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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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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.

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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•].

Although 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-depressant-like 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