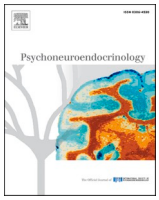
Psychoneuroendocrinology 177 (2025) 107455

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen



Estrogen receptor alpha (ERα) partially modulates ketamine's sustained anxiolytic effects without altering its antidepressant properties in female rats

Ece Idil, Bahar Yuksel, Zeynep Sen, Gunes Unal *

Behavioral Neuroscience Laboratory, Department of Psychology, Boğaziçi University, Istanbul 34342, Turkey

ARTICLE INFO

Keywords:
Ketamine
Sex difference
Estrogen
ERα
Depression
Anxiety

ABSTRACT

Ketamine is a rapid-acting antidepressant with sexually dimorphic effects. Female animals exhibit a higher sensitivity to its antidepressant properties, which has been associated with their ovarian hormone levels. One factor contributing to this sex difference is the faster rate of ketamine metabolism observed in females, potentially regulated by estrogen receptor alpha (ERα) through modulation of enzymatic activity. In this study, we explored the role of ERα in mediating the therapeutic effects of ketamine in adult female Wistar rats. To inhibit ERα, we administered its antagonist, methyl-piperidino-pyrazole (MPP; 1 mg/kg, IP), 24 h and 1 h prior to a single antidepressant dose of ketamine (10 mg/kg, IP) or saline (vehicle). We tested the animals in the forced swim test (FST), open field test (OFT), elevated plus maze (EPM), and auditory fear conditioning. Ketamine administration ameliorated behavioral despair observed in the vehicle group, and ERα antagonism did not affect this outcome. An interaction between MPP and ketamine was observed in anxiety-like behaviors assessed in the OFT and EPM; however, this effect did not reach significance in post-hoc analyses. Neither MPP nor ketamine affected fear memory, as measured in cued fear conditioning. These findings suggest that the sexually dimorphic antidepressant effects of ketamine occur independently of ERα activity, although ERα may influence neural circuits related to anxiety.

1. Introduction

Ketamine, an NMDA receptor antagonist, exhibits rapid antidepressant and anxiolytic effects (Zanos et al., 2016; Gokalp and Unal, 2024). However, these therapeutic effects show significant sex differences in preclinical studies, with lower doses being sufficient for female animals, but not for males (Carrier and Kabbaj, 2013). Ovarian hormones are likely mediators of these differences, as female mice in proestrus respond to ketamine at doses that do not affect females in diestrus. Ketamine sensitivity in diestrus mice increases to proestrus levels following estrogen receptor activation (Dossat et al., 2018). Additionally, ovariectomy abolishes the sensitivity of female animals to ketamine, while estrogen and progesterone treatment restores this sensitivity (Carrier and Kabbaj, 2013). Notably, the administration of progesterone enhanced male sensitivity to ketamine, further emphasizing the role of ovarian hormones and their receptors in the sex-dependent effects of ketamine (Saland et al., 2016).

Ketamine is metabolized by CYP enzymes in the liver, first into norketamine and then into hydroxynorketamine (HNK) through the actions of CYP2A6 and CYP2B6 (Portmann et al., 2010). These enzymes are inducible by estrogen via estrogen receptor alpha (ERα), which also serves as a key regulator of several other CYP enzymes (Higashi et al., 2007; Wang et al., 2019). Notably, (2 *R*,6 *R*) HNK, which exerts potent independent antidepressant effects, is found at higher concentrations in the plasma and brain tissue of female rodents (Zanos et al., 2016; Highland et al., 2022). Therefore, estrogen receptors play a crucial role in the therapeutic action of ketamine through its metabolism. It has been suggested that ERα triggers a metabolic cascade, enhancing the conversion of ketamine into its active metabolites (Ho et al., 2018). Ketamine and HNK exhibit comparable affinity to ERα, both of which upregulate this receptor to induce CYP2A6 and CYP2B6, facilitating further metabolism into HNK. These effects are blocked by pharmacological inhibition or knockdown of ERα (Ho et al., 2018). While these studies provide important evidence, they have not directly tested the contribution of ERα to the sex-dependent therapeutic effects of ketamine.

* Corresponding author.
E-mail address: gunes.unal@bogazici.edu.tr (G. Unal).

https://doi.org/10.1016/j.psyneuen.2025.107455
Received 24 November 2024; Received in revised form 26 February 2025; Accepted 31 March 2025
Available online 1 April 2025

In this study, we addressed this question by pharmacologically silencing ERα using its selective antagonist methyl-piperidino-pyrazole (MPP) prior to IP ketamine (10 mg/kg) administration in female Wistar rats. We assessed behavioral despair in the forced swim test (FST), locomotor activity in the open field test (OFT), anxiety-like behavior in the elevated plus maze (EPM), and fear memory processes through cued fear conditioning.

2. Methods

2.1. Subjects

Thirty-two adult female Wistar rats (4–6 months old; $M = 195.54$ g, $SD = 13.01$ g) were used in the experiment. Animals were housed under standard laboratory conditions (21 ± 1 °C; ~50 % humidity; 12:12 day/night cycle) with *ad libitum* access to food and water. All procedures were approved by the Boğaziçi University Institutional Ethics Committee for the Use of Animals in Experiments (2023–11).

2.2. Pharmacological agents

MPP (Cayman Chemical, MI, USA) was prepared by dissolving it in 20 % dimethyl sulfoxide (DMSO) and further diluting it with 0.9 % saline. Animals received two intraperitoneal (IP) injections of either 1 mg/kg MPP (1 ml/kg volume) or 20 % DMSO in saline as a vehicle. Ketamine (Keta-control, Doğa İlaç, Turkey) was diluted to a concentration of 10 mg/kg in 0.9 % saline. Animals were administered a single IP injection of either ketamine or saline as a vehicle.

2.3. Experimental design

To control for estrous cycle phases and ensure their even distribution across groups, the phases were monitored daily via vaginal lavage for nine days following the handling procedure (Fig. 1 A). Vaginal smears were air-dried, stained with cresyl violet or toluidine blue, and examined under a light microscope (Fig. 1B). Animals were randomly assigned to four groups ($n = 8$ per group) based on their estrous phases on Day 14, body weights, and home cages: vehicle (20 % DMSO in saline + saline), ketamine (20 % DMSO in saline + ketamine), MPP (MPP + saline), or MPP + ketamine. Ketamine was administered 30 minutes prior to forced swim test 2 (FST-2), while MPP injections were given immediately after forced swim test 1 (FST-1) and 90 minutes before FST-2 (Fig. 1 A). This treatment regimen was chosen to inhibit ERα activity during ketamine administration and its subsequent metabolization. The timing of MPP administration was based on previous studies that applied MPP either 24 h before a behavioral test (Jiang et al., 2021) or 24 h prior to and during the behavioral tests (Munive et al., 2016; Zhao et al., 2017).

FST sessions were analyzed using EthoVision XT 17 (Noldus, Netherlands), while the OFT, EPM and fear conditioning were coded using ezTrack open-source software. Arm entry counts in the EPM, headshaking and diving in the FST, rearing and grooming in the OFT, and darting and jumping behaviors during fear conditioning were manually analyzed by trained researchers blinded to the experimental conditions.

2.4. Forced swim test (FST)

A two-day FST protocol was conducted as previously described (Gokalp and Unal, 2024; water temperature = 25 ± 1°C). The first 5 minutes of FST-1 were analyzed and compared to FST-2 within each group, and FST-2 scores were compared across groups to assess behavioral despair. Time spent struggling and swimming were also measured in both sessions.

2.5. Open field test (OFT)

We conducted a 5-minute OFT session as described in Gokalp and Unal (2024), using an opaque square arena (70 × 70 cm), virtually divided into center and periphery zones, characterized by differing light intensities (center: 120 ± 10 lx; periphery: 60 ± 10 lx). Locomotor activity was analyzed based on the distance traveled (cm), while anxiety-like behavior was assessed by measuring the time spent in the center of the maze (s).

2.6. Elevated plus maze (EPM)

A plus-shaped elevated apparatus was used to assess anxiety-like behavior as described previously (Gokalp and Unal, 2024). Light intensities were measured to confirm a significant difference between the closed arms (30 ± 10 lx) and open arms (120 ± 10 lx). The time spent (s) in each type of arm and the number of arm entries were recorded.

2.7. Fear conditioning

We followed a three-day auditory fear conditioning paradigm. The acquisition phase consisted of five pairings of a conditional stimulus (CS, tone) and an unconditional stimulus (US, mild foot shock), with a random intertrial interval, in a conditioning chamber (Context A). This was followed by two days of extinction in a different apparatus (Context B), where 15 CS presentations occurred without the US. Fear response was measured as the percentage of time animals spent freezing during CS presentations, compared to baseline periods (10 minutes for the fear acquisition session and 3 minutes for the extinction sessions) (refer to Gokalp and Unal, 2024).

2.8. Statistical analysis

All statistical analyses were conducted using GraphPad Prism (9.5.1). A mixed-design analysis of variance (ANOVA; 2×2×2) was performed to assess the effects of ketamine and MPP on immobility, struggling, and swimming behaviors during FST sessions, as well as on freezing responses to the CSs during the fear conditioning phases (2×2×5). Two-way independent measures ANOVA was used for the EPM and OFT analyses, as well as for baseline fear responses. One animal was excluded from the FST analyses after being identified as an outlier, based on Tukey's fence outlier test ($k = 1.5$), due to floating for approximately 4 minutes.

3. Results

3.1. Estrus cycle measurement

The estrus cycle consists of four main phases, each lasting a different duration (Ajayi and Akhigbe, 2020). Fig. 1B illustrates how vaginal smear samples are classified into estrous phases in this study. The animals exhibited a regular estrous cycle (Fig. 1 C), and their phases on Day 14 indicated a balanced distribution across experimental groups (Fig. 1D).

3.2. Behavioral despair

Animals in the vehicle group spent significantly more time immobile in the FST-2 session compared to FST-1, indicating behavioral despair (Table 1; Fig. 1E). An interaction between session and ketamine treatment was observed, with the ketamine groups showing lower immobility in FST-2 compared to the vehicle group. However, MPP did not affect immobility, either alone or in interaction with ketamine. Struggling behavior was higher in FST-2 than in FST-1 (Table 1; Fig. 1 F), with an interaction among all three variables. Increased struggling behavior was observed only in the ketamine group, suggesting that MPP occluded

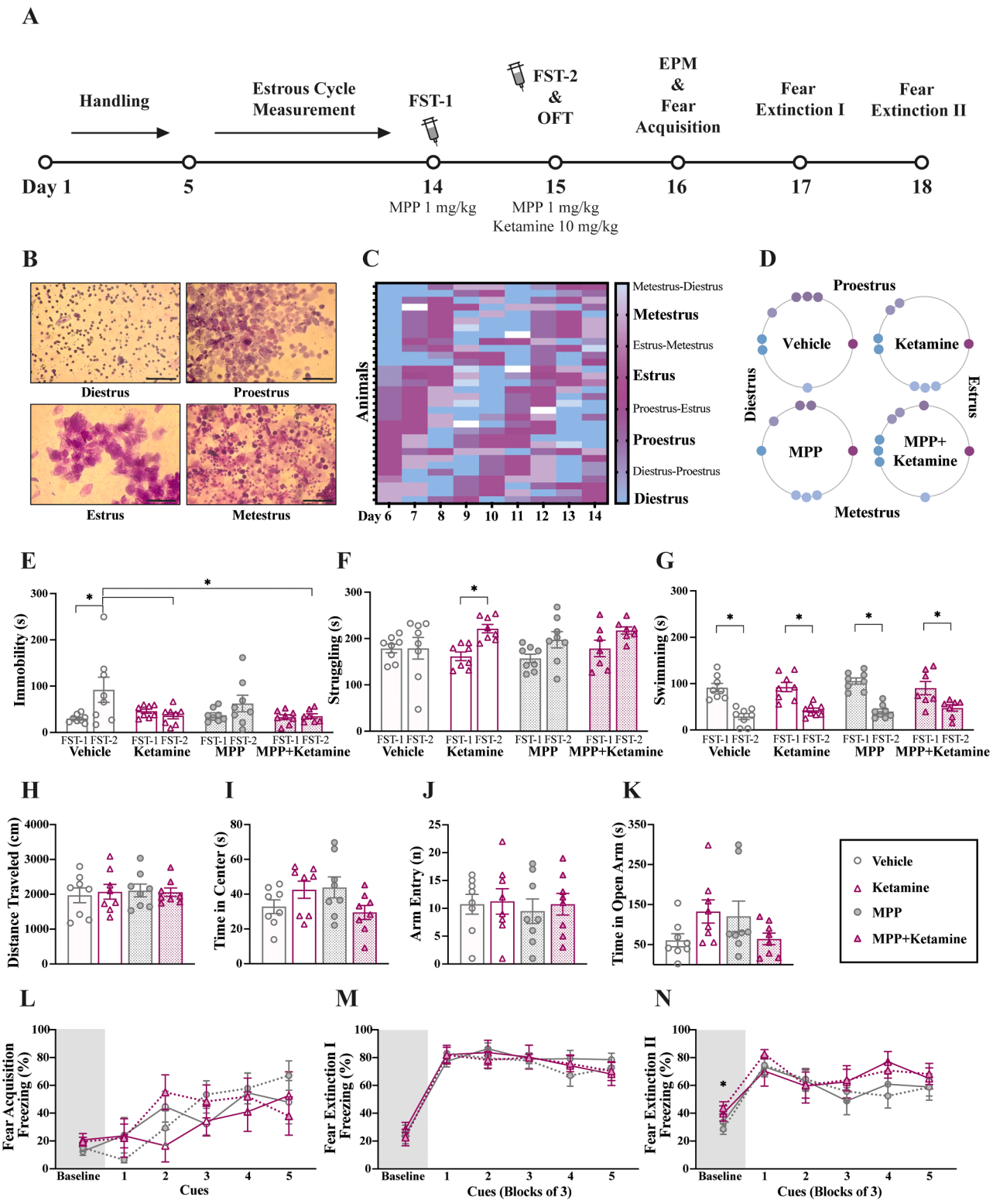


Fig. 1. Experimental design, procedures and results. **(A)** Experimental timeline showing the days of handling, vaginal lavage, behavioral tests and IP injections of MPP and ketamine. **(B)** Photographs of vaginal smears as examples of different phases of the estrus cycle. Scale bars represent 200 μm. **(C)** Heat map of the estrus phases of individual animals ($N = 32$) over 9 days, from the end of handling (Day 6) to the beginning of behavioral testing (Day 14). White boxes indicate missing data points. **(D)** Representative illustration of the distribution of animals into experimental groups based on their cycle phase on Day 14. **(E-G)** FST bar charts showing the time spent (E) immobile, (F) struggling, and (G) swimming in both sessions. **(H-I)** OFT results showing (H) locomotor activity levels and (I) the time spent at the center of the arena. **(J-K)** EPM results showing (J) arm entry counts and (K) the duration spent in the open arms. **(L-N)** Line graphs illustrating the freezing percentages of animals to the CSs during (L) fear acquisition, (M) Extinction I, and (N) Extinction II. Baseline recordings are shown with gray backgrounds. Asterisks (*) indicate statistical differences ($p < 0.05$). Error bars represent SEM.

Table 1
Statistical test results for the FST, OFT (left columns), EPM and fear conditioning (right columns).

Test	Variable	Statistical Test	Factor/comparison	*df*	*F/t*	*p*	*η2/d*	Test	Variable	Statistical Test	Factor/comparison	*df*	*F/t*	*p*	*η2/d*
FST	Immobility	3-way RMANOVA	Sessions	1,27	6.638	.016 *	7.017	EPM	Arm Entries	Two-way ANOVA	Ketamine	1,28	0.181	0.674	0.637
			SessionsxKetamine	1,27	8.555	.007 *	9.042				MPP	1,28	0.181	0.674	0.637
			SessionsxMPP	1,27	0.523	0.476	0.552				KetaminexMPP	1,28	0.033	0.857	0.117
			KetaminexMPP	1,27	0.027	0.87	0.045	EPM	Time in Open Arm	Two-way ANOVA	Ketamine	1,28	0.083	0.775	0.245
			SessionsxKetaminexMPP	1,27	2.556	0.122	2.701				MPP	1,28	0.025	0.875	0.074
FST	Immobility	Sidak corrected *t*-test	FST−1 vs. FST−2 (Vehicle)	27	3.981	.003 *	1.134				KetaminexMPP	1,28	5.966	.021 *	17.51
FST	Immobility	Sidak corrected *t*-test	Vehicle vs. Ketamine (FST−2)	54	3.179	.017 *	1.001	FC Acquisition	Baseline Freezing	Two-way ANOVA	Ketamine	1,24	3.475	0.075	12.59
											MPP	1,24	0.037	0.849	0.134
FST	Immobility	Sidak corrected *t*-test	Vehicle vs. MPP	54	1.673	0.522	0.454				KetaminexMPP	1,24	0.309	0.584	1.119
FST	Immobility	Sidak corrected *t*-test	Vehicle vs. MPP+Ketamine	54	3.117	0.020 *	1.029	FC Acquisition	Freezing to CSs	3-way RMANOVA	Cues	4,96	5.964	< .001 *	12.3
FST	Struggling	3-way RMANOVA	Sessions	1,27	22.89	< .001 *	16.6				Ketamine	1,24	0.21	0.651	0.246
			SessionsxKetamine	1,27	3.916	0.058	2.841				MPP	1,24	0.611	0.442	0.717
			SessionsxMPP	1,27	0.430	0.518	0.312				CuesxKetamine	4,96	0.519	0.722	1.069
			KetaminexMPP	1,27	0.114	0.739	0.225				CuesxMPP	4,96	0.891	0.473	1.836
			SessionsxKetaminexMPP	1,27	4.378	.046 *	3.175				KetaminexMPP	1,24	0.25	0.622	0.293
FST	Struggling	Sidak corrected *t*-test	FST−1 vs. FST−2 (Vehicle)	27	0.029	0.999	0.008				CuesxKetaminexMPP	4,96	2.17	0.078	4.476
FST	Struggling	Sidak corrected *t*-test	FST−1 vs. FST−2 (Ketamine)	27	4.173	.002 *	2.32	FC Extinction I	Baseline Freezing	Two-way ANOVA	Ketamine	1,24	0.118	0.734	0.476
FST	Struggling	Sidak corrected *t*-test	FST−1 vs. FST−2 (MPP)	27	2.826	0.06	1.027				MPP	1,24	0.522	0.477	2.111
FST	Struggling	Sidak corrected *t*-test	FST−1 vs. FST−2 (MPP+Ketamine)	27	2.535	0.115	1.067				KetaminexMPP	1,24	0.117	0.736	0.471
								FC Extinction I	Freezing to CSs	3-way RMANOVA	Cues	4,96	3.126	.018 *	5.766
FST	Swimming	3-way RMANOVA	Sessions	1,27	199.3	< .001 *	59.59				Ketamine	1,24	0.019	0.89	0.037
			SessionsxKetamine	1,27	5.100	.032 *	1.525				MPP	1,24	0.26	0.615	0.496
			SessionsxMPP	1,27	0.062	0.805	0.019				CuesxKetamine	4,96	0.552	0.698	1.019
			KetaminexMPP	1,27	0.608	0.442	0.63				CuesxMPP	4,96	0.547	0.702	1.008
			SessionsxKetaminexMPP	1,27	0.414	0.525	0.124				KetaminexMPP	1,24	0.164	0.689	0.312
FST	Swimming	Sidak corrected *t*-test	FST−1 vs. FST−2 (Vehicle)	27	8.131	< .001 *	2.843				CuesxKetaminexMPP	4,96	0.595	0.667	1.097
FST	Swimming	Sidak corrected *t*-test	FST−1 vs. FST−2 (Ketamine)	27	6.488	< .001 *	2.245	FC Extinction II	Baseline Freezing	Two-way ANOVA	Ketamine	1,24	4.589	.043 *	15.26
FST	Swimming	Sidak corrected *t*-test	FST−1 vs. FST−2 (MPP)	27	8.533	< .001 *	3.837				MPP	1,24	0.013	0.912	0.042
FST	Swimming	Sidak corrected *t*-test	FST−1 vs. FST−2 (MPP+Ketamine)	27	5.219	< .001 *	1.435				KetaminexMPP	1,24	0.801	0.38	2.664
								FC Extinction II	Freezing to CSs	3-way RMANOVA	Cues	4,96	5.152	< .001 *	7.128
OFT	Locomotion	Two-way ANOVA	Ketamine	1,28	0.020	0.888	0.072				Ketamine	1,24	1.144	0.296	2.487
			MPP	1,28	0.112	0.741	0.395				MPP	1,24	0.032	0.86	0.069
			KetaminexMPP	1,28	0.163	0.689	0.577				CuesxKetamine	4,96	2.016	0.098	2.79
OFT	Time in Center	Two-way ANOVA	Ketamine	1,28	0.226	0.638	0.655				CuesxMPP	4,96	0.839	0.504	1.161
			MPP	1,28	0.048	0.829	0.138				KetaminexMPP	1,24	0.027	0.871	0.058
			KetaminexMPP	1,28	6.262	.018 *	18.13				CuesxKetaminexMPP	4,96	0.284	0.887	0.394

this effect. In addition, swimming duration decreased in the second session for all groups (Table 1; Fig. 1 G), with a ketamine-session interaction, but no significant group differences (all $ps > .05$, Sidak corrected t-tests). Ketamine also reduced diving in FST-2 ($F(1,27) = 8.433$, $p = .007$, $\eta 2 = 19.890$, two-way ANOVA), while MPP had no effect. Neither treatment altered headshaking (all $ps > .05$, two-way ANOVAs).

3.3. Locomotor activity and anxiety

Similar distances were traveled by all groups in the OFT, indicating that pharmacological treatments did not affect locomotor activity (Table 1; Fig. 1H). Rearing and grooming counts were also not different (all $ps > .05$, two-way ANOVAs). However, an interaction between ketamine and MPP was observed in the time spent in the center of the arena (Table 1; Fig. 1I), with no post-hoc differences (all $ps > .05$, Sidak corrected t-tests). Similarly, the time spent in the open arms of the EPM was influenced by the interaction between ketamine and MPP treatments (Table 1; Fig. 1 K), despite the lack of significant pairwise differences (all $ps > .05$, Sidak corrected t-tests). Neither ketamine nor MPP treatments altered the number of arm entries in the EPM, suggesting comparable activity and exploration levels across groups (Table 1; Fig. 1 J).

3.4. Fear memory

Animals underwent successful fear conditioning, showing an increased freezing response to the cues as the pairing progressed ($n = 28$; Table 1; Fig. 1 L). During the extinction phases, freezing percentages were analyzed across five blocks, each consisting of an average of three cues. Conditioned animals exhibited a reduction in freezing responses across the blocks in each session (Table 1; Fig. 1 M, N). However, neither ketamine nor MPP treatments had any effect in any of the sessions (Table 1; Fig. 1L-N), including jumping and darting instances during fear acquisition (all $ps > .05$, two-way ANOVAs). Interestingly, ketamine increased baseline freezing responses during the second extinction session (Table 1; Fig. 1 N), suggesting fear generalization.

4. Discussion

Our results showed that intraperitoneal administration of ketamine (10 mg/kg) produced antidepressant-like effects by reducing behavioral despair in female Wistar rats. However, this effect was not altered by pretreatment with MPP, suggesting that ERα activation may not be a key mechanism underlying the heightened antidepressant sensitivity observed in females. Notably, ketamine-treated animals exhibited significantly increased struggling behavior, characterized by high mobility (Aykan et al., 2024), in the FST-2 compared to FST-1. This increase, however, was diminished and lost statistical significance following MPP pretreatment. These findings suggest that ERα activation may partially contribute to the active stress response typically observed with ketamine treatment. It is important to note that the MPP+Ketamine group showed high variability in FST-1, which may have contributed to the loss of this significant effect.

In contrast to its limited role in behavioral despair, ERα antagonism appeared to modulate the relatively higher open space preference observed in the OFT and EPM, which are typically interpreted as measures of anxiety-like behavior (Schmitt and Hiemke, 1998; Gencturk and Unal, 2024), but have also been used to evaluate risk-taking (Rodgers and Dalvi, 1997; Gencturk and Unal, 2024). While group-level differences were not statistically significant, both the ketamine-only and MPP-only groups spent more time in the open, brighter areas of these mazes. Given previous reports suggesting anxiogenic effects of ERα (Spiteri et al., 2010; 2012), this relative preference for open spaces could be interpreted as enhanced exploratory behavior. Interestingly, this trend was abolished when ketamine and MPP were administered together, potentially because ERα may regulate ketamine's metabolism, with (*R,S*)-ketamine and its metabolites exerting different effects on risk-taking or exploratory behavior, consistent with their varying antidepressant efficacy (Zanos et al., 2016; Zhang et al., 2023). Hence, previous studies on the effects of (*R,S*)-ketamine and its metabolites on anxiety-like behavior have shown mixed results, with these effects strongly dependent on the specific experimental protocol used (Chen et al., 2020; Chen et al.; 2023). Alternatively, our findings might suggest competition between MPP and ketamine for ERα binding, which could prevent both substances from exerting their full effects (Ho et al., 2018). Additionally, the treatment timepoints at which the behavioral tests were applied may have obscured the overall behavioral effects of ketamine and MPP on anxiety-like and fear memory measures. We implemented the EPM and fear conditioning tests one day after drug administration, which did not allow for testing their potential acute effects. In fact, the effects of ketamine on anxiety and fear-related behavior are especially diverse, depending on factors such as the time of administration and dosage (Silote et al., 2020).

It is important to note that ovarian hormones and ERα likely interact with ketamine at multiple levels beyond the regulation of its metabolism. Estrogens have therapeutic effects of their own, primarily mediated by ERβ (Osterlund, 2010), while ERα inhibition can abolish the antidepressant effects of estradiol in a sex- and age-dependent manner (Jiang et al., 2021). Furthermore, the selective expression of ERα in limbic structures (Shughrue et al., 1997), such as the lateral habenula, which is implicated in ketamine's therapeutic effects (Kingir et al., 2023), underscores the circuit-level contributions to the complexity of the ERα-ketamine interaction.

Taken together, our results suggest that the interaction between ERα and ketamine observed in vitro (Ho et al., 2018) has minimal translation into the behavioral effects of ketamine. While the acute antidepressant effects of ketamine appear to occur independently of ERα activity, ERα may influence neural circuits involved in anxiety-like behavior and partially modulate ketamine's sustained anxiolytic effects. Ovarian hormones likely mediate the therapeutic effects of ketamine through various mechanisms, and further research is necessary to clarify the contribution of the ERα to the sexually dimorphic effects of ketamine.

Funding

this work was supported by EMBO (grant no: 4432)

CRediT authorship contribution statement

Unal Gunes: Writing – review & editing, Project administration, Methodology, Conceptualization. **Sen Zeynep:** Methodology, Investigation. **Yuksel Bahar:** Writing – original draft, Methodology, Investigation. **Idil Ece:** Writing – original draft, Methodology, Investigation, Conceptualization.

Declaration of Competing Interest

None.

Acknowledgements

The authors thank Dilan Gökalp for her contributions to the experimental procedures.

References

Ajayi, A.F., Akhigbe, R.E., 2020. Staging of the estrous cycle and induction of estrus in experimental rodents: an update. Fertil. Res. Pract. 6, 5. https://doi.org/10.1186/s40738-020-00074-3.

Aykan, D., Genc, M., Unal, G., 2024. Environmental enrichment enhances the antidepressant effect of ketamine and ameliorates spatial memory deficits in adult

rats. Pharmacol. Biochem. Behav. 240, 173790. https://doi.org/10.1016/j.pbb.2024.173790.
Carrier, N., Kabbaj, M., 2013. Sex differences in the antidepressant-like effects of ketamine. Neuropharmacology 70, 27–34. https://doi.org/10.1016/j.neuropharm.2012.12.009.
Chen, B.K., Luna, V.M., LaGamma, C.T., Xu, X., Deng, S.X., Suckow, R.F., Denny, C.A., 2020. Sex-specific neurobiological actions of prophylactic (R, S)-ketamine,(2 R, 6 R)-hydroxynorketamine, and (2 S, 6 S)-hydroxynorketamine. Neuropsychopharmacology 45 (9), 1545–1556.
Chen, Y., Yan, P., Wei, S., Zhu, Y., Lai, J., Zhou, Q., 2023. Ketamine metabolite alleviates morphine withdrawal-induced anxiety via modulating nucleus accumbens parvalbumin neurons in male mice. Neurobiol. Dis. 186, 106279.
Dossat, A.M., Wright, K.N., Strong, C.E., Kabbaj, M., 2018. Behavioral and biochemical sensitivity to low doses of ketamine: influence of estrous cycle in C57BL/6 mice. Neuropharmacology 130, 30–41. https://doi.org/10.1016/j.neuropharm.2017.11.022.
Gencturk, S., Unal, G., 2024. Rodent tests of depression and anxiety: construct validity and translational relevance. Cogn., Affect. Behav. Neurosci. 24 (2), 191–224. https://doi.org/10.3758/s13415-024-01171-2.
Gokalp, D., Unal, G., 2024. The role of mGluR5 on the therapeutic effects of ketamine in Wistar rats. Psychopharmacology 241 (7), 1399–1415. https://doi.org/10.1007/s00213-024-06571-3.
Higashi, E., Fukami, T., Itoh, M., Kyo, S., Inoue, M., Yokoi, T., Nakajima, M., 2007. Human CYP2A6 is induced by estrogen via estrogen receptor. Drug Metab. Dispos. 35 (10), 1935–1941. https://doi.org/10.1124/dmd.107.016568.
Highland, J.N., Farmer, C.A., Zanos, P., Lovett, J., Zarate Jr, C.A., Moaddel, R., Gould, T. D., 2022. Sex-dependent metabolism of ketamine and (2 R, 6 R)-hydroxynorketamine in mice and humans. J. Psychopharmacol. 36 (2), 170–182.
Ho, M.-F., Correia, C., Ingle, J.N., Kaddurah-Daouk, R., Wang, L., Kaufmann, S.H., Weinshilboum, R.M., 2018. Ketamine and ketamine metabolites as novel estrogen receptor ligands: Induction of cytochrome P450 and AMPA glutamate receptor gene expression. Biochem. Pharmacol. 152, 279–292. https://doi.org/10.1016/j.bcp.2018.03.032.
Jiang, X., Chen, Z., Yu, X., Chen, J., Sun, C., Jing, C., Xu, L., Liu, F., Ni, W., Chen, L., 2021. Lipopolysaccharide-induced depression is associated with estrogen receptor-α/SIRT1/NF-κB signaling pathway in old female mice. Neurochem. Int. 148, 105097. https://doi.org/10.1016/j.neuint.2021.105097.
Kingir, E., Sevinc, C., Unal, G., 2023. Chronic oral ketamine prevents anhedonia and alters neuronal activation in the lateral habenula and nucleus accumbens in rats under chronic unpredictable mild stress. Neuropharmacology 228, 109468. https://doi.org/10.1016/j.neuropharm.2023.109468.
Munive, V., Santi, A., Torres-Aleman, I., 2016. A concerted action of estradiol and insulin like growth factor I underlies sex differences in mood regulation by exercise. Sci. Rep. 6 (1), 25969.
Osterlund, M.K., 2010. Underlying mechanisms mediating the antidepressant effects of estrogens. Biochim. Biophys. Acta 1800 (10), 1136–1144. https://doi.org/10.1016/j.bbagen.2009.11.001.
Portmann, S., Kwan, H.Y., Theurillat, R., Schmitz, A., Mevissen, M., Thormann, W., 2010. Enantioselective capillary electrophoresis for identification and characterization of human cytochrome P450 enzymes which metabolize ketamine and norketamine in vitro. J. Chromatogr. A 1217 (51), 7942–7948.
Rodgers, R.J., Dalvi, A., 1997. Anxiety, defence and the elevated plus-maze. Neurosci. Biobehav. Rev. 21 (6), 801–810.
Saland, S.K., Schoepfer, K.J., Kabbaj, M., 2016. Hedonic sensitivity to low-dose ketamine is modulated by gonadal hormones in a sex-dependent manner. Sci. Rep. 6 (1), 21322.
Schmitt, U., Hiemke, C., 1998. Combination of open field and elevated plus-maze: a suitable test battery to assess strain as well as treatment differences in rat behavior. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 22 (7), 1197–1215.
Shughrue, P.J., Lane, M.V., Merchenthaler, I., 1997. Comparative distribution of estrogen receptor-α and -β mRNA in the rat central nervous system. J. Comp. Neurol. 388, 507–525. https://doi.org/10.1002/(SICI)1096-9861(19971201)388:4< 507::AID-CNE1> 3.0.CO;2-6.
Silote, G.P., de Oliveira, S.F., Ribeiro, D.E., Machado, M.S., Andreatini, R., Joca, S.R., Beijamini, V., 2020. Ketamine effects on anxiety and fear-related behaviors: current literature evidence and new findings. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 100, 109878.
Spiteri, T., Musatov, S., Ogawa, S., Ribeiro, A., Pfaff, D.W., Ågmo, A., 2010. The role of the estrogen receptor α in the medial amygdala and ventromedial nucleus of the hypothalamus in social recognition, anxiety and aggression. Behav. Brain Res. 210 (2), 211–220.
Spiteri, T., Ogawa, S., Musatov, S., Pfaff, D.W., Ågmo, A., 2012. The role of the estrogen receptor α in the medial preoptic area in sexual incentive motivation, proceptivity and receptivity, anxiety, and wheel running in female rats. Behav. Brain Res. 230 (1), 11–20.
Wang, D., Lu, R., Rempala, G., Sadee, W., 2019. Ligand-free estrogen receptor α (ESR1) as master regulator for the expression of CYP3A4 and other cytochrome P450 enzymes in the human liver. Mol. Pharmacol. 96 (4), 430–440. https://doi.org/10.1124/mol.119.116897.
Zanos, P., Moaddel, R., Morris, P.J., Georgiou, P., Fischell, J., Elmer, G.I., Alkondon, M., Yuan, P., Pribut, H.J., Singh, N.S., Dossou, K.S.S., Fang, Y., Huang, X.-P., Mayo, C.L., Wainer, I.W., Albuquerque, E.X., Thompson, S.M., Thomas, C.J., Zarate Jr, C.A., Gould, T.D., 2016. NMDAR inhibition-independent antidepressant actions of ketamine metabolites. Nature 533 (7604), 481–486. https://doi.org/10.1038/nature17998.
Zhang, K., Yao, Y., Hashimoto, K., 2023. Ketamine and its metabolites: potential as novel treatments for depression. Neuropharmacology 222, 109305. https://doi.org/10.1016/j.neuropharm.2022.109305.
Zhao, Y., He, L., Zhang, Y., Zhao, J., Liu, Z., Xing, F., Zhang, J., 2017. Estrogen receptor alpha and beta regulate actin polymerization and spatial memory through an SRC-1/mTORC2-dependent pathway in the hippocampus of female mice. J. Steroid Biochem. Mol. Biol. 174, 96–113.