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REVIEW ARTICLE

Sex Differences in the Antidepressant Effects of Ketamine in Animal Models of Depression

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Abstract

Major depressive disorder (MDD) is the most common psychiatric disease and it affects millions of people across the world. Patients suffering from MDD consistently complain about cognitive disturbances, significantly worsening the burden of this illness. The second most frequent mental illness in Europe is mood disorders and they are dominated by MDD, affecting 7% of the population. The recent discovery that the N-methyl-D-aspartate receptor (NMDAR) antagonist, ketamine; a revolutionary novel antidepressant, rapidly relieves depressive symptoms and suicidal imaginations, particularly amongst those with treatment-resistant depression have generated a new wave of excitement. This article discusses the sex differences that exist in depressive patients, summarizes the antidepressant activity of ketamine and reviews the mechanisms underlying the rapid antidepressant effects of ketamine. It further discusses the sexual differences in the antidepressant activity of ketamine in preclinical studies.

Keywords

Depression, Ketamine, Antidepressant, Sex differences, NMDA antagonist

Abbreviations

MDD: Major Depressive Depression; NMDAR: N-methyl d-aspartate receptor; WHO: World Health Organization; SSRIs: Selective Serotonin Reuptake Inhibitors; TCAs: Tricyclic Antidepressants; MAOIs: Monoamine Oxidase Inhibitors; mPFC: Medial Prefrontal Cortex; AMPA: α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; mTOR: mammalian/mechanistic Target of Rapamycin; BDNF: Brain Derived Neurotrophic Factor; GABA: γ -aminobutyric acid;

VDCC: Voltage-Gated Calcium Channels; TrkB: Tropomyosin receptor kinase B; GluR1: Glutamate Ionotropic Receptor AMPA type subunit 1; PSD-95: Post-Synaptic Density 95; eEF2: eukaryotic Elongation Factor 2; FST: Forced Swim Test; NSFT: Novelty Suppressed Feeding Test; NIHT: Novelty-Induced Hypophagia Test; LH: Learned Helplessness; CUMS: Chronic Unpredictable Mild Stress; CSDS: Chronic Social Defeat Stress; CIS: Chronic Immobilization; CRS: Chronic Restraint Stress; TST: Tail Suspension Test; SCVS: Sub-Chronic Variable Stress; CPP: Conditioned Place Preference; 5-HIAA: 5-Hydroxyindoleacetic Acid; 5-HT: 5-Hydroxytryptamine; VGLUT1: Vesicular Glutamate Transporter 1; FKBP: FK506 Binding Protein; NAC: Nucleus Accumbens; CaMKII: Calcium Calmodulin Kinase II; SPT: Sucrose Preference Test; OFT: Open Field Test; OVX: Ovariectomized; PPT: 4, 4', 4''-(4-Propyl-[1H]-pyrazole-1,3,5-triyl) Trisphenol; DPN: Diarylpropionitrile; MAPK: Mitogen-Activated Protein Kinase; GSK-3: Glycogen Synthase Kinase 3; SNARE: Soluble NSF Attachment Protein Receptor; VTA: Ventral Tegmental Area

Background

Major depressive disorder (MDD), a severe mood disorder has a high prevalence in almost all developed countries and the disease has also been referred to as clinical depression. This disease is extensively spread out all over the world, applying a huge toll in terms of mortality and morbidity [1,2]. It was estimated in a study from the World Health Organization (WHO) in 2007 that depression affected health more deeply compared to many other chronic diseases [3]. Mood disorders are

the second most frequent group of mental disorders in Europe, and these mood disorders are dominated by MDD, affecting 7% of the population [2]. MDD patients experience loss of self-esteem, disturbed sleep, grumpiness, increased fatigue, reduced pleasure and concentration [4]. Depression is a very important risk factor of suicide [5]. MDD affects people of a wide range of ages, and the disease can be recurrent throughout an individual's lifetime. Depression caused a million deaths the world over and also contributed to 12.5% of all suicide cases caused by mental disorders in 2012 [6,7], representing a serious public health concern until today.

Antidepressants

Currently available treatment options for people suffering from MDD depend on the use of antidepressant medications, which are mostly monoaminergic agents, such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), selective norepinephrine or dual serotonin-norepinephrine reuptake inhibitors (SNRIs) and monoamine oxidase inhibitors (MAOIs) [8]. There are over twenty different antidepressant medications that are targeting monoamine systems. These drugs basically work by increasing the amount of serotonin or norepinephrine in the brain. While effective in most patients, sustained remission is achieved only in one-third of patients after treatment which puts them at greater risk of alcohol and drug abuse, hospitalization, and even suicide attempts [9]. The efficacy of these pharmacological agents is based on the concept that monoamine neurotransmitters (primarily norepinephrine, dopamine and serotonin) are hypoactive, particularly in brain areas such as the hippocampus and medial prefrontal cortex (mPFC); which have been strongly implicated in the pathophysiology of MDD [8,10-13]. The full clinical benefits of conventional antidepressants take weeks to months to start working [14]. This time lag to therapeutic efficacy is a serious problem especially in considering the high suicide risk associated with MDD. Patients experiencing severe depression as well as those having thoughts of harming themselves, immediate relief is very much needed and may even be life-saving. Accordingly, there is a dire need of rapid-acting, well-tolerated and much more effective treatment method particularly for patients who are at high risk of suicide.

Method

To identify current information available on ketamine and its mechanism of action, a literature and Internet search of databases including PubMed was conducted. Key search words used in these searches included, for example, 'ketamine', 'antidepressant', 'mechanism of action', 'rapid acting', 'sex differences', 'preclinical studies', 'animal models of depression', combinations of these and others. The search terms were chosen to get information that would encompass the well-known, as well as the less well-known, basic science information

about the pharmacologic properties of ketamine; to identify recent preclinical studies undertaken to test the efficacy of ketamine as an antidepressant; and, in particular, to identify and summarize the hypotheses about the mechanism of ketamine's antidepressant action. The 'hits' that arose from these searches were used as sources and starting points for further searches. All were reviewed, evaluated and summarized.

Ketamine

The burden of depression continues to increase worldwide as the major cause of disability globally [15], the urgent need for more effective treatments is dire. A new wave of excitement, however, has been generated by the recent discovery that, ketamine, NMDAR antagonist, rapidly alleviates symptoms of depression and suicidal ideation, particularly amongst those with treatment-resistant depression [16].

Ketamine is a noncompetitive NMDA glutamate receptor antagonist used for the induction and maintenance of anesthesia and it has been in clinical use since the 1960s. Antidepressant effects of ketamine have been demonstrated in many antidepressant-relevant tests in experimental animals [17-23]. The actions of ketamine to induce rapid antidepressant effects are in contrast with the delayed effect of currently approved antidepressant treatments, which is particularly vital in cases of depressive patients who have suicidal fantasies, where the increased risk for suicidal behavior has been associated with a lag in the onset of antidepressant action [24]. Ketamine has been also shown to induce a rapid amelioration of suicidal ideation in major depressed patients [25,26] and to rapidly reduce anhedonia [27-29]. These rapid and potent antidepressant effects of ketamine have also been demonstrated in patient groups known to respond poorly to current antidepressants, such as patients diagnosed with bipolar disorder and patients with depressive symptoms that did not respond to electroconvulsive therapy [30,31]. 1-2 h after the acute perceptual disturbances of ketamine have abated, the antidepressant effects tend to arise. The disturbances can persist for two weeks or longer in some patients even though the plasma redistribution half-life is approximately 4 min and overall terminal plasma half-life is 1-3 h [32]. Ketamine has seen a recent surge in interest following findings that sub-anesthetic doses have rapid antidepressant effects [33]. An early study in treatment-refractory MDD patients revealed that a single sub-anesthetic dose of ketamine had a robust antidepressant effect within 4 hours [33].

Mechanism of action of ketamine

The antidepressant effects of ketamine are believed to be the result of a cascade of events, which include

- Blockade of interneuronal NMDA receptors, [34].
- Glutamate surge resulting from the disinhibition of

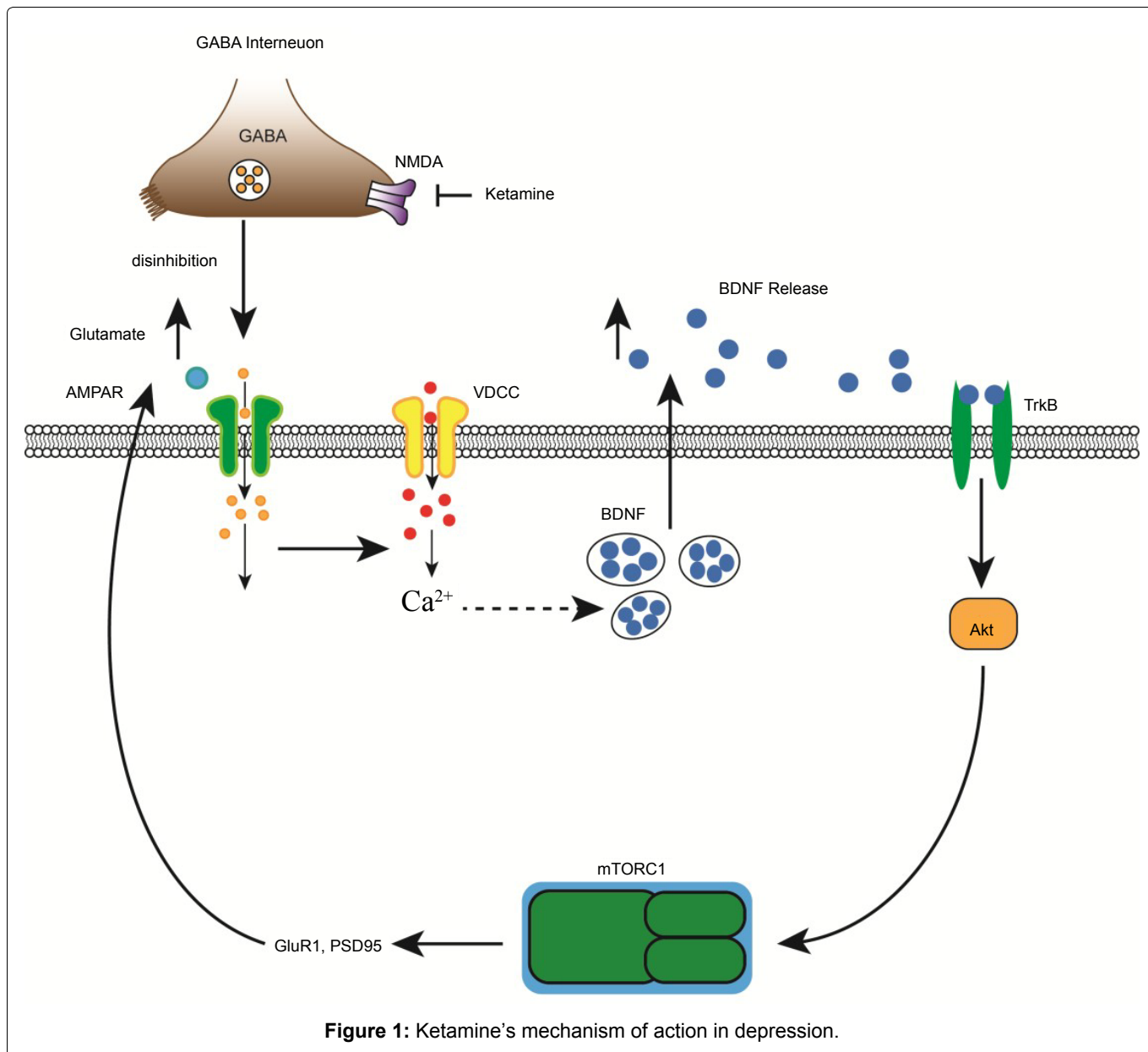


Figure 1: Ketamine's mechanism of action in depression.

pyramidal cells, [35].

- Activation of the pro-synaptogenic α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, [17].
- Blockade of the excitotoxic extrasynaptic NMDA receptors, [18].
- Activation of synaptogenic intracellular signaling, including mTORC1 [36] and BDNF pathways (Figure 1) [37].

At low doses, ketamine is thought to preferentially bind to and block NMDARs on γ -aminobutyric acid (GABA)ergic interneurons resulting in reduced excitability of these inhibitory interneurons, which then causes disinhibition of glutamatergic neurons.

There is a surge of glutamate release resulting from an increased depolarization of the presynaptic neuron, as reported in the mPFC. Released glutamate binds to and activates postsynaptic AMPA receptors, which

conduct Na⁺ and Ca²⁺ into the cell.

The influx of calcium and depolarization cause the activation of the voltage-gated calcium channels (VDCCs). This high local intracellular Ca²⁺ concentration set off the activity-dependent vesicular release of brain-derived neurotrophic factor (BDNF) into the synaptic space. BDNF binds to its surface receptor, tropomyosin receptor kinase B (TrkB), and activates it. TrkB then activates two major downstream signaling cascades involving MEK-ERK, and PI3K-Akt.

These two pathways converge onto the mammalian/mechanistic target of rapamycin (mTOR), a key regulator of protein synthesis and synaptic plasticity. These events lead to disinhibition of synaptic protein translation (e.g., GluR1-2, PSD95, synapsin1) as well as BDNF, in part through the suppressed phosphorylation of eukaryotic elongation factor 2 (eEF2). I) Ketamine at low doses preferentially binds to and inhibits NMDARs on GABAergic interneurons; II) This inhibition leads to decreased excitability of these inhibitory interneurons,

which then causes disinhibition of glutamatergic neurons; III) The presynaptic neuron becomes increasingly depolarized which leads to a surge in the release of glutamate, as reported in the mPFC. Glutamate that is released binds to and activates postsynaptic AMPA receptors, which channels Na^+ and Ca^{2+} into the cell. IV) VDCCs are activated by calcium influx and depolarization; V) The high intracellular Ca^{2+} concentration set off the activity-dependent vesicular release of BDNF into the synaptic space; VI) The released BDNF binds to and activates TrkB, which in turn activates two major downstream signaling cascades involving MEK-ERK and PI3K-Akt. These two pathways assemble onto mTOR; an important regulator of protein synthesis and synaptic plasticity; VII) These events result in the disinhibition of synaptic protein translation (e.g., GluR1-2, PSD95, synapsin1) as well as BDNF, in part through the suppressed phosphorylation of eEF2; VIII) These newly synthesized proteins are then inserted into the postsynaptic density, leading to further increases in AMPAR-mediated synaptic transmission and dendritic spine density, thus causing massive synaptogenesis.

Sex Differences in Depression and Antidepressant Activity

Much like genetic and environmental factors, sex is a naturally-occurring disease and treatment modifier [38,39], such that factors either protecting against disease or enhancing treatment response in one sex may indicate prevention or treatment strategies in the other sex [40]. More women than men are diagnosed with

depression in any given year [41-43]. This difference in number has been attributed to the pronounced sex differences existing in both the anatomy as well as the function of the brain, and also to the sexually dimorphic hormonal environment [1,44]. In males and females, the current available antidepressants have grave limitations in that the drugs require weeks to months to ameliorate symptoms, and only one third of patients respond to the first prescribed antidepressant [45,46]. Interesting gender differences exist in the prevalence rate of depression [1,41]; the symptoms of depressive disorders [47,48] and the efficacy of antidepressant medication [49-51].

Animal Models of Depression

Animal models are very useful tools which are employed in investigating the etiology of depression, as well as progress in the development of effective and novel therapeutic targets for its treatment. Tests in rodents predictive of antidepressant activity of different drugs have been widely used for mechanism of action studies and drug development purposes [52]. Such validated tests include the forced-swim test (FST) assessed 24 h after drug administration (i.e., 24-h forced-swim test), novelty-suppressed feeding test (NSFT), novelty-induced hypophagia test (NIHT), learned helplessness (LH), social avoidance, long-term corticosterone administration, chronic unpredictable mild stress (CUMS), chronic social defeat stress (CSDS), chronic immobilization stress (CIS), chronic restraint stress (CRS), maternal deprivation or early life stress, and the reversal of the

Table 1: Criteria for the validity of an animal model of depression.

Criteria	Manifestation
Face validity	Cardinal symptoms of depression manifested by patients should be simulated in animals.
Construct validity	Realistic use of inducing conditions to bring about pathophysiological changes that occur in patients with depression, such as changes in the HPA axis, hippocampal atrophy, and neurotransmitters in animal.
Predictive validity	Behavioral changes should be responsive to appropriate antidepressant drugs.

Table 2: Animal models of depression and their criteria for validity.

Model	Criteria		
	Face	Construct	Predictive
Forced swim test (FST)	-	-	+
Tail suspension test (TST)	-	-	+
Chronic unpredictable mild stress (CUMS)	+	+	+
Chronic social isolation stress (CSIS)	+	+	+
Chronic social defeat stress (CSDS)	+	+	+
Learned helplessness (LH)	+	+	+
Maternal deprivation Stress	+	+	+
Olfactory bulbectomy	+	+	+
Lipopolysaccharide	+	+	+
Sub-chronic variable stress (SCVS)	+	+	+

-: Negative; +: Positive.

hyperlocomotor effects following olfactory bulbectomy. Shown in Table 1 is a list of some existing models of depression and whether they meet each of the criteria for validity presented in Table 2. The validity of animal models of depression is usually assessed using approaches in which a model is evaluated in respect of its predictive validity, face validity and construct validity. Although animal models greatly help our understanding of psychiatric disorders, they do have some limitations. For example, animal cannot observe feelings of sadness, guilt, or suicidal thoughts, symptoms mainly limited to humans [53]. A summary of these criteria for animal models of depression is presented in Table 2.

Sex Differences in the Anti-Depressant Activity of Ketamine

The encouraging clinical findings of ketamine's usefulness in the treatment of MDD have inspired a wave of preclinical research aimed at throwing more light on the molecular mechanisms underlying the robust antidepressant effects of ketamine. Numerous studies have successfully duplicated the positive effects of ketamine in rodent tests or models of depression, including the FST (the most commonly used preclinical screen for antidepressant activity) and the CUMS paradigm (the most commonly used animal model of depression) [54]. In addition to mirroring the rapid and sustained antidepressant effects of ketamine seen in the clinic, animal studies have also yielded further intriguing observations. Despite the prevalence of MDD in women being roughly twice as high as in men, preclinical research investigating the mechanisms underlying ketamine's antidepressant effects has been conducted almost exclusively in male rodents [11]. The unequal numbers of male and female animals utilized in preclinical studies has resul-

ted in less molecular and behavioral data concerning the female animal response to a sub-anesthetic dosage of ketamine. Many of these experiments only employed male animals, but most recent findings indicate that there exist sex differences in the antidepressant effects of ketamine [55]. The exception to these findings is a work by Chang and his colleagues who did not find any sex differences in the acute antidepressant actions of (R)-ketamine in an inflammatory model of depression [56].

Sex differences in ketamine's antidepressant response at baseline conditions

Preclinical studies that include both males and females indicate a heightened sensitivity to ketamine in females. Stress-naïve female rodents consistently respond to a lower dose of ketamine than males on behavioral assays related to depression: Specifically using measures of antidepressant efficacy (FST) and anxiety-induced neophagia (NSFT) [21,57-59], these observations were shown to be mediated by the gonadal hormones estrogen and progesterone [57].

On the other hand, there is also emerging evidence that repeated ketamine treatment (daily injections of 10 mg/kg for 21 days) effectively sustains the antidepressant response in male mice, whereas it may actually worsen depression and anxiety-related phenotypes in female mice [60] (Table 3). Therefore, further research into the sex specific effects of ketamine is warranted. It is also important to note that such preclinical studies involving prolonged exposure to ketamine over several days have also reported neurotoxicity in animal models of schizophrenia [61]. Thus, approaches that extend the therapeutic effects of ketamine without the onset of severe neurotoxicity and other side effects are much

Table 3: This table outlines studies that have assessed the antidepressant-like effects of ketamine in commonly used behavioral tests. Molecular alterations of relevance to ketamine's molecular mechanism of action are also reported.

Species	Behaviour	Molecular Alteration			References
		mPFC	Hippocampus	NAc	
SD Rats	↓ Latency to feed in the NSF 24 h post-injection (5 & 10 mg/kg)	↑ mTOR phosphorylation in males & females	↓ eEF2 phosphorylation in males (5 mg/kg)	N/A	[57]
	↑ Sucrose consumption of males 48 h post-injection in SPT				
	↓ Immobility in FST in males & females 30 min post-injection				
C57BL/6/J	↓ FST immobility time in males & free cycling females (3 mg/kg)	p-CaMKIIα & p-MAPK ↔ in all groups	p-CaMKIIα ↔ in D1 females ↑ in males (3 mg/kg) ↑ in Pro females (1.5 & 3 mg/kg)	N/A	[59]
	↓ Immobility time in D1 females treated with PPT or DPN but not P4 (1.5 mg/kg)	p-GluR1 & BDNF ↔ in D1 females ↑ in males & Pro Females (3 mg/kg)	p-GluR1 ↔ D1 females ↑ in males & Pro females (3 mg/kg)		

	↓immobility time in males and D1 females (3 mg/kg)	p-Akt ↔in D1 females ↑in males at 3 mg/kg ↑in Pro females (1.5 & 3 mg/kg)	BDNF ↔in Pro females ↑in males & D1 females (3 mg/kg)		
	↓immobility time in Pro females (1.5 & 3 mg/kg)	p-GSK-3β ↔in D1 females ↑in males & Pro females (1.5 & 3 mg/kg)	p-MAPK ↑in males & Pro females (3 mg/kg) ↑in D1 females (1.5 & 3 mg/kg)		
		mTOR ↔in Pro females ↑in males & D1 females (3 mg/kg)	p-Akt↔in D1 females ↑in males (3 mg/kg) ↑in Pro females (1.5 & 3 mg/kg)		
			p-GSK-3β ↑in males (1.5 & 3 mg/kg) ↑in D1 & Pro females (3 mg/kg)		
C57BL6/J	Females were more sensitive in the FST than males (Females responded to lower dose (3 mg/kg) and the higher doses while males responded to higher doses (5 & 10 mg/kg))	↑aspartate levels in females ↓5-HIAA/5HT ratio in females	↓glutamate conc. in males ↓5-HIAA/5HT in females	N/A	[58]
ICR	↓immobility time in FST in both sexes (10 mg/kg acute administration)	↔beclin-1 & p62 (5 & 10 mg/kg chronic administration)	N/A	N/A	[75]
	↔in immobility time in FST, locomotor activity in the OFT, in both sexes (5 & 10 mg/kg chronic administration)				
SD Rats	Ketamine at 10, 20 & 40 mg/kg caused ↑locomotor activity ↔grooming in both sexes of preadolescent rats	N/A	N/A	N/A	[92]
	Ketamine at 20 or 40 mg/kg caused female adolescent rats to exhibit more locomotor activity than males ↔grooming				
	↔ conditioned activity after Ketamine administration in both sexes of the preadolescent rats				
SD Rats	2.5 mg/kg ↑in sucrose preference in OVX females + E2 + P4	N/A	Protein levels of BDNF ↑in OVX female + E2 + P4	N/A	[91]
	↔in sucrose preference in OVX females + E2		↔in OVX females + E2 ↔in OVX females + P4		
	↔in sucrose preference in OVX females + P4		↔ in intact males + P4 ↓in intact males + E2		
	↑in sucrose preference in intact males + P4		↑in intact males + E2 + P4 ↔ in intact males + P4		

	↔in sucrose preference in intact males + E2		protein levels of Akt & -p-Akt ↔in all groups		
	↔in sucrose preference in females + testosterone		protein levels of p-ERK ↑in OVX females + E2 ↔ in all other groups		
	↔in sucrose preference in gonadectomized males + testosterone		protein levels of CaMKIIα & p-CaMKIIα ↓OVX females + E2 of CaMKIIα ↑in intact males + E2 ↑in intact males + E2 + P4		
SD Rats	↔Conditioned placed preference in both sexes	5 mg/kg ↑spine density in the NAcSh in males	N/A	N/A	[62]
		↑spine density in NAcSh & NAcC in females			
		↑ΔfosB, CaMKIIα, GluA1 and BDNF in males			
		↔ΔfosB, CaMKIIα and BDNF in females ↑GluA1 in females			
C57BL6/J	↑time spent in the center in OFT in males ↓time spent in the center in the OFT in females	↔glutamate & aspartate in levels in males ↑5-HIAA/5HT ratio in males	N/A	N/A	[60]
		↑Synapsin I & SNARE levels in males ↓glutamate & aspartate levels in females			
		↔5-HIAA/5HT ratio in females			
		↔ Synapsin I & SNARE levels in females			
SD Rats	5 & 10 mg/kg chronic administration ↑time in males in the drug-paired chamber (10 mg/kg)	N/A	N/A	↑ΔfosB expression in both sexes but it was higher in females than in males	[63]
	↓time in females in the drug-paired chamber (5 mg/kg)				
	↑in running in locomotor activity in both sexes but the females ran more than the males				

FST: Forced swim test; NSF: Novelty suppressed feeding; SPT: Sucrose preference test; OFT: Open field test; mPFC: Medial prefrontal cortex; NAcSh: Nucleus accumbens shell; NAcC: Nucleus accumbens core; eEF2: Eukaryotic elongation factor 2; D1: Diestrus 1; Pro: Proestrous; E2: Estradiol; P4: Progesterone; OVX: Ovariectomized; PPT: 4,4',4''-(4-Propyl-[1H]-pyrazole-1,3,5-triyl) trisphenol; DPN: Diarylpropionitrile; mTOR: Mechanistic target of rapamycin; CaMKIIα: Calcium calmodulin kinase II alpha; GluA1: Glutamate ionotropic receptor AMPA type subunit 1; MAPK: Mitogen-activated protein kinase; BDNF: Brain derived neurotrophic factor; GSK-3: Glycogen synthase kinase 3; 5-HIAA: 5hydroxyindoleacetic acid; 5-HT: 5-hydroxytryptamine; SNARE: Soluble NSF attachment protein receptor; ↑: Increasing; ↓: Decreasing; ↔: Propositional.

needed.

The assessment of ketamine's effects on anhedonia, a signature feature of depression that is measured in rodents using the sucrose preference test (SPT), has produced conflicted findings. This is in part due to sex differences in baseline sucrose intake and ceiling effects [57]. When chronic ketamine is tested (10 mg/kg daily, for 21 days), males displayed an antidepressant-like phenotype but females showed pro-depressive and anxiogenic behavioral traits [60].

Preclinical studies used to characterize ketamine's addiction-like properties involve behavioral assays such as locomotor sensitization, conditioned place preference (CPP), and intravenous self-administration, and sex difference studies have recently started to emerge. Female rats show increased locomotor sensitization to intermittent (weekly and every other day, respectively) repeated ketamine at depression-relevant doses (2.5-10.0 mg/kg intraperitoneally, i.p.) [62,63]. Locomotor sensitization after repeated exposure to drugs of abuse is indicative of plasticity in the reward circuitry that may underlie the transition to addiction. Interestingly in these studies, the same rats that displayed sensitization did not form a CPP to ketamine at any dose tested [62,63]; in fact, females displayed a conditioned place aversion to 5.0 mg/kg. Together, these findings suggest that divergent mechanisms may underlie the locomotor activating effects and the associative rewarding effects of ketamine. However another group testing higher ketamine doses (6-14 mg/kg, daily) found females displayed a greater CPP than males [64]. This study also found distinct urine metabolic profiles in males and females, warranting further research into sex-specific pharmacokinetics of ketamine.

Ketamine treatment induces sex-dependent rapid and sustained neurochemical antidepressant-like effects in naive C57BL/6J mice. Tissue levels of the excitatory amino acids glutamate and aspartate, as well as serotonergic activity, were affected in a sex-dependent manner in the PFC and the hippocampus. Ketamine caused a rapid decrease of glutamate concentrations in the hippocampus of male mice and an increase in aspartate levels in the PFC of female mice 30 minutes after administration while at 24 hours after ketamine administration, 5-HIAA/5-HT turnover ratio in the PFC and the hippocampus were decreased in female mice [58]. The glutamatergic system is abnormally affected in MDD, atypical expression of glutamate receptors (NMDA, mGluR, and AMPA) are reported in postmortem brain [65]. Inhibition of glutamatergic transmission occurs following repeated stressful and depressive events and can be attributed to the down-regulation of presynaptic proteins, such as synapsin I and III, synaptophysin [66] and the vesicular glutamate transporter 1 (VGLUT1) [67-69].

mTOR regulates synaptic protein synthesis in response to activity leading to altered spine density and morphology [70,71]. In particular, chronic inhibition of mTOR was shown to reduce dendrite complexity and spine density in hippocampal neurons [72]. Consistent with this, the activation of mTOR enhanced synaptic responses and increased synapse number from both glutamatergic and GABAergic neurons by increasing the readily releasable pool of synaptic vesicles. Ketamine administration was shown not to have any effect on the phosphorylation status of mTOR in total protein preparations from the mPFC of either female or male rats but an increased phosphorylation of mTOR specifically within synaptoneuroosomes isolated from the mPFC in both male and female rats was observed [57].

Autophagy is important for most cells in various tissues including the central nervous system (CNS); it is sensitive to the accumulation of toxic proteins/damaged organelles [73]. Hence, change of autophagy during neurodevelopment and synaptic plasticity might bring about abnormal development as well as synaptic malfunction. Many antidepressants have been found to be involved in the neuronal autophagy signaling pathway including the co-chaperone FKBP5/FKBP51 acting as an antidepressant plays a role in autophagy [74]. These findings suggest that neuronal autophagy signaling pathways play an important role in MDD. Ketamine also has been demonstrated to have no effect in the autophagy pathway. Acute and chronic administration of ketamine did not alter frontal cortex levels of autophagy markers p62/beclin-1 ratio in both males and females [75].

The way and manner dendritic spine number, size, and shape are regulated is of much importance to the synaptic plasticity, as well as learning and memory [76,77]. Many psychiatric diseases have been shown to be associated with dendritic spine pathology [78-81]. Formation, growth, and elimination of dendritic spines are under a precise control, requiring reorganization of the neural network in response to acute stress or learning processes. These processes are frequently dysregulated or disrupted in chronically stressed animals [82,83]. Therefore, understanding dendritic spines is fundamental in uncovering the mechanisms underlying depression and also anti-depressant activities. Dendritic spine density was increased in the nucleus accumbens (NAc) of both males and females administered with ketamine, and this effect was specific to the NAc shell (NAcSh) in both sexes but also to the NAc core (NAcC) in females [62].

Calcium calmodulin kinase II (CaMKII) α and β are neuron-specific kinases, expressed at high molar concentrations in the brain [84] and are activated in response to glutamate-induced NMDA receptor activation, following which the receptor becomes permeable to calcium as well as Na^+ and K^+ [85]. The elevation of

intracellular calcium triggers the auto-phosphorylation of a threonine residue in the catalytic domain of CaMKII, leading to its activation. This auto-phosphorylation is critical for synaptic plasticity [86]. Neurotrophic factors, especially BDNF, have been widely studied in the context of synaptic plasticity and in relation to depressive and anxiety disorders. Human patients suffering from depression display decreased serum levels of BDNF [87,88] and in rodents, BDNF mRNA decreases following stress in the hippocampus [89]. BDNF upregulates expression of several synaptic proteins such as synapsin-I, PSD-95, and GluR1 [90]. Ketamine affected the expression levels of certain proteins including CaMKII α and BDNF in the synapse in a sexual dimorphic manner. Males administered ketamine displayed increased protein expression of Δ fosB, CaMKII α , and BDNF, this effect was not seen in females. However, males and females administered ketamine displayed increased protein expression of AMPA receptors (GluA1) [62]. Repeated ketamine treatment also induced sustained sex-differentiated neurochemical and molecular effects, as it enhanced hippocampal synapsin protein levels and serotonin turnover in males, but attenuated glutamate and aspartate levels in female mice [60].

A study by Saland, et al. that looked into the influence of testosterone, estradiol and progesterone on initiation and maintenance of hedonic response to low-dose ketamine in intact and gonadectomized male and female rats revealed that ketamine induced a prolonged increase in SPT of female, but not male rats. Although testosterone was unable to alter male treatment response, simultaneous administration of progesterone (P4) alone in intact males improved hedonic response to low-dose ketamine. Greater hippocampal BDNF levels, but

not activation of key downstream signaling effectors, were associated with treatment responsiveness in female rats. Saland and colleagues further provided novel evidence supporting activational roles for ovarian-, but not testicular-, derived hormones in mediating hedonic sensitivity to low-dose ketamine in female and male rats, respectively. They concluded that organizational differences may, in part, account for the persistence of sex differences following gonadectomy and selective involvement of BDNF in treatment response [91] (Table 3).

Sex differences in ketamine's antidepressant response under stress

Acute administration of ketamine has been demonstrated to reverse chronic stress-induced depressive-like behaviours in male rodents but it had opposite effects in female counterparts. Ketamine induced sex-dependent behavioral effects in mice subjected to the CUMS model of depression as female mice were more reactive to the earlier effects of ketamine, as assessed in the OFT and the FST (at 30 min and 24 h post-treatment, respectively) but the antidepressant potential of the drug proved to be longer lasting in males, as assessed in the splash test and the FST (days 5 and 7 post-treatment, respectively). CUMS-induced anhedonia and anxiety (measured by the increased number of marbles buried by mice) were not reversed by ketamine treatment in either sex [58] (Table 4). These opposite effects observed may point to sexually biased mechanisms underlying the maintenance of ketamine's lasting antidepressant-like effects in animals chronically stressed.

In male and female rats which were chronically socially isolated, a single administration of ketamine at 2.5

Table 4: This table outlines studies that used various animal models of depression to assess the antidepressant-like effects of ketamine in commonly used behavioral tests. Molecular alterations of relevance to ketamine's molecular mechanism of action are also reported.

Species	Stress	Behavioural	Molecular Alterations	References
C57BL6/J	CUMS	ketamine did not reverse CUMS-induced anhedonia & marble burying in either sex	N/A	[58]
		↓locomotor activity, time spent in the center in females in OFT		
		↓immobility time in FST in both sexes		
		The antidepressant effect lasted longer in males than in females as seen in the FST & splash test		
SD Rats	CUMS	↓in immobility time in the FST in both sexes	↑VTA dopamine neuron activity	[99]
		↑latency to immobility in females	↔firing rates and percentage of burst firing	
SD Rats	Social Isolation	5 mg/kg ↑SPT in males but not in females	5 mg/kg ↑spine density, PSD95, Synapsin 1 & GluA1 in males	[93]
		↓immobility time in FST in both sexes	↔spine density, PSD95, Synapsin 1 & GluR1 in females	
		2.5 mg/kg ↔in SPT & immobility time in FST in males	2.5 mg/kg ↔ spine density, PSD95, Synapsin 1 & GluA1 in both sexes	

		↓immobility time in FST females	
C57BL6/J	LPS (0.5 mg/kg)	10 mg/kg ↓immobility time in FST in both sexes	[56]

FST: Forced swim test; OFT: Open field test; GluA1: Glutamate ionotropic receptor AMPA type subunit 1; VTA: Ventral tegmental area; PSD95: Post-synaptic density 95; SPT: Sucrose preference test; LPS: Lipopolysaccharide; ↑: Increasing; ↓: Decreasing; ↔: Propositional.

Table 5: This Table Summarizes A Study That Assessed The Pharmacokinetic Properties Of Ketamine.

Species	metabolites			References
	Serum	mPFC	Hippocampus	
SD Rats	Females had higher serum NK levels 30 min after administration	Females had higher levels of ketamine & NK than males	Females had higher levels of ketamine & NKT than males	[100]
	Males had higher serum DHNK levels after 10 & 30 min			
C57BL6/J	10 & 3 mg/kg post LPS (0.5 mg/kg) injection, both sexes had similar levels	10 & 3 mg/kg post LPS (0.5 mg/kg) injection, both sexes had similar levels		[56]

NK: Norketamine; DHNK: Dehydronorketamine.

and 5 mg/kg restored the stress-induced behavioural despair in females whereas only the 5 mg/kg ketamine was effective in males [93]. These findings give credence to the higher female sensitivity to ketamine's antidepressant-like effects at baseline [57,91]. They observed that female rats appear to be more resilient to social isolation stress, as they do not display a decrease in SPT after 8 weeks of social isolation, which is sufficient to induce anhedonia in males. The ketamine administration at 5 mg/kg in males also reversed stress-induced decrease in spine density and reductions in synapsin I, PSD95 and GluR1 in the mPFC, but neither 2.5 nor 5 mg/kg was able to reverse these stress-induced reductions in dendritic loss synaptic proteins expression in females [93].

Ventral tegmental area (VTA) dopaminergic neurons increase the dopamine level in the striatum and modulate medium spiny neuron sensitivity to a glutamatergic projection from the PFC and limbic regions [94]. This dopaminergic connection from the VTA is crucial for the functioning of the dorsal striatum and Vstr [95], regions associated with guiding motivation and reward anticipation [96,97]. MDD is characterized by dopamine depletion, which could lead to hedonic deficits [98]. Following CUMS, there was greater immobility duration in both sexes and reduced VTA dopamine neuron activity in both males and females but the reduction was greater in the females than the males. These stress-induced changes were restored by ketamine and post-FST VTA dopamine activity for up to 7 days in both male and female CUMS-exposed rats [99].

In a lipopolysaccharide induced inflammation model of depression, saline or (R)-ketamine was administered 23 hours post lipopolysaccharide administration to C57BL6/J mice. (R)-ketamine (10 mg/kg) significantly attenuated the increased immobility time of FST in the lipopolysaccharide-treated mice but there was no diffe-

rences in this effect between the two sexes. The authors concluded that there are no sex-specific differences in the acute antidepressant effects of (R)-ketamine [56].

It can be speculated that this study; which did not find sex differences after acute ketamine treatment; might be as a result of the different depression model employed by the researchers as compared to the other models used by the other investigators who found sex differences in their various studies. Also, it is possible that chronic treatment of ketamine in this model may be able to elicit sexual dimorphism in the response by the mice.

Sex differences in preclinical ketamine pharmacokinetics

Sex is a variable that have an influence on almost all the pharmacokinetic processes; absorption, distribution, metabolism and elimination (ADME); which may or may not impact treatment response [40]. Ketamine is predominantly metabolized through N-demethylation into norketamine (NK), which is subsequently transformed into dehydronorketamine (DHNK) and six diastereomeric hydroxynorketamine (HNK) metabolites [32]. Females exhibited greater concentrations of ketamine and NK in the plasma and brain than males 30 minutes after 2.5 mg/kg ketamine administration. Males had higher serum DHNK levels after 10 & 30 minutes. There were regional differences observed when the mPFC and hippocampus were examined individually [100] (Table 5).

Sex differences in ketamine's pharmacokinetics under stress was also undertaken by Chang and colleagues in which (R)-ketamine was given 23 hours post lipopolysaccharide administration to C57BL6/J male or female mice and the concentration of (R)-ketamine and its 2 major metabolites, (R)-norketamine and

(2R,6R)-hydroxynorketamine, was measured in the plasma and brain after the administration of (R)-ketamine in the mice. There were no sex-specific differences in the pharmacokinetic profile of (R)-ketamine as no differences were seen in the concentrations of (R)-ketamine and its 2 metabolites in the plasma and brain [56].

Conclusion

Preclinical studies highlighting the importance of including females in these studies, and furthermore illustrate that sex differences can emerge following exposure to various drug dosages and treatment regimens, or exposure to different types of stressful stimuli. Therefore, future ketamine antidepressant research must include analysis of female animals, for enhanced research reproducibility, and for more accurate translation to clinical populations.

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