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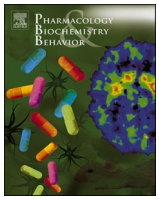

Ketamine retards recovery from reward downshift and supports conditioned taste aversion

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ABSTRACT

Ketamine is a noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist with antidepressant, anxiolytic, and memory effects in clinical and preclinical studies. The present studies investigated the behavioral effects of ketamine in animals exposed to a consummatory successive negative contrast (cSNC) task involving unexpected reward downshift, negative emotion (frustration), and aversive memory. Food-restricted male rats had 5-min access to 32 % sucrose in each of 10 preshift sessions followed by 4 % sucrose in 4 postshift sessions. Unshifted controls had access to 4 % sucrose during all 14 sessions. Ketamine (10 mg/kg, ip) was injected 30 min before sessions 11 and 12 (Experiment 1) or immediately after session 11 (Experiment 3). The results showed that both pre- and postdownshift session injection of ketamine increased consummatory suppression, as Group 32-4/Ket exhibited lower sucrose intake than Groups 32-4/Sal, 4-4/Ket, and 4-4/Sal. These effects extended beyond the day(s) of injection. Experiments 2 and 4 showed that the same dose, route of administration, and time of injection induced significant conditioned taste aversion to 4 % sucrose, in the absence of reward downshift. These data suggest that ketamine induces an aversive state that may summate with frustration induced by reward downshift in the cSNC task and also support a conditioned taste aversion to 4 % sucrose in the absence of reward downshift. Implications for these and other experiments involving pre- and postsession administration of ketamine are discussed.

1. Introduction

In the Research Domain Criteria initiative, loss is characterized as responses to the removal of a motivationally significant stimulus, whereas frustrative nonreward (FNR) refers to responses to the withdrawal or prevention of rewards following repeated efforts (Cuthbert and Insel, 2013; Hasratian et al., 2022). Both constructs are thus related to situations involving the unexpected omission, reduction, or inaccessibility of rewards. These situations have been considered as triggers for negative emotions (frustration, disappointment, conflict, psychological pain; Amsel, 1992; Flaherty, 1996; Gray, 1987; Papini et al., 2015), which, in turn, increase the risk of anxiety, depression, posttraumatic stress, and drug abuse, among others (Huston et al., 2013; Konopka et al., 2013; Ortega et al., 2017; Papini et al., 2015; Ramírez-Castillo et al., 2019). Several experimental paradigms have been developed to study loss and FNR in both human and nonhuman animals, including reward devaluation, omission, and delay; partial reinforcement; increased response effort; response and reward blockade; etc. The impact of these manipulations has been analyzed in terms of behavior, subjective affect reports, physiological and hormonal responses, and brain function (Torres et al., 2021).

The successive negative contrast (SNC) task is commonly used to induce frustration in nonhuman animals. SNC consists of a transient reduction in responding for a small reward (e.g., 4 % sucrose) after previous exposure to a large reward (32 % sucrose) in the same situation (reward downshift), in comparison to the behavior observed in unshifted controls always exposed to the small reward (Flaherty, 1996). Adjustments to unexpected reward downshifts involve reward detection and comparison, negative emotion (FNR), aversive memory, and memory update (Torres and Papini, 2017).

The consummatory SNC (cSNC) effect involving a 32 %-to-4 % sucrose downshift has predictive validity to identify pharmacological agents that alleviate FNR induced by reward downshift. GABAergic anxiolytics (benzodiazepines, alcohol, barbiturates), selective and nonselective opioids agonists, and cannabinoids reduce or abolish the cSNC effect in a session-dependent manner when administered before

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reward downshift (Flaherty, 1996; Genn et al., 2004; Papini, 2009). These results have been explained in terms of the anxiolytic and analgesic effects of these drugs (Flaherty, 1996; Papini et al., 2015). The cSNC effect is, in turn, enhanced by the administration of some drugs immediately after downshift sessions. Post-training drug effects have been explained in terms of interference with memory update of the downshifted reward (e.g., benzodiazepines: Ortega et al., 2014a), enhancement of the emotional memory of the downshift (e.g., corticosterone: Bentosela et al., 2006; Ruetti et al., 2009; D-cycloserine: Norris et al., 2011), or conditioned taste aversion (e.g., anisomycin: Ortega et al., 2014b).

Surprisingly, there is a paucity of studies analyzing the sensitivity of the cSNC effect to antidepressants, given that FNR procedures have been also proposed as models for depression (Huston et al., 2013; Nikiforuk and Popik, 2009; Komorowski et al., 2012). Moreover, FNR events have been shown to be risk factors for mood disorders in humans (Papini et al., 2015). Some studies involving pre-downshift session administration have yielded negative or inconclusive results, including acute and subchronic imipramine administration (Flaherty, 1990), chronic fluoxetine administration (Flaherty, 1996; Nikiforuk and Popik, 2009), and acute citalopram administration (Phelps et al., 2015). There is also behavioral evidence consistent with a connection between reward loss and depression. Rats exposed to a downshift from 32 % sucrose to water exhibit suppression of aggressive behavior (Mustaca et al., 2000), an effect reminiscent of the suppression of aggressive responses in rats exposed to inescapable shocks (Williams, 1982). These results suggest that the potential of SNC paradigms as models for depression requires further examination.

The present experimental series examines the effects of ketamine (Ket) on cSNC. Ket is a noncompetitive *N*-methyl-D-aspartate receptor (NMDAR) compound with fast antidepressant effects (Matveychuk et al., 2020). Ket inhibits ion currents in voltage-gated channels for Na^+ and K^+; decreases serotonin and dopamine reuptake; reduces GABAergic-mediated inhibition; modulates molecular pathways dependent on glycogen synthase kinase-3 (GSK3), rapamycin (mTOR), and TrkB signaling; and activates CREB and the brain-derived neurotrophic factor (BDNF), thus promoting synaptic plasticity that mediates its antidepressant effects (Alshammari, 2020; Kang et al., 2022; Li et al., 2010). In rodents, acute presession administration of Ket has been reported to have anxiolytic, anxiogenic, and no effects on anxiety/fear tests such as the open field, social interaction, elevated plus maze, one-way escape, fear conditioning, hole-board test, and light-dark box (see Silote et al., 2020). The ability of acute Ket to reduce depressive-like behaviors has also been shown in the forced swimming, tail suspension, novelty- and stress-induced suppressed feeding and sucrose preference, chronic mild stress, social defeat, and learned helplessness tests, although some of the findings have not been replicated (see Browne and Lucki, 2013; Rincón-Cortés and Grace, 2020). Whether the behavioral effects of Ket extend to situations involving loss and FNR, including the cSNC effect, is unknown.

Unlike presession effects, posttraining Ket administration facilitates fear extinction when administered between acquisition and extinction sessions (Girgenti et al., 2017; Sala et al., 2022; Wei et al., 2020). However, null and even opposite effects have also been reported (Clifton et al., 2018; Juven-Wetzler et al., 2014). In the cSNC task, the initial rejection of the devalued solution has been hypothesized to support aversive conditioning based on Pavlovian associations between the taste of the downshifted reward (4 % sucrose) and the internal state of frustration induced by the downshift (Papini et al., 2015). Such aversive conditioning is supported by NMDARs, as shown by the retardation of behavioral recovery after a 32-to-4 % sucrose downshift induced by post-downshift administration of the memory enhancer D-cycloserine, a partial agonist/antagonist at the glycine site of the NMDAR (Norris et al., 2011). Because Ket's effects on memory are mediated by NMDARs (Newcomer et al., 2000), it was expected that it would also modulate the aversive memory of the downshift in the cSNC task.

The present studies investigated the effects of the pre- and post-downshift administration of Ket on the cSNC effect. Ket was administered either 30 min before (Experiment 1) or immediately after (Experiment 3) exposure to a 32 %-to-4 % sucrose downshift. Because previous studies showed that Ket can act as an aversive unconditioned stimulus in taste aversion learning in rodents (Aguado et al., 1997; Etscorn and Parson, 1979; Lin et al., 2017), Experiments 2 and 4 explored the possibility that the pre- and postdownshift session effects of Ket could also support a conditioned taste aversion to 4 % sucrose even in the absence of reward downshift.

2. Experiment 1

The lack of previous studies analyzing the effect of Ket on loss and NFR, along with the inconsistent effects of antidepressants on the cSNC effect (Flaherty, 1996), make it difficult to predict whether Ket would attenuate or enhance the initial reaction and/or the subsequent recovery of behavior following reward downshift. Experiment 1 started this series by examining the effects of Ket administration before the first and the second postshift sessions of a cSNC task. The selected dose of Ket (10 mg/kg) was previously shown to affect behavior in animal tests for depression involving feeding and sucrose intake (Li et al., 2011; Lin et al., 2016).

2.1. Method

2.1.1. Subjects

A total of 24 male Wistar rats, experimentally naïve and approximately 90 days old at the start of the experiment, served as subjects. Only male rats were used in this and subsequent experiments for consistency with previous pharmacological studies involving the cSNC effect (e.g., Castejón et al., 2023; Donaire et al., 2022; Ortega et al., 2014a; Ortega et al., 2014b; Norris et al., 2011), to have a more homogeneous sample in terms of body size, and also because previous studies indicated more labile reward devaluation effects in female rats (Castejón et al., 2022). The generalizability of the present results to female rats must also be taken with caution given documented sex differences in the effects of Ket on behavior (e.g., Ponton et al., 2022; Saland and Kabbaj, 2018). Rats were purchased from Envigo (Barcelona, Spain). Their mean (±SEM) ad lib weight was 369 g (± 5,29) at the beginning of the experiment. Rats were housed individually in polycarbonate cages with water and environmental enrichment continuously available, in a room with constant temperature (18–22 °C) and humidity (50–60 %). The colony room was lighted between 08:00 and 20:00 h. Animals were food restricted and maintained within 82–85 % of their ad lib weight. Some amount of standard rat chow was provided each day during the duration of the experiment, at least 30 min after the end of each session. Water was always available in the cage. Animals were maintained according to the EU Directive 2010/63/EU and Spanish Law (6/2013; R.D.53/2013) for animal experiments. Experimental procedures were approved by the institutional animal care and use committee.

2.1.2. Apparatus

cSNC training was carried out in eight boxes, each measuring 30 × 15 × 30 cm (L × W × H). The walls, floor, and ceiling of these boxes were made of clear Plexiglas; the floor was covered with a layer of sawdust. A sipper attached to a graduated cylinder was inserted through a hole in the front wall. The 32 % (or 4 %) sucrose solution was prepared *w*/w by mixing 32 g (or 4 g) of sucrose for every 68 g (or 96 g) of distilled water. Sucrose was dissolved with a magnetic mixer (Nahita Magnetic Stirrer 680–9, Beriain, Spain). Session length was measured with a manual stop watch (Extech, model 365,510, Madrid, Spain).

2.1.3. Procedure

Fig. 1 describes the sequence of procedures used in this and subsequent experiments. Subjects were matched by weight and randomly

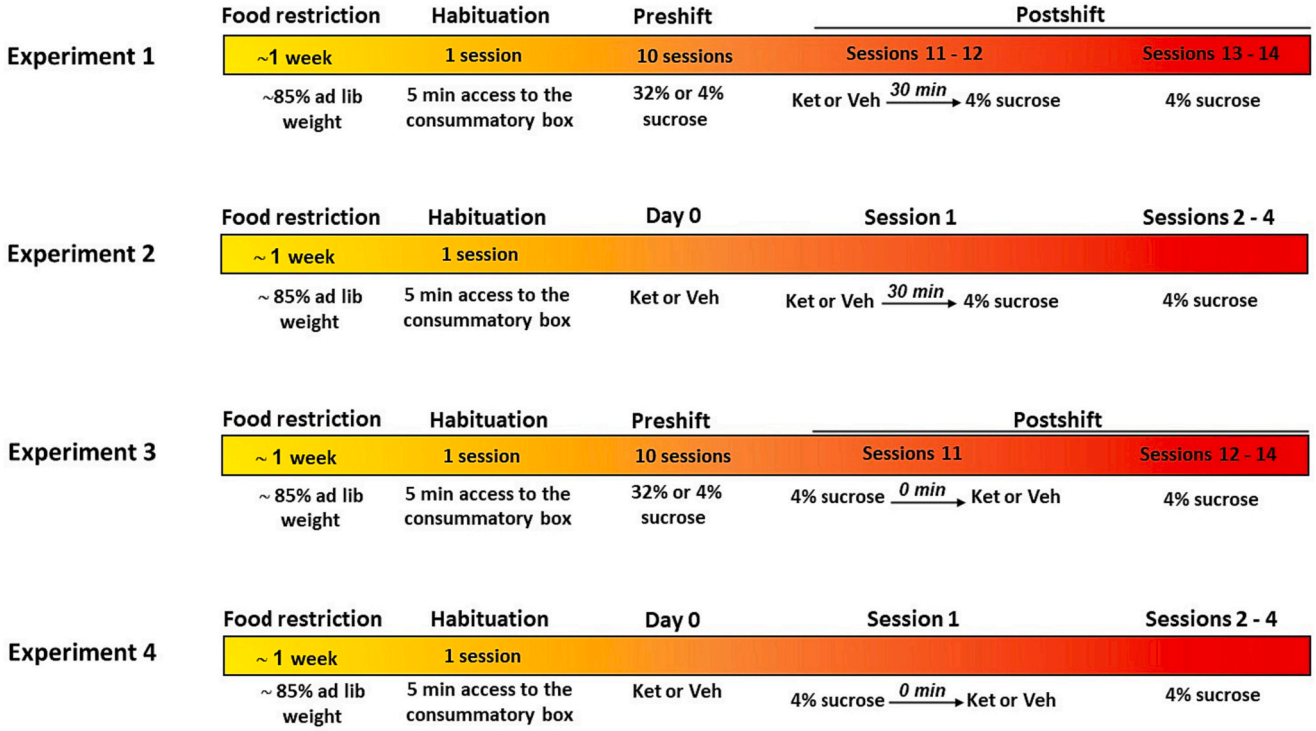

Fig. 1. A description of the sequence of procedures used in each experiment. Ket: ketamine. Veh: vehicle (saline injection).

assigned to Groups 32–4/Ket, 32–4/Veh, and 4–4/Ket ($n = 8$). Additional animals to complete the design were not available, so a 4–4/Veh condition was not included because it was deemed the least informative condition. Animals were run in squads of eight (squads included at least one animal from each group). Animals were tested from Monday to Friday. A 5-min habituation session in the consummatory box without fluids preceded training. On sessions 1–10, animals had free access to 32 % (Groups 32–4/Ket and 32–4/Veh) or 4 % sucrose (Group 4–4/Ket), and on sessions 11–14, all animals received access to 4 % sucrose. Ket (10 mg/kg, ip) or saline (equal volume, ip) was administered 30 min before sessions 11 and 12. Each session lasted 5 min starting from the first contact with the sipper tube. Consummatory boxes were cleaned and the saw dust replaced every other day. The amount of sucrose solution consumed during each 5-min session was transformed to mL/kg based on the animal's weight recorded on the same day.

2.1.4. Drug preparation

An injectable solution of Ket (Ketaset 100 mg/mL, Ecuphar, Barcelona, Spain) was dissolved in saline to administer 10 mg/kg of Ket ip (0,1 mL of Ket solution in 0,9 mL of saline). The isotonic saline solution was used as vehicle. Drug concentration and vehicle were adjusted to a volume of 1 mL/kg.

2.1.5. Statistics

In all the experiments reported in this article, analyses of variance were calculated for the dependent variable (consumption, mL/kg) with an alpha value set at the 0.05 level. Session was a repeated-measure factor in all the analyses reported in this article. Pairwise Bonferroni tests derived from the main analysis were computed to identify the source of significant interactions. Partial eta square scores (η^2) were used to estimate effect size. The specific designs were described in the Results sections of each experiment. All statistical tests were conducted with the IBM SPSS Statistics 27 package.

2.2. Results and discussion

Fig. 2 shows the results in terms of mL/kg of sucrose intake as a function of sessions for each of the three groups. A Group by Session (1−10) analysis indicated only a significant increase across sessions, $F(9, 189) = 38.88$, $p < 0.001$, $\eta^2 = 0.65$. The Group and Group by Session interaction were nonsignificant, $Fs < 2.19$, $ps > 0.08$, $\eta^2 s < 0.18$.

Fig. 2 also shows the results during postshift sessions. There was substantial suppression of consummatory behavior in downshifted groups on session 11, but behavior recovered more slowly in animals treated with Ket vs. vehicle before sessions 11 and 12. A Group by Session (11–14) analysis yielded significant effects for all factors, $Fs > 3.19$, $ps < 0.007$, $\eta^2 s > 0.23$. Pairwise Bonferroni tests indicated that Group 32–4/Ket was significantly more suppressed than Group 4–4/Ket on each postshift session, $ps < 0.05$, and more suppressed than Group

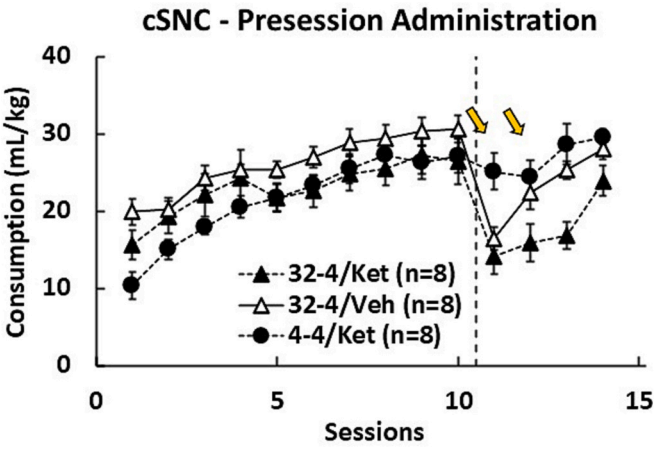

Fig. 2. Sucrose consumption (mL/kg) (means ±SEMs) of groups of rats given access to reward downshift (32 %-to-4 % sucrose) or to 4 % sucrose and an injection of Ket (or Veh) 30 min before trial 11 and 12. Results from Experiment 1.

32–4/Veh on session 13, $p < 0.02$. Other comparisons were nonsignificant.

Fig. 2 also shows a hint of consummatory suppression in Group 4–4/Ket on sessions 11–12, relative to session 10, followed by an increase in behavior on sessions 13–14. To assess the possibility that Ket caused suppression in the absence of reward downshift in these animals, a one-way analysis was computed on sessions 9–14 (two sessions before and after the two sessions involving Ket administration). There were significant differences across sessions in Group 4–4/Ket, $F(5,35) = 3.73$, $p < 0.009$, $\eta^2 = 0.35$. However, pairwise Bonferroni tests only found a significant difference between sessions 12 and 13, $p < 0.02$. Other comparisons were nonsignificant, $ps > 0.12$.

Ket administration before postshift sessions 11 and 12, the first and the second downshift sessions, enhanced suppression of consummatory behavior, an effect that extended to subsequent drug-free sessions. According to the sensitivity of the cSNC effect to drugs actions that either reduce (e.g., benzodiacepine anxiolytics) or increase (e.g., opioid antagonists) the emotional reaction to reward devaluation, these results would suggest an anxiogenic/pro-frustrating effect of Ket in the cSNC situation. In that case, the present data agree with previous studies showing anxiogenic effects of Ket in animal models involving negative emotion (e.g., Alijanpour and Rezayof, 2023; Babar et al., 2001; Loss et al., 2012; Pietersen et al., 2006; Silvestre et al., 1997). The suppressive effect of Ket on consummatory behavior observed in Experiment 1 is consistent with results showing that Ket administration can elevate glucocorticoid levels in monkeys (e.g., Crockett et al., 2000; Springer and Baker, 2007). Glucocorticoids are also elevated during reward downshift (Pecoraro et al., 2009).

3. Experiment 2

In Experiment 1, presession Ket administration retarded recovery from reward downshift in the cSNC task, but it also resulted in some suppression of behavior in the absence of reward downshift (Group 4–4/Ket). Reduced sucrose intake after Ket administration could reflect the acquisition of a conditioned taste aversion (CTA). CTA involves learning to reject consumption of a taste (the conditioned stimulus, CS) after pairings with sickness or some aversive state (the unconditioned stimulus, US; Verendeev and Riley, 2012). In the cSNC task, sucrose would act as a CS and Ket's posteffects would act as a US. Although Ket was administered before access to the sucrose in Experiment 1, we assumed following Woods and Ramsay (2000) that the US was not the injection per se, but the posteffects of the drug. We could not find pharmacokinetic information on Ket under the same conditions used in these experiments, but the common use of a 30-min interval between injection and behavioral testing in studies using similar Ket doses (e.g., Acevedo et al., 2023) coupled with the short duration of sucrose sessions (5 min) suggested that Ket's posteffects would be present before, but also during and after access to sucrose. These conditions could thus support the development of a CTA to the downshifted sucrose solution. CTA is known to be especially strong when rats are exposed to relatively novel CSs, but retarded when the CS is familiar (Cannon et al., 1983). The latter is referred to as latent inhibition, the retardation of acquisition after nonreinforced preexposure to the CS (Lubow, 2009). In the cSNC situation, 4 % sucrose was relatively novel to animals that had received access to 32 % sucrose during the 10 preshift sessions, but it was familiar to unshifted controls that were preexposed to 4 % sucrose during 10 preshift sessions in the absence of any consequence. Therefore, the difference in novelty of the 4 % sucrose would explain a reduced intake in Group 32–4/Ket relative to Group 4–4/Ket. Ket is known to support CTA in rodents (Aguado et al., 1997; Etscorn and Parson, 1979). Moreover, long-lasting dizziness and nausea/vomiting side effects associated with Ket use have been reported in humans (Niesters et al., 2014). Although Ket was administered before sessions 11 and 12 in Experiment 1, it is possible that its effects extended in time and overlapped with tasting 4 % sucrose intake, thus supporting CTA. The possible role of CTA was tested in Experiment 2 by implementing a backward Ket-sucrose pairing in the absence of reward downshift and under the same temporal parameters used in Experiment 1.

3.1. Method

3.1.1. Subjects and apparatus

The subjects were 24 experimentally naïve male Wistar rats, approximately 90 days old, purchased from Envigo (Barcelona, Spain). Their mean (±SEM) ad lib weight was 335 g (± 1,99) at the beginning of the experiment. All other details of maintenance and the apparatus used were described in Experiment 1.

3.1.2. Procedure

The sequence of procedures is described in Fig. 1. Rats were randomly assigned to one of three groups ($n = 8$): Groups P (paired), UP (unpaired), and Veh (vehicle). All animals had access to 4 % sucrose during four trials (5 min) and received two ip injections, one 24 h before session 1 and the other 30 min before session 1. For animals in Group P, the first injection was a saline injection (equal volume, ip) and the second was Ket (10 mg/kg, ip). For animals in Group UP, Ket was administered 24 h before session 1 and saline 30 min before session 1; this group controlled for nonassociative effects of Ket. For animals in Group Veh, both injections were saline injections; this group equated exposure to the injections and provided an additional control for the nonassociative effects of Ket behavior. To minimize the number of vehicle and ketamine injections and equate them to the number of injections administered in Experiment 1, Ket was administered only once in this experiment. Other details of the training procedure, drug preparation, and statistics were as described in Experiment 1.

3.2. Results and discussion

Fig. 3 shows the results for each of the three groups across four sessions. Groups P and UP performed at a similar level, but both were below Group Veh. Statistically, a Group by Session (1–4) analysis confirmed a significant increase across sessions, $F(3, 63) = 17.03$, $p < 0.001$, $\eta^2 = 0.45$. There was also a significant Group effect, $F(2,21) = 3.63$, $p < 0.05$, $\eta^2 = 0.26$, but the interaction effect was not significant, $F(6, 63) = 1.51$, $p > 0.19$, $\eta^2 = 0.13$. Pairwise Bonferroni comparisons based on the significant Group effect indicated that Group P consumed significantly less sucrose than Group Veh, $p < 0.05$, but Group P and UP did not differ significantly, $p = 1.00$. Groups UP and Veh also failed to differ from each other, $p > 0.22$.

There was little support for a conventional CTA effect in these

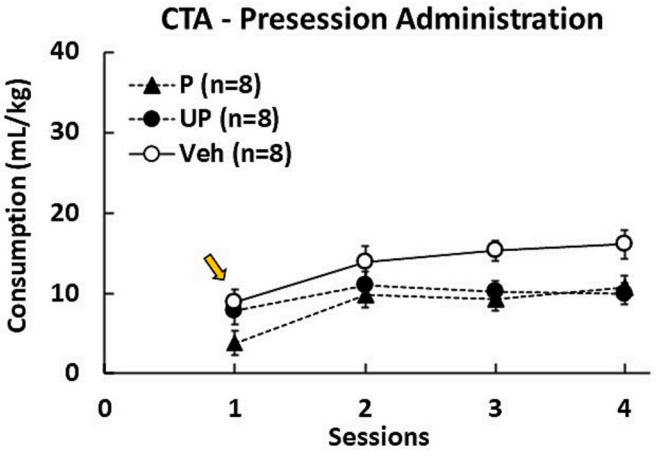

Fig. 3. Sucrose consumption (mL/kg) (means ±SEMs) of groups of rats given access to 4 % sucrose and pre-trial 1 Veh or Ket 24 h (UP: unpaired) or 30 min (P: paired) before 4 % sucrose. Results from Experiment 2.

results, since Groups P and UP did not differ from each other. However, Ket might have nonassociative effects on sucrose consumption that might account for the results of Experiment 1, as indicated by the difference in behavior between Groups P and Veh, and the nonsignificant trend in the same direction between Groups UP and Veh. Such effects might be potentiated after two Ket administrations, as in Experiment 1.

In sum, an injection of Ket either followed or not by 4 % sucrose induced similar (low) sucrose intake, thus making it difficult to interpret the results obtained in Experiment 1 in terms of CTA. The lack of significant differences in Groups UP vs. Veh, as opposed to Groups P vs. Veh, suggests the potential involvement of both associative and nonassociative processes in the effect of Ket on consummatory behavior observed in Experiment 1.

4. Experiment 3

In the cSNC task, at least two relevant memories have been proposed to explain the initial behavioral suppression and its subsequent recovery across postshift sessions (Papini, 2003): (1) the *FNR memory* (or egocentric memory) triggered by the negative disparity between the obtained (4 % sucrose) and expected rewards (32 % sucrose) that leads to consummatory suppression, and (2) a *memory update* process (or allocentric memory) that adjusts the expected reward to the new, downshifted conditions such that the obtained vs. expected disparity is reduced across postshift sessions and consummatory behavior recovers to the level of unshifted animals. Previous research suggests that memory enhancers that increase consummatory suppression reflect the strengthening of the FNR memory, including postdownshift administration of the stress hormone corticosterone (Bentosela et al., 2006; Ruetti et al., 2009) and the partial agonist/antagonist of the NMDAR D-cycloserine (Norris et al., 2011). By contrast, memory interfering drugs that also increase consummatory suppression are assumed to disrupt memory update, such as is the case with the benzodiazepine anxiolytic chlordiazepoxide (Ortega et al., 2014a). Although postdownshift administration of the protein synthesis inhibitor anisomycin also reduced consummatory behavior, this drug (unlike corticosterone, D-cycloserine, and chlordiazepoxide) also induced CTA. In the case of anisomycin, CTA provides a more parsimonious explanation of its effects on cSNC than memory disruption (Ortega et al., 2014b). Overall, this evidence shows that the cSNC task is sensitive to the action of drugs that modulate memory. The effects of posttraining Ket administration on aversive memory have been widely described in fear conditioning studies, where they were shown to depend on the route, dose, and timing of administration, among other factors (Choi et al., 2020). Under conditions analogous to those used in the present study (10 mg/kg, ip), Ket administration immediately after fear conditioning training facilitated fear extinction in rodents (Girgenti et al., 2017; Radford et al., 2018), suggesting that Ket interfered with the consolidation of fear memory. The goal of Experiment 3 was to determine whether, similar to fear conditioning, Ket modulates aversive memory when administered immediately after the initial experience with the downshifted reward.

4.1. Method

4.1.1. Subjects

A total of 32 male Wistar rats, experimentally naïve and approximately 90 days old at the start of the experiment served as subjects. Rats were purchased from Envigo (Barcelona, Spain). Their mean (±SEM) ad lib weight was 374 g (± 6,84) at the beginning of the experiment. All other details of maintenance and the apparatus used were described in Experiment 1.

4.1.2. Procedure

The sequence of events in Experiment 3 are summarized in Fig. 1. Subjects were matched by weight and randomly assigned to Groups 32–4/Ket, 32–4/Veh, 4–4/Ket, and 4–4/Veh (n = 8). The training procedure was the same as that described in Experiment 1. The only exception was that Ket (or saline) was administered immediately after session 11. Drug preparation and statistics were also as described in Experiment 1.

4.2. Results and discussion

The results are plotted in Fig. 4 for each group across preshift (1–10) and postshift (11–14) sessions in terms of mL/kg of sucrose consumption. Preshift sessions showed the typical increase in sucrose consumption across sessions. A Contrast (32–4 vs. 4–4) by Drug (Ket vs. Veh) by Session (1–10) analysis indicated that the Contrast by Session interaction and the change across Sessions were significant, $Fs > 2.03$, $p < 0.04$, η^2s > 0.07. All other effects were nonsignificant, $Fs < 1.04$, $ps > 0.40$, η^2s < 0.04. Consistent with its relatively small effect size, pairwise Bonferroni comparisons indicated that animals receiving access to 32 % sucrose consumed significantly more than animals with access to 4 % sucrose only on session 2, $p < 0.05$. This was the only evidence of differential consumption of 32 % vs. 4 % sucrose. Such general lack of differentiation is not uncommon with these sucrose concentrations (see Flaherty, 1996).

Fig. 4 also shows that postsession 11 Ket administration disrupted sucrose intake in animals that experienced reward downshift, but not in unshifted controls. A similar analysis involving sessions 11–14 provided significant effects for Contrast by Session, $F(3, 84) = 19.89$, $p < 0.001$, $\eta^2 = 0.42$; Drug by Session, $F(3, 84) = 3.69$, $p < 0.02$, $\eta^2 = 0.12$; Contrast, $F(1, 28) = 33.27$, $p < 0.001$, $\eta^2 = 0.54$; and Session, $F(3, 84) = 19.59$, $p < 0.001$, $\eta^2 = 0.41$. All other effects failed to achieve significance, $Fs < 2.87$, $ps > 0.10$, η^2s < 0.10. To clarify the effects of postsession Ket, the performance of downshifted and unshifted groups was compared independently across sessions 12–14, that is, the sessions after Ket administration. A Drug by Session analysis of downshifted groups yielded significant main effects for Session, $F(2,28) = 16,42$, $p < 0.0001$, $\eta^2 = 0.54$, and Drug, $F(1,14) = 7,34$, $p < 0.02$, $\eta^2 = 0.34$, thus indicating that, regardless of the session, Group 32–4/Ket consumed less sucrose than Group 32–4/Veh. A similar analysis for unshifted groups, 4–4/Ket and 4–4/Veh, produced nonsignificant differences for all three factors, $Fs < 1.74$, $ps > 0.21$, η^2s < 0.11.

Postsession 11 Ket administration did not affect behavior in animals exposed to unshifted reward, but retarded recovery of consummatory behavior after a reward downshift in the cSNC task. If Ket is viewed as a memory interfering drug (e.g., Girgenti et al., 2017; Radford et al., 2018), then the results of Experiment 3 are consistent with a disruption of the memory update process (see Ortega et al., 2014a). The present results are also consistent with the CTA hypothesis on the assumption

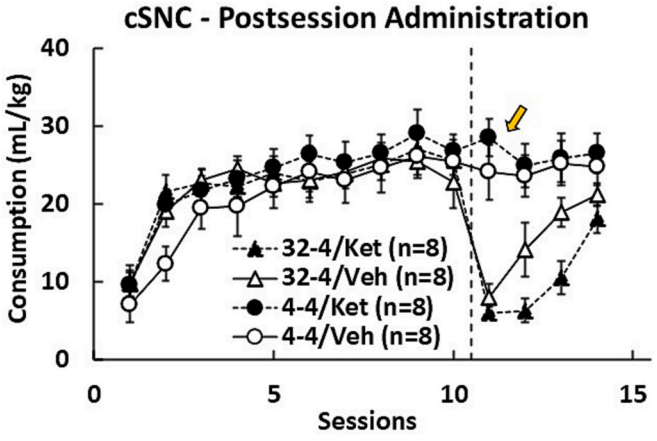

Fig. 4. Means (±SEMs) Sucrose consumption (mL/kg) of groups of rats given access to reward downshift (32 %-to-4 % sucrose) or to 4 % sucrose and an injection of Ket (or Veh) immediately after trial 11. Results from Experiment 3.

that CTA was weaker in unshifted controls due to their extensive exposure to 4 % sucrose during preshift sessions (i.e., latent inhibition).

5. Experiment 4

In addition to its effects on depression, anxiety, and memory, Ket can also induce a state of sickness causing emesis in cats, primates, and humans (Fox et al., 1990; Niesters et al., 2014). Saccharine and sucrose intake preceding these aversive consequences of Ket can lead to CTA (Etscorn and Parson, 1979; Lin et al., 2017). For example, pairings of 4 % and 20 % sucrose (CSs) with Ket (US; 10 and 25 mg/kg) reduce sucrose intake (Aguado et al., 1997; Etscorn and Parson, 1979). Thus, any demonstration of an effect of postdownshift Ket administration on sucrose consumption in the cSNC task must test for the possibility that the behavioral effects were due to CTA, rather than to reward downshift per se. As indicated in Experiment 2, the differential novelty of the 4 % sucrose could explain the greater intake suppression in downshifted than in unshifted animals via latent inhibition (Lubow, 2009). The goal of Experiment 4 was to assess whether post-session Ket under conditions similar to those used in Experiment 3, but in the absence of reward downshift, would suppress sucrose intake based on a CTA effect. An unpaired group similar to that of Experiment 2 was included to further characterize the involvement of nonassociative factors in the effects of Ket on sucrose intake.

5.1. Method

5.1.1. Subjects and apparatus

The subjects were 24 male Wistar rats purchased and maintained as described in Experiment 1. Their mean (±SEM) ad lib weight was 372 g (± 4,26) at the beginning of the experiment. All other details and the apparatus used were described in Experiment 1.

5.1.2. Procedure

Procedural features of Experiment 4 are described in Fig. 1. Rats were randomly assigned to one of three groups (n = 8): Groups P (paired), UP (unpaired), and Veh (vehicle). All animals had access to 4 % sucrose during four trials (5 min) and received two ip injections, one 24 h before session 1 and the other immediately after session 1. For animals in Group P, the first injection was a saline injection (equal volume, ip) and the second was Ket (10 mg/kg, ip). For animals in Group UP, Ket was administered 24 h before session 1 and saline immediately after session 1. For animals in Group Veh, both injections were saline injections. Other details of the training procedure, drug preparation, and statistics were as described in Experiment 1.

5.2. Results and discussion

Fig. 5 shows the results for the three groups during the four sessions in terms of mL/kg of 4 % sucrose intake. There was a clear CTA effect with extensive suppression of sucrose consumption in Group P relative to Groups UP and Veh, which, in turn, did not differ much from each other. A Group by Session (1–4) analysis indicated that all three factors were significant, $Fs > 12.35$, $ps < 0.001$, $\eta^2 s > 0.51$. Pairwise Bonferroni tests indicated that groups were not different on session 1, before the administration of Ket, $ps > 0.18$, but Group P differed significantly from Groups UP and Veh in subsequent sessions, $ps < 0.001$. Groups UP and Veh did not differ in any of the sessions, $ps > 0.37$.

Postsession Ket administration acted as a US that promoted CTA to the 4 % sucrose solution under the same general conditions used in Experiment 3, except for the absence of a reward downshift. The results of Experiment 3 can be parsimoniously explained in terms of CTA, rather than as a selective effect of Ket on memory after a reward downshift event. Furthermore, the nonsignificant differences between the UP and Veh animals rule out the involvement of nonassociative processes in the obtained results.

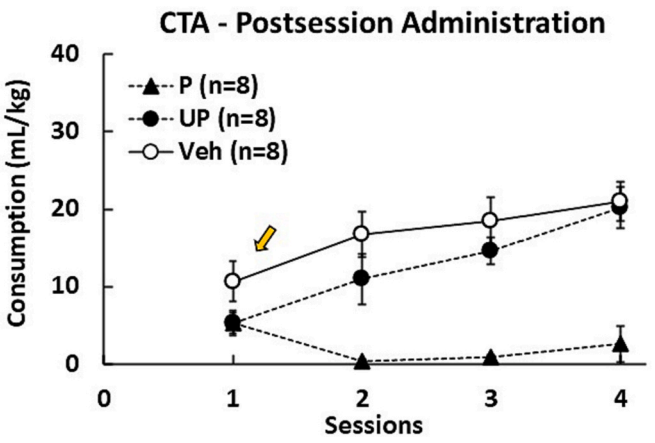

Fig. 5. Sucrose consumption (mL/kg) (means ±SEMs) of groups of rats given access to 4 % sucrose and post-trial 1 Ket (or Veh), either 24 before or immediately after the trial. Results from Experiment 4.

6. General discussion

Four experiments investigated the effects of Ket on cSNC and CTA tasks. Reduced sucrose intake was observed in animals receiving Ket before or after reward downshift sessions, suggesting anxiogenic (Experiment 1) and memory interfering effects (Experiment 3) in the cSNC task. Ket also induced consummatory suppression when administered before (Experiment 2) or after (Experiment 4) access to 4 % sucrose in the absence of reward downshift. Overall, these results suggest that ketamine administration (10 mg/kg, ip) induced an aversive internal state that added to the aversive state of FNR induced by reward downshift and promoted CTA to the 4 % solution.

CTA experiments usually induce visceral sickness with lithium chloride (e.g., Sakai and Yamamoto, 1997) or intragastric hypertonic sodium chloride (e.g., Agüera and Puerto, 2015), but other drugs have been used to induce taste rejection, including abuse drugs with reinforcing properties such as amphetamine, cocaine, nicotine, phencyclidine, and Δ9-tetrahydrocannabinol, among others (Lin et al., 2014). There is evidence showing that Ket (10 and 25 mg/kg, alone or in combination with xylazine) can be used as a US to induce CTA when associated with 4 % or 20 % sucrose, relative to unpaired controls (Aguado et al., 1997) or to saline controls (Etscorn and Parson, 1979; Lin et al., 2017). While the use of saline controls leaves open the possibility that Ket's behavioral effects are caused by nonassociative actions (e.g., direct effects on drinking, motor effects, etc.), results based on a comparison against an unpaired control (as in Aguado et al., 1997; current Experiment 4) confirm that Ket's aversive posteffects support CTA. In the present Experiments 1 and 3, unshifted controls treated with Ket exhibited little or no evidence of a reduction in sucrose intake, a fact suggesting that consuming sucrose was not aversive to these animals. A CTA hypothesis would also explain the absence of consummatory suppression in these animals in terms of familiarity with 4 % sucrose developing during the 10 preshift sessions that preceded Ket administration. Such a latent inhibition effect in CTA has been extensively documented (Lubow, 2009) and it could apply to the present results in unshifted animals.

Alternatively, Ket-induced consummatory suppression could be interpreted as an indication that the incentive value of 4 % sucrose was devalued because it was followed by a more rewarding stimulus (i.e., Ket's posteffects), a phenomenon referred to as anticipatory contrast (Flaherty, 1996). However, the present experimental procedures differ in several respects from those used in studies of anticipatory contrast using drugs of abuse. First, such studies usually involved forced/intraoral administration of the taste solution (e.g., Colechio et al., 2018), whereas in the present study sucrose was available for voluntary

consumption. Second, saccharine, rather than sucrose, is frequently used as the tastant CS (Colechio et al., 2018; Grigson and Twining, 2002; Imperio and Grigson, 2015; Twining et al., 2009). This may or not be a relevant factor, but it is worth noting. Third, apart from some exceptions (e.g., Parker, 1993), these studies usually involved voluntary drug self-administration (e.g., Grigson and Twining, 2002; Imperio and Grigson, 2015), whereas a forced administration procedure (ip) was used in the present studies. There is evidence suggesting that drugs of abuse, such as alcohol, can produce appetitive or aversive effects depending on whether their administration is voluntary or forced (Spanagel, 2003). There is also evidence indicating that the unpredictable/uncontrollable delivery of drugs of abuse (e.g., cocaine, via yoked delivery) is aversive and can protect against the subsequent motivation for the drug (Twining et al., 2009). Fourth, according to Colechio et al. (2018), the difficulty with using voluntary intake as dependent variable is that consummatory suppression could be interpreted as an indication that the rat finds the tastant aversive (based, for example, on a CTA effect; see, e.g., Etscorn and Parson, 1979) or that the otherwise palatable taste cue is merely devalued because it is followed by a more rewarding stimulus (i.e., the drug). Support for this latter interpretation would require independent evidence that Ket is reinforcing under conditions like those used in the present study (e.g., 10 mg/kg, ip).

The present results may have implications for other studies involving pre- and postsession Ket administration. With respect to studies involving pretrial Ket administration, there is evidence that presession acute (10 mg/kg) and chronic (15 mg/kg, 7 days) administration of Ket increased sucrose consumption in both stressed and nonstresses animals (García et al., 2009; Li et al., 2011). Presession Ket administration (10 mg/kg) also attenuated the suppression of feeding induced by novelty (Li et al., 2010). These results rule out the possibility that pre-session ketamine administration consistently induces aversive states and promotes CTA. Such a conclusion is hardly surprising, given the multiple effects of systemic Ket administration, which are usually handled by including control conditions (see Introduction for references).

Alternatively, postsession administration studies showed that Ket (10 mg/kg, ip) reduced a conditioned place preference induced by sucrose (10 %, *w/v*, oral) if injected after sucrose-place pairings and 30 min before the place test (McKendrick et al., 2020). Although these results were interpreted in terms of Ket-induced memory impairment, it seems possible that the positive affect elicited by sucrose-associated place cues was counteracted by the aversive state induced by Ket administration, thus leading to no change in the preference score. According to this view, Ket induces aversive internal states that may not only promote CTA under particular conditions, but also subtract from positive affective states or invigorate aversive motivational states by motivational summation. The latter process might have been at work in the present Experiments 1 and 3, in addition to the development of CTA. In these experiments, increased consummatory suppression may have resulted from a summation of the aversive state induced by Ket injection, and the aversive affect (FNR) triggered by reward downshift. The absence of a summation effect in Experiment 1, session 11, may reflect a floor effect on licking responses, whereas similar performance in Experiment 2, session 11, is simply due to the fact that ketamine was administered after this session in this case. Similar interactions were demonstrated by adding peripheral pain (Ortega et al., 2011) or restraint stress (Ortega et al., 2013) to reward downshift.

Ultimately, an explanation of the present results in terms of Ket's aversive effects and CTA challenges the utility of the cSNC task (and other procedures involving taste stimuli) for analyzing Ket's effects on anxiety, depression, and memory. Modifications to reduce the likelihood of drug-induced aversion to the FNR event are needed. One possibility is to take advantage of the extensive exposure to water in the lab environment to implement a downshift from sucrose to water, rather than a sucrose devaluation. Latent inhibition would substantially reduce the ability of water to acquire aversive value. Such consummatory extinction procedure (e.g., Mustaca et al., 2002) might help uncover selective effects of Ket on FNR. One contribution of the present experiments is to have identified some limitations of the cSNC task to detect the behavioral effects of Ket. Changes to this task can enhance its reliability and predictive validity as a tool to study the behavioral pharmacology of FNR.

Data availability

Data will be made available on request.

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