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Short communication

Effect of a positive reinforcing stimulus on fear memory reconsolidation in ethanol withdrawn rats: Influence of D-cycloserine

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HIGHLIGHTS

- Fear memory reconsolidation can be disrupted by a positive reinforcing stimulus in control rats.
- Ethanol withdrawal induces a fear memory trace that becomes insensitive to the disruptive effect of a reinforcing stimulus on the reconsolidation process.
- Pre-retrieval D-cycloserine restores the vulnerability to the disruptive effect of a reinforcing stimulus on reconsolidation process in ethanol withdrawn rats.

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ABSTRACT

The pharmacological blockade of memory reconsolidation has been suggested as a potential treatment to the attenuation of maladaptive memories associated to psychiatric disorders and drug addiction. To interfere with the process of fear memory reconsolidation using a manipulation safer than pharmacological interventions, here we examined whether a positive reinforcing stimulus (non-alcoholic beer, NB) post-memory retrieval can decrease the fear response in ethanol withdrawn (ETOH) animals. We first evaluated the potential interfering effect of NB on memory reconsolidation in non-ethanol dependent (control, CON) rats. Non-alcoholic beer intake shortly after memory retrieval attenuated the fear response in CON rats. A resistance to destabilization/reconsolidation process was previously observed in ETOH rats, which was reversed by the activation of NMDA receptor induced by pre-retrieval D-cycloserine (DCS) administration. Therefore, the influence of DCS (5 mg/kg; i.p.) to facilitate the disruptive effect of NB on fear memory was examined in ETOH animals. As expected, NB was ineffective to attenuate the fear response in ETOH rats, with DCS being necessary to promote the disruptive effect of NB on the reconsolidation in these animals. Hence, DCS/reinforcing stimulus in combination with memory reactivation can be considered as an alternative approach for disrupting resistant fear memories.

Alcoholism is a chronic relapsing disorder with economic, health and domestic consequences that require more effective treatments. Emotional disturbances such as increased anxiety and fear observed during the withdrawal period are a major factor in maintaining alcohol addiction [1,2] and therefore represent a relevant therapeutic target. Alcohol affects the neural circuitry involved in learning and memory processes, with repeated/chronic ethanol administration facilitating the emergence of a robust and persistent fear memory [3–6]. Moreover, as the retrieval of contextual fear memory increases ethanol consumption in ethanol withdrawn animals [7], manipulations that attenuate fear memories may be relevant for alcohol addiction treatment.

Accumulated evidence has demonstrated that under certain conditions, previously established memories can become temporarily labile following their retrieval and require a further protein synthesis-dependent stabilization phase in order to persist, a process referred to as reconsolidation [8–10]. Different pharmacological interventions during this unstable phase have been used in pre-clinical and clinical studies to alter the original memory trace and, in turn, to reduce the impact of the maladaptive memories presumably implicated in diverse psychiatric disorders, including drug addiction [11].

Interestingly, the emotional valence of fear memory can be modified by the presentation of an appetitive stimulus [12,13].

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Considering the importance of fear memory attenuation in the context of alcoholism and that the use of a positive reinforcing stimulus after memory retrieval could provide a therapeutic approach safer than pharmacological interventions, the main goal of the present study was to examine whether a positive reinforcing stimulus can disrupt the fear memory reconsolidation in ethanol withdrawn (ETOH) animals. Given that non-alcoholic beer (NB) is highly accepted by rats and they also have a remarkable preference for it compared to water [14], NB was used as a positive reinforcing stimulus. The NB has never been used as an interfering agent with the reconsolidation process. Therefore, we first established the key parameters necessary to block the reconsolidation with NB. Thus, we examined the effect of NB consumption after fear memory reactivation on subsequent fear memory in control rats (CON, rats not submitted to ethanol dependence).

It has been reported that fear memory in ETOH rats, under similar conditions of training and reactivation to those used in the present study, is resistant to post-reactivation pharmacological interference [15], so a similar resistance to the disruptive effects induced by the appetitive stimulus could be expected in ETOH rats. Moreover, this resistant fear memory may become vulnerable to disruption by pre-retrieval D-cycloserine (DCS, NMDA receptor partial agonist) administration [15]. Therefore, the second aim was to examine the effect of NB consumption after memory retrieval on the reconsolidation process in ETOH rats treated or not with pre-retrieval DCS administration.

Experiments were performed using adult male Wistar rats (240–260 g; 70 days of age at the beginning of the study) of our breeding stock, which were housed in groups of 3 per cage, with food and water *ad libitum* except when stated otherwise in the protocol [15]. Animals were maintained in a 12 h light-dark cycle (lights on at 0700) at a room temperature of 21–22 °C. The protocols used were approved by the Animal Care Committee of the Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, and are consistent with the NIH Guide for the Care and Use of Laboratory animals.

Each experiment consisted of five phases: diet administration, fear conditioning, habituation phase to NB (or water in Exp. 1) consumption, memory reactivation followed by access to NB (or water in Exp. 1) and memory retention tests as described below.

Rats were made dependent on ethanol by administration of 6% (v/v) of ethanol in a nutritionally complete liquid diet (Ensure, chocolate flavor, Abbott Laboratories B.V.), as previously described [15]. Control animals were pair-fed with the same diet, but with dextrose substituted isocalorically for ethanol. After 14 days, liquid diet administration was interrupted and animals were subsequently fed with laboratory chow.

Contextual fear conditioning (FC) took place in standard training chambers as previously described [15]. On the training day, rats were individually placed in the chamber and after 3 min received 3 unsignaled scrambled footshocks (0.5 mA of 3 s duration with a 30 s intershock interval). Animals were kept in the chamber for an additional 50 s, before being immediately brought back to the colony room.

One day after FC, the habituation phase began. Animals were individually placed in a cage with the same characteristics and bedding as their home cages, and given a 2 h access either to NB or water (experiment 1) or to NB alone (experiment 2) in the colony room, for 3 days. Non-alcoholic beer (NB, Lieber, Quilmes, Argentina, 0.4% alcohol by volume, 45.9 Kcal/ml) was decarbonated by stirring vigorously for at least 2 h, and presented in graduated cylinders (50 ml) fitted with sipper spouts at room temperature. This shaking was also needed for evaporation of the low alcohol content of the "Lieber" beer [16]. The amount of fluids consumed was expressed in terms of ml/kg. Throughout this procedure, rats were not subjected to either food or water deprivation.

Table 1
Non-alcoholic beer and water consumption after the reactivation session for Experiment 1. All data are expressed as the mean ± SEM for NB or water consumption (ml/kg).

Group	Fluid (ml/kg)	n
Water	8.2 ± 1.5*	6
NB–15 min	34.5 ± 4.0	7
NB–7 h	36.4 ± 3.6	7

NB: non-alcoholic beer.
* Significantly different from the remaining groups $p < 0.05$.

Memory reactivation took place 24 h after the end of the habituation period, and consisted of re-exposing rats to the training context for 5 min without shock delivery. After this re-exposure, animals were given access to NB or water intake (experiment 1) or NB (experiment 2) for 2 h. To asses fear memory retention, animals were reintroduced into the training context without shock delivery for 10 min, one (Test 1) and eight (Test 2) days after the reactivation session. The freezing response was scored during the reactivation and testing sessions. The total time spent freezing was scored by a trained observer blind to the experimental conditions. Freezing, a commonly used index of fear in rats [17], was defined as the total absence of body and head movements except those associated with breathing.

Results were expressed as the means ± S.E.M. The data were analyzed by the student's *t*-test or ANOVAs followed by Tukey HSD post-hoc ($p < 0.05$ was regarded as significant).

Experiment 1 was conducted to evaluate the potential disruptive effect of NB consumption on fear memory reconsolidation in control (CON) rats. Animals were treated with the control liquid diet (without ethanol) for 14 days, and 3 days after received the contextual fear training as described above. Twenty-four hours later, the habituation phase began and rats were given access to either NB or water. All animals were submitted to the reactivation session one day after the habituation phase. Fifteen minutes after the reactivation, half of the animals habituated with NB were given access to NB (NB–15 min group). The other half of rats habituated with NB were given access to NB 7 h after memory reactivation (NB–7 h group), in order to determine whether a delayed access to NB could affect the freezing levels. The group which was habituated with water received water fifteen min after memory reactivation (Water–15 min group). Memory retention was evaluated 1 (Test 1) and 8 days later (Test 2). The timeline of the experimental procedure is shown in Fig. 1A.

As illustrated in Fig. 1B, all animals displayed equivalent levels of freezing during the reactivation session. For Test 1, a significant reduction of freezing was detected only in the NB–15 min group [$F(1,17) = 27.46$; $p < 0.05$], which lasted up to one week as shown for Test 2 [$F(1,17) = 27.44$; $p < 0.05$] (Fig. 1C). In both tests, the post hoc analysis revealed that the NB–15 min group exhibited significantly less freezing than the remaining groups. As observed in Table 1, rats drank less water than NB after the reactivation session [$F(1,17) = 20.78$; $p < 0.05$]. Furthermore, the NB–15 min and the NB–7 h groups displayed similar levels of NB consumption after the reactivation session. Therefore, to induce a persistent memory deficit, NB consumption must occur 15 min after memory reactivation.

Experiment 2 was designed to test whether the memory reconsolidation process could be impaired by the consumption of NB after memory reactivation in ETOH rats pre-treated or not with DCS. D-Cycloserine (Sigma-Aldrich, St. Louis, MO, USA) was dissolved in sterile saline (0.9% w/v; SAL) at concentrations of 5 mg/ml for i.p. injection [15], with the total volume of drug or an equivalent amount of SAL being 1.0 ml/kg. Animals were treated with control liquid diet or ethanol-containing liquid diet (CON and ETOH groups, respectively) for 14 days, and 3 days after received the contextual

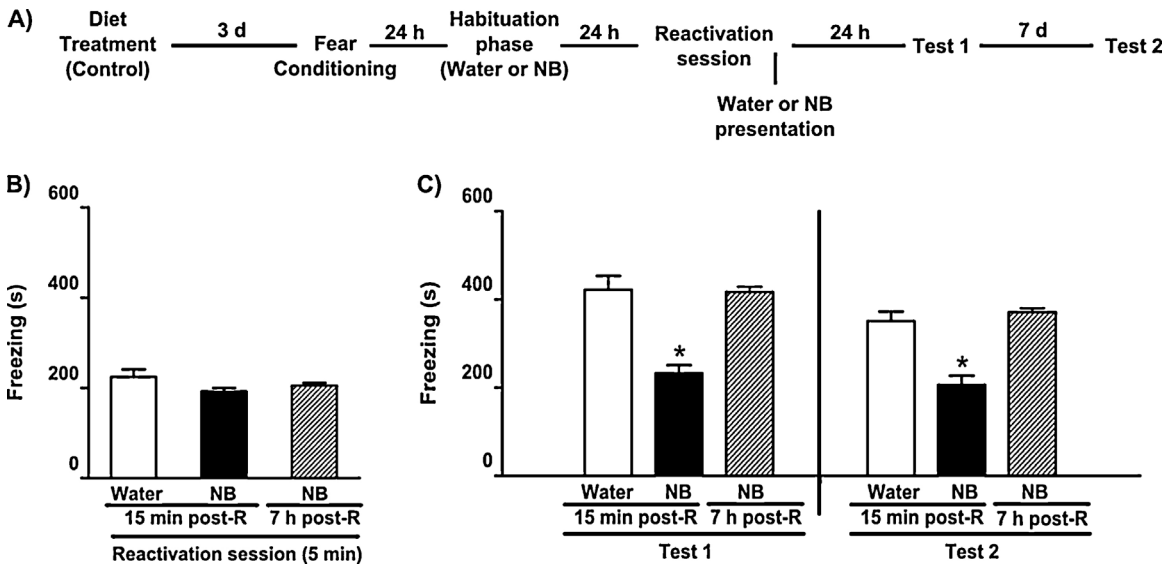

Fig. 1. Effect of appetitive stimulus consumption on fear memory reconsolidation in control animals. (A) Timeline for Experiment 1. (B) Fear response during the 5 min reactivation session. (C) Freezing behavior during Test 1 and Test 2 (10 min) for Water–15 min (n = 6), NB–15 min (n = 7) and NB–7 h (n = 7) groups. All data are expressed as the mean ± SEM of time spent freezing during the reactivation session, Test 1 and Test 2. (*) Significantly different from the remaining groups $p < 0.05$. NB: non-alcoholic beer. Post-R: after reactivation session.

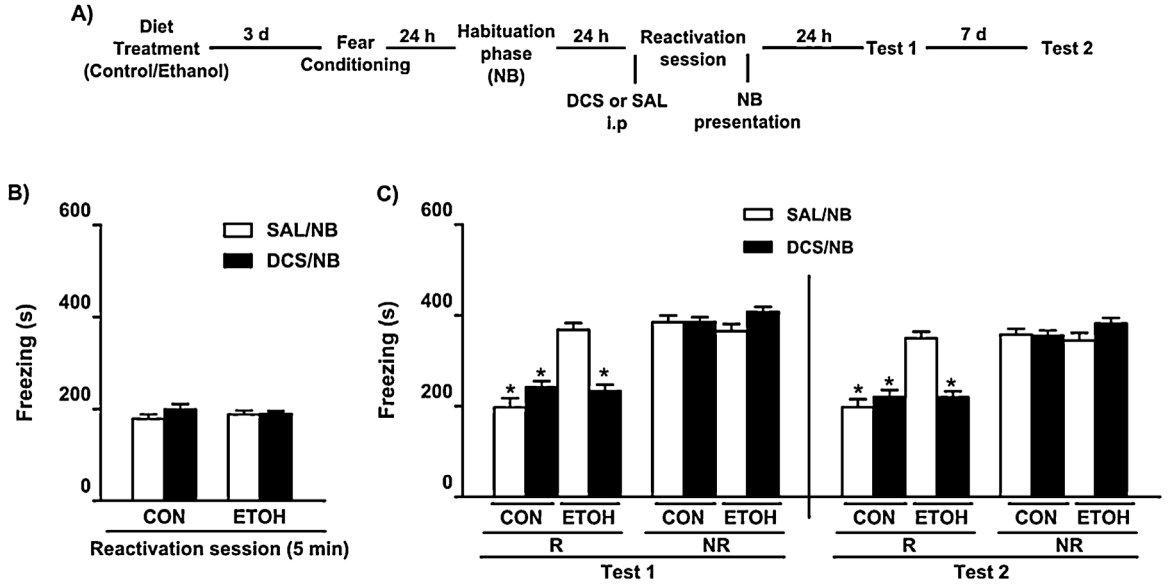

Fig. 2. Effect of appetitive stimulus consumption on fear memory reconsolidation in ethanol withdrawn rats: Influence of DCS. (A) Timeline for Experiment 2. (B) Fear response during the 5 min reactivation session. (C) Freezing behavior during Test 1 and Test 2 (10 min) for CON-SAL/NB (n = 10), CON-DCS/NB (n = 12), ETOH-SAL/NB (n = 8) and ETOH-DCS/NB (n = 12), and CON-SAL/NB (n = 9), CON-DCS/NB (n = 9), ETOH-SAL/NB (n = 9) and ETOH-DCS/NB (n = 9) for reactivated (R) and non-reactivated (NR) groups, respectively. All data are expressed as the mean ± SEM of time spent freezing during the reactivation session, Test 1 and Test 2. (*) Significantly different from the remaining groups $p < 0.05$. CON: control (non-ethanol dependent) animals. ETOH: rats withdrawn from chronic ethanol consumption. NB: non-alcoholic beer. DCS: D-cycloserine. SAL: saline.

fear training as described above. The habituation phase began one day later and all animals were habituated only to NB consumption. One day after the end of the habituation phase, rats received either DCS (5 mg/kg i.p) or saline (SAL) 30 min prior to the reactivation session. Fifteen minutes after memory reactivation, animals were offered NB for 2 h. Additional groups of rats from the CON and ETOH groups that underwent the same training, NB habituation and drug treatments in their home cages served as non-reactivated controls. The fear memory retention was evaluated 1 (Test 1) and 8 days (Test 2) later. The timeline of the experimental procedure is shown in Fig. 2A.

As observed in Fig. 2B, all reactivated rats showed comparable levels of freezing during the 5 min reactivation session. The influence of pre-reactivation DCS administration on the NB disruptive effects on memory reconsolidation is shown in Fig. 2C. Regardless of the treatment performed prior to the reactivation session, CON animals showed reduced levels of freezing. Non-alcoholic beer was ineffective to reduce the fear response in ETOH rats that received pre-reactivation SAL injection. Reactivated ETOH animals treated with DSC-NB exhibited a decrease in the freezing levels which did not differ from those shown by the reactivated CON groups [$F(1,70) = 29.14$; $p < 0.05$]. All these effects lasted up to one week [$F(1,70) = 21.23$; $p < 0.05$]. For both tests, all non-reactivated

Table 2
Non-alcoholic beer consumption after the reactivation session for Experiment 2. All data are expressed as the mean ± SEM for NB consumption (ml/kg).

Group	NB (ml/kg)	n
CON-R-SAL	29.7 ± 2.9	10
CON-R-DCS	28.7 ± 2.9	12
ETOH-R-SAL	29.2 ± 2.1	8
ETOH-R-DCS	26.7 ± 2.0	12
CON-NR-SAL	27.8 ± 2.2	9
CON-NR-DCS	25.4 ± 3.4	9
ETOH-NR-SAL	25.8 ± 2.9	9
ETOH-NR-DCS	26.5 ± 1.3	9

CON: control (non-ethanol dependent) animals. ETOH: rats withdrawn from chronic ethanol consumption. NB: non-alcoholic beer. R: reactivated rats. NR: non-reactivated rats. DCS: D-cycloserine. SAL: saline.

groups displayed similar elevated freezing levels, which did not vary from those shown by the reactivated ETOH group treated with SAL-NB. The post hoc test confirmed that freezing levels of DCS-NB and of SAL-NB from the reactivated CON groups and DCS-NB from the reactivated ETOH group did not differ and were significantly lower than the remaining group. Finally, as shown in Table 2, no significant differences were detected on NB consumption after the reactivation session. Together, these results suggest that pre-reactivation DCS facilitated the attenuating effect of NB on the fear memory in ETOH rats.

The present findings demonstrate that the consumption of an appetitive stimulus (NB) after memory reactivation can reduce fear memory in CON rats at testing, with fear memory being attenuated in CON animals that were given access to NB but not to water 15 min after the reactivation session. Although animals from NB–15 min and NB–7 h groups consumed similar levels of NB, NB intake outside the reconsolidation window did not affect fear memory (Fig. 1C, NB–7 h group; [10]). In addition, reduced freezing in the NB–15 min group was also noticeable eight days after the reactivation session (Test 2), indicating the absence of fear recovery and therefore, suggesting that fear memory extinction was not facilitated. The high NB consumption compared to water can be attributed to the palatable and reinforcing properties of NB, because animals were not subjected to any water deprivation schedule. Finally, the NB disruptive effect was dependent on memory reactivation since the reactivated group (CON-SAL) showed a decreased fear response compared with its respective non-reactivated group, despite similar levels of NB consumption (Experiment 2). Summing up, these results suggest that fear memory reconsolidation can be interfered with the consumption of a positive reinforcing agent after memory reactivation.

Recently, it has been reported that the presentation of an appetitive stimulus during contextual fear memory reactivation can modify the emotional valence of the memory trace by the incorporation of positive information through reconsolidation [12]. Similarly, a counter-conditioning study which used maltose as a reinforcing stimuli showed a comparable effect [13]. Despite the differences regarding the type of positive stimulus employed or when it was offered (during or after the recall), our results reinforce the idea that an appetitive stimulus in combination with memory reactivation can be effective for reducing fear memories. In contrast, according to our hypothesis, this disruptive effect was not observed in ETOH rats pretreated with SAL. Moreover, these animals exhibited a similar NB intake to that shown by the remaining groups. Therefore, these findings support the notion that ethanol withdrawal facilitates the formation of a fear memory resistant to the destabilization process following retrieval as previously suggested [15].

Similar to previous evidence using pharmacological interference, the current study shows that pre-retrieval DCS administration promotes the instability following reactivation, since memory became vulnerable to NB interference in ETOH rats. This proposal is supported by the following results: (1) NB was able to induce memory interference in ETOH animals that received pre-reactivation DCS but not SAL; (2) in the reactivated groups, ETOH rats treated with DCS displayed similar freezing levels to those exhibited by CON rats treated or not with DCS; (3) DCS/NB treatment was ineffective in the absence of the reactivation session, thus indicating that such interference is selectively dependent on memory reactivation and (4) DCS was ineffective in CON rats, because SAL/NB and DCS/NB reactivated groups exhibited similar freezing responses during Test 1 and Test 2. Thus, the above findings support the contention that memory destabilization induced by DCS is selectively evident in resistant memories. As previously reported [15,18,19], DCS administration before the brief reactivation session did not influence freezing expression because all rats showed comparable levels of freezing during this reactivation. In conclusion, DCS is presumably capable of inducing the destabilization process in resistant fear memories, thereby facilitating the disruptive effect of both pharmacological [15] and non-pharmacological agents on the reconsolidation process. In addition, rats treated or not with DCS did not exhibit differences in NB intake, thus indicating that NB consumption is not modified by this drug. Finally, all reactivated and non-reactivated groups showed similar levels of NB intake, suggesting that fear recall did not affect NB consumption.

Recent evidence has demonstrated that the activation of the ubiquitin/proteasome system (UPS) is necessary for the occurrence of retrieval-induced destabilization process of fear and drug-associated memories [20,21]. In addition, the inhibition of proteasome activity prevented the DCS-induced enhancement of memory extinction, suggesting that the DCS effect is mediated by the activation of the UPS [22]. Therefore, although the mechanism by which DCS promotes retrieval-induced memory destabilization in resistant memories is still unknown, it seems likely that it is mediated by the UPS activation. Further studies are necessary to address such proposal.

Given that dopamine is involved in learning and memory processes [23], and that NB is a reinforcing stimulus for rats, we can tentatively suggest that the interfering effect is mediated by dopamine release in the brain circuitry involved in fear memory reconsolidation, such as the BLA. Related to this, Rosenkranz and Grace [24] have demonstrated that dopamine release in the BLA attenuated the firing of BLA projection neurons, which could be involved in fear memory deficit. Further experiments are now necessary to elucidate this possibility.

A large body of evidence has demonstrated that post-training presentation of reinforcers that influence reward processes, such as food, rewarding electrical and chemical brain stimulation or amphetamine, can strengthen memory traces in various aversively motivated tasks [25]. Similarly, intracranial self-stimulation (SS) at the lateral hypothalamus or a reminder exposure improved memory retrieval in an active avoidance paradigm [26]. Even more, a better performance was obtained with the combination of both treatments. However, no statistical interaction was reported between SS and the reminder exposure, suggesting that this influence is not due to an effect on memory reconsolidation [26]. On the other hand, it was recently reported that a monetary reward after reactivation disrupts a skill memory in humans [27]. Therefore, the effect of a rewarding/reinforcing stimulus seems to be dependent on the phase and kind of memory under study.

Collectively, our results: (1) confirm that a positive reinforcing stimulus can act as a disruptive agent of the fear memory reconsolidation process; (2) strengthen our assumption that ethanol withdrawal induces the formation of fear memory resistant to labilization after recall, and (3) indicate that DCS/reinforcing stimulus presentation in combination with memory reactivation can be con-

sidered as an alternative approach for disrupting resistant fear memories such as those formed under ethanol withdrawal.

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