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Brain expression of pCREB in rats exposed to consummatory successive negative contrast

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HIGHLIGHTS

- A 32-to-4% sucrose devaluation induces a suppression of consummatory behavior.
- An episode of reward devaluation can trigger a memory consolidation process.
- pCREB expression, a marker of synaptic plasticity, was assessed in several brain regions.
- High expression in prelimbic cortex, anterior cingulate, and dorso-medial striatum.
- These are potential brain regions for memory consolidation in reward devaluation.

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ABSTRACT

A 32-to-4% sucrose devaluation leads to suppression of consummatory behavior relative to unshifted 4% sucrose controls. This is accompanied by an emotional response inducing memory consolidation. Expression levels of phosphorylated cyclic adenosine monophosphate response element-binding protein (pCREB, a marker of synaptic plasticity) were higher after the first devaluation session than after the second in prelimbic cortex, anterior cingulate cortex, and dorso-medial striatum. The central nucleus of the amygdala showed a tendency to differential pCREB expression. This evidence contributes to identifying the brain circuit for one form of traumatic memory involving reward loss.

1. Introduction

A surprising reward devaluation can induce a negative emotional response and switch behavior from an appetitive/consummatory to an escape/search mode [1,11,12]. In consummatory successive negative contrast (cSNC), animals typically receive access to 32% sucrose for ten 5 min sessions and then are downshifted to 4% sucrose for 4–5 additional sessions. Downshifted animals consume less 4% sucrose than animals that have always received 4% sucrose; the cSNC effect typically lasts 1–3 sessions and then behavior recovers to the level of unshifted controls [12]. Drugs administered after the first downshift session (usually session 11) suggest that reward devaluation involves memory processes. Thus, cSNC is enhanced by memory modulators including corticosterone [6,30], D-cycloserine [23], and chlordiazepoxide [24], administered after session 11. These treatments do not affect unshifted controls, suggesting that they modulate the consolidation of a new memory. Because these drugs are known to facilitate (corticosterone, D-cycloserine) and interfere (chlordiazepoxide) with memory consolidation, and yet have the same behavioral effect (i.e., enhance cSNC), these results suggest that reward devaluation induces the consolidation of different memories. Candidates for new memories include the downshift experience and the new reward [28].

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Systemic pharmacological treatments narrow down the possible synaptic receptors involved in memory processes, but provide no information about the brain circuit engaged during reward devaluation. Brain lesions point to cortical [21,25,27,29] and limbic [4] involvement in the cSNC effect. However, the paucity of lesion data and the large number of potential brain locations suggest the need for a different approach. We assessed brain levels of phosphorylated cyclic-adenosin monophosphate response-element binding (pCREB) as a tool to identify brain locations potentially involved in memory during reward devaluation. pCREB levels, chosen because of its established role in synaptic plasticity and memory consolidation [5,17], were assessed in prefrontal cortex (insular, orbital, infralimbic, and prelimbic areas), striatum (nucleus accumbens core and shell, and medial, intermediate, and lateral dorsal striatum), and limbic system (basolateral and central amygdala, anterior cingulate cortex (ACC), and hippocampal CA3 areas).

CREB is a transcription factor crucial for the transduction of events that occur at cell membranes into alterations of gene expression. CREB binds as dimers to the cyclic adenosine monophosphate-response element (CRE), a specialized stretch of DNA found within the regulatory region of numerous genes. Membrane-dependent events elicited by a behavioral experience stimulate intracellular cascades that cause the phosphorylation of CREB (pCREB) and initiate its transcriptional activity [9]. These molecular changes stabilize modifications in synaptic strength, thereby encoding the memory for that experience [5,7]. Available evidence suggests that CREB is necessary for the stability of new and reactivated fear memories [17], regulates anxiety-like behaviors [2], and constitutes a key regulator of the individual sensitivity to emotional stimuli [3]. The CREB pathway has been implicated in learning, memory, addiction, perception, cognition, neural development and protection, and a variety of neuropsychiatric disorders [5,18,31].

Pharmacological evidence suggests that a significant episode of memory consolidation in the cSNC situation occurs after the first downshift session, although memory update probably occurs beyond session 11 as the animal experiences the devalued solution [23]. To selectively target potential brain sites of plasticity activated by this initial reward-devaluation event, we compared pCREB expression in animals sacrificed after session 11 vs. 12. pCREB expression levels were predicted to be higher after the first than after the second downshift session.

2. Method

2.1. Subjects

Forty four experimentally naïve, male wistar rats, derived from breeders purchased at Charles River (Wilmington, MA) and Harlan (Houston, TX), served as subjects. Animals were group housed from weaning until about 40 days of age and subsequently individually housed with free food and water. At 90 days of age, food was restricted until animals were 81–84% of the free-feeding weight. Temperature (23 °C) and humidity (50%) were maintained relatively constant. The colony was lighted from 07:00 to 19:00 h. Behavioral testing occurred during the light phase.

2.2. Apparatus

Eight conditioning boxes (MED Associates, St. Albans, VT) made of aluminum and Plexiglas (29.3 × 21.3 × 26.8 cm, $L \times W \times H$) were used. The floor consisted of steel rods parallel to the feeder wall. A tray filled with corncob bedding was placed below the floor to collect feces and urine. A sipper tube (diameter: 1 cm) was inserted through an elliptical hole, 1 × 2 cm ($W \times H$), 3.5 cm from the floor. When fully inserted, the sipper tube was flush against the wall. A computer located in an adjacent room controlled the presentation of the sipper tube and detected contact with the sipper tube via a circuit involving the steel rods in the floor. Each box was in a sound-attenuating chamber containing a house light, a speaker that delivered white noise, and a fan (masking noise: 80.1 dB, SPL, Scale C).

2.3. Procedure

2.3.1. Behavior

Animals were randomly assigned to one of four conditions depending on the sucrose concentration (32% or 4%) administered during preshift sessions 1–10 and the postshift session in which they were sacrificed (11 or 12). Two groups were exposed to 32-to-4% sucrose reward devaluation: 32/11 ($n = 16$) and 32/12 ($n = 16$). Two groups received only access to 4% sucrose: 4/11 ($n = 6$) and 4/12 ($n = 6$).

Each session lasted 5 min from the first contact with the sipper tube. 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. At the start of each session, the computer turned on the house light and started a variable interval (mean: 30 s ± 15) ending with the presentation of the sipper tube. The cumulative time in contact with the sipper tube (goal-tracking time) was recorded in 0.01 s units. Retraction of the sipper tube was followed by a variable interval (mean: 30 s ± 15). Then the house light was turned off and the rat was placed back in its cage. At least 15 min after the session ended, rats were fed enough food to maintain deprivation levels. Following each session, boxes were wiped with a damp sponge, feces removed from the tray, and bedding replaced as needed.

2.3.2. pCREB assessment

Immediately following session 11 or 12, depending on the group, animals were deeply anesthetized with a single 1 ml ip injection of chloral hydrate (400 mg/ml in 0.9% saline) and perfused transcardially with 200 ml of 0.01-M phosphate-buffered saline (PBS) followed by 400 ml of 4% paraformaldehyde made in 0.01 M PBS. Brains were removed, placed in 4% paraformaldehyde and stored at 4 °C. The next day, brains were placed in 20% glycerol for a minimum of 24 h.

Brains were sectioned (40 μm) on a freezing microtome and coronal sections stored in 0.01% sodium azide dissolved in 0.01-M PBS at 4 °C. Brains were immunohistochemically stained for pCREB. Tissue was rinsed with 3% hydrogen peroxide to destroy any endogenous peroxidases. Next, sections were blocked for 1 h with 3% normal goat serum (Jackson ImmunoResearch, West Grove, PA) and 0.3% Triton X followed by incubation in rabbit pCREB antibody (1:1500; Millipore Billerica, MA) for approximately 20 h with 1% normal donkey serum. A biotinylated goat anti-rabbit secondary antibody (Vector BA-1000) was used at a dilution of 1:200. Tissue was then incubated with avidin-biotin complex (Vectastain ABC Elite kit; Vector Laboratories, Burlingame, CA) for 1.5 h and pCREB immunoreactive nuclei were visualized by using a DAB kit (Vector Laboratories, Burlingame, CA). After staining, sections were rinsed in PBS, mounted onto microscope slides, dehydrated, and cover-slipped prior to cell counting.

Pictures were taken of each brain area of interest at a magnification of 20X. Thirteen brain areas were targeted based on previous research on cSNC and related phenomena (see Discussion for references) and grouped according to conventional neuroanatomical regions [8]: (1) Prefrontal cortex: insular, orbital, infralimbic, and prelimbic areas; (2) Striatum: nucleus accumbens core and shell, and medial, intermediate, and lateral dorsal striatum; (3) Limbic

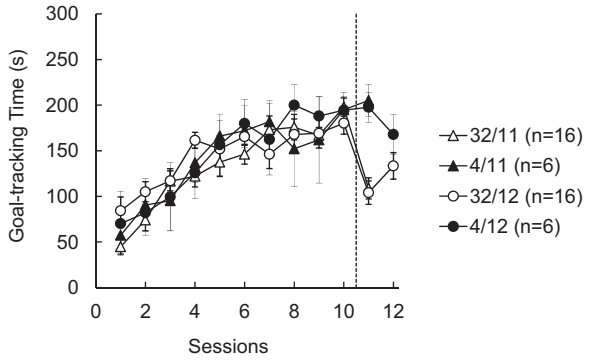

Fig.1. Mean (±SEM) goal-tracking time of groups exposed to reward downshift (32) or unshifted controls (4), and sacrificed after session 11 or 12. The vertical dotted line separates preshift from postshift sessions.

system: basolateral and central amygdala, ACC, and hippocampal CA3. pCREB-positive cells were identified and counted using Image J software. Images were converted to greyscale and thresholded with the default filter. The watershed function was applied to separate clumps of cells into individual cells for counting. Next, cells were quantified using the Analyze Particle function with the parameters of 13 for size and 0.6 for circularity. A subset of 156 pictures was hand counted for validation. Pearson's correlation coefficient between hand counting and automated counting was significant, $r(154) = 0.94$, $p < 0.001$.

3. Results

3.1. Behavior

Preshift performance of animals exposed to 32% vs. 4% sucrose was nondifferential. A sucrose (32%, 4%) × session (1–10) analysis yielded only a significant increase in goal tracking across sessions, $F(9, 378) = 35.20$, $p < 0.001$. There were clear cSNC effects on session 11 in animals sacrificed after session 11 or after session 12 (i.e., downshifted groups performed significantly below unshifted controls); the cSNC effect had dissipated by session 12 (Fig. 1). A contrast (32%, 4%) × session (10–11) analysis computed on Groups 32/11 vs. 4/11 indicated a significant contrast by session interaction, $Fs(1, 20) = 33.44$, $p < 0.001$. The session, $F(1, 20) = 21.15$, $p < 0.001$, and the contrast main effects were also significant, $F(1, 20) = 6.52$, $p < 0.02$. LSD pairwise comparisons derived from the main analysis indicated that groups did not differ during session 10, $F < 1$, but Group 32/11 was significantly below Group 4/11 on session 11, $F(1, 20) = 19.73$, $p < 0.001$.

A contrast × session (10–12) analysis for the animals sacrificed after session 12 also revealed a significant interaction, $F(2, 40) = 7.36$, $p < 0.003$, and significant session, $F(2, 40) = 6.85$, $p < 0.004$, and contrast main effects, $F(1, 20) = 4.60$, $p < 0.05$. The source of the interaction was a greater consummatory suppression in Group 32/12 than 4/12 on session 11, $F(1, 20) = 16.06$, $p < 0.002$. The groups were not different on session 10, $F < 1$, and were recovered by session 12, $F(1, 20) = 1.12$, $p > 0.30$.

The cSNC effect was observed on session 11 in terms of 2 × 2 analysis of Groups 32/11, 32/12, 4/11, and 4/12. The contrast effect was highly significant, $F(1, 40) = 35.52$, $p < 0.001$, but the sacrifice session and contrast by sacrifice session interaction effects were negligible, $Fs < 1$.

3.2. pCREB

Data were normalized to minimize fluctuations in cell counts across sessions. Cell counts in each downshifted animal, for each area, were expressed as a percentage change relative to the mean cell count for the unshifted controls for that area according to the formula: $(D_{i,j} - U_{i,j})/U_j \times 100$, where "D" stands for downshifted individuals, "U" stands for unshifted mean, "i" stands for an individual animal, and "j" for a particular brain area. A positive number indicates that pCREB expression was $D > U$, a negative number indicates $D < U$, and a zero indicates $D = U$. Data from animals sacrificed after sessions 11 or 12 were separately transformed. Two tests were calculated for each area. First, one-way analyses of variance for independent samples were computed to compare scores from session 11 vs. 12. Second, the score from each session was compared to the zero baseline to determine whether scores differed from the indifference point. One-sample, two-tailed *t*-Tests were used in this case. A $p < 0.05$ was used as the alpha level in all tests.

For prefrontal areas (Fig. 2a), prelimbic cortex exhibited a higher pCREB expression after session 11 than after session 12, $F(1, 30) = 7.02$, $p < 0.02$. For other areas: $Fs < 1$. A *t*-Test indicated only a significant reduction in expression on session 12 in prelimbic cortex, $t(15) = -2.77$, $p < 0.02$.

For striatal areas (Fig. 2b), Group 32/11 was significantly higher than Group 32/12 in the dorsomedial striatum (dmSt), $F(1, 30) = 5.18$, $p < 0.04$. For other areas: $F(1, 30) < 1.84$, $ps > 0.18$. One-sample *t*-Tests indicated that pCREB expression was higher than zero on session 11 only for the intermediate dorsal striatum (diSt), $t(15) = 2.92$, $p < 0.02$. For the dmSt, the increase in expression was marginal, $t(15) = 2.04$, $p = 0.059$.

For limbic areas (Fig. 2c), the amygdala showed higher pCREB expression in both the basolateral (BLA) and the central nuclei (CeA), but the differences were not significant. For the CeA,

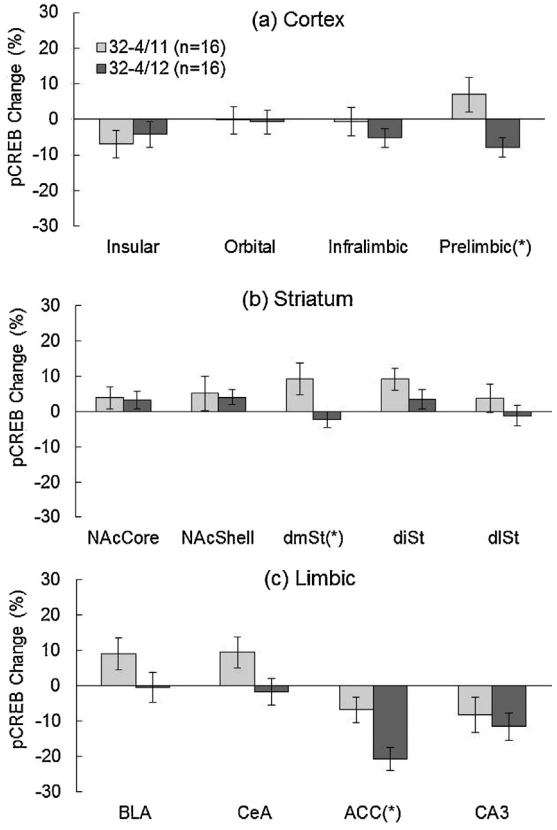

Fig. 2. Mean (±SEM) of change in cells expressing pCREB in downshifted groups (32/11, 32/12) relative to their respective unshifted controls. (a) Cortical areas. (b) Striatal areas; NAc: nucleus accumbens. dmSt: dorso medial striatum. diSt: dorso intermediate striatum. dlSt: dorso lateral striatum. (c) Limbic areas; BLA: basolateral amygdala. CeA: central nucleus of the amygdala. ACC: anterior cingulate cortex. CA3: hippocampal CA3 area. (*): $p < 0.04$.

the effect was marginal, $F(1,30) = 3.65$, $p = 0.066$. Because of this marginal effect and given the potential role of the amygdala in the cSNC effect [4], we computed an additional two-way analysis involving Area (BLA, CeA) and session (11, 12) as independent-sample factors. In this case, the session effect was significant, $F(1, 58) = 5.94$, $p < 0.02$ (the area and interaction effects were nonsignificant, $Fs < 1$). A clear effect was observed in the ACC, but pCREB expression was lower in downshifted than in unshifted animals for both days. In relative terms, however, there was more pCREB expression after session 11 than 12 in the ACC, $F(1,30) = 8.37$, $p < 0.008$. One-sample t-Tests indicated a significant increase relative to zero in the CeA, $t(15) = 2.18$, $p < 0.05$, and a marginal effect for the BLA, $t(15) = 2.02$, $p = 0.061$. After session 12, however, both the ACC, $t(15) = -6.28$, $p < 0.001$, and the hippocampal CA3 area, $t(14) = -2.97$, $p < 0.02$, were significantly below the zero baseline.

4. Discussion

In this experiment, the cSNC effect was observed during the first downshift session (session 11), but it had dissipated by the second downshift session (session 12). Posttraining pharmacological treatments suggest that the recovery of consummatory behavior involves memory processes triggered during the initial devaluation experience [6,23,30]. The present experiment was an attempt to determine potential sites of memory consolidation activated after the initial downshift event. This does not imply that all memory consolidation occurs after the initial downshift experience. For example, the memory-interfering benzodiazepine drug chlordiazepoxide affects performance whether administered immediately after the first or second postshift session [24]. The present research, however, aims at distinguishing between memory sites potentially and selectively implicated in memory consolidation triggered by the initial reward devaluation event. How does the information provided by pCREB levels relate to the results of experiments using lesion and microinfusion techniques in the cSNC situation?

The view adopted here is that cSNC involves telencephalic modulation of a brain stem circuit controlling the taste-licking action pattern [4,16]. The two main sources of modulation identified thus far involve the prefrontal cortex and the amygdala. Data on the effect of lesions in four cortical areas on cSNC are available: ACC, insular, orbital, and medial prefrontal cortex (mPFC). ACC lesions enhance cSNC by interfering with the memory update of the new downshifted reward [27]. Consistent with these results, pCREB expression, while lower than baseline levels, was higher for session 11 than 12. While consistent in relative terms, the fact that expression levels were below those of the unshifted controls is difficult to explain. Thus, this result should be considered with caution until additional data are available. Lesions of the insular cortex abolished cSNC without disrupting the behavior of unshifted controls [21]. Insular animals adjusted their consummatory behavior to the devalued reward without producing a contrast effect. It is unclear whether this effect is related to memory consolidation or to an adjustment to the palatability of the devalued reward. There was no evidence that pCREB levels differed in the insular cortex, so the present results discourage further consideration of this prefrontal area as a potential site for plasticity in the cSNC situation, although it certainly plays an active role in this paradigm. A similar active role, probably unrelated to memory, was reported for the ventrolateral orbital cortex [25]. Orbital animals exhibited a reduced cSNC effect only during the first downshift session, and only restricted to the later portions of that session. In the same study, orbital lesions also eliminated the enhancement of anticipatory performance by partial reinforcement training, an effect that has been attributed to increased drive induced by reward uncertainty [1]. Likewise, selective breeding for fast recovery from reward downshift also eliminated the activation of anticipatory behavior during partial reinforcement training [26]. These results suggest that the ventrolateral orbital cortex controls drive levels during reward devaluation or omission. The lack of evidence for differential pCREB expression in the orbital cortex is consistent with this conclusion.

There is contradictory evidence about the function of the mPFC in the cSNC effect. Evidence of enhanced recovery from reward downshift after lesions of the mPFC [29] is difficult to interpret because unshifted controls were not included. A study that included such controls found no evidence of an effect of mPFC lesions on cSNC [25]. The present study sampled from two sections of the mPFC, the infralimbic and prelimbic areas. The former yielded no evidence of involvement in terms of pCREB expression, but the prelimbic cortex showed higher relative expression on session 11 than session 12, suggesting that it might be a plasticity site. Prior evidence suggests that the rat prelimbic cortex is linked to taste and olfactory learning. Extinction of a conditioned taste aversion with saccharin induces significant activation in the prelimbic area, as measure by c-fos expression, suggesting that this area plays a role in the reacceptance of a previously aversive taste [22]. This finding is analogous to the recovery of consummatory behavior to a 4% sucrose solution previously made aversive by the reward devaluation procedure used in the present study. Furthermore, blockage of NMDA receptors in this area with the competitive antagonist 2-amino-5-phosphonoeptanoic acid (APV) immediately after appetitive odor conditioning induced a deep retention impairment [32]. Microinfusions of D-cycloserine, an NMDA partial agonist, or S18986, a positive allosteric modulator of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, enhanced the relearning and retention of appetitive odor conditioning [33,34]. Thus, the prelimbic portion of the mPFC needs to be included in an exploratory search for sites of plasticity in the cSNC situation as it might play a role in memory consolidation.

Disruption of amygdala function either via large lesions [4] or by infusion of the benzodiazepine diazepam [20] attenuates the cSNC effect. In a direct comparison of Groups 32/11 and 32/12, the present results for BLA and CeA were in the right direction (i.e., increased pCREB expression after session 11), but statistically marginal. The effect was significant only when the two areas were combined in the analysis. Moreover, pCREB was significantly elevated in the CeA relative to the zero baseline on session 11, but not on session 12 (a similar, but marginal, effect was found for BLA). Thus, a role of the amygdala in memory encoding in the cSNC paradigm cannot be discarded.

Unlike the amygdala, lesion experiments provide no evidence that the hippocampus is involved in the cSNC effect. Whereas the hippocampus is critical in some fear conditioning paradigms, such as contextual and trace conditioning [15], and its damage impairs instrumental successive negative contrast in the runway situation [13], large lesions do not seem to affect cSNC [13]. Consistent with these results, there was no evidence of enhanced pCREB expression in the CA3 hippocampal region in a direct comparison of Groups 32/11 and 32/12.

The function of the nucleus accumbens in the cSNC effect is difficult to grasp. The role of this structure in reward processes [10] suggests a priori that it should be an essential component of the circuit. A microdialysis study revealed that the 32-to-4% sucrose downshift in an operant analog of the cSNC situation was accompanied by a reduction in dopamine efflux in the NAc below that of unshifted controls [14]. This result suggests that the output from the accumbens could integrate information about the expected and obtained rewards. However, electrolytic lesions of the NAc disrupted iSNC, but had no effect on cSNC [19]. Because the current experiment involved a cSNC paradigm, the absence of differential

pCREB expression among downshifted groups, whether in the NAc core or shell, agrees with previous results. The different response requirements of iSNC and cSNC apparently determine whether the NAc is involved in reward comparisons.

Two potential types of information may be encoded in memory during reward devaluation in the cSNC situation [28]. First, the animal may acquire information about its emotional reaction to the downshift, called egocentric memory. When retrieved in subsequent sessions, egocentric memory would tend to enhance the cSNC effect by increasing rejection/avoidance of the devalued reward. Second, the animal may acquire information about the new, downshifted reward, called allocentric memory. Allocentric memory would tend to alleviate consummatory suppression by minimizing the discrepancy between expected and obtained rewards, thus reducing the cSNC effect. Based on the present results, we hypothesize that the prelimbic cortex, ACC, dmSt, and (tentatively) CeA are involved in one or both of these memory processes. Lesion and microinfusion procedures may now target these structures to determine their role in the egocentric and allocentric memory components thought to be implicated in recovery from reward devaluation in the cSNC situation.

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