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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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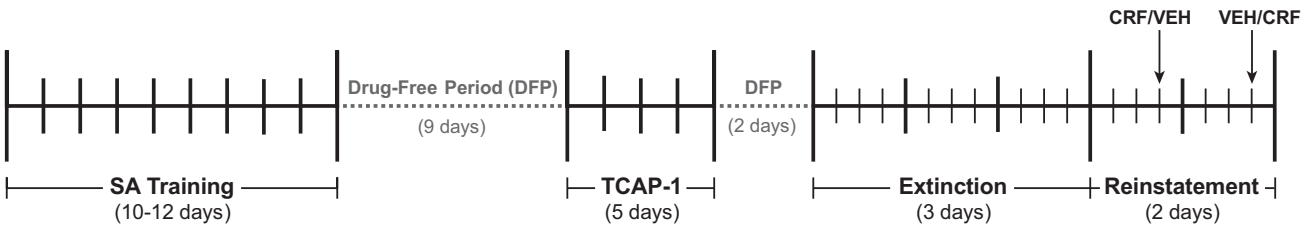

Fig. 1. Time-line of experimental procedures. *SA training*: Rats self-administered cocaine during once daily 3 (ShA) or 6 (LgA) h sessions. *Drug-free period (DFP) and TCAP-1 Pre-exposure*: Rats were given a 16-day DFP, and 9 days into this period they were given 5 daily injections of TCAP-1 (IV). *Extinction*: 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).

Fig. 2. Mean (±SEM) number of cocaine infusions administered (left axis) and mean (±SEM) total cocaine intake (right axis) on the first (Day 1) and last (Day 10) training sessions in ShA and LgA rats. #Day 1 different from Day 10 ($p < .001$). *ShA different from LgA on Day 10 ($p < .01$).

Although there was no effect of TCAP-1 on the time-course of extinction responding, there were significant main effects of Day ($F[2,146] = 106.452$; $p < .001$) and Drug history ($F[1,73] = 296.18$; $p < .001$), and a significant interaction between these factors ($F[2,146] = 5.216$; $p < .01$). It can be seen in Fig. 3, that in both ShA (*A*) and LgA rats (*B*), there was a gradual decrease in responding over the 3 days of extinction training and that ShA rats exhibited a somewhat higher initial number of responses relative to LgA rats. Although this relatively higher number of responses in ShA rats was unexpected, it should be noted that the difference is primarily

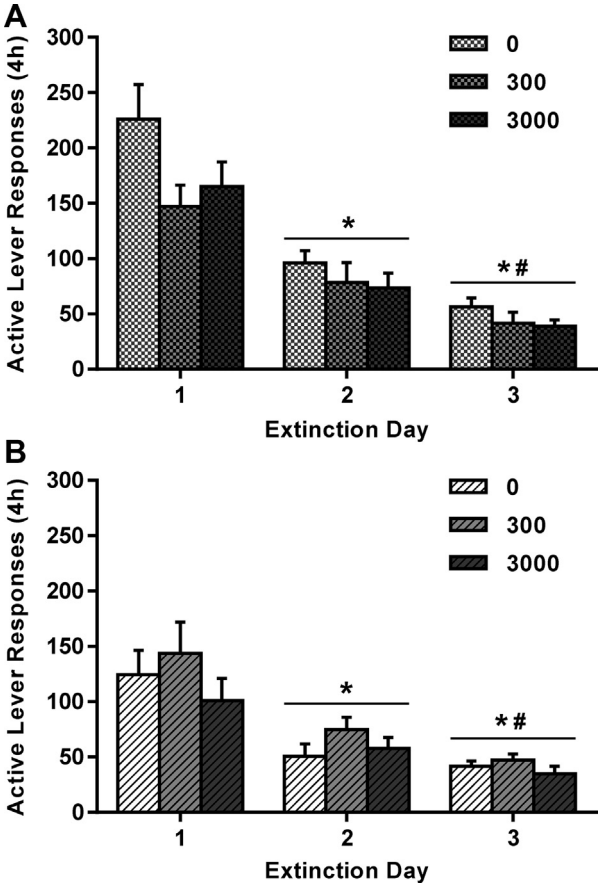

Fig. 3. Mean (±SEM) total number of active lever responses over 3 days of extinction after exposure to 0, 300, or 3000 pmol, IV, TCAP-1. Data are presented separately for ShA (A) and LgA (B). *Different from Day 1; #Different from Day 2.

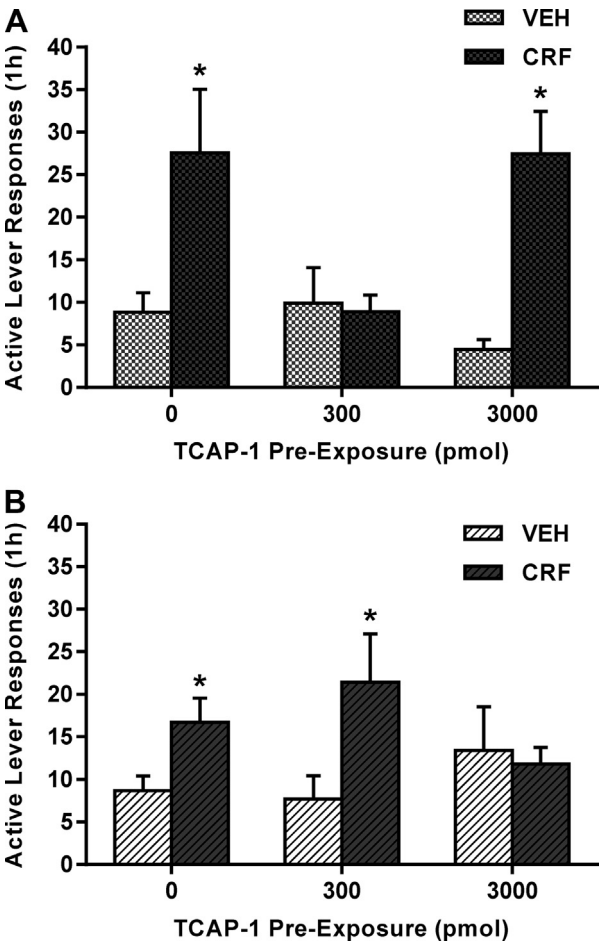

Fig. 4. Mean (±SEM) total number of active lever responses during tests for reinstatement in response to ICV injections of corticotropin-releasing factor (CRF) or Vehicle (VEH), following exposure to 0, 300, or 3000 pmol, IV, TCAP-1. Data are presented separately for ShA (A) and LgA (B). *Different from VEH test condition, same TCAP-1 condition.

attributable to an unusually high level of responding in the 0 TCAP-1 condition, a level higher than what we typically observe in rats trained under this cocaine schedule [12]. Moreover, in a previous study comparing extinction responding between ShA and LgA rats that had self-administered under similar conditions, no group differences were observed [13]. We do not believe, therefore, that this is a difference that should complicate the current interpretation of our findings.

In contrast to its lack of effect in extinction, repeated TCAP-1 strongly affected responding during the test phase. In this case, a mixed-factor ANOVA for responses on the active lever revealed a significant main effect of Test condition ($F[1,730] = 24.44$; $p < .001$) and a significant 3-way interaction of drug history by TCAP-1 condition by test condition ($F[2,73]$; $p < .01$).

To follow up on the 3-way interaction, separate 2-way ANOVAs were carried out for each drug history. In the case of ShA rats (see Fig. 4A), this analysis yielded a significant main effect of Test ($F[1,37] = 16.97$; $p < .001$) and a Test by TCAP-1 interaction ($F[2,37] = 4.51$; $p < .03$). Separate paired samples *t*-tests between test conditions were significant only in the 0 ($t[14] = 2.67$; $p < .03$) and 3000 ($t[14] = 5.13$; $p < .001$) pmol conditions; thus a dose of 300, but not 3000, TCAP-1 was effective in blocking the effect of CRF on reinstatement of cocaine seeking.

In the LgA condition, a 2-way ANOVA carried out for number of responses on the active lever revealed a significant main effect of Test condition ($F[1,36] = 7.62$; $p < .01$) and an interaction of Test by

TCAP-1 that narrowly missed significance ($F[2,36] = 3.14$; $p < .06$). In contrast to the effect of TCAP-1 in ShA rats, only the high dose was effective in blocking CRF-induced reinstatement in LgA rats (see Fig. 4B). Indeed, in LgA rats, separate planned comparisons between test conditions were significant for the 0 ($t[14] = 3.269$; $p < .01$) and 300 ($t[14] = 2.90$; $p < .01$) pmol conditions, but not for the 3000 pmol condition.

It should be noted that in the 0 TCAP-1 condition, CRF-induced responding was modestly higher in ShA relative to LgA rats. Although this difference was not significant, it is noteworthy that it is opposite in direction to what might have been expected based on a previous study [13]. In that study, LgA relative to ShA rats exhibited enhanced CRF-induced reinstatement of cocaine seeking. The reason for the differences in the relative magnitude of effects between ShA and LgA rats between studies is not obvious. However, given that in the present study, both ShA and LgA rats showed reliable CRF-induced reinstatement of cocaine seeking in the 0 pmol TCAP-1 condition, we do not believe that interpretation of the effect of TCAP-1 on that reinstatement is complicated by the magnitude of the initial CRF effect.

The main finding in the present study is that repeated IV injections of TCAP-1 significantly inhibited the effects of CRF on reinstatement of cocaine seeking. The effective IV doses of TCAP-1, however, differed depending on whether rats had self-administered cocaine under ShA or LgA conditions. Whereas in ShA rats the lower IV dose of 300 pmol TCAP-1 was effective in preventing CRF-induced reinstatement, in LgA rats the higher dose of 3000 pmol was required to achieve the same effect. The robust effect of 300 pmol IV TCAP-1 in blocking CRF-induced reinstatement of cocaine seeking in ShA rats is consistent with our previous work involving ICV injections of TCAP-1 in rats that had self-administered under similar conditions [12].

The finding that the lower dose of TCAP-1 was sufficient to block CRF-induced reinstatement in ShA rats, whereas the higher dose was required to achieve this effect in LgA rats, was not unexpected. Indeed, it would seem reasonable to expect that a more stringent history of cocaine SA, as occurs under LgA relative to ShA conditions, would result in more profound neuroadaptations within circuitry that may, in turn, enhance resistance to interference in relapse.

At least at first glance, one somewhat puzzling aspect of our findings is that in ShA rats, the higher 3000 pmol IV dose of TCAP-1 failed to interfere in CRF-induced reinstatement of cocaine seeking, while the lower 300 pmol dose was effective in completely blocking the effect. That said, neuropeptides, that are neuromodulatory in action, typically do not show linear dose-response curves and, in fact, frequently show inverse U relationships [14], like the one observed in our study. This relationship has been noted, for example, with the behavioral actions of the CRF receptor antagonist, alpha-helical CRF_{9-41}, where sufficiently high doses produce partial agonist effects; moreover, these dose effects of alpha-helical CRF are dependent on the baseline sensitivity of the animals [14,15]. Our findings of TCAP-1 are consistent with this type of interpretation and, interestingly, suggest that cocaine may alter sensitivity to TCAP-1.

In our previous work on the effects of ICV TCAP-1 on CRF-induced reinstatement of cocaine seeking, we speculated on possible cellular and neuroanatomical mechanisms of action [see 12]. Briefly, although the brain loci in which TCAP-1 and CRF interact to alter behavior are currently unknown, it is known that TCAP-1 uptake is widespread and particularly pronounced in limbic and prefrontal brain regions rich with CRF receptors, such as the amygdala, hippocampus, and cingulate cortex [16]. TCAP-1 has also been shown to attenuate CRF-induced increases in c-fos expression in similar regions, including the amygdala [10], which have been implicated in the effects of CRF on the reinstatement of cocaine seeking [3,26] and the expression of cocaine-induced behavioral sensitization [17]. Although, unlike in the amygdala, acute TCAP-1 was without effect on CRF-induced c-fos expression in the BNST [10], repeated TCAP-1 may act in the BNST to counteract the behavioral effects of CRF. Indeed, intra-BNST injections of CRF induce reinstatement of cocaine seeking [5], as well as several other stress-related behaviors (e.g. [18,19]). Moreover, excitotoxic lesions of BNST, and intra-BNST infusion of the CRF receptor antagonist, α-helical CRF_{9-41}, like repeated ICV treatment with TCAP-1 [20], block the enhanced acoustic startle observed in rats following ICV CRF administration [18].

The mechanisms by which TCAP-1 and CRF interact at the cellular level also remain unclear. Evidence suggests, however, that the TCAP-1 receptor is β-dystroglycan, a transmembrane protein that stimulates the MEK-ERK1/2 signal cascade [20] and induces intracellular internalization via calveoli-mediated endocytosis [21]. Through numerous experiments, we have established that TCAP-1 does not act directly on CRF receptors to mediate its effects [22], and that TCAP-1, in cell culture, acts independently of CRF receptors to modulate cAMP [8]. Moreover, TCAP-1 induces a modification of neurite and filopodia outgrowth, axonal fasciculation, dendritic arborization and spine density [7,23–25] to regulate synaptic plasticity by TCAP-1-dependent phosphorylation of stathmin and filamin [7,20]. Given these findings, we postulate that TCAP-1 inhibits the actions of CRF by indirectly reducing its efficacy. We propose that this reduced efficacy occurs through structural changes in synaptic plasticity on key circuits that, through repeated cocaine exposure, induce long-lasting changes in cell signaling and structure. These changes, which may also result in a down-regulation of CRF receptors with repeated TCAP-1 treatment in vivo, may also serve to alter and perhaps inhibit the cellular and behavioral effects of CRF-induced reinstatement of cocaine seeking.

In conclusion, the present results extend our previous work on the effects of ICV TCAP-1 administration on CRF-induced reinstatement of cocaine seeking, by showing the efficacy of a more clinically relevant route of TCAP-1 administration (i.e., IV). Indeed, our results demonstrate that repeated IV administration of TCAP-1 can dramatically alter the reinstatement of cocaine seeking behavior in rats, and to a degree comparable to that induced by injections of the peptide directly into the brain. Our work also extends previous findings demonstrating TCAP-CRF interactions in the modulation of behavior more generally, and provides validation of the potential clinical utility of TCAP-1 in modulating drug seeking.

Conflict of interest

Dr. DA Lovejoy is the Chief Scientific Officer of Protagenic Therapeutics Inc (PTI).

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