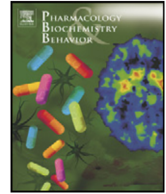
Pharmacology, Biochemistry and Behavior 116 (2014) 96–106

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

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



Memory interfering effects of chlordiazepoxide on consummatory successive negative contrast

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ARTICLE INFO

Article history:
Received 7 June 2013
Received in revised form 19 November 2013
Accepted 23 November 2013
Available online 4 December 2013

Keywords:
Chlordiazepoxide
Successive negative contrast
Memory consolidation
Allocentric memory
Egocentric memory
Memory reconsolidation

ABSTRACT

Long–Evans rats downshifted from 32% to 4% sucrose solution exhibit lower consummatory behavior during downshift trials than rats exposed only to 4% sucrose. In Experiment 1, this effect, called consummatory successive negative contrast (cSNC), was attenuated by administration of the benzodiazepine anxiolytic chlordiazepoxide (CDP, 5 mg/kg, ip) before the second downshift trial (Trial 12), but was not affected when CDP was administered before the first downshift trial (Trial 11). In Experiment 2, CDP administered after Trial 11 actually enhanced the cSNC effect on Trial 12. This posttrial effect of CDP was reduced by delayed administration (Experiment 3). This CDP effect was not present in the absence of incentive downshift (Experiments 4–5), or when animals were tested with the preshift incentive (Experiment 6) or after complete recovery from cSNC (Experiment 7). The posttrial CDP effect was observed after an 8-day interval between Trials 11 and 12 (Experiment 8) and when administered after Trial 12, rather than Trial 11 (Experiment 9). Experiment 10 extended the effect to Wistar rats. Because CDP is a memory interfering drug, it was hypothesized that its posttrial administration interferes with the consolidation of the memory of the downshifted incentive, thus prolonging the mismatch between expected (32% sucrose) and obtained (4% sucrose) incentives that leads to the cSNC effect.

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1. Introduction

In a typical experiment on consummatory successive negative contrast (cSNC), two groups of food-deprived rats receive access to either 32% or 4% sucrose solution during 10 daily trials, followed by access to 4% sucrose during subsequent trials. cSNC involves the transient suppression of consummatory behavior in the group exposed to an incentive downshift from 32% to 4% sucrose, relative to the 4-to-4% sucrose, unshifted controls (Flaherty, 1996). An intriguing property of cSNC is the apparent selectivity with which consummatory performance can be affected by the benzodiazepine anxiolytic chlordiazepoxide (CDP) on Trials 11 and 12—the first and second downshift trials (Flaherty et al., 1986, 1990). Whereas CDP significantly reduces cSNC on the second downshift trial, it has no apparent effects on the first downshift trial. A similar trial selectivity was observed with other anxiolytics (Flaherty, 1996). Additional studies demonstrated that CDP can have a contrast-reducing effect on the first downshift trial provided that trial is longer than the typical 5 min (Flaherty et al., 1986) or that rats are exposed to repeated cycles of incentive downshift (Flaherty et al., 1996).

Flaherty (1996) considered several hypotheses that could explain this trial selectivity of CDP, but none of them includes a direct reference to a memory process. He favored the idea that CDP reduces the negative emotion induced by incentive downshift, which would peak on the second downshift trial. To explain CDP's lack of action on the first downshift trial, Flaherty (1996) argued that the initial reaction to the downshift involves search behavior, rather than emotional activation. Unlike Flaherty's (1996) account, the present view incorporates memory processes to account for the cSNC effect. We suggest that the dependence of these CDP effects on experience with the downshifted solution, as illustrated by experiments with trials longer than the typical 5 min and with repeated downshifts (see above), suggests a memory-related mechanism (Bentosela et al., 2006; Norris et al., 2011). In the cSNC situation, there are at least three relevant memory sources: (1) the memory of the preshift incentive, formed during the initial trials of exposure to 32% sucrose; (2) the memory of the emotional response to the downshift event, formed during and after the first downshift trial (usually Trial 11); and (3) the memory of the downshifted solution, formed during subsequent downshift trials. Because (1) and (3) are incentive memories (i.e., environmental events), they were called "allocentric" (the prefix "allo" implies external to the organism), but because (2) is an emotional memory (i.e., internal event) it was called "egocentric" (the prefix "ego" implies internal to the organism; Papini, 2003). Therefore, during downshift trials, animals are assumed to encode two different memories: The egocentric memory of the negative emotional experience and the allocentric memory update of the new, less valued incentive. With posttrial administration, drugs that enhance egocentric memory or interfere with allocentric memory should promote consummatory suppression, whereas drugs that interfere with egocentric memory or enhance allocentric memory should promote the recovery

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http://dx.doi.org/10.1016/j.pbb.2013.11.031

of consummatory behavior. Posttrial drug administration is routinely used to modulate memory consolidation (McGaugh, 2000). The drug was not present when the memory is acquired (during the downshift event) and it is excreted before the next trial is administered, 24 h later. In rats, a single oral dose of CDP (10 mg/kg) has a half-life of 4–6 h (Koechlin and D'Arconte, 1963). Therefore, CDP could only influence consummatory behavior if it had memory effects, either on memory consolidation or via conditioned taste aversion.

Generally speaking, drugs affecting memory are either memory enhancing or memory interfering drugs (Amadio et al., 2004; Hirshman, 2004; McGaugh and Izquierdo, 2000). Thus, the working hypothesis is that if the administration of a memory enhancing drug after Trial 11 in the cSNC situation increases the cSNC effect, it can only act by potentiating the egocentric emotional memory of the downshift (i.e., enhancing allocentric memory should lead to attenuated cSNC because the expected incentive would tend to match the obtained incentive). Recent research with memory enhancing drugs administered after Trial 11, such as corticosterone (Bentosela et al., 2006; Ruetti et al., 2009) and D-cycloserine (Norris et al., 2011), have shown that the cSNC can indeed be increased and extended, thus retarding the recovery of consummatory behavior. The present series of experiments follows a similar logic, but using the anxiolytic CDP, a drug that acts at the benzodiazepine site of the type-A gamma-amino butyric acid receptor. CDP was selected because it has been shown to affect cSNC, as described above, and it has been shown to affect memory in other situations. CDP and other benzodiazepines have been described as causing memory impairment in avoidance conditioning, spatial learning, and step-down inhibitory avoidance (Flood et al., 1998; Ghoneim, 1992; Herzog et al., 2000; Izquierdo et al., 1990; Olaman and McNaughton, 2001; Silva and Frussa-Filho, 2000). If CDP is a memory-interfering drug in the cSNC situation, then it should either (1) cause animals to recover faster from the downshift (interpreted as interference with egocentric memory), or (2) cause animals to recover more slowly (interpreted as interference with allocentric memory). This series of experiments starts by asking whether the trial-selectivity of pretrial CDP in the cSNC situation is reproduced under the current conditions. Subsequent experiments explore the effects of posttrial CDP administration on cSNC and the extent to which such effects depend on an experience of incentive downshift.

2. Experiment 1: Pretrial 11 vs. 12

The main outcome consistent with an anxiolytic effect of CDP on cSNC is the selective attenuation of this effect with pretrial drug administration before the second downshift trial (Trial 12), but not when CDP is administered before the first downshift trial (Trial 11). Although several studies reported such a trial selectivity of CDP administration on cSNC (see above), in one study (Genn et al., 2004), pretrial CDP (5 mg/kg, ip) administration reduced cSNC on both the first and second downshift trials. Experiment 1 had two aims: first, to demonstrate the anxiolytic effect under the conditions used in the rest of the experiments and, second, to determine whether the attenuating effect of CDP under these conditions is trial selective (i.e., present on Trial 12, but not on Trial 11).

The Genn et al. (2004) study differed from previous research (see above) in terms of the dependent measure (solution intake, rather than lick frequency), testing environment (home cage, rather than separate conditioning box), and the rat strain (hooded Lister rats, rather than Sprague–Dawley or other commercially available strains). The procedure used in the present and previous studies from our lab differed from other studies in several respects (e.g., Norris et al., 2008, 2011). First, we routinely use goal-tracking time (cumulative time in contact with the sipper tube) as the dependent measure. Goal-tracking time has produced orderly results in a variety of experiments (see Papini, 2009; Papini et al., 2006) and it has been shown to significantly and positively correlate with fluid intake (Mustaca et al., 2002). Similar results were obtained when both goal-tracking time and fluid intake were recorded in the same experiment (Papini et al., 1988; Riley and Dunlap, 1979). Second, training was carried out in a separate conditioning box. Finally, we used Long–Evans rats.

2.1. Method

2.1.1. Subjects

The subjects were 60 experimentally naïve, male Long–Evans rats, approximately 90 days of age at the start of the experiment. Animals were bred in the TCU colony, housed in wire-bottom cages with water continuously available during the course of the experiment. At 90 days of age, food was restricted until animals were 81–84% of the free food weight. Temperature (around 23 °C) and humidity (around 50%) were maintained relatively constant and the colony was on a 12 h of light–dark cycle (lights on at 07:00 h). Behavioral testing occurred during the light phase of the cycle. Housing and testing were carried out in an USDA-inspected research facility. All experimental procedures were approved by the Institutional Committee on Animal Care and Use. Animal health was evaluated daily by researchers and periodically by a consulting veterinarian.

2.1.2. Apparatus

Animals were tested in 4 conditioning boxes constructed of aluminum and Plexiglas, 29.3 cm long, 21.3 cm high, and 26.8 cm wide. The floor was made of steel rods 0.4 cm in diameter and 1.6 cm apart that ran parallel to the feeder wall. A tray filled with corncob bedding was placed below the floor to collect fecal pellets and urine. A sipper tube (1 cm in diameter and protruding 1.5 cm from the feeder wall when fully inserted) was automatically inserted and retracted to deliver the sucrose solution. This sipper tube was inserted through an elliptical hole in the feeder wall, 1 cm wide, 2 cm high, and 4 cm from the floor. Contact with the sipper tube was recorded automatically by the closing of an electric circuit between the sipper tube and the steel floor. Each conditioning box was enclosed in a sound-attenuating chamber 57.5 cm long, 36.9 cm high, and 39.4 cm wide. This chamber also had a speaker and a fan, which together register 80.1 dB (SPL, scale C). The control of the sipper tube and recording of the response were performed by a computer located in an adjacent room.

2.1.3. Training procedure

When the weights reached the target deprivation criterion, animals were randomly assigned to one of six groups ($n = 10$) depending on the drug administered before Trial 11 or 12, either saline or CDP: 32/Sal/Sal, 32/CDP/Sal, 32/Sal/CDP, 4/Sal/Sal, 4/CDP/Sal, and 4/Sal/CDP. In this design, the same saline controls can be used for each of the two CDP conditions, Trial 11 or Trial 12. For two groups (one downshifted and one unshifted), the two injections were equal-volume saline injections (32/Sal/Sal and 4/Sal/Sal). Two other groups received CDP (5 mg/kg, ip) before Trial 11 and vehicle before Trial 12 (32/CDP/Sal and 4/CDP/Sal). The final two groups received the vehicle injection before Trial 11 and CDP before Trial 12 (32/Sal/CDP and 4/Sal/CDP).

All animals received training during 12 daily trials each lasting 5 min starting after the first contact with the sipper tube was detected. For 3 groups (downshifted groups), 32% sucrose was available during Trials 1–10, followed by 4% sucrose during Trials 11–12. For the other three groups, 4% sucrose was available during the 12 trials. Solutions were prepared w/w by mixing 32 g (or 4 g) of commercial sugar with 78 g (or 96 g) of distilled water and administered at room temperature. All animals received two injections (before Trials 11 and 12), 30 min before the start of each trial.

Rats received training in squads of four. Each animal was always in the same squad and trained in the same conditioning box, but the order of squads was randomized across days. Conditioning boxes were cleaned with a damp paper towel after each trial. Each trial started with a variable interval of 30 s (range: 15–45 s). At the end of this interval, the sipper tube was automatically presented. A recording period

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