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Short Communication

Repeated intravenous administrations of teneurin-C terminal associated peptide (TCAP)-1 attenuates reinstatement of cocaine seeking by corticotropin-releasing factor (CRF) in rats

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HIGHLIGHTS

- The results extend our previous work with intracranial administrations of TCAP-1.
- Here, repeated IV injections of TCAP-1 attenuated the CRF-induced reinstatement of cocaine seeking in rats.
- The TCAP-1 regimen had a differential effect in rats that self-administered cocaine for 6, relative to 3, hours per day.
- The results point to a potential therapeutic benefit of TCAP-1 in attenuating cocaine seeking behaviors.

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ABSTRACT

The teneurin c-terminal associated peptides (TCAP) have been implicated in the regulation of the stress response, possibly via a corticotropin-releasing factor (CRF)-related mechanism. We have previously shown that repeated intracerebroventricular (ICV) injections of TCAP-1 attenuate the reinstatement of cocaine seeking by CRF in rats. Here, we determined whether intravenous (IV) administrations of TCAP-1 would likewise attenuate CRF-induced reinstatement, and whether this effect would vary depending on the rat's history of cocaine self administration. Rats were trained to self-administer cocaine for 10 days, during once daily sessions that were either 3 h ("short access"; ShA) or 6 h ("long access"; LgA). Rats were then given five daily injections of TCAP-1 (0, 300, or 3000 pmol, IV) in their home cage. Subsequently, they were returned to the self-administration chambers where extinction of cocaine seeking and testing for CRF-induced reinstatement of cocaine seeking was carried out. Repeated IV administrations of TCAP-1 were efficacious in attenuating CRF-induced reinstatement of cocaine seeking, but at different doses in ShA and LgA rats. Taken together, the findings extend previous work showing a consistent effect of repeated ICV TCAP-1 on CRF-induced reinstatement of cocaine seeking, and point to a potential therapeutic benefit of TCAP-1 in attenuating cocaine seeking behaviors.

Stress has long been considered an important factor contributing to relapse to drug use in humans. Studies using an animal model of relapse known as the reinstatement procedure indicate that stressors, such as footshock, serve as powerful triggers for drug seeking in rats [1,2]. CRF, a principle neuropeptide in the mammalian stress response, has been found to be critically involved in the effects of footshock on reinstatement of drug seeking [2–4]. Specifically, CRF receptor antagonists block footshock-induced reinstatement of drug seeking, whereas central injections of CRF induce reinstatement [5,6]. These effects have been localized to the extended amygdala and, more specifically, the central nucleus of the amygdala (CeA) and bed nucleus of the stria terminalis (BNST) [2,3].

The TCAPs have been shown to modulate the CRF stress response, as assessed using various animal models of anxiety and depression. For example, repeated (5-day) pretreatment with a synthetic variant of TCAP-1 inhibits CRF-induced behavioral responses in the elevated plus maze, open field, and acoustic startle tests [7]. Interestingly, TCAP-1 is expressed in brain regions of the extended amygdala [8], which contain high

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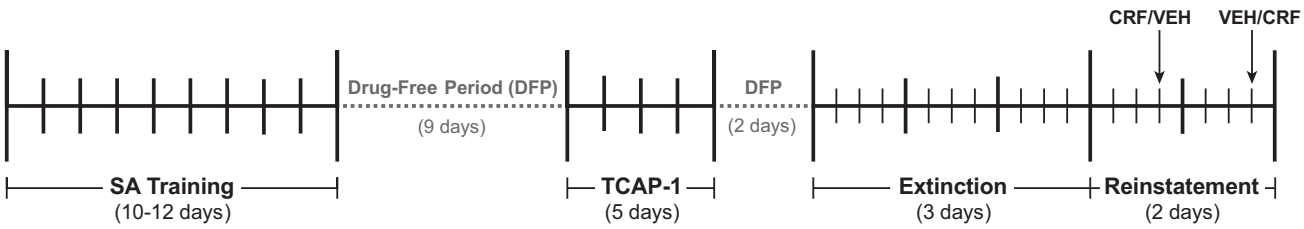

Fig. 1. Time-line of experimental procedures. *SA training*: Rats self-administered cocaine during once daily 3 (ShA) or 6 (LgA) h sessions. *Drug-free period (DFP) and TCAP-1 Pre-exposure*: Rats were given a 16-day DFP, and 9 days into this period they were given 5 daily injections of TCAP-1 (IV). *Extinction*: Over 3 days, rats were given 4 daily 1-h extinction sessions in the SA chambers. *Reinstatement*: Rats were given two 1-h tests for reinstatement, on consecutive days and in a counterbalanced order; one test was in response to an ICV injection of corticotropin-releasing factor (CRF) and one was in response to vehicle (VEH). Before each of the tests for reinstatement, rats were given three 1-h extinction sessions.

densities of CRF cell bodies and terminals [9] and play a critical role in stress-induced reinstatement of drug seeking [2,3]. Moreover, pretreatment with TCAP-1 before a CRF challenge attenuates CRF-induced c-fos immunoreactivity within this circuitry [10].

Given the known modulatory effects of TCAP on the CRF stress response, and the neuroanatomical convergence between TCAP and CRF systems, we carried out a series of experiments to study the effect of ICV injections of TCAP-1 on subsequent cocaine-related behavioral responses to CRF. In those experiments, 5 daily ICV injections of TCAP-1 completely blocked the reinstatement of cocaine seeking induced by ICV injection of CRF [12].

Based on prior evidence that systemic administration of TCAP-1 can penetrate the blood-brain barrier and modulate measures of behavioral anxiety in rodent models [2], the current work was carried out to determine whether IV administrations of TCAP-1 would be effective in altering CRF-induced reinstatement of cocaine seeking, as were ICV administrations of TCAP-1 [12]. *Indeed, prior behavioral studies indicating efficacy of systemic TCAP-1 in the modulation of stress and anxiety responses point to a potential therapeutic benefit of the peptide* [7]. In addition, we determined whether the daily schedule of cocaine self-administration (SA) would alter the subsequent effects of IV TCAP-1 on CRF-induced reinstatement of cocaine seeking. To this end, we compared the effect of repeated IV TCAP-1 administrations in rats that had self-administered cocaine during daily 3- versus 6-hour sessions.

Eighty-five male Long–Evans rats (Charles River, Montreal, QC; 275–300 g) were used in the experiment. Rats were individually housed in plastic cages in a temperature- ($21 \pm 1\,^{\circ}C$) and humidity-controlled vivarium, and maintained on a reverse light-dark schedule (lights on 1900–0700) with free access to water and standard laboratory rat chow.

Under isoflurane anesthesia (3–5% in O_2; Benson Medical, Markham ON), rats were implanted with a 22-gauge cannula (Plastics One, Roanoke, VA, USA) aimed 1 mm above the right lateral ventricle (A/P: −1.0 mm from bregma; M/L: −1.4 mm from bregma; D/V: −2.7 mm from dura [11]). Rats were also implanted with a silastic intravenous catheter (Dow Corning, Midland, MI; inner diameter: 0.51 mm; outer diameter: 0.94 mm) into the right jugular vein, according to procedures described in detail elsewhere [12].

The experiment was conducted in five phases: (1) SA training, (2) Drug-free Period (DFP), (3) TCAP-1 pre-exposure, (4) extinction, and (5) testing for reinstatement. A time-line of these procedures is included in Fig. 1.

Before the start of training, rats were habituated to the SA chambers (Med Associates, St. Albans, VT, USA) during one 2-h session. Twenty-four to 48 h later, rats were trained to self-administer cocaine HCl (0.35 mg in 65 μl physiological saline, IV; Medisca Pharmaceuticals, St. Laurent, QC) on a FR-1 schedule of reinforcement, during once daily 3-h (ShA condition) or 6-h (LgA condition) sessions for 10 days. At the start of each session, availability of cocaine was signaled by the introduction of the active lever, illumination of the white houselight (which remained lit throughout the session), and illumination of the white stimulus light above the active lever for 20 s. During SA training, responses on the active lever activated an infusion pump (Razel Scientific Instruments, Stamford, CN, USA), resulting in a 3-s infusion of cocaine and 20-s illumination of the stimulus light, which signaled a "time-out" period during which additional responses were not reinforced. Responses on a second lever (inactive lever) were recorded but did not result in activation of the pump.

The DFP was 16 days in duration, such that the subsequent extinction and reinstatement testing phases occurred outside of the initial cocaine withdrawal period. Daily TCAP-1 (American Peptide Company, Sunnyvale, CA) injections were begun 9 days into the DFP. TCAP-1 was administered IV at concentrations of 0, 300, or 3000 pmol/0.3 ml physiological saline. This regimen of TCAP-1 exposure was chosen based on our previous work with ICV and IV TCAP-1 (see [7,12]).

After the DFP, rats were given 3 consecutive days of extinction training. Days 1 and 2 consisted of four 60-min sessions (separated by 30-min intervals) during which all conditions present during training were maintained, except that lever presses were not reinforced. On Day 3 of extinction, conditions were the same as on Days 1 and 2, except that rats were given a sham ICV injection at the start of the 30-min interval between the third and fourth sessions. Sham injections were given to familiarize animals with the manipulations associated with testing for reinstatement.

In the two days after extinction, rats were tested for reinstatement. The start of each test day began with three 60-min extinction sessions. Rats responding 20 or fewer responses on the active lever during the second and third sessions (combined) were subsequently tested for reinstatement. Rats that did not reach this criterion were given an additional extinction session and tested the next day. Immediately after the third session, rats were injected with CRF (0.5 μg, ICV) or vehicle and 30 min later tested for reinstatement. Testing occurred under extinction conditions. Each animal was tested in both conditions on consecutive days and in a counterbalanced order.

Over the 10-day training period, the mean (±SEM) total number of cocaine infusions administered by ShA ($n = 40$) and LgA ($n = 40$) rats was 203.20 (±9.71) and 424.15 (±25.72), respectively. Overall, LgA rats took relatively more infusions of cocaine than ShA rats on both the first and last days of training (main effect of Drug history: $F[1,82] = 26.78$, $p < .001$), and the magnitude of this difference was relatively greater on the last relative to first day of training (interaction of Drug history by Training Day: $F[1,82] = 17.54$; $p < .001$; see Fig. 2).

Because TCAP-1 exposure occurred before extinction and testing for reinstatement, it was of interest to look at its effects on responding during both of these subsequent phases. A mixed-factor ANOVA for the factors of Drug History, TCAP-1 Condition, and Day yielded no significant main or interaction effects of TCAP-1 (see Fig. 3).