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# Effects of Sodium Benzoate Treatment in Combination with an Extinction Training on the Maintenance of Cocaine-Supported Memory

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## Abstract

**Activation of N-methyl-D-aspartate (NMDA) receptor can facilitate the extinction of various maladaptive memories. Sodium benzoate (NaB) has been known to enhance a naturally occurring full agonist on the glycine binding site of the NMDA receptor. This study aimed to test whether systemic NaB treatment can affect the extinction of a cocaine-supported memory, the cocaine-induced conditioned place preference (CPP). Following the establishment of the cocaine (10 mg/kg/conditioning × 3)-induced CPP, an extinction protocol, consisting of two consecutive extinction training bouts at an 8-h interval, was used. NaB (500 mg/kg) or an equivalent volume of saline was given immediately following each extinction training bout to test the modulating effect of NaB on the maintenance of cocaine-induced CPP. Moreover, NaB was bilaterally micro-infused into the medial prefrontal cortex (mPFC) to validate the involvement of this brain region in mediating systemic NaB treatment-produced effect on cocaine-induced CPP. Systemic (500 mg/kg) and intra-mPFC (10 μg/side) NaB treatment significantly decreased subsequent cocaine-induced CPP magnitude, although the NaB treatment or the extinction training alone did not affect such CPP magnitude. It was of importance to note that systemic or intra-mPFC NaB delivery did not affect mouse locomotor activity in the retests. These results, taken together, suggest that NaB treatment in combination with the extinction training may facilitate the extinction of the cocaine-supported memory. Moreover, systemic NaB treatment exerts such effects, at least in part, *via* its effect in the mPFC.**

**Key Words: cocaine, conditioning, memory, sodium benzoate**

## Introduction

Cocaine-related memory has long been regarded as a major risk factor in causing the cocaine relapse and recurrence in addicts (12). Thus, erasing cocaine-related memory has become one of the most promising targets for treating cocaine addiction (5). Although many studies have demonstrated that the extinction training may change the originally formed memories in both animals and humans (2, 4, 10, 13, 14, 20), curing the maladaptive memory-motivated symptoms through the exposure therapy and the indwelt extinction techniques in clinical trials are lackluster and sometimes short-lived (14, 15). Such short-lasting nature of the exposure therapy can be explained in two ways. First, the exposure therapy alone is incapable

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of reversing the abused drug-induced long-term neuronal plasticity. Second, the exposure therapy is more prone to favoring the expression of the exposure therapy-related memory than to ameliorating the original abused drug-associated memory. Thus, we decided to use a combination of exposure therapy and pharmacological treatment to extinguish cocaine-supported memory. In this study, cocaine-induced conditioned place preference (CPP) was used for modeling cocaine-supported memory. In an attempt to test the efficacy of the exposure therapy combined with pharmacological treatment, an extinction protocol, consisting two extinction training bouts, in combination with an N-methyl-D-aspartate (NMDA) agent delivery was employed. Moreover, multiple retests and the cocaine reminding (cocaine re-exposure) test were used to reveal the plausible changes in cocaine-associated memory.

NMDA receptor activation has been known to modulate the extinction of cocaine-supported and fear memories (1, 4, 6, 8, 9, 17, 21). Sodium benzoate (NaB) can drastically enhance glutamate efflux from the hepatic cells (11) and NaB also serves as an inhibitor of D-amino acid oxidase, the catabolizing enzyme of D-serine, which is a naturally occurring full agonist on the glycine binding site of the NMDA receptor (16). Systemic NaB treatment is anticipated to enhance glutamate availability and to render NMDA receptor activation. In an attempt to test the modulating effects of NaB treatment combined with an extinction protocol on the maintenance of cocaine-induced CPP, systemic NaB administration was done immediately after each extinction training bout. Neuronal plasticity in the medial prefrontal cortex (mPFC) has been known to be critical in acquiring the cocaine-induced CPP (9). Thus, NaB was bilaterally infused into mPFC immediately after the extinction training bout to assess the possible involvement of mPFC NMDA activation in mediating the systemic NaB-exerted effect on the cocaine-induced CPP.

## Materials and Methods

*Ethics Statement*

This study was performed in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23) revised in 1996. All procedures were approved by the local Animal Care Committee at National Cheng Kung University College of Medicine.

*Animals*

Male C57BL/6 mice, approximately 10 weeks of age, were group housed in plastic cages (five per cage) in a temperature- and humidity-controlled colony room on a 12-h light/dark cycle with lights on at 07:00. Mice had access to food (Purina Mouse Chow, Richmond, IN, USA) and tap water *ad libitum*. All experiments were conducted in a temperature (23 ± 1°C)- and humidity (70%)-controlled laboratory.

*Cocaine-Induced CPP Training and Test*

Cocaine hydrochloride was obtained from Sigma Chem (St. Louis, MO, USA) and freshly dissolved in saline before use. Cocaine-induced CPP training and test were conducted in commercial chambers designed for mice (Med Associates Inc., Georgia, VT, USA) as described in our previous reports (7, 18, 19). Chambers were deodorized by a thorough cleaning with an isopropyl alcohol (70%)-rinsed paper towel wiping and then dried before each training and test bout. First, mice were placed in the central compartment of any randomly chosen chamber and the time spent in each compartment of the chamber was measured for their unconditioned preference in a 15-min pretest. Mice spending less than 40% of the time in any side compartment (17 × 13 × 13 cm with white or black walls and ceilings, steel bar grid or wire-mesh floors, strong or dim roof light) or center compartment (9 × 13 × 13 cm with gray walls and ceilings, platform floor) were included in the study. For cocaine-induced CPP training, mice receiving an intraperitoneal (i.p.) saline injection between 08:00 and 10:00 were immediately confined in their previously preferred compartment for 30 min. At least 8 h later, mice receiving a cocaine (10 mg/kg) injection were immediately confined in their previously non-preferred compartment for 30 min. These procedures were repeated for another two days. Approximately 20 h (around noon) after the conclusion of the last bout of the cocaine conditioning, mice were placed in the central compartment with guillotine doors open and a 15-min CPP test was started at a cocaine-free status in their respective chambers. Durations (in sec) for mice exploring each of the three compartments were recorded. Cocaine-induced CPP magnitude was represented by subtracting the time spent in the saline-conditioned compartment from the time spent in the cocaine-conditioned compartment.

*The Extinction Protocol, Retest and Cocaine Reminding Test*

Starting approximately 20 h after the CPP test, the extinction protocol consisting of two consecutive, cocaine-free, extinction training bouts at an 8-h interval was conducted. In brief, mice receiving an i.p. saline injection between 08:00 and 10:00 were immediately confined in their previously saline-conditioned compartment for 30 min. Approximately 8 h later, mice

receiving another saline injection were immediately confined in their previously cocaine-conditioned compartment for 30 min. After the extinction protocol, mice received 2 consecutive daily cocaine-free CPP retests. Approximately 48 h after the second retest, mice received the cocaine reminding test. A half (5 mg/kg) of the cocaine dose (10 mg/kg) used for the cocaine-induced CPP training was used in the cocaine reminding test. Immediately after the cocaine injection, mice were placed in the center with guillotine doors open and the 15-min retest and reminding test were started in their corresponding chambers. Cocaine-induced CPP magnitude was represented by subtracting the time spent in previously saline-paired compartment from the time spent in previously cocaine-paired compartment in the retests and the cocaine reminding test. In an attempt to assess the modulating effects of NaB and the extinction training on the maintenance of cocaine-induced CPP, four groups of mice (n = 96) were used. Two groups (n = 54) received the extinction training, while the remaining two groups (n = 42) stayed at their home cages at the respective time points. One half of these two groups (n = 27 out of 54 and n = 21 out of 42) received NaB treatment, while the remaining halves (n = 27 and n = 21) received an equivalent volume of saline injection. To further examine the roles of the mPFC NMDA activation in modulating the maintenance of the cocaine-induced CPP, a total of 30 mice were used. Following histological check, 16 mice receiving intra-mPFC NaB infusion and 14 mice receiving intra-mPFC saline infusion immediately after each forced extinction training bout were included for further data analysis.

*Stereotaxic Surgery and Guide Cannula Implantation*

Stereotaxic surgery and the 26-gauge guide cannula implantation [coordinates: anteroposterior, 1.6 mm; lateral, ± 3.0 mm (9° angle); dorsoventral, -1.6 mm] were performed under sodium pentobarbital anesthesia (40 mg/kg) one week prior to the beginning of the CPP training. Clearance through the guide cannula was maintained with dummy cannulas. The infusion cannula, a 33-gauge dental needle, was inserted into the guide cannula and was lowered 0.7 mm below the guide cannula. The infusion cannula was mostly in or bordered on the lateral and ventral parts of the medial prefrontal cortex (mPFC, including both infralimbic and prelimbic region). Following histological examination, mice found to have infusion cannula outside the above-mentioned range were not included for further statistical analyses. NaB (10 μg/0.25 μl/side) or 0.25 μl/side saline was infused into bilateral mPFC with a Hamilton 10-μl microsyringe driven by a microdialysis pump (CMA/Microdialysis, Stockholm, Sweden) at a rate of 0.5 μl/min.

*Locomotor Activity*

To evaluate whether NaB treatment may impair the maintenance of cocaine-induced CPP by decreasing mouse motor activity, a total of 37 mice were used for monitoring their locomotor activity at approximately 20 h after the second treatment with NaB (500 mg/kg, i.p., n = 11), saline (i.p., n = 10) or NaB (10 μg/0.25 μl/side for two sides, intra-mPFC, n = 8), saline (0.25 μl/side for two sides, intra-mPFC, n = 8). Locomotor activity (ambulatory activity and vertical rearing in combination) was monitored in a custom-made transparent Plexiglas chamber (41 × 41 × 30 cm) inside the Optovarimax (Columbus Instrument, Columbus, OH, USA). In brief, mice were individually placed in the center of the chamber and allowed free navigation for three consecutive bins (10 min/bin). The vertical infrared (IR) beam break count was used as an index for vertical rearing and the horizontal IR beam break was recorded as a count of ambulatory activity. Locomotor activity stood for the sum of rearing and ambulatory activity.

*Statistics*

Repeated measure ANOVAs were employed to assure reliable establishment of cocaine-induced CPP. Likewise, one-way (NaB *vs.* saline) or two-way (extinction training × NaB) repeated measure ANOVAs were used to assess NaB- and extinction training-produced differences on the cocaine-induced CPP magnitude. Finally, one-way repeated measure ANOVAs were used to test the differences between NaB and saline treatment (in systemic or intra-mPFC experiments) on the locomotor activity in three 10-min bins across 30 minutes. ANOVAs were followed by Bonferroni's post hoc tests if appropriate. The levels of statistical significance were set at $P < 0.05$.

## Results

*Systemic NaB Treatment Following Each Extinction Training Bout Facilitates the Extinction of Cocaine-Induced CPP*

Since no group effect or group × pretest-test interactive effect was noticed, a repeated measure ANOVA revealed that there was a significant main effect of pretest-test on the cocaine-induced CPP magnitude, indicating that the mice had acquired reliable and comparable cocaine-induced CPP [$F(1,92) = 302$, $P < 0.0001$] (Fig. 1). Two-way repeated measured ANOVA revealed that the main effect of test-retest-reminding test on the cocaine-induced CPP magnitude was evident [$F(3,276) = 4.30$, $P = 0.0055$] (Fig. 1). Moreover, the main effect of group [$F(3,276) =$

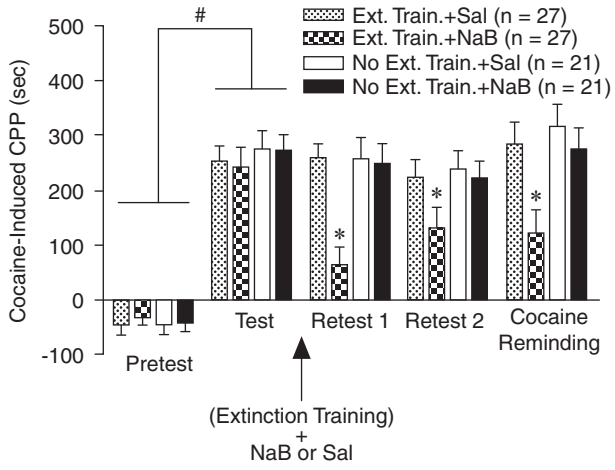


Fig. 1. Impact of systemic NaB treatment and the extinction training on the maintenance of cocaine-induced CPP. NaB or saline was given immediately following each extinction bout (two in total at an 8-h interval). Systemic NaB treatment (500 mg/kg) following each extinction training bout facilitated the extinction of cocaine-induced CPP in retests and cocaine reminding test. NaB, sodium benzoate; Sal, saline. #Significantly greater than pretest. *Significantly lower than test.

8.86, $P < 0.0001$] and the interactive effect of test-retest-reminding test and group [$F(9,276) = 2.30$, $P = 0.0165$] on the cocaine-induced CPP magnitude were also noticed (Fig. 1). *Post hoc* tests further indicated that mice receiving the extinction training protocol immediately followed by systemic NaB injection displayed significant decreases in cocaine-induced CPP in retest 1, 2 and the cocaine reminding test (Fig. 1).

*Bilateral Intra-mPFC NaB Infusion Following the Extinction Training Facilitates the Extinction of Cocaine-Induced CPP*

No group effect or group × pretest-test interactive effect was noticed, but a significant main effect of pretest-test [$F(1,28) = 141.2$, $P < 0.0001$] on the cocaine-induced CPP magnitude was noticed in a one-way repeated measured ANOVA. These results indicated that the two groups of mice had acquired reliable and comparable cocaine-induced CPP after the CPP training (Fig. 2). A one-way (NaB *vs*. saline) repeated measured ANOVA revealed that there was a main effect of test-retest-reminding test [$F(3,60) = 3.75$, $P = 0.0155$] on the cocaine-induced CPP magnitude (Fig. 2). Moreover, there was a main effect of NaB treatment [$F(1,84) = 10.02$, $P = 0.0037$] on the cocaine-induced CPP magnitude (Fig. 2). Furthermore, there was an interactive effect of NaB treatment and test-retest-reminding test on the cocaine-induced CPP magnitude [$F(3,84) = 2.93$, $P = 0.0384$] (Fig. 2). *Post hoc* analysis further indicated that intra-mPFC NaB-infused mice exhibited lower cocaine-induced CPP in retest 1, 2, and the cocaine reminding test as compared

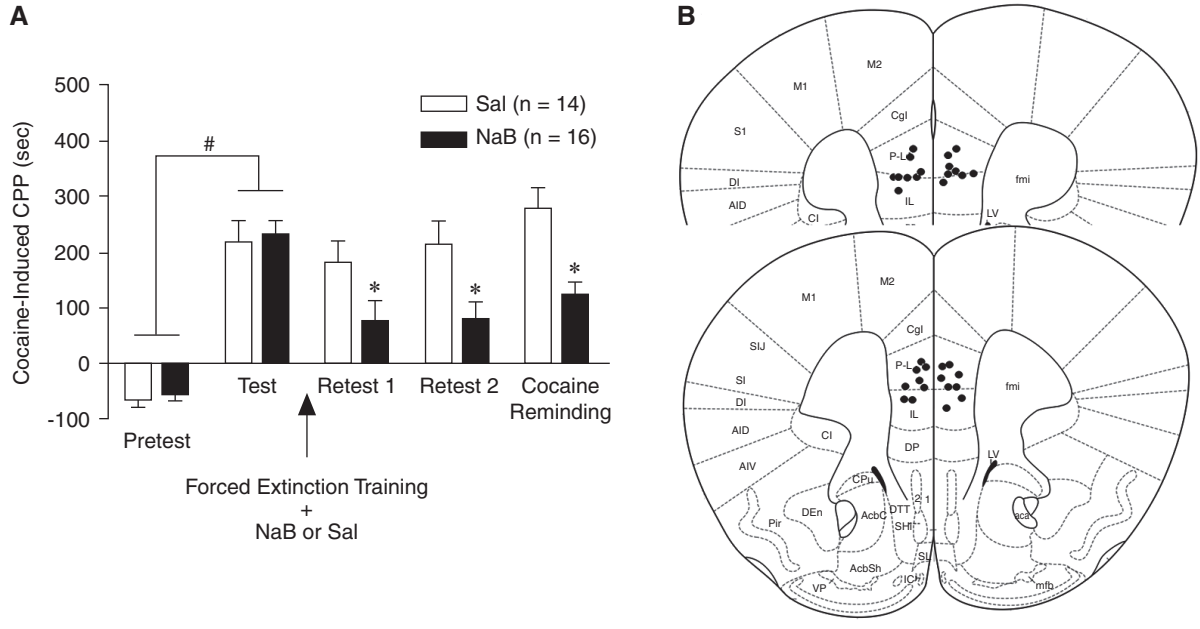


Fig. 2. Modulating effects of intra-mPFC NaB infusion on the extinction of cocaine-induced CPP using the extinction training protocol. (A) Mice receiving the extinction training protocol followed by bilateral intra-mPFC NaB (10 μg/side) injection displayed significant decreases in the cocaine-induced CPP magnitude in retest 1, 2 and the cocaine reminding (5 mg/kg) test. #Significantly greater than the value in the pretest. *Significantly lower than the corresponding value in the test. NaB, sodium benzoate; Sal, saline; mPFC, medial prefrontal cortex. (B) Representative schematics of correct cannula placement in the mPFC. Solid circles stand for the injection sites for the NaB-treated mice.

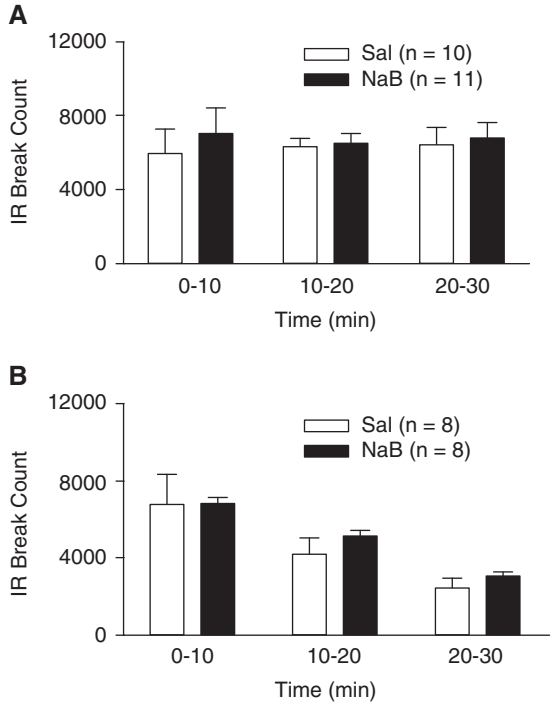


Fig. 3. Mouse locomotor acitivity following systemic or intra-mPFC NaB administration. Neither (A) intra-peritoneal (500 mg/kg/injection for two times) or (B) intra-mPFC (10 μg/side for two sides of the mPFC for two times) NaB delivery altered mouse locomotor acitivity in any of the three 10-min bins observed at approximately 20 h after the second NaB administration.

to it in the test (Fig. 2).

*Systemic or Intra-mPFC NaB Administration Does Not Affect Mouse Locomotor Acitivity*

Regardless of systemic or intra-mPFC NaB delivery, two consecutive NaB administrations (500 mg/kg/injection for i.p. injection or 10 μg/side for two sides of the mPFC) at an 8 h interval did not affect mouse locomotor acitivity in any of the three 10-min bins observed at approximately 20 h after the second NaB administration (Fig. 3, A and B).

## Discussion

Although systemic NaB treatment (at a dose of 500 mg/kg for a total of 1000 mg/kg) or two consecutive extinction training bouts alone did not affect subsequent cocaine-induced CPP magnitude, the extinction protocol followed immediately by the NaB treatment was found to effectively facilitate the extinction of cocaine-induced CPP (Fig. 1). Decreases in cocaine-induced CPP magnitude were evident in both retests and the cocaine reminding test. Since NaB treatment was given immediately after the extinction protocol in the present design, NaB was suspected to strengthen the consolidation of the extinction training in this regard. Since our extinction protocol consisted of free navigation with the conditioning chamber at a cocaine-free status, such extinction protocol can be regarded as a method for recalling original cocaine-induced CPP (3). Another possibility was that NaB could diminish the cocaine-induced CPP magnitude by disrupting the reconsolidation of the original cocaine-induced CPP. Nonetheless, our extinction training took much longer than the time window for reactivating such a memory (20). Thus, NaB was less likely to impair the reconsolidation of the original cocaine-induced CPP.

To carefully look into several systemic NaB delivery-related issues, including NaB distribution, metabolism and the primary targets in brain, we decided to bypass these pharmaco-dynamic processes and micro-injected NaB into the mouse mPFC to test the possible involvement of mPFC NMDA receptor activation in this regard. We found that bilateral intra-mPFC NaB infusion (10 μg/side) immediately after each extinction training bout also produced significant decreases in the cocaine-induced CPP magnitude in retests and the cocaine reminding test (Fig. 2). The implication of this result was that systemic NaB treatment in combination with the extinction protocol may facilitate the extinction of cocaine-induced CPP, at least in part, by activating the NMDA receptor in the mPFC. Importantly, systemic or intra-mPFC NaB treatment (500 mg/kg or 10 μg/side) did not affect mouse locomotor activity because neither of the NaB administrations affected mouse locomotor activity at the time point of the retest 1 (Fig. 3).

Two groups of investigators have previously suggested that curbing pathological memory-motivated symptoms and behaviors through the exposure therapy frequently fail because the extinction learning strengthens specifically the extinction learning-activated controls in the medial prefrontal cortex (14, 15). That is, the extinction training-activated controls in the medial prefrontal cortex alone may not affect original pathological memories. In this study, we provided another line of evidence that NaB treatment in combination with the extinction training, but not extinction training alone, can effectively facilitate the extinction of a cocaine-supported memory. Considering collectively the published data and our results, a scenario was provided here to generalize the extinction learning-specific controls to original cocaine learning and memory. We speculate that moderate activation of the NMDA receptor in the medial prefrontal cortex is beneficial in spreading extinction learning-produced controls over the cocaine-supported learning and memory. In fact, immediately following the extinction protocol, NaB produced decreases in subsequent

cocaine-induced CPP magnitude and such decreased CPP magnitudes remained low at the cocaine reminding test. The implication of the latter finding is that such decreased CPP magnitudes could be resistant to cocaine-produced craving. Thus, we conclude that systemic administration of NaB in combination with the extinction training have the potential to be translated into clinical applications in curbing cocaine craving and seeking behavior in cocaine addicts.

In a previous report, we have reported that D-cycloserine treatment in combination of CPP test can effectively diminish cocaine-induced CPP magnitude (21). Paradoxically, D-serine, a naturally occurring full agonist on glycine site of NMDA receptor, can suppress cocaine-induced CPP preference for a short period of time (21). Accordingly, it was reasonable to speculate that NMDA activation was not sufficient to suppress cocaine memory recall. In parallel with this notion, we reported in here that NaB, also a full agonist on glycine site of NMDA receptor, in part suppressed the expression of cocaine-induced CPP (Figs. 1 and 2).

These results, taken together, suggest that systemic NaB treatment combined with forced extinction training may afford a potentially therapeutic advance in facilitating the extinction of cocaine-supported memory, thus curbing the risks of cocaine craving and relapse in addicts at abstinence.

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