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Research Paper

Ketamine attenuates the effects of intermittent social defeat on anxiety, social interaction and cocaine-induced conditioned place preference in male mice

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ABSTRACT

Mice exposed to intermittent social defeat (ISD) stress in late adolescence exhibit short-term anxiety- and depression-like behaviours and demonstrate greater sensitivity to the rewarding effects of cocaine in adulthood. Furthermore, the development of depression-like symptoms predicts subsequent enhanced vulnerability to cocaine reward. The aim of this study was to investigate whether ketamine, a non-competitive glutamate N-methyl-D-aspartate (NMDA) receptor antagonist with antidepressant properties, could prevent the short-term effects of ISD on anxiety- and depression-like behaviours and the long-term effects of ISD on the cocaine-induced conditioned place preference. Four groups of late adolescent C57BL/6 male mice were used. One non-stressed group (control) and three ISD-exposed groups treated with ketamine (0, 10 or 30 mg/kg). After the last defeat episode, the mice were tested in the elevated plus maze, social interaction, splash and tail suspension tests. Three weeks later, the mice were conditioned with cocaine (1 mg/kg). Stressed mice showed anxiety, displayed a deficit in social interaction, spent less time immobile in the tail suspension test and developed a cocaine place preference. Ketamine attenuated ISD-induced anxiety, social avoidance and cocaine reward potentiation. These results support the usefulness of ketamine in preventing some effects of social stress.

1. Introduction

Exposure to stressful life events is one of the environmental factors more closely associated with an increased risk of developing psychiatric illnesses [1] and drug use disorders [2–4]. In previous studies we have observed that exposure to intermittent social defeat (ISD), an ethological model of social stress, during late adolescence (post-natal days (PND) 47, 50, 53 and 56) caused short-term behavioural changes in male mice, including anxiety-like effects in the elevated plus maze (EPM), as indicated by reduced time spent in the open arms of the EPM; depression-like effects, such as social avoidance in the social interaction test and reduced grooming in the splash test; and decreased immobility in the tail suspension test [5–7]. Furthermore, mice exposed to ISD during late adolescence exhibited heightened sensitivity to the rewarding effects of cocaine in the conditioned place preference (CPP) paradigm, as defeated mice acquired CPP with a cocaine dose ineffective in inducing rewarding effects in non-stressed mice [5–9]. The development of depression-like behaviour (social avoidance) in the short term after ISD has been shown to predict subsequent enhanced vulnerability to cocaine reward [5]. Absence of depression-like behaviour is a trait associated with the resilience to cocaine CPP potentiation induced by ISD [5]. Additionally, environmental manipulations that reduce depression-like behaviour in the social interaction and splash tests such as exposure to voluntary physical activity [6] or a brief episode of maternal separation [7], also reduce enhanced sensitivity to cocaine CPP.

Regarding the neurobiological substrates of the effects of ISD on cocaine reward, we have previously observed that administering the glutamate N-methyl-D-aspartate (NMDA) antagonist memantine [8] or the neuronal nitric oxide synthase (nNOS) inhibitor 7-nitroindazole

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(7-NI) [9] before each defeat episode (PND 47, 50, 53 and 56) prevented ISD-induced potentiation of cocaine CPP in adult mice. Furthermore, a similar ISD protocol (on PND 54, 56, 58 and 60) reduced the expression of several NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunits, primarily GluN1 and GluA1, in the striatum and hippocampus [10], and increased nitrite levels in these structures [11] 48 h after the last episode of defeat. Therefore, these results suggest that glutamate receptors and nNOS, a downstream signal molecule of NMDA receptor activation, play a role in the effects of ISD stress on cocaine reward and that compounds modulating glutamatergic-nitric oxide signalling could enhance resilience to stress.

Ketamine is a rapid-onset antidepressant, which acts as a non-competitive antagonist of the NMDA glutamate receptor. It blocks synaptic NMDA receptors more effectively than extra-synaptic ones [12] subsequently inducing stimulation of AMPA receptors [13]. The effects of ketamine on the behavioural responses to social stress, including depression- and anxiety-like symptoms, have been studied using acute social defeat (ASD) and chronic social defeat stress (CSDS) protocols. In particular, the CSDS protocol, in which experimental animals are exposed to daily episodes of defeat for 10 consecutive days, is a validated animal model of depression [14,15]. A single dose of ketamine reversed social avoidance induced by ASD [16]. Similarly, the acute administration of ketamine prevented depression-like effects and impairment of social behaviour induced by CSDS [13,17–24]. Treatment with ketamine for two consecutive days following the last CSDS episode reversed social deficits and depression-like behaviours [25], while repeated ketamine administration during adolescence prevented the depressive-like behaviours induced by CSDS [26]. Ketamine has also been shown to attenuate impairments in spatial working memory [27] and goal-directed behaviour [28] induced by CSDS. However, the effects of ketamine on the short- and long-term behavioural consequences of ISD have yet to be evaluated. As previously mentioned, the ISD protocol is a valuable tool for modelling the effects of social stress, particularly the heightened vulnerability to the rewarding effects of cocaine. It also allows for the evaluation of environmental and pharmacological strategies designed to enhance resilience to these effects [5–9]. In this regard, we previously observed that an intermediate dose of the NMDA antagonist memantine prevented the ISD-induced potentiation of cocaine CPP; however, in this study we did not assess the effects of memantine on the depression-like behaviour induced by ISD [8]. The profile of ketamine on the glutamate receptors and its antidepressant efficacy suggest that this drug can be effective in preventing the depression-like effects and the potentiation of cocaine reward induced by ISD, adding evidence to the role of glutamate in the effects of ISD.

Therefore, the aim of the present study was to evaluate whether treatment with ketamine could prevent the short-term effects of ISD exposure on anxiety- and depression-like behaviours in young mice, as observed in the EPM, social interaction, splash and tail suspension tests. Additionally, we investigated whether ketamine could counteract the impact of adolescent ISD exposure on the enhancement of cocaine-induced CPP in adult mice. Given the antidepressant effects of ketamine and its mechanism of action as an NMDA antagonist, we hypothesise that this drug could effectively prevent the negative consequences of social defeat stress.

2. Materials and methods

2.1. Subjects

A total of 56 male mice (40 C57BL/6 and 16 OF1) from Charles River (France) were delivered to our laboratory at 21 days and 42 days of age, respectively. The experimental mice (C57BL/6) were housed in groups of four to five in plastic cages (25×25×14.5 cm). The mice used as aggressive opponents (OF1) were housed individually in plastic cages (23×32×20 cm) to induce heightened aggression [29]. All mice were housed under standard laboratory conditions: a constant temperature; a reversed light schedule (white lights on from 19:30 to 07:30); and food and water available ad libitum, except during behavioural tests. Experimental protocols were initiated 26 days after the mice arrived at the laboratory. All procedures involving the mice and their care were conducted in accordance with Directive 2010/63/EU and were approved by the Ethics Committee for Experimental Research at the University of Valencia and the regional government (2023-VSC-PEA-0229).

2.2. Drugs

Sixty minutes prior to each defeat episode, the experimental mice were injected with either 10 or 30 mg/kg of ketamine (Sigma Aldrich, St Louis, MO, USA), dissolved in physiological saline (NaCl 0.9 %). These doses and the timing of administration were based on a review of the literature concerning the effects of this compound on stress-induced alterations in rodents [21,30–33]. To induce CPP, the experimental mice were injected with 1 mg/kg of cocaine (Alcaliber Laboratory, Madrid, Spain) dissolved in physiological saline. All compounds were injected intraperitoneally at a volume of 0.01 ml/g of body weight. The cocaine dose was selected on the basis of previous studies carried out in our laboratory that demonstrated that 1 mg/kg is a subthreshold dose in naïve male mice and allow us to detect an increase in the sensitivity of stressed mice to the rewarding effects of cocaine in the CPP [5,11].

2.3. Experimental design

Four groups of mice were used according to the treatment received: a control group (Saline+No stress, $n = 8$); a stressed group (Saline+ISD, $n = 8$); and two stressed groups that were treated with ketamine (10 or 30 mg/kg) before each episode of ISD (K10+ISD and K30+ISD, $n = 12$). Shortly after the last episode of stress (within 24–48 h), the mice were tested in the EPM, social interaction test (SIT), splash test (SPT) and tail suspension test (TST). All experiments took place during the dark period (8:30–16:30) in an environment different to that of the confrontation sessions. To facilitate adaptation, the mice were transported to the dimly illuminated experimental room 1 h prior to testing. During the behavioural tests the experimental room was illuminated with a dim red light (40 lx at 1 m above floor level). The order of the behavioural tests was based on previous studies according to the degree of stress that the same tests induced in the mice. This was done to prevent previous experience from affecting performance in subsequent tests [5]. As open arm measurements are very sensitive to environmental conditions and prior manipulation of the animals, we decided to perform the EPM first. Following the same logic, the TST was performed last because it is the most stressful test. Subsequently, after an interval of 3 weeks, all mice were conditioned in the CPP paradigm with a subthreshold dose of cocaine (1 mg/kg). Exposing mice to repeated testing shortly after ISD could have confounding effects, particularly with regard to the potential influence of stress induced by the TST. However, it is important to note that both the ISD and control groups underwent the same behavioural tests and experienced their potential stressful effects. Additionally, more than three weeks elapsed between the TST and the final CPP reward evaluation, during which time the mice were left undisturbed.

Intermittent Social Defeat (ISD)

The ISD procedure consisted of four encounters, each separated by an interval of 72 h (PND 47, 50, 53 and 56) - with an isolated conspecific mouse (OF1). This resulted in the experimental animal being defeated. Each 25-min encounter consisted of three phases, begin with the experimental animal (intruder) being introduced to the home cage of the aggressive opponent (resident) for 10 min. During this initial phase, the intruder was protected from attack by a wire mesh wall, which permitted social interaction and threats from the aggressive male resident. The wire mesh was then removed from the cage, allowing confrontation between the two mice for 5 min. In the third phase, the

wire mesh was returned to the cage to separate the two animals once again for a further 10 min, allowing social threats from the resident. Intruder mice were exposed to a different aggressor mouse during each episode of social defeat. An animal was defined as defeated if it adopted a posture signifying defeat, characterised by an upright submissive position, limp forepaws, an upwardly angled head and retracted ears [34,35]. All of the experimental mice displayed defeat, given that they all faced resident mice with high levels of aggression as mentioned above. The first and fourth agonistic encounters were videotaped and evaluated by an observer who was blind to the treatment [36] using a computerised system (Raton Time 1.0 software; Fixma SL, Valencia, Spain). The time spent in avoidance/flee and defence/submission by the experimental mice and the time spent in threat and attack by the aggressive resident mice were measured, as were the frequencies and latencies of these behaviours. The control (non-stressed) group underwent the same protocol, without a resident mouse in the cage.

Elevated Plus Maze (EPM)

The effects of ISD on anxiety were evaluated on PND 57 using the EPM paradigm. This test is based on mice's natural aversion to open, elevated areas and their spontaneous exploratory behaviour in novel environments. The apparatus consisted of four arms (two open and two enclosed, each measuring 30 × 5 cm) which formed a central platform (5 × 5 cm) at their junction. The maze's floor was made of black Perspex and the enclosed arms' walls were made of transparent Perspex. The open arms had a small raised edge (0.25 cm) to provide the animals with additional grip. The entire apparatus was elevated 45 cm above floor level. Total time spent in the open and closed arms, number of entries into the open and closed arms, and percentage of time and entries into the open arms are commonly considered indicators of anxiety induced by open spaces in mice. Therefore, anxiety levels are considered to be lower when the measurements in the open arms are higher and those in the closed arms are lower, and vice versa [37]. Furthermore, the total number of entries into the arms is regarded as a measure of locomotor activity [38]. At the start of each trial, the mice were placed on the central platform facing an open arm and allowed to explore it for 5 min. The maze was cleaned with a 7 % alcohol swab after each test and left to dry completely. The behaviour of the mice was video recorded and later analysed by a researcher who was unaware of the experimental conditions, using a computerised method (Raton Time 1.0 software; Fixma SL, Valencia, Spain). Values recorded during the test period included the frequency of entries and the time spent in each section of the apparatus (open arms, closed arms and central platform). An arm was considered to have been visited when the animal placed all four paws on it. The following measures were taken into account in the statistical analyses: latency to first enter the open arms (LOA); time spent in the open arms (TOA); number of entries into the open arms (EOA); percentage of time spent in the open arms (%TOA), calculated as [(open/open + closed) × 100]; percentage of open arm entries (%EOA); and total entries into the arms (TotalE).

2.4. Social interaction test (SIT)

Twenty-four hours after the final defeat or exploration (PND 57), the social behaviour of the mice was assessed using an open field (37 × 37 × 30 cm). A perforated Perspex cage (10 × 6.5 × 30 cm) was placed on one of the walls of the open field. Once the animals were habituated to the room, each one was placed in the centre of the open field and allowed to explore it twice under two different experimental conditions. The first time (object phase) the perforated Perspex cage was empty. After 10 min of exploration, the experimental mouse was returned to its home cage for 2 min. Next, to safeguard the experimental mouse from attack, a mouse of the OF1 strain was confined to the perforated cage and the experimental mouse was reintroduced into the open field for 10 min (social phase). The OF1 mouse was unfamiliar to the experimental mouse (i.e., a different mouse to the one used in the ISD episodes). In both phases, the time spent in the 8 cm area surrounding the perforated cage – the interaction zone – was recorded automatically using the Ethovision 2.0 software package (Noldus, Wageningen, The Netherlands). An index of social interaction (ISI) was obtained [time spent in the interaction zone during the social phase/(time spent in the interaction zone during the social phase + time spent in the interaction zone during the object phase); 39]. The ISI is commonly used as an index of social preference-avoidance [40].

2.5. Splash test (SPT)

The SPT test was conducted on PND 58 to evaluate depressive-like symptoms [41]. In this test, each mouse was placed in a transparent cage (15×30×20 cm) and sprayed with a 10 % sucrose solution on the dorsal coat. The behaviour of the mice was then videotaped and analysed using a computerised method (Raton Time 1.0 software; Fixma SL, Valencia, Spain). The behaviour of the mice was evaluated based on three parameters: time spent in grooming, the latency to the first grooming, and the frequency of grooming.

2.6. Tail suspension test (TST)

The TST measures the behavioural variable of immobility, which is considered to indicate despair [42]. It is based on the observation that rodents develop an immobile posture after making initial escape-oriented movements when placed in an inescapable, stressful situation. In the case of the TST, this situation involves the hemodynamic stress of being suspended by the tail in an uncontrollable manner [43]. This has been used as a measure of behavioural depression because when antidepressant treatments are administered prior to the test, rodents exhibit in escape-directed behaviours for longer than after treatment with a placebo [42]. Forty-eight hours after the last social defeat or exploration (PND 58), we investigated whether our social defeat procedure modified the length of time spent in immobile positions in the TST. In accordance with the protocol described by Vaugeois [44], mice were suspended by the tail using adhesive tape from a hook during a 6-min test period. Their behaviour was video recorded and later analysed by an observer who was unaware of the treatment received by the animal, using a computerised method (Raton Time 1.0 software; Fixma SL, Valencia, Spain). The parameters considered for statistical analysis were total time spent immobile and latency to become immobile.

2.7. Conditioned place preference (CPP)

Three weeks after the last episode of social defeat (PND 77), the animals underwent the CPP procedure. Place conditioning was carried out using eight identical Perspex boxes, each with two equal-sized compartments (30.7 cm long × 31.5 cm wide × 34.5 cm high) separated by a grey central area (13.8 cm long × 31.5 cm wide × 34.5 cm high). The compartments had differently coloured walls (black vs. white) and distinct floor textures (fine grid in the black compartment and wide grid in the white one). Four infrared light beams in each compartment of the box and six in the central area allowed us to record the animals' positions and their movements between compartments. The equipment was controlled by three IBM PC computers using MONPRE 2Z software (Cibertec SA, Madrid, Spain). The CPP consisted of three phases and took place during the dark cycle following an unbiased procedure in terms of initial spontaneous preference (see [45] for detailed explanations of the procedure). In brief, during pre-conditioning (Pre-C), the time spent by the animal in each compartment over a period of 15 min was recorded. Animals showing a strong unconditioned aversion or a preference for a given compartment were excluded from the study ($n = 3$). In the second phase (conditioning), which lasted for 4 days, the experimental animals received saline before being confined to the vehicle-paired compartment for 30 min. After an interval of 4 h, they were injected with 1 mg/kg of cocaine immediately before being confined to the drug-paired compartment for

a further 30 min. During the third phase (post-conditioning, Post-C), the time spent by the untreated mice in each compartment during a 15-min period was recorded.

2.8. Statistical analyses

The data obtained from the tests performed in the short term after ISD were analysed using a one-way ANOVA with a between-subjects variable – Treatment – with four levels (Saline+No stress (control), Saline+ISD, K10+ISD and K30+ISD). The following measurements were included in the statistical analyses: TOA, EOA, LOA, %TOA, %EOA and TotalE in the EPM, ISI, Immobility and Latency of Immobility in the TST, Time spent in Grooming, Latency of Grooming, and Frequency of Grooming in the Splash test. In addition, the data of the time spent in the drug-paired compartment was analysed using a repeated measures two-way ANOVA with a between-subjects variable – Treatment – with four levels (Saline+No stress (control), Saline+ISD, 7 K10+ISD and K30+ISD) and a within-subjects variable – Days – with two levels (Pre-C and Post-C). In all cases, post-hoc comparisons were performed with Tukey tests. All statistical analyses were performed using the SPSS program.

3. Results

3.1. Role of ketamine in the short-term behavioural effects of ISD

ANOVA of the data obtained in the EPM regarding the percentage of time spent in the open arms (%TOA) was significant [$F(3,36)=3.772$; $p < 0.05$]. As shown in Fig. 1, the post-hoc comparison of the Treatment variable revealed that only the group of defeated mice treated with saline showed a reduction in the percentage of TOA compared to the control group ($p < 0.05$), indicating the presence of anxiety-like symptoms in mice exposed to ISD. ANOVA of TOA also revealed significant effects of the variable Treatment [$F(3,36)=3.672$; $p < 0.05$]. Post-hoc comparison showed that defeated mice treated with saline showed a reduction in TOA compared to the groups of defeated mice treated with the high dose of ketamine or without stress exposure ($p < 0.05$). These results suggested that ketamine, particularly at a dose of 30 mg/kg, could mitigate the anxiety-like effects of ISD, as defeated mice treated with this drug exhibited similar behaviour to the control group. ANOVAs of the other measurements obtained in the EPM (EOA, %EOA, LOA and TotalE) did not reveal significant effects ([$F(3,36)=2.017$; $p = 0.129$], [$F(3,36)=2.191$; $p = 0.106$], [$F(3,36)=0.365$; $p = 0.779$] and [$F(3,36)=0.974$; $p = 0.416$)], respectively).

ANOVA of the social interaction data also confirmed significance [$F(3,36)=5.083$; $p < 0.01$]. Post-hoc comparison of the Treatment variable (see Fig. 2) revealed that the group of defeated mice treated with saline exhibited a reduction in the ISI compared to both the control group ($p < 0.01$) and the group of stressed mice treated with 30 mg/kg of ketamine ($p < 0.05$). These results indicated that ISD-induced social avoidance was prevented by treatment with the high dose of ketamine.

The ANOVA of time spent immobile in the tail suspension test was also significant [$F(3,36)=8.324$; $p < 0.001$]. Post-hoc comparison of the variable Treatment (Fig. 3) revealed that all mice exposed to ISD spent less time immobile than the control group mice, irrespective of whether they were treated with saline or ketamine ($p < 0.05$, $p < 0.01$ and $p < 0.001$, for the SAL+IDS, K10+ISD, K30+ISD groups, respectively). These results indicated that ketamine did not prevent the effects of ISD

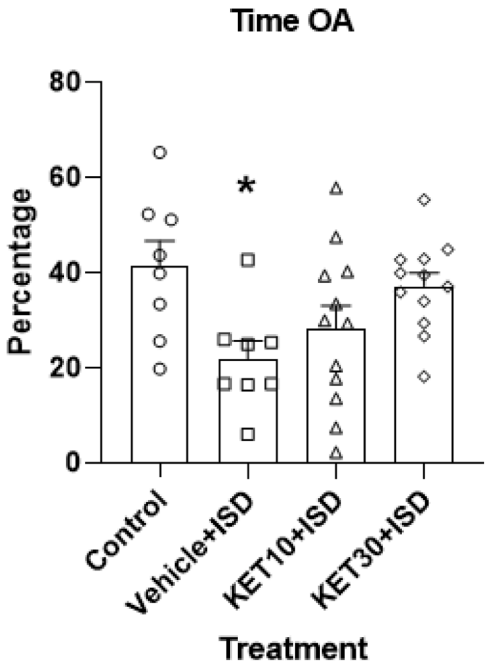

Fig. 1. Effects of intermittent social defeat (ISD) and ketamine (KET) treatment on the percentage of time spent in the open arms (Time OA) of the EPM. Control group was treated with physiological saline and not exposed to stress while the Vehicle+ISD group received an injection of physiological saline before each episode of social defeat. The groups KET10+ISD and KET30+ISD received an injection of ketamine 10 or 30 mg/kg, respectively, before each episode of social defeat. ISD reduced the percentage of time spent in the OA, while the administration of 10 and 30 mg/kg of ketamine before each episode of social defeat attenuated this effect of ISD. Bars represent the mean (±SEM) percentage of time spent in open arms (OA) of the EPM. *$P < 0.05$, significant difference compared to the control group.

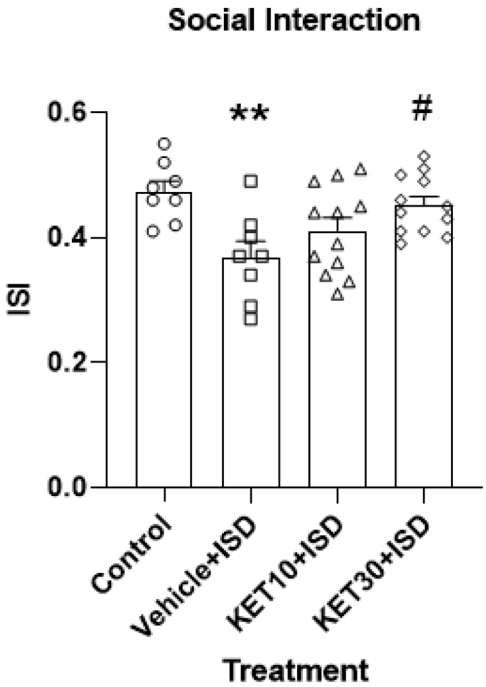

Fig. 2. Effects of intermittent social defeat (ISD) and ketamine (KET) treatment on the index of social interaction (ISI) in the social interaction test. Control group was treated with physiological saline and not exposed to stress while the Vehicle+ISD group received an injection of physiological saline before each episode of social defeat. The groups KET10+ISD and KET30+ISD received an injection of ketamine 10 or 30 mg/kg, respectively, before each episode of social defeat. ISD decreased social interaction while the administration of 10 and 30 mg/kg of ketamine before each episode of social defeat attenuated and completely prevent, respectively, this effect of ISD. Bars represent the mean (±SEM) index of social Interaction (ISI) in each group. *$P < 0.05$ significant difference compared to the control group. # $P < 0.05$ significant difference compared to the Vehicle + ISD group.

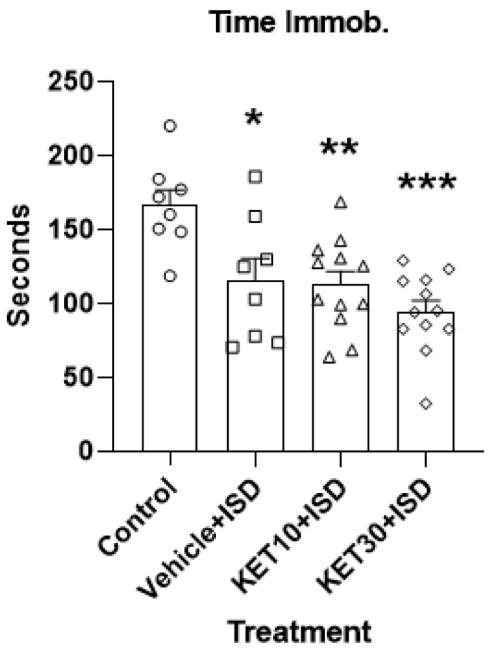

Fig. 3. Effects of intermittent social defeat (ISD) and ketamine (KET) treatment on the time spent in immobility (Time Immob) in the tail suspension test. Control group was treated with physiological saline and not exposed to stress while the Vehicle+ISD group received an injection of physiological saline before each episode of social defeat. The groups KET10+ISD and KET30+ISD received an injection of ketamine 10 or 30 mg/kg, respectively, before each episode of social defeat. ISD reduced the immobility while administration of 10 and 30 mg/kg of ketamine before each episode of social defeat did not modify this effect of ISD. Bars represent the mean (±SEM) time spent in immobility. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, significant difference compared to the control group.

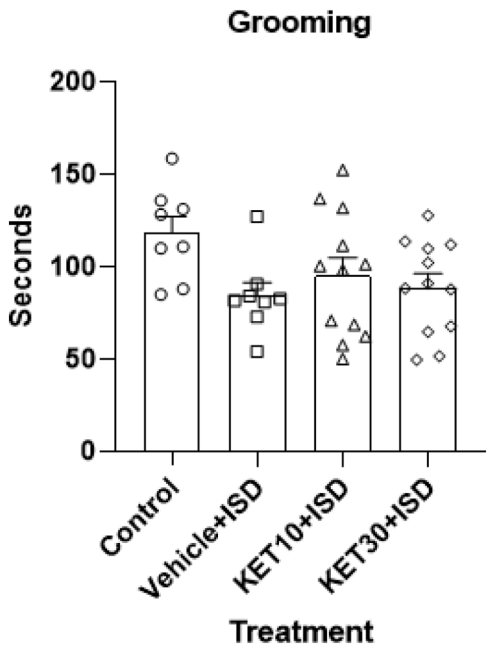

Fig. 4. Effects of intermittent social defeat (ISD) and ketamine (KET) treatment on the time spent in grooming in the splash test. Control group was treated with physiological saline and not exposed to stress while the Vehicle+ISD group received an injection of physiological saline before each episode of social defeat. The groups KET10+ISD and KET30+ISD received an injection of ketamine 10 or 30 mg/kg, respectively, before each episode of social defeat. Bars represent the mean (±SEM) time spent in grooming.

in the tail suspension test. ANOVA of the latency of immobility did not reveal significant effects ([F(3,36)=1.504; $p = 0.23$]).

ANOVA of time spent in grooming in the splash test (Fig. 4) did not reveal significant values [F(3,36)=2.556; $p = 0.07$]. Similarly, ANOVA of the other measurements obtained in the splash test (frequency and latency of grooming) did not reveal significant effects ([F(3,36)=2.363; $p = 0.087$] and [F(3,36)=1.156; $p = 0.34$], respectively).

3.2. Role of ketamine on the long-term effects of ISD on cocaine CPP

ANOVA of time spent in the drug-paired compartment revealed that Days [F(1,35)=1.565, $p = 0.219$], Treatment [F(3,35)=2.176, $p = 0.108$] and the Interaction Days X Treatment [F(3,35)=1.256, $p = 0.304$] were not significant (Fig. 5).

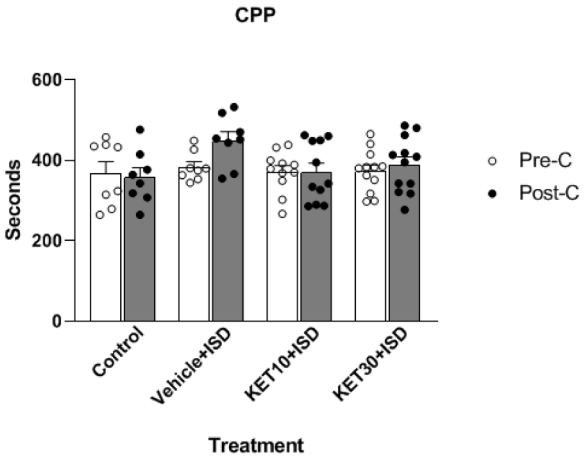

Fig. 5. Effects of intermittent social defeat (ISD) and ketamine (KET) treatment in the CPP paradigm. Control group was treated with physiological saline and not exposed to stress while the Vehicle+ISD group received an injection of physiological saline before each episode of social defeat. The groups KET10+ISD and KET30+ISD received an injection of ketamine 10 or 30 mg/kg, respectively, before each episode of social defeat. Bars represent the mean (±SEM) time spent in the drug-paired compartment in the pre-conditioning (Pre-C) and post-conditioning (Post-C) by mice conditioned with 1 mg/kg of cocaine.

4. Discussion

The results of the present study suggest that the administration of ketamine attenuated certain short-term behavioural effects of ISD, including anxiety-like symptoms in the EPM and impaired social behaviour in the social interaction test. However, ketamine did not prevent the reduction in grooming behaviour in the splash test and immobility in the tail suspension test induced by ISD. Furthermore, we found that the dose of cocaine administered was ineffective in inducing rewarding effects in the CPP paradigm.

Exposure to ISD during late adolescence reduced the percentage of time that mice spent in the open arms of the EPM indicating the presence of anxiety-like symptoms in defeated mice, in line with previous studies carried out in our laboratory [5,6]. As was expected, treatment with ketamine prior to each defeat episode attenuated the anxiogenic effects of ISD in the EPM. While the effects of ketamine on anxiety-like behaviours induced by social defeat protocols have not been evaluated, studies using other stress paradigms such as footshock exposure [18], chronic psychosocial stress (predator exposure plus social instability) [46], chronic unpredictable stress [30–32] and chronic mild stress [33] have reported that ketamine reduces anxiety-like behaviour of stressed animals in the EPM. These results are consistent with those observed in our study. However, ketamine (1 mg/kg, 60 min prior to the test) did not

affect the anxiety-like effects induced by social isolation stress in the hole board or open field tests [47].

In agreement with previous studies conducted in our laboratory [5,7], mice exposed to ISD displayed a reduction in social interaction. Treatment with ketamine before each episode of social defeat attenuated the social avoidance induced by ISD, completely preventing it at the high dose. The same beneficial effect was observed in mice that received a single dose of ketamine [17] or 15 injections [26] prior exposure to CSDS, or that were treated with ketamine acutely [13,24] or for two consecutive days following CSDS [25]. Furthermore, administration of a ketamine dose during re-exposure to acute social defeat also reversed the deficit in social interaction induced by defeat in mice [16]. Interestingly, not all mice displaying social avoidance following CSDS exposure respond to the positive effects of ketamine. One study showed that, of 13 stress-susceptible mice with a reduced social interaction ratio, only 6 mice increased their social interaction ratio following the acute administration of ketamine [22]. In our study we observed a similar effect with the low dose of ketamine, which only reversed the ISD-induced social avoidance in approximately half of the stressed mice.

Unexpectedly, we have not observed effects in the splash test. In previous studies, we have observed that ISD induced a significant reduction of the frequency of grooming or the time spent in this behaviour [5–7]. A plausible explanation for this lack of effect of ISD is that all groups of stressed mice exhibited similar grooming behaviour, irrespective of treatment with vehicle or ketamine, suggesting that ketamine did not induce depression-like effects in the splash test. These results contrast with previous studies that reported an increase in grooming time in naïve mice following ketamine administration, consistent with its antidepressant effects [48]. In addition, several studies have demonstrated that a single dose of ketamine can prevent depression-like effects induced by other stress protocols in the splash test, such as a reduction in grooming time and/or an increase in latency of this behaviour. For instance, the administration of ketamine (5 mg/kg) one week prior to the administration of corticosterone [49], LPS or TNF-α [50], or chronic restraint [51], was effective in counteracting the effects of these stressors in the splash test. In another study, the increase in grooming latency induced by chronic corticosterone was reversed by an acute injection of ketamine (90 mg/kg) administered one week prior to the stress protocol; however, lower doses (10 and 30 mg/kg) were ineffective [17]. Similarly, a single dose of ketamine (10 mg/kg) administered 15 days after chronic mild stress and 5 days before the test reversed the decrease in grooming behaviour induced by this type of stress [52]. The same effect was observed after the acute administration of ketamine (1 mg/kg, 60 min before the test) in mice that had been exposed to social isolation stress [47]. Conversely, neither unpredictable chronic mild stress nor a single dose of ketamine (1 mg/kg) induced any effects in the splash test with regard to grooming latency and time spent in grooming [53]. The divergence between these results and those obtained in the present study can be explained by differences in the stress protocol (social defeat) and the ketamine treatment schedule (administered before each episode of social defeat).

ISD reduced immobility time in the TST, in line with previous studies conducted in our laboratory [5,6] and ketamine did not reverse this effect. According to the conventional interpretation of immobility in the TST as behavioural despair or depression-like behaviour, several studies have indicated that ketamine reduces increased immobility in mice exposed to various stress protocols, such as CSDS [19], unpredictable chronic stress [31,40], chronic restraint stress [51], corticosterone administration [49], and inflammatory stressors such as lipopolysaccharide and tumour necrosis factor-alpha [50]. However, rather than an increase in immobility, we observed a reduction in the time spent immobile in mice exposed to ISD. In previous studies, we have observed the same results [5,6], which indicated that our protocol of defeat does not induce despair, and have interpreted this reduction in immobility as an enhanced reactivity of defeated mice to the stressful situation implied by the TST (see a more detailed discussion in [5]). Alternatively, it could be considered that exposure to the predictable stress of ISD induced subsequent resilience to the stressful effects of TST. Defeated mice treated with ketamine also showed a reduction of immobility, that indicated that this drug did not prevent stress-induced resilience.

A main objective of the present work was to evaluate whether administering ketamine prior to each episode of social defeat in late adolescence could reverse the long-term effects of ISD on mice's sensitivity to cocaine reward in adulthood that we have observed in previous studies [5–9]. In the present study no group of mice acquired CPP after conditioning with 1 mg/kg of cocaine. We expected to observe this lack of CPP in the control group (because we used a subthreshold dose of cocaine that does not induce CPP in naïve non-stressed mice) and in groups of defeated mice treated with ketamine (based on our previous studies, in which the blockade of NMDA receptors prevented the effects of ISD [8]). Conversely, we expected to observe CPP in mice exposed to ISD because we have observed this result repeatedly [5–9]. However, in the present study the exposure to ISD alone did not induce significant effects on cocaine reward. While there are no previous studies on the role of ketamine in the effects of social defeat on the rewarding properties of cocaine, our previous research has shown that blocking the NMDA receptors with memantine [8] and inhibiting nNOS with 7-NI [9], which is closely related to NMDA receptor antagonism, also reversed the effects of ISD on cocaine reward. Furthermore, memantine and 7-NI reversed the short-term effects of social defeat on MDMA-induced CPP [10,11]. As ISD alone did not induce statistically significant effects, it remains unknown to what extent ketamine can reverse the effects of ISD on sensitivity to cocaine reward.

It is difficult to explain why ketamine reversed the anxiety-like behaviour in the EPM and social avoidance induced by ISD, while not modifying the effects of ISD on other tests of depression-like behaviour such as the splash or in tail suspension test. These specific effects of ketamine may be related to its action on different glutamate receptors. Previous studies have shown that the reversal of social avoidance induced by ketamine was blocked by a selective AMPA receptor antagonist, suggesting that the protective effects of ketamine were mediated by the activation of AMPA receptors [13]. However, the GluN2C- and/or GluN2D-containing NMDA receptors also appear to play a role, since the administration of a drug that potentiates these subunits partially inhibited the ketamine-induced attenuation of the impairment of social behaviour in defeated mice [24]. Conversely, the administration of NMDA receptor antagonists reversed the depression-like effects of social isolation stress in the splash test but not the anxiety-like effects in the hole-board and open field tests [47]. Furthermore, a low-affinity NMDA receptor antagonist failed to prevent depressive-like behaviour in the tail suspension and splash tests induced by chronic restraint stress in mice [51]. These results suggest that blocking NMDA receptors may be more effective in reducing depression-like behaviours than anxiety-like behaviours, and that stimulating AMPA receptors may prevent stress-induced deficits in social interaction. As ketamine is a non-competitive glutamate NMDA receptor antagonist [12] and stimulates AMPA receptors [13], it could be hypothesised that the administration schedule and dose (30 mg/kg) of ketamine that we observed to selectively reduce the anxiety-like effects and social avoidance induced by social defeat stimulate AMPA receptors to a greater extent than they block NMDA receptors. This hypothesis remains to be tested in future studies.

A limitation of the present study was the fact that we have not tested the effects of ketamine on its own (i.e., in mice without stress exposure). Ketamine induces dissociative effects and has pleasurable and aversive properties [54]. Exposure to ketamine during adolescence (PND 35–49) subsequently (3 weeks later) increased the rewarding effects of cocaine in the CPP paradigm in male mice, although this effect was not observed when adolescent male mice were exposed to both ketamine and social stressors (PD35–44) or when mice were treated with ketamine during adulthood (PND 70–84) [55]. Conversely, exposure to ketamine during early adolescence (PND 21–30) attenuated alcohol-induced CPP in

adolescent (PND 32–39) male and female rats [56]. The balance between the positive and the aversive effects of ketamine may be different in adolescent and adult animals and may explain the different abuse potential of this drug in function of age and in comparison with other drugs of abuse [54]. The lack of ketamine-treated control groups limited the use of more appropriate statistical analyses (two-way ANOVAs Stress × Drug), which allow proper evaluation of the main effects of each factor and their potential interaction. Another limitation of the present study is its exclusive use of male mice, given that sex differences have been reported in the effects of ketamine on rodents. Behavioural effects induced by psychosocial stress (predator exposure) in rats were mitigated by ketamine in a sex- and dose-dependent manner [46]. Furthermore, female mice exposed to chronic mild stress were more sensitive than males to the antidepressant-like effects of ketamine in the forced swim test; however, the opposite was observed in the splash test, and the antidepressant potential of ketamine was found to be longer-lasting in males in both tests [52]. Finally, adolescent ketamine exposure increases the reward value of sucrose and cocaine in later life in a sex-specific manner in non-stressed mice [55].

In conclusion, our results support the involvement of glutamate receptors in the short-term effects of ISD stress, such as anxiety-like behaviour and deficits in social interaction. However, ketamine did not prevent the effects of ISD in the splash and tail suspension tests. The results of the present study suggest that ketamine could be used as a novel therapeutic strategy to enhance resilience to stress-related anxiety and increased cocaine sensitivity in individuals who have experienced adverse events during adolescence.

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Data availability

Data will be made available on request.

CRediT authorship contribution statement

M.A. Martínez-Caballero: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis. **M.P. García-Pardo:** Writing – original draft, Methodology, Investigation. **C. Calpe-López:** Writing – original draft, Visualization. **M.C Arenas:** Writing – review & editing, Conceptualization. **C Manzanedo:** Writing – review & editing, Supervision. **M.A. Aguilar:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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