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Integrative analysis of sex differences in the rapid antidepressant effects of ketamine in preclinical models for individualized clinical outcomes

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Abstract

In major depressive disorder, women exhibit higher lifetime prevalence and different antidepressant response rates than men, which illustrates the importance of examining individual differences in the pathophysiology of depression and therapeutic response. In recent years, the consideration of sex in related preclinical research has thus gained interest—particularly in light of novel evidence for rapid-acting antidepressants. Notably, the literature recently revealed a higher sensitivity of females to the antidepressant effects of the N-methyl-D-aspartate receptor antagonist ketamine, in both baseline and preclinical conditions. Combined with its fast-acting and relatively sustained properties, this evidence highlights ketamine as a particularly interesting therapeutic alternative for this sensitive population, and supports the value in considering sex as a critical factor for improved individualized therapeutic strategies.

Introduction

As the global burden of depression continues its rise as the leading cause of disability worldwide [1], the urgent need for more effective treatments is dire. A new wave of excitement, however, has been generated by recent discovery that the N-methyl d-aspartate receptor (NMDAR) antagonist, ketamine, rapidly relieves depressive symptoms and suicidal ideation, particularly amongst those with treatment-resistant depression [2]. Since then, a significant amount of effort has gone into understanding the underlying mechanisms by both preclinical and clinical researchers alike, with the hope of developing novel rapid-acting treatments effective in a broader range of patients [2].

In the era of personalized medicine, a greater focus on identifying biomarkers or predictors of rapid antidepressant response to ketamine has emerged [3], but despite the well-established female preponderance in depressive disorders [1] and sex differences in antidepressant efficacy [4], sex has yet to be investigated as a potential moderating variable. Much like genetic and environmental factors, sex is a naturally-occurring disease and

treatment modifier [4,5], such that factors either protecting against disease or enhancing treatment response in one sex may indicate prevention or treatment strategies in the other sex [6]. This review will highlight recent preclinical evidence demonstrating sex differences in the rapid antidepressant-like response to acute low-dose ketamine, and discuss how a variety of factors including stress, hormonal state, context, and the presence of baseline sex differences, significantly contribute to behavioral or molecular readout following ketamine treatment. This new evidence encourages that sex be seen as an important factor influencing the individual's response to antidepressant treatment rather than a phenotypic dichotomy.

Sex differences in effects of ketamine under baseline conditions

Sex differences in the rapid antidepressant-like effects of ketamine were first reported only a few years ago by work from our lab revealing the heightened sensitivity of female rats to these effects compared to males. These conclusions were demonstrated by the lower dose (2.5 mg/kg) required to rapidly reduce immobility in the forced swim test (FST) and latency to feed in the novelty-suppressed feeding test (NSFT) in naturally-cycling female rats compared to their male counterparts [7]. This finding, using FST measures as a behavioral readout, has since been replicated by our lab in rats [8], and corroborated in mice [9,10].

While studies conducted in mice to date have focused solely on intact females, our work in rats demonstrated that this heightened female sensitivity required cyclic fluctuations of both gonadal estradiol and progesterone in female rats [7,11]. This finding has significance, as we recently reported that cyclic progesterone administration to males was sufficient to significantly enhance their sucrose preference following the same acute low-dose of ketamine to which they have repeatedly been non-responsive [7,8,11]—providing an important example of how one facilitator of treatment response in females may enhance response in males. Conversely, testosterone does not influence male sensitivity to low-dose ketamine in rats in measures of hedonic behavior, but blocks hedonic response of naturally-cycling female rats to low-dose ketamine, likely via disruption of normal cyclic hormonal fluctuations [11].

The higher sensitivity of females to low-dose ketamine interestingly does not simply translate to greater activation of known molecular mediators mammalian target of rapamycin (mTOR) in the medial prefrontal cortex (mPFC), and eukaryotic elongation factor 2 in the hippocampus [7], suggesting that behavioral sex differences in response to ketamine extend beyond differential sensitivity at the molecular level, but rather involve distinct mechanisms in a dose-dependent manner.

Interestingly, daily injections of 10 mg/kg ketamine in mice for 21 days induce anti- or pro-depressant-like effects in males or females, respectively [12], which, while still potentially linked to the females' higher sensitivity to ketamine, highlights the importance of administration paradigm in preclinical studies and warrants further investigations into the interaction between the treatment regimen and ketamine's sex-dependent behavioral outcome.

Sex differences in antidepressant response under stress

Although substantial data on brain dysregulations in human depressed subjects are now available, preclinical studies have brought a detailed understanding of their underlying molecular mechanisms and response to therapeutic interventions. In this context, repeated exposures to stress triggers behavioral, molecular, and functional alterations resembling depressive symptoms observed in humans [13]. Notably, because several key mediators of the antidepressant response are sexually biased at baseline or following stress itself, it is critical to first investigate their regulation under chronic stress to better understand how males and females differ in response to antidepressants under pathological conditions.

Sex differences in response to chronic stress

Stress triggers a fast endocrine response characterized by the release of glucocorticoids, which, in the brain, directly control neurotransmission at multiple levels [14]. In addition to being highly dependent on the nature and intensity of the stressor, the consequences of this regulation are affected by both sex and hormonal fluctuations. In male rodents, prolonged exposure to stress or glucocorticoids impairs learning and memory, cognitive performances, and induces anxiety and depressive-like behaviors [13–15], whereas in females, the effects of chronic stress differ in a stress-specific manner [16,17]. For instance, chronic social defeat, restraint, isolation, or unpredictable stress, provoke learning and memory impairments as well as anxiety and depressive-like behaviors in male rats and mice [13], whereas chronic restraint stress induces memory deficits in male but not female rats [18,19]. Similarly, males generally appear more sensitive to the development of anhedonia following chronic mild or isolation stress [8,18,20], whereas females are more sensitive to induction of depressive-like symptoms by subchronic variable stress [21].

These behavioral sex differences are paralleled by coherent adaptations in neuronal activity underlined by dendritic and spine plasticity in key structures such as the hippocampus and mPFC. In these structures, chronic stress generally results in spine loss in both rats and mice [8,22], with concomitant down-regulation of synaptic proteins including synapsin I, PSD-95, and GluR1 [8,23,24], and reduced synaptic function and depressive-like behaviors, as observed in human depressed patients [25]. These effects are specific to males, however, as females show greater spine density in hippocampal CA1 [26,27] and infralimbic neurons projecting to the basolateral amygdala [28]. Notably, we recently found that chronic isolation stress down-regulates spine density and synaptic proteins in the mPFC of both male and female rats [8], indicating that sex differences in stress-induced spinogenesis in the mPFC are stress-specific. Furthermore, these sex differences are also species-specific as while observed in rats, both male and female mice exhibit hippocampal spine loss following chronic restraint stress [22], requiring further consideration when investigating sex-differences in the effects of ketamine on hippocampal spinogenesis.

Despite the lack of data in females, glutamatergic neurotransmission is critically involved in these events, as chronic stress-induced dendritic atrophy is prevented by NMDAR antagonists in males [29–31]. Importantly, stress-induced spine alterations can recover following interruption of the stress [32], in addition to illustrating the highly dynamic nature

of neuronal and synaptic plasticity, opens the way for novel therapeutic intervention, and warrants targeting the glutamatergic neurotransmission for antidepressant treatment.

Sex differences in antidepressant response following chronic stress

Since the original detailed description of ketamine's antidepressant effect in a preclinical model [23], the study of its underlying molecular mechanisms led to the development of a model whereby acute ketamine—through NMDAR inhibition on GABAergic interneurons—increases synaptic strength and subsequent activation of postsynaptic neuroplasticity-promoting pathways such as mTOR and brain-derived neurotrophic factor (BDNF), which, when coupled with extrasynaptic NMDAR inhibition, enhances synaptogenesis [2]. This model, however, originates from studies conducted solely in males. In light of the aforementioned sex differences in synaptic plasticity following chronic stress, and the higher sensitivity of stress-naive females to ketamine's antidepressant-like effects when compared to males, it is difficult to directly extrapolate these findings to both sexes.

Accordingly, while acute ketamine can reverse chronic stress-induced depressive-like behaviors in male rats and mice, its effects differ in females (Table 1). For instance, although 10 mg/kg ketamine reduces chronic mild stress-induced behavioral despair in the FST 24 hours after acute treatment in both male and female mice, this effect is more pronounced in females but lasts longer in males [9], suggesting that the mechanisms underlying maintenance of ketamine's lasting antidepressant-like effects in chronically stressed animals may be sexually biased. Alternatively, this sex discrepancy could result from the activation of sexually-distinct molecular mechanisms. Accordingly, we recently analyzed the dose-dependent effects of acute ketamine on spine density on apical dendrites of prelimbic pyramidal neurons of the socially-isolated male and female rat mPFC [8]. Similar to unstressed rats, a single dose of ketamine at 5 but not 2.5 mg/kg reversed isolation-induced behavioral despair in males, whereas both doses were effective in females [8]—findings coherent with the higher female sensitivity to ketamine's antidepressant-like effects [7,11]. Consistent with the current model for ketamine's effects on spinogenesis, ketamine reversed the stress-induced spine loss in the male mPFC only at the 5 mg/kg dose, associated with increases in synapsin I, PSD-95, and GluR1. In females, however, neither dose affected synaptic proteins expression or spine density within the mPFC, despite behavioral antidepressant-like effects [8]. Although pharmacokinetic differences or stress-specificity cannot be ruled out, these findings indicate that the molecular mechanisms underlying the reversal of stress-induced depressive-like behaviors differ between sexes.

We do possess several elements of interest for such alternative mechanisms, originating from the dependence of females' higher sensitivity to ketamine on estrogen, progesterone, and hippocampal BDNF [11]. First, hippocampal spinogenesis is markedly influenced by ovarian hormones, and as such varies across the estrous cycle [33]. Second, BDNF is a critical regulator of the antidepressant and spinogenesis-enhancing effects of ketamine in the mPFC [34]. Interestingly, although controversial, multiple studies report differential stress-induced hippocampal BDNF regulation between male and female rodents [35–37], which places hippocampal BDNF as a potential critical mediator of sex differences in sensitivity to both the induction of a depressive-like state, as well as response to ketamine.

While behavioral responses to low-dose ketamine discussed thus far are generally consistent between rats and mice, they can vary between strains. In mice, for example, while ketamine's antidepressant-like effects can be observed for up to 2 weeks [38], they dissipate by 7 days post-treatment in the male CD-1 strain [39]. Similarly, both male and female ICR mice exhibit an antidepressant-like response to acute 10 mg/kg ketamine, but not 5 mg/kg [40], a dose effective in C57BL6/J mice (Table 1). Moreover, ketamine dose-dependently reduces immobility in the FST in Wistar-Kyoto female rats but not in their relative control Wistar strain [41]. Although the non-response of Wistar rats could result from a flooring effect, these studies illustrate the need for an appropriate selection of strain based on study design. The Wistar-Kyoto strain, for instance, meets several criteria for modeling treatment-resistant depression [42], and given the interest in ketamine's efficacy in treatment-resistant patients [43], represents an interesting choice for deciphering ketamine's potential in this population.

Pharmacokinetic considerations and relevance to clinical populations

Once administered, ketamine is predominantly N-demethylated into norketamine (NK), which is further transformed into dehydronorketamine (DHNK) and six diastereomeric hydroxynorketamine (HNK) metabolites [44]. As a highly lipophilic, weak base, ketamine is rapidly distributed to the brain where it readily penetrates the blood-brain barrier via passive diffusion, along with its pharmacologically active metabolites—albeit to a slightly lesser extent as a result of greater hydrophilicity (SK Saland *et al.*, unpublished; [10,45]). As a prerequisite, ketamine's therapeutic efficacy in a given individual is limited by the availability of unbound drug (and/or metabolites) present at its relevant site(s) of action within the brain, making pharmacokinetic processes fundamental in understanding the heterogeneity in treatment response within and between sexes. Importantly, sex is a variable that influences nearly all pharmacokinetic processes—absorption, distribution, metabolism, and elimination—which may or may not ultimately influence treatment response [6].

Preclinical sex differences in ketamine pharmacokinetics

To this point, recent preclinical work has found that higher HNK, but not ketamine or NK, levels are observed in the brain of female mice following acute administration of 10 mg/kg ketamine (*i.p.*), in addition to *greater* female behavioral sensitivity to ketamine's antidepressant-like effects when compared to males [10]. Excitingly, further experiments showed that systemically administered HNK is able to cross the blood-brain barrier and elicit antidepressant-like activity in mice without inducing ketamine-like side effects. However, sex differences were not examined in this case, so it is unclear whether behavioral sensitivity to HNK differs between males and females. Here, it should be noted that females, but not males, exhibited an antidepressant-like response to 3 mg/kg ketamine, whereas both sexes responded to the 10 mg/kg dose used for pharmacokinetic analysis. Therefore, a direct association between greater HNK levels and enhanced female antidepressant-like response to ketamine cannot be conclusively inferred. Interestingly, new findings from our lab demonstrated greater ketamine and NK exposure in the plasma and brain of cycling female versus male rats following 2.5 mg/kg ketamine—a dose behaviorally effective in females but not males—with regional differences observed when the mPFC and hippocampus were

examined independently (SK Saland *et al.*, unpublished). These findings further suggest species differences in not only behavioral, but also pharmacokinetic parameters following low-dose ketamine exposure, and highlight the need for pharmacokinetic analysis across multiple behaviorally-relevant doses across species in both sexes.

Human sex differences in ketamine pharmacokinetics and relationship to clinical response

Surprisingly, very little evidence exists regarding sex differences in ketamine pharmacokinetics in humans, primarily owing to a lack of studies investigating such effects. However, Zarate and colleagues (2012) recently identified modest sex differences in metabolism of low-dose ketamine in MDD and bipolar patients, where females displayed greater plasma levels of DHNK and HNK4a/c metabolites compared to males—however, these differences had no association with treatment response, and no sex differences in antidepressant response were observed. In fact, HNK was *negatively* associated with treatment response in bipolar depression patients (independent of sex) [46], suggesting that pharmacokinetic sex differences may not actually impact treatment response in clinical depression. Of note, hormone levels were not controlled for in these studies, which may have obscured potential differences in clinical response between sexes. These observations are likely dose-dependent, however, as 20% greater ketamine and NK clearance and lower drug/metabolite concentrations are observed in women than men following ketamine infusion at a higher dose [47]. These sex differences were also reflected at the behavioral level in healthy men and women, with greater effects on cardiac output and heat pain-related indices in men compared to women [48]. Together, the limited clinical data available do not currently support sex differences in rapid antidepressant-response to acute low-dose ketamine; however, preclinical evidence discussed herein may warrant further investigation through the use of proper experimental design and controls for within- and between-sex differences in hormone levels.

Possible explanations for sex- and species-specific pharmacokinetic differences—While underlying factors responsible for these varying differences in ketamine metabolism observed between males and females remain unknown, sex differences in hepatic expression and activity of ketamine-metabolizing cytochrome P450 enzymes are well-known [49]—and subject to hormonal regulation by estrogen, progesterone and testosterone, which also happen to be substrates of several P450 enzymes responsible for ketamine metabolism [6,49]. As well, physiological differences influencing xenobiotic distribution, metabolism and clearance (i.e., body weight, adipose tissue levels and distribution) are present between males and females of a variety of species [6]. Ultimately, whether sex-dependent pharmacokinetic processes contribute to differences between males and females in ketamine's antidepressant response is unclear, but the evidence strongly supports their consideration both preclinically and clinically. Likewise, non-negligible pharmacokinetic-related species differences have been highlighted herein, encouraging further examination to better translate findings between rodents and humans—an appreciable barrier currently hindering translational neuroscience.

Conclusions

In this review, we discussed the recent advances on sex differences in antidepressant response, while focusing on the novel fast-acting drug ketamine. The increasing inclusion of females in animal models of depression and antidepressant response in the recent years revealed sex-specificities reflected in the case of ketamine by an overall higher sensitivity of females to its antidepressant properties. These observations, however, aren't consistent, but rather depend on a variety of additional factors including hormonal state, context, and most importantly the presence of baseline sex differences likely to interfere with the behavioral or molecular readout following ketamine treatment. It becomes important to investigate the multiple factors influencing one's behavior together, revealing the advantage of an individualized approach over a group-based strategy (Figure 1). Indeed, the integration of sex as covariate among other factors would bring preclinical experimental designs closer to the reality of the clinical population's heterogeneity. Leveraging this heterogeneity in preclinical studies would thus help improve the translatability from preclinical to clinical, and ultimately promote our understanding of sex and individual differences in antidepressant response.

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Highlights

- Ketamine’s antidepressant effects in preclinical models are sexually different
- The higher sensitivity of females to ketamine is modulated by hormonal fluctuations
- Ketamine response is controlled by interactions between sex, hormones, and context
- Sparse clinical consideration of sex differences limits translation from preclinical
- Greater consideration of sex would help improve individualized therapeutic approaches

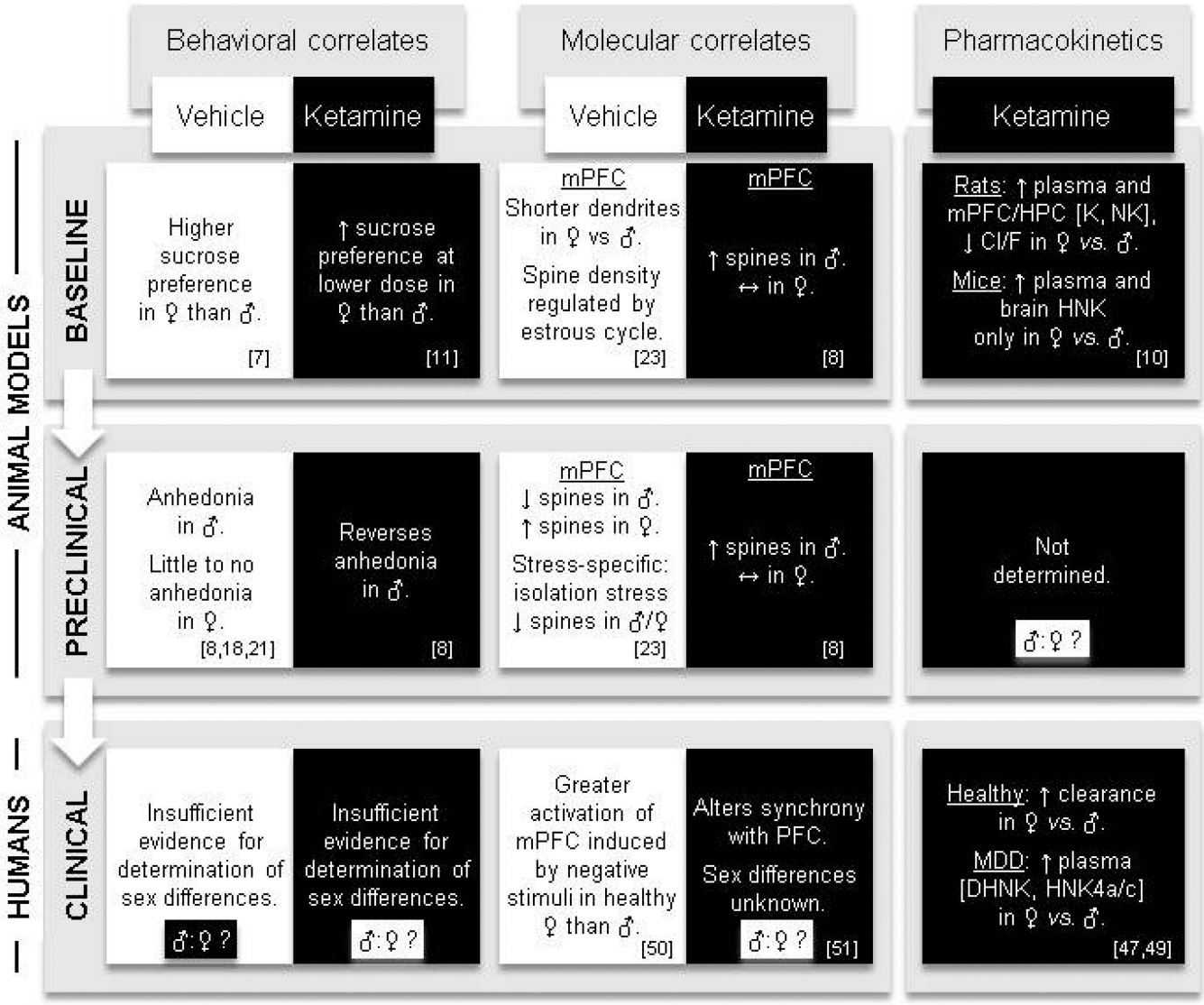

Figure 1.

Conceptual framework for an individualized multi-domain analysis of antidepressant response, applied to sex differences in anti-anhedonic effects of ketamine (as discussed throughout this review). In this diagram, key findings on the current state of knowledge of sex differences in ketamine's effects on hedonic behaviors across three primary domains of investigation ("Behavioral correlates", "Molecular correlates", and "Pharmacokinetics") are depicted at three main study levels ("Baseline", "Preclinical", and "Clinical"). Furthermore, each level × domain combination is summarized with (black background) and without (white background) ketamine treatment, thereby accounting for baseline sex differences when analyzing the drug's effect(s). Note that all changes in the "Ketamine" category refer to comparisons with vehicle-treated controls ("Vehicle" category of the same "level"). Despite a previous sparsity in experimental evidence, growing preclinical research further characterizes the similarities and inconsistencies in sex differences in the effects of ketamine between rodents and humans across the three study levels defined (baseline, preclinical, and

clinical). In this example, for instance, a parallel comparison reveals a consistent sex difference in ketamine-induced spinogenesis in rats between baseline and a preclinical model, whereas such a comparison can be limited either by the presence of a sex difference in the preclinical model itself (as seen for the development of anhedonia in males but not females, “Behavioral correlates” domain), or by the absence of data on eventual sex differences (as seen in the “Pharmacokinetics” domain). Moreover, this example also illustrates the missing consideration of sex differences in clinical populations—both in vehicle- and drug-treated groups—that further limits the translation from the preclinical to clinical level and thus represents a significant barrier to progress in individualized treatment approaches. For each description, corresponding references are listed in the lower right corner. Cl/F: oral clearance, DHNK: dehydronorketamine, HNK: hydroxynorketamine, HPC: hippocampus, K: ketamine, MDD: major depressive disorder, mPFC: medial prefrontal cortex, NK: norketamine.

Table 1

Summary of sex differences in response to acute ketamine treatment.

Reference	Species	Stress	Ketamine dose (i.p.)	Readout	Time post injection	Ketamine effects in Males vs Females
Behavioral correlates						
Carrier and Kabbaj, 2013	Rats (SD)	No stress	2.5–10 mg/kg	FST + NSFT	30 min	Reduced immobility and latency to feed at 2.5, 5, and 10 mg/kg in females, but only at 5 and 10 mg/kg in males.
Carrier and Kabbaj, 2013	Rats (SD)	No stress	2.5–10 mg/kg	Acute SPT	48 hrs	Increased sucrose preference at 5 and 10 mg/kg in males only (ceiling effect in females).
Franceschelli *et al*., 2015	Mice (C57BL/6J)	No stress	3, 5, 10 mg/kg	FST	30 min	Reduced immobility at 3, 5, and 10 mg/kg in females, but only at 5 and 10 mg/kg in males.
Franceschelli *et al*., 2015	Mice (C57BL/6J)	No stress	3, 5, 10 mg/kg	FST	24 hrs	Reduced immobility at 5 and 10 mg/kg in females, but only at 10 mg/kg in males.
Saland *et al*., 2016	Rats (SD)	No stress	2.5 mg/kg	Continuous SPT monitoring	Up to 7 days	Hedonic effect sustained up to 7 days in females only, in an ovarian hormones-dependent manner.
Zanos *et al*., 2016	Mice (CD-1)	No stress	1, 3, 10 mg/kg	FST	24 hrs	Reduced immobility at 3 and 10 mg/kg in females, but only at 10 mg/kg in males.
Franceschelli *et al*., 2015	Mice (C57BL/6J)	Stress (CMS)	10 mg/kg	Acute SPT	6 days	No effect in either sex.
Franceschelli *et al*., 2015	Mice (C57BL/6J)	Stress (CMS)	10 mg/kg	FST	1 or 7 days	Reduced immobility at day 1 and 7 in males, but only at day 1 in females.
Franceschelli *et al*., 2015	Mice (C57BL/6J)	Stress (CMS)	10 mg/kg	Splash test	5 days	Reversed CMS-induced reduction in grooming behavior in males, but not females.
Sarkar and Kabbaj, 2016	Rats (SD)	No stress + Stress (IS)	2.5, 5 mg/kg	FST	3–5 days	Reduced immobility at 2.5, and 5 mg/kg in females, but only at 5 mg/kg in males.
Molecular correlates						
Carrier and Kabbaj, 2013	Rats (SD)	No stress	2.5, 5 mg/kg	Protein expression in mPFC	30 min	Increased mTOR phosphorylation in both males and females at 5, but not 2.5 mg/kg. Reduced eEF2 in the male HPC at 5 mg/kg; no effect in females.
Saland *et al*., 2016	Rats (SD)	No stress	2.5 mg/kg	Protein expression	24 hrs	Up-regulation of BDNF in treatment-responsive females, but not males.
Sarkar and Kabbaj, 2016	Rats (SD)	Stress (IS)	2.5, 5 mg/kg	Dendritic spine density in mPFC	3 hrs	Reversed stress-induced spine loss at 5 mg/kg in males but not in females.
Sarkar and Kabbaj, 2016	Rats (SD)	Stress (IS)	2.5, 5 mg/kg	Synaptic protein expression in mPFC	3 days	Reversed stress-induced down-regulation of synapsin I, PSD95, and GluR1 at 5 mg/kg in males but not in females.
Pharmacokinetics						

Reference	Species	Stress	Ketamine dose (i.p.)	Readout	Time post injection	Ketamine effects in Males vs Females
Zanos *et al.*, 2016	Mice (CD-1)	No stress	10 mg/kg	Ketamine metabolites	0–60 min	Higher HNK but not K or NK levels in the brain of females following ketamine administration.
Saland *et al.*, unpublished	Rats (SD)	No stress	2.5 mg/kg	Ketamine metabolites	0–180 min	Greater K and NK levels in the plasma and brain of females at early timepoints, but HPC and mPFC specificities in magnitude.
Zarate *et al.*, 2012	Humans	MDD/BP patients	0.5 mg/kg (*i.v.*)	Ketamine metabolites	40–1,440 min	Higher DHNK and HNK4a/c plasma levels in female MDD and bipolar patients than males.
Sigtermans *et al.*, 2009	Humans	Healthy	40 ng/ml/15 min (*i.v.*); 320 ng/ml max	Ketamine, Norketamine	2–300 min	Higher S(+)-K and -NK plasma levels in healthy females compared to males, associated with greater female clearance.

Only experimental data displaying a sex difference are reported. BP: Bipolar Disorder, CMS: Chronic Mild Stress, DHNK: Dehydronorketamine, FST: Forced Swim Test, HNK: Hydroxynorketamine, HPC: Hippocampus, IS: Isolation Stress, K: Ketamine, mPFC: medial Prefrontal Cortex, MDD: Major Depressive Disorder, NSFT: Novelty-suppressed Feeding Test, NK: Norketamine, SD: Sprague-Dawley, SPT: Sucrose Preference Test.