Sex Differences in Glutamate Pathologies: Implications in Ketamine Treatment for Depression and Alcohol Use Disorder

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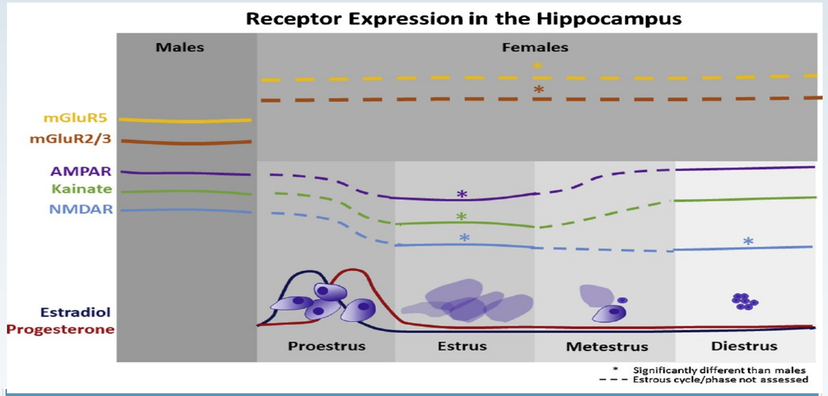
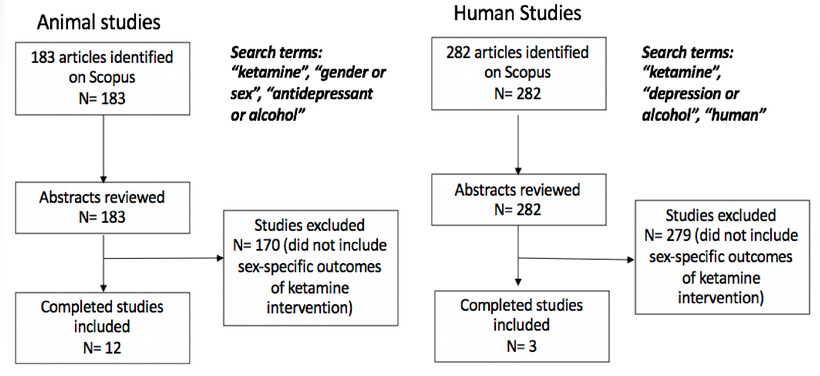
Background

- Major depressive disorder (MDD) and alcohol use disorder (AUD) are prevalent psychiatric conditions known to occur at different rates and have different treatment outcomes in men and women
- MDD and AUD are associated with glutamatergic dysregulation[1]
- Ketamine, an N-methyl d-aspartate glutamate receptor (NMDAR) antagonist, has shown efficacy in treatment of MDD and AUD[1,9]
- Numerous studies show differences in glutamate system regulation between men and women, suggesting there may be sex-dependent differences in ketamine treatment response[1,2]
- Animal studies suggest NMDAR density is regulated by gonadal hormones- increases during follicular phase/reduces during luteal phase[3]
- **The purpose of this review is to summarize the current knowledge of sex-specific outcomes of ketamine treatment for MDD and AUD.**



Methods



Results

Animal Studies

Reference	Condition	Animal Model	Hormonal Effects Measured	Primary Outcome	Ketamine Dose	Results
4	Depression	Sprague-Dawley rats	Yes	Forced Swim Test	0, 2.5, 5.0, 10.0 mg/kg	• Females more sensitive to ketamine than males
5	Depression	C57BL/6J mice	No	Forced Swim Test	0, 3, 5, 10 mg/kg	• Females responded to all ketamine doses; males responded to highest dose
6	Depression	C57BL/6J mice	No	Forced Swim Test	0, 3, 5, 10 mg/kg	• Males: antidepressant effects; females: anxiety/depression-like behaviors
7	Depression	Sprague-Dawley rats	Yes	Forced Swim Test	0, 2.5, 5 mg/kg	• Ketamine reversed depression symptoms in females more than males
8	Depression	Sprague-Dawley rats	Yes	Sucrose Preference Test	0, 2.5 mg/kg	• Females had greater increase in sucrose preference than males • Exogenous progesterone increased sensitivity to ketamine
9	Depression	ICR mice	No	Forced Swim Test	0, 5, 10 mg/kg	• No significant differences in behavior between the sexes
10	Depression	Sprague-Dawley rats	No	Forced Swim Test	0, 10 mg/kg	• Stress affected females more than males • Females more sensitive to ketamine treatment than males
11	Depression	C57BL6/J mice	Yes	Forced Swim Test	0, 1.5, 3.0 mg/kg	• No different outcomes between the sexes • P4 stage rats had antidepressant response to ketamine at a lower dose than other groups
12	Alcohol Use Disorder	C57BL/6J mice	No	Ethanol consumption	0, 3 mg/kg	• Ketamine decreased binge-like ethanol consumption in females, not males
13	Alcohol Use Disorder	Sprague-Dawley rats	No	Alcohol consumption	0, 0.5 mg/kg	• Males' alcohol consumption reduced more than females'
14	Alcohol Use Disorder	Alcohol preferring rats	No	Alcohol consumption	0, 5 , 7.5 , 10 mg/kg	• Females' alcohol consumption decreased more significantly with ketamine than males'

Human Studies

Reference	Sample size	Condition	Intervention	Main Outcome Measures	Results
15	N=99	Depression	0.1, 0.2, 0.5, 1.0 mg/kg ketamine/ 0.045 mg/kg midazolam	HAM-D6[a]	• No significant differences between the sexes • Ketamine decreased depression symptoms acutely in both sexes
16	N=27	MDD and BD	0.5 mg/kg ketamine	HDRS	• Men more likely to reach 50% better outcomes than women with ketamine
17	N=108	Depression	0.5 mg/kg ketamine	HDRS	• Gender not associated with antidepressant response to ketamine

Conclusions

- Preclinical studies implicate sex as a moderator of treatment outcomes in MDD and AUD animal models
- However, there were few analyses in human trials of this potential confounder
- Two of the three clinical trials showed null findings, while one showed a small sex-based effect
- Future studies should continue to evaluate sex-specific differences and the effects of female hormone levels on ketamine treatment outcomes
- Studies should characterize if female participants are on exogenous hormones- and if so, which type

References

Scan QR code for references.

Acknowledgements

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