closer to the center of the distribution, with the other farther to the left, where far leftward points represent a paradoxical *increase* in immobility. Quantitatively, the distribution of the standard difference in means has a skewness (measured by the adjusted Fisher-Pearson standardized moment coefficient) of −0.9085, which indicates that it is moderately negatively skewed and that the majority of points fall to the right of the expected value. This may be due to the presence of an underlying non-gaussian, and possibly multi-modal, distribution or a variety of other factors. Finding more points to the right in Figure 1 is consistent with findings from the larger number of studies we summarized in Table 1, which also reported a high proportion of decreases in immobility in the FST after a single injection of (*R,S*)-ketamine. It remains unclear where the spread of data comes from and whether the increased numbers of points toward the right of the graph compared to the left is worth specific consideration. One possibility is that "unstressed" conditions vary in different labs' experimental procedures or housing (lighting, staff handling, enrichment, etc.), and that such differences could drive variability with respect to the mean observed in Figure 1. Also, opposing effects of (*R,S*)-ketamine based on the stress state of mice would be represented as both leftward and rightward points in the funnel plot. This may be expected given that a recent study in human subjects found opposing effects of (*R,S*)-ketamine based on whether the individuals had major depression or not, since depression can be induced by psychological stress (Nugent et al., 2018). If there is an under-representation of negative (i.e., no change in immobility) or contrary (i.e., paradoxical increase in immobility) results in the published literature, it may be because it is more difficult to publish these types of results at this stage since the decrease in immobility result is well-established.

To further investigate how (*R,S*)-ketamine and stress effects may vary across individuals, we compared FST effects in different mouse strains. Figure 2 shows strain comparison data from our lab, previously unpublished except for the C57BL/6J data that were contained in Fitzgerald et al. (2019) and for that mouse strain represent the first of our two experiments described in the previous paragraph (Figure 1, our leftmost point), with the addition of C57BL/6J mice that received a 30 mg/kg dose (Fitzgerald et al., 2019). The data in Figure 2 depict FST immobility in five strains of *unstressed* mice, averaged over the last four minutes of the six minute test (Fig. 2A,B), and also binned by minute (Fig. 2C,D) for these two post-injection tests (see Table S1 for a statistical summary). Since different strains of mice are known to exhibit widely differing amounts of immobility in the FST, it is not surprising that at both the 24 hour post-injection timepoint (Fig. 2A) and when the same animals were tested again 7 days post-injection (Fig. 2B), there is a main effect of strain in the two-way (strain x drug) ANOVA (24 hours: $F(4,105) = 21.06$, $p < 0.01$; 7 days: $F(4,105) = 21.9$, $p < 0.01$) (see Table S1 for a summary of which strains differed significantly from one another).

However, at the 24 hour timepoint there is also a main effect of drug ($F(2,105) = 3.3$, $p < 0.05$), with 30 mg/kg (*R,S*)-ketamine on average showing a trend toward an *increase* in immobility relative to vehicle (Tukey's multiple comparisons test; $p = 0.089$) and the 10 mg/kg ($p = 0.059$) groups, where the latter two groups tend to be similar to one another across strains. When we parsed the data into one minute bins for the 24 hour post-ketamine test (Fig. 2C) and 7 days post-ketamine test (Fig. 2D), repeated measures ANOVA did not reveal a significant effect of drug or a drug-by-time interaction (each $p > 0.05$) for any mouse strain, but there was a significant effect of time for all strains (each $p < 0.0001$). The results in Figure 2 are perhaps paradoxical and suggest (*R,S*)-ketamine is not antidepressant-like in the FST across a range of mouse strains that have not been subjected to marked stress, extending findings that we previously reported for C57BL/6J mice (Fitzgerald et al., 2019). It is also interesting to note that while there was no strain-by-drug interaction in the two-way ANOVA, the C57BL/6J strain seems to differ from the other strains in that both the 10 and 30 mg/kg doses increase immobility 24 hours post-injection (Fitzgerald et al., 2019).

Another poorly understood factor at this time may be how sex of the (human) experimenter may interact with sex of the animals being tested in the FST. This phenomenon has already been repeatedly demonstrated in psychological studies investigating behavior in human subjects (Chapman, Benedict, & Schiöth, 2018), a concept that may extend to rodent experiments (Georgiou et al., 2018). Since (*R,S*)-ketamine treatment has different effects on male versus female mice and rats (Carrier & Kabbaj, 2013; Franceschelli et al., 2015; Thelen, Sens, Mauch, Pandit, & Pitychoutis, 2016), perhaps experimenter sex could interact with these pharmacological effects. The potential effects of sex of the experimenter are, however, not well characterized at this time and future studies should address whether it has significant effects on rodent behavior.

Animal age is an additional factor to consider in rodent antidepressant studies, since these drugs can be less effective in elderly human populations (Patel, Abdool, Rajji, & Mulsant, 2017). Another variable, or set of variables, in rodent drug studies comprises the setting or context of the injection itself. For example, is the room in which the injection takes place the same as the testing room? After the injection and before the test, are the animals placed in a cage with other vehicle only animals, or instead in a cage with only animals that received drug? These factors could contribute to the variability that we report here in the ketamine literature.

In summary, there is some degree of consistency in the reported antidepressant-like effects of (*R,S*)-ketamine across a range of differing variables, including in the rodent FST (Table 1) but we may need to pay specific attention to whether animals are stressed or unstressed. Our brief "meta analysis" of a subset of these data (Figure 1) suggests that, in animals not subjected to marked psychosocial stress, negative results or paradoxical increases in immobility have not been emphasized in the literature. Our own mouse strain comparison data (Figure 2) suggest that a number of unstressed strains show mild increases in immobility in the 24-hour post-injection FST, after a single injection of 30 mg/kg (*R,S*)-ketamine.

SUMMARY AND CONCLUSIONS

Here we have reviewed two intriguing topics in the (*R,S*)-ketamine literature: first, the putative antidepressant-like mechanism of action of this drug, and second, its widely reported similar therapeutic effects across a range of factors and testing parameters. We suggest that (*R,S*)-ketamine's antidepressant effects (in humans and rodents) require an initial glutamatergic (and possibly noradrenergic) "excitatory burst", whether mediated principally by NMDAR antagonism or partly by AMPAR potentiation. This burst is followed by compensatory suppression of neural activity that decreases the E:I ratio to achieve its antidepressant-related effects. This effect may be spread across multiple brain regions simultaneously and each may be crucial. In the second portion of the paper, we suggest that there has been an under-emphasis of the potential stress-sensitivity of (*R,S*)-ketamine in rodent depression-related tests, including the FST. Gaining a greater understanding of the experimental conditions under which this drug exhibits antidepressant-like properties (or depression-like ones) has translational relevance for modeling major depression in human subjects (Fitzgerald et al., 2019), where opposing effects of (*R,S*)-ketamine have recently been reported based on whether the individuals were suffering from major depression or not (Nugent et al., 2018). Many studies of this drug have been conducted only in unstressed animals, so including animals that have been exposed to chronic psychosocial stress, such as CSDS, to induce a depression-like state may be critical for understanding the therapeutic properties of (*R,S*)-ketamine (Bale et al., 2019; Hashimoto & Shirayama, 2018).

We suggest that researchers view the variability and current lack of clarity on many points in the field as potentially helpful in the long term. If we can understand the source of variance in these data we can better study the complex biology we are attempting to understand. The variance is there, most likely, due to a combination of "noise" but also possibly some systematic differences in factors such as animal housing, drug administration, animal handling, recording methodologies, analytical techniques, animal strain, sex, dosing and test timing, circadian differences and others. Human psychiatric conditions are also expressed in individuals within a context that includes huge variability in background conditions. If, as a field, we can understand how the variance in our laboratories influences the effects of (*R,S*)-ketamine and other drugs, we stand a better chance of understanding variability among individuals in patient populations. Considering variability as not a barrier but as a tool can lead to more effective and often personalized interventions on our way to better understanding neurobiology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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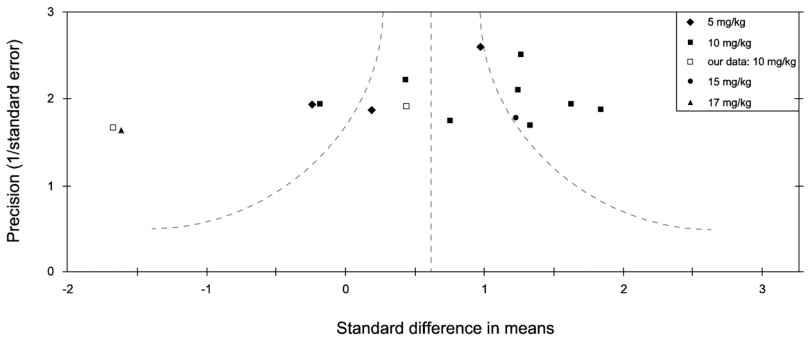

Figure 1.

Funnel plot "meta analysis" of a subset of 13 unstressed forced swim studies from Table 1. The abscissa is effect size which quantifies the difference in immobility between the (*R,S*)-ketamine and vehicle groups in a given study, whereas the ordinate is the "precision" also known as the inverse standard error, a measure of sample size. The curved lines represent the 95% confidence interval. Cohen's *d* was used to determine effect sizes. Positive effect sizes represent decreases in immobility induced by (*R,S*)-ketamine, whereas negative values indicate increases in immobility on this drug. As noted in the legend, our own data (Fitzgerald et al. 2019) are depicted as open squares in this graph. This figure only includes studies of mice (various strains) at the 24 hour post-injection timepoint, in a moderate subanesthetic dose range between 5-20 mg/kg (see legend).

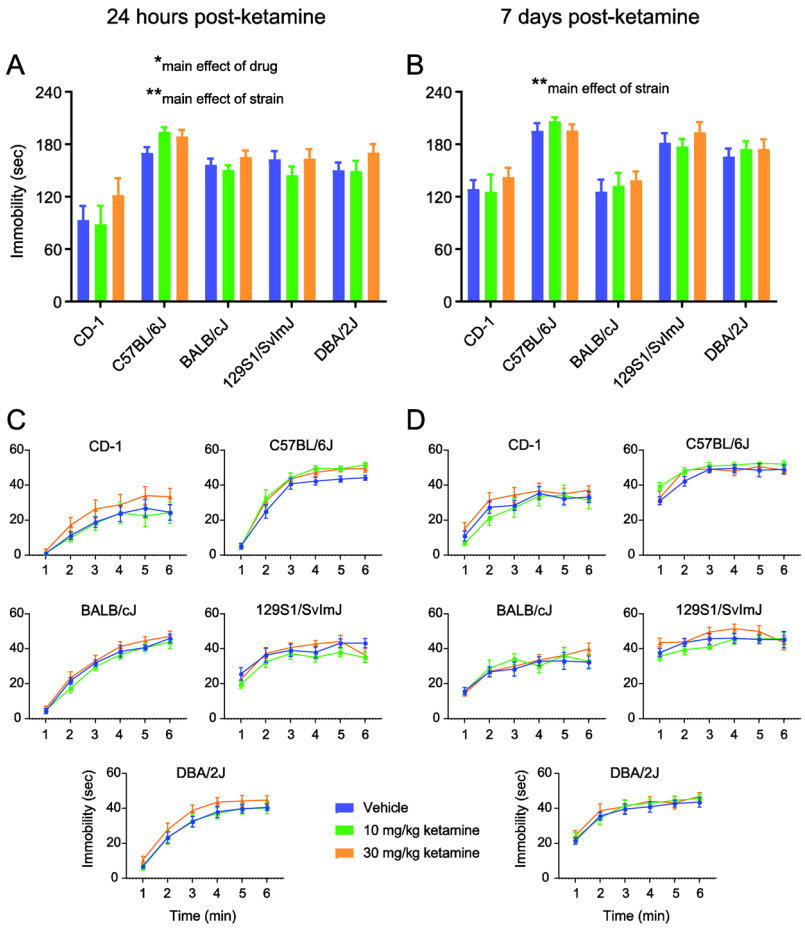

Figure 2.

Strain comparison data reveal increased forced swim immobility after (*R,S*)-ketamine in unstressed mice. Immobility in this test: **A**, 24 hours after a single injection of (*R,S*)-ketamine, averaged across the last four minutes of the six minute test; **B**, the same animals were tested again seven days after this injection, also averaged across the last four minutes; **C**, 24 hour post-injection data binned in one minute intervals; **D**, 7 day post-injection data binned in one minute intervals. Strain-by-drug two-way ANOVAs reveal a main effect of strain at both timepoints in **A** and **B**, and a main effect of drug only at the 24 hour point. Vehicle solution is 0.9% saline. Bars and points in **A**-**D** depict mean ± standard error of mean (SEM). Significance indicators for the two-way ANOVAs (centered over each graph) are marked by $*p < 0.05$, $**p < 0.01$. See Fitzgerald et al. (2019) for detailed methodology.

Table 1.

Summary of literature on sustained effects of (*R,S*)-ketamine in the rodent forced swim test (FST). Criteria for studies to be included in this table. 1) wild type mouse or rat, 2) single intraperitoneal injection of 1-30 mg/kg (*R,S*)-ketamine, 3) FST carried out 24 hours or more post-injection. "Sex" refers to sex of the animals used. "Change in Immobility" column indicates whether (*R,S*)-ketamine decreased or increased this measure relative to vehicle-injected animals subjected to the same stress condition (i.e., stressed or unstressed); "Stat Sig" column indicates whether the difference between (*R,S*)-ketamine and vehicle immobility was statistically significant, for $p < 0.05$. Other abbreviations are defined within the table when they first appear. All experiments that used chronic stress are marked in red. Experiments that showed a statistically significant decrease in immobility are marked in dark green, whereas those with a decrease that was not significant are marked in light green. Experiments that exhibited a statistically significant increase in immobility are colored dark blue, whereas those with an increase (or "no change") that was not significant are light blue.

Publication	Species	Strain	Sex	Dose(s) (mg/kg)	Time Delay	Stressor/Unstressed	Δ Immobility	Stat Sig
(Autry et al., 2011)	Mouse	C57BL/6	M	3	24 hr	Unstressed	Decrease	Yes
		C57BL/6	M	3	7 days	Unstressed	Decrease	Yes
(Liu et al., 2012)	Mouse	C57BL/6	M	10	24 hr	Unstressed	Decrease	Yes
(Ma et al., 2013)	Mouse	C57BL/6J	M	10	48 hr	Chronic Mild Stress (CMS)	Decrease	Yes
		C57BL/6J	M	10	48 hr	Unstressed (control)	Decrease	No
(Pozzi et al., 2014)	Mouse	C57BL/6N	M	3	24 hr	Unstressed	Decrease	Yes
		C57BL/6N	M	3	7 days	Unstressed	Decrease	No
(Gideons et al., 2014)	Mouse	C57BL/6	M	3	24 hr	Unstressed	Decrease	Yes
(Nosyreva et al., 2014)	Mouse	C57BL/6	M	3	24 hr	Unstressed	Decrease	Yes
(Franceschelli et al., 2015)	Mouse	C57BL/6J	M	3	24 hr	Unstressed	Decrease	No
		C57BL/6J	M	5	24 hr	Unstressed	Decrease	No
		C57BL/6J	M	10	24 hr	Unstressed	Decrease	Yes
		C57BL/6J	F	3	24 hr	Unstressed	Decrease	No
		C57BL/6J	F	5	24 hr	Unstressed	Decrease	Yes
		C57BL/6J	F	10	24 hr	Unstressed	Decrease	Yes
		C57BL/6J	M	10	24 hr	CMS	Decrease	Yes
		C57BL/6J	M	10	7 days	CMS	Decrease	Yes
		C57BL/6J	F	10	24 hr	CMS	Decrease	Yes
		C57BL/6J	F	10	7 days	CMS	Decrease	No
		C57BL/6J	F	10	5 days	CMS	Decrease	Yes
(Dong et al., 2017)	Mouse	C57BL/6	M	10	48 hr	Social Defeat Stress	Decrease	Yes
(Zhang et al., 2018)	Mouse	C57BL/6	M	10	24 hr	Chronic Unpredictable Stress (CUS)	Decrease	Yes
		C57BL/6	M	10	3 days	CUS	Decrease	Yes
		C57BL/6	M	10	5 days	CUS	Decrease	Yes
		C57BL/6	M	10	7 days	CUS	Decrease	Yes

Publication	Species	Strain	Sex	Dose(s) (mg/kg)	Time Delay	Stressor/Unstressed	Δ Immobility	Stat Sig
(Fukumoto et al., 2018)	Mouse	C57BL/6J	M	30	24 hr	Unstressed	Decrease	Yes
(Wang et al., 2018a)	Mouse	C57BL/6	M	30	28 days	Unstressed	Decrease	Yes
		C57BL/6	M	30	28 days	Unpredictable Chronic Mild Stress (UCMS)	Decrease	No
(Shen et al., 2018)	Mouse	C57BL/6J	M	10	5 days	Chronic Social Defeat Stress (CSDS)	Decrease	Yes
(Huang et al., 2019)	Mouse	C57BL/6	M	10	25 hr	Lipopolysaccharide (Induced Inflammation)	Decrease	Yes
(Hare et al., 2019)	Mouse	C57BL/6J	M & F	10	24 hr	Unstressed	Decrease	No
(Fitzgerald et al., 2019)	Mouse	C57BL/6J	M	10	24 hr	Unstressed	Increase	Yes
		C57BL/6J	M	30	24 hr	Unstressed	Increase	Yes
		C57BL/6J	M	10	7 days	Unstressed	Increase	No
		C57BL/6J	M	30	7 days	Unstressed	Decrease	No
		C57BL/6J	M	10	24 hr	UCMS	Increase	No
		C57BL/6J	M	30	24 hr	UCMS	Decrease	No
		C57BL/6J	M	10	7 days	UCMS	Increase	No
		C57BL/6J	M	30	7 days	UCMS	Decrease	No
(Wang et al., 2018b)	Mouse	ICR	M	10	24 hr	Unstressed	Decrease	Yes
(Botanas et al., 2017)	Mouse	ICR	M	5	24 hr	Unstressed	Decrease	Yes
		ICR		10	24 hr	Unstressed	Decrease	Yes
(Lin et al., 2016)	Mouse	ICR	M	3	7 days	Unstressed	Decrease	No
		ICR	M	10	7 days	Unstressed	Decrease	Yes
		ICR	M	15	7 days	Unstressed	Decrease	Yes
(Pham et al., 2017)	Mouse	BALB/cJ	M	10	24 hr	Unstressed	Decrease	Yes
(Wu et al., 2017)	Mouse	BALB/cJ	M and F	30	24 hr	Offspring of Female Mice with Post Partum Depression (PPD)	Decrease	Yes
(Pham et al., 2018)	Mouse	BALB/cJ	M	10	24 hr	Unstressed	Decrease	Yes
(Xia et al., 2016)	Mouse	BALB/cJ	F	30	24 hr	Prepregnancy Stress and Parturition (SP)	Decrease	Yes
(Tao et al., 2014)	Mouse	Kunming	M	30	24 hr	Unstressed	Decrease	Yes
(Tang et al., 2015)	Mouse	Kunming	M	30	24 hr	CMS	Decrease	Yes
(Popik et al., 2017)	Mouse	CD-1	M	5	24 hr	Unstressed	Increase	No
		CD-1	M	10	24 hr	Unstressed	Increase	No
		CD-1	M	15	24 hr	Unstressed	Decrease	No
		CD-1	M	25	24 hr	Unstressed	Increase	No
(Clarke et al., 2017)	Mouse	CD-1	M	10	2 days	Unstressed	Decrease	No
		CD-1	M	10	5 days	Unstressed	Decrease	No
		CD-1	M	10	8 days	Unstressed	Decrease	No
(Bechtholt-Gompf et al., 2011)	Mouse	CD-1	M	2.5	7 days	Unstressed	Decrease	No

Publication	Species	Strain	Sex	Dose(s) (mg/kg)	Time Delay	Stressor/Unstressed	Δ Immobility	Stat Sig
		CD-1	M	12.5	7 days	Unstressed	Decrease	No
(Zanos et al., 2015)	Mouse	CD-1	M	10	24 hr	Unstressed	Decrease	Yes
(Zanos et al., 2016)	Mouse	CD-1	M	1	24 hr	Unstressed	Decrease	No
		CD-1	M	3	24 hr	Unstressed	Decrease	No
		CD-1	M	10	24 hr	Unstressed	Decrease	Yes
		CD-1	M	30	24 hr	Unstressed	Decrease	No
		CD-1	F	1	24 hr	Unstressed	Decrease	No
		CD-1	F	3	24 hr	Unstressed	Decrease	Yes
		CD-1	F	10	24 hr	Unstressed	Decrease	Yes
(Yuen et al., 2017)	Mouse	NIH- Swiss	M	17	24 hr	Unstressed	Increase	No
(Popik et al., 2008)	Mouse	Albino Swiss	M	1.25	14 days	Unstressed	Decrease	No
		Albino Swiss	M	2.5	14 days	Unstressed	Decrease	No
		Albino Swiss	M	5	14 days	Unstressed	Decrease	No
		Albino Swiss	M	10	14 days	Unstressed	Decrease	No
(Maeng et al., 2008)	Mouse	Not Specified	M	2.5	14 days	Unstressed	Decrease	Yes
(Wang et al., 2011)	Rat	Sprague-Dawley	M	10	24 hr	Spared Nerve Injury (SNI)	Decrease	Yes
(Gigliucci et al., 2013)	Rat	Sprague-Dawley	M	25	24 hr	Unstressed	Decrease	Yes
		Sprague-Dawley	M	25	24 hr	Restraint Stress	Increase	No
(Koike & Chaki, 2014)	Rat	Sprague-Dawley	M	10	24 hr	Unstressed	Decrease	Yes
(Lepack et al., 2015)	Rat	Sprague-Dawley	M	10	24 hr	Unstressed	Decrease	Yes
(Dwyer et al., 2015)	Rat	Sprague-Dawley	M	10	24 hr	Unstressed	Decrease	Yes
(Jett et al., 2015)	Rat	Sprague-Dawley	M	10	7 days	Unstressed	Decrease	Yes
(Sun et al., 2016)	Rat	Sprague-Dawley	M	10	72 hr	UCMS	Decrease	Yes
(Sarkar & Kabbaj, 2016)	Rat	Sprague-Dawley	M	2.5	3 days	Isolation Stress (IS)	Decrease	No
		Sprague-Dawley	M	5	3 days	IS	Decrease	Yes
		Sprague-Dawley	M	2.5	3 days	Unstressed (Pair Housed)	Decrease	No
		Sprague-Dawley	M	5	3 days	Unstressed	Decrease	Yes
		Sprague-Dawley	F	2.5	3 days	IS	Decrease	No
		Sprague-Dawley	F	5	3 days	IS	Decrease	Yes
		Sprague-Dawley	F	2.5	3 days	Unstressed	Decrease	Yes
		Sprague-Dawley	F	5	3 days	Unstressed	Decrease	Yes
(Chowdhury et al., 2017)	Rat	Sprague-Dawley	M	3	24 hr	Unstressed	Decrease	No
		Sprague-Dawley	M	30	24 hr	Unstressed	Decrease	Yes
(Podkowa et al., 2016)	Rat	Sprague-Dawley	M	3	24 hr	Unstressed	Decrease	No
		Sprague-Dawley	M	10	24 hr	Unstressed	Decrease	Yes
		Sprague-Dawley	M	30	24 hr	Unstressed	Decrease	No

Publication	Species	Strain	Sex	Dose(s) (mg/kg)	Time Delay	Stressor/Unstressed	Δ Immobility	Stat Sig
(Zhang et al., 2016)	Rat	Sprague-Dawley	M	20	24 hr	CFA	Decrease	Yes
(Donegan & Lodge, 2017)	Rat	Sprague Dawley	M	10	7 days	Unstressed	Decrease	Yes
(Xie et al., 2017)	Rat	Sprague-Dawley	M	20	48 hr	Unstressed	No change	No
		Sprague-Dawley	M	20	48 hr	SNI	Decrease	Yes
(Jiang et al., 2017)	Rat	Sprague-Dawley	M	10	24 hr	CUS	Decrease	No
		Sprague-Dawley	M	10	7 days	CUS	Decrease	Yes
(Hou et al., 2018)	Rat	Sprague-Dawley	M	5	23.5 hr	SPS&S (Single Prolonged Shock and Electric Foot Shock)	Decrease	No
		Sprague-Dawley	M	10	23.5 hr	SPS&S	Decrease	Yes
		Sprague-Dawley	M	15	23.5 hr	SPS&S	Decrease	Yes
		Sprague-Dawley	M	20	23.5 hr	SPS&S	Decrease	No
(Shepard et al., 2018)	Rat	Sprague-Dawley	M	20	24 hr	Unstressed (Postnatal (P)42-P50)	Decrease	No
		Sprague-Dawley	M	20	24 hr	Maternal Deprivation (MD)	Decrease	Yes
		Sprague-Dawley	M	20	24 hr	Unstressed (P21-P28)	Increase	No
		Sprague-Dawley	M	20	24 hr	MD	Increase	Yes
(Pałucha-Poniewiera et al., 2019)	Rat	Sprague-Dawley	M	3	24 hr	Unstressed	Decrease	No
(Maciel et al., 2018)	Rat	Wistar	M	15	8 days	CMS	Decrease	Yes
		Wistar	M	15	8 days	Maternal Deprivation	Decrease	Yes
(Réus et al., 2014)	Rat	Wistar	M	15	23.5 hr	Unstressed	Decrease	Yes
(Chindo et al., 2012)	Rat	Wistar	M	30	24 hr	Unstressed	No change	No
(Liu et al., 2013)	Rat	Not Specified	M	10	24 hr	Unstressed	Decrease	Yes
		Not Specified	M	10	7 days	Unstressed	Decrease	Yes
		Not Specified	M	10	14 days	Unstressed	Increase	No
		Not Specified	M	1	24 hr	Unstressed	Increase	No