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Pituitary Adenylate Cyclase–Activating Polypeptide Disrupts Motivation, Social Interaction, and Attention in Male Sprague-Dawley Rats

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ABSTRACT

BACKGROUND: Severe or prolonged stress can trigger psychiatric illnesses including mood and anxiety disorders. Recent work indicates that pituitary adenylate cyclase–activating polypeptide (PACAP) plays an important role in regulating stress effects. In rodents, exogenous PACAP administration can produce persistent elevations in the acoustic startle response, which may reflect anxiety-like signs including hypervigilance. We investigated whether PACAP causes acute or persistent alterations in behaviors that reflect other core features of mood and anxiety disorders (motivation, social interaction, and attention).

METHODS: Using male Sprague-Dawley rats, we examined if PACAP (.25–1.0 μg, intracerebroventricular infusion) affects motivation as measured in the intracranial self-stimulation test. We also examined if PACAP alters interactions with a conspecific in the social interaction test. Finally, we examined if PACAP affects performance in the 5-choice serial reaction time task, which quantifies attention and error processing.

RESULTS: Dose-dependent disruptions in motivation, social interaction, and attention were produced by PACAP, as reflected by increases in reward thresholds, decreases in social behaviors, and decreases in correct responses and alterations in posterror accuracy. Behavior normalized quickly in the intracranial self-stimulation and 5-choice serial reaction time task tests but remained dysregulated in the social interaction test. Effects on attention were attenuated by the corticotropin-releasing factor receptor-1 antagonist antalarmin but not the κ opioid receptor antagonist JDTic.

CONCLUSIONS: Our findings suggest that PACAP affects numerous domains often dysregulated in mood and anxiety disorders, but that individual signs depend on brain substrates that are at least partially independent. This work may help to devise therapeutics that mitigate specific signs of these disorders.

Keywords: Anhedonia, Attention, Model, Pituitary Adenylate Cyclase–Activating Peptide (PACAP), Rat, Social Interaction

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Severe or prolonged stress is linked to the etiology of mood and anxiety disorders such as major depressive disorder (MDD) and posttraumatic stress disorder (PTSD) (1–3). These disorders are often associated with persistent dysregulation of domains including motivation, social behavior, and attention (4,5). Despite the broad impact of these illnesses, the mechanisms by which stress induces maladaptive behavioral responses are not fully understood.

Pituitary adenylate cyclase–activating polypeptide (PACAP) is a neuropeptide that plays an important role in regulating stress effects and is modified by stressful experiences (6,7). PACAP and its cognate receptor (PAC1) are widely expressed in stress- and anxiety-associated brain regions, including the amygdala and bed nucleus of the stria terminalis (8,9). In rodents, chronic stress increases expression of PACAP messenger RNA within these regions (9,10), raising the possibility that neuroadaptive changes in PACAP systems alter sensitivity to subsequent stressors. Mice that are deficient in PACAP exhibit reduced corticosterone responses (11), anxiety-like behavior (12–14), and sensitivity to chronic social defeat stress (15). Exogenous PACAP administration produces many of the same physiologic and behavioral effects of severe or chronic stress, including hypothalamic-pituitary adrenal axis activation (16), elevations in plasma corticosterone levels (17), increases in corticotropin-releasing factor (CRF) expression (17), and increases in anxiety-like behavior (9,18,19). Importantly, a single administration of PACAP produces a persistent (lasting at least 1 week) elevation in the acoustic startle response, a putative indicator of hypervigilance (9). PACAP also has been associated with fear responses in humans (20) and the development of affective disorders, including PTSD (21–23) and MDD (24). Thus, PACAP is implicated in both the acute and long-lasting effects of stress.

Mood and anxiety disorders involve many domains, including domains affecting motivational, cognitive, and social

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function. It was reported recently that PACAP produces acute anhedonia (reduced sensitivity to reward), and this effect is dependent on CRF systems (19). Considering that psychiatric illnesses are persistent, the present studies were designed to investigate the dose-dependent and time-dependent effects of exogenous PACAP on motivation, social behavior, and attention as assessed by the intracranial self-stimulation (ICSS) test, social interaction (SI) test, and 5-choice serial reaction time task (5CSRTT). Because addiction is often comorbid with stress and anxiety disorders (25,26), we also evaluated whether PACAP exposure would affect sensitivity to the reward-related effects of cocaine. Finally, we evaluated whether CRF receptor (CRF-R) or κ opioid receptor (KOR) antagonists attenuate PACAP effects on attention; we focused on this domain because our previous work suggested that it depends critically on interactions between CRF-Rs and KORs. (19,27).

METHODS AND MATERIALS

Animals

Male Sprague-Dawley rats (Charles River Laboratories, Inc, Raleigh, North Carolina) weighing 250–275 g at the start of experiments were pair-housed and maintained on a 12-hour light-dark cycle (lights on at 7 AM). Rats in the ICSS and SI experiments were given free access to food (Purina Rat Chow; Purina Mills LLC, St. Louis, Missouri). Rats in the 5CSRTT experiments had their food restricted to 85% of their free-feeding weight beginning 2 days before training. All rats had free access to water while in their home cages. Experiments were approved by the McLean Hospital Animal Care and Use Committee in accordance with National Institutes of Health guidelines.

Drugs

PACAP-38 (Bachem Americas, Inc, Torrance, California) was dissolved in artificial cerebrospinal fluid (Harvard Apparatus, Hollister, Massachusetts). Vehicle (VEH; artificial cerebrospinal fluid) or PACAP (.25, .5, 1.0 μg) was infused into the lateral right ventricle with a Hamilton microsyringe (10 μL; Hamilton Company, Reno, Nevada) attached to polyethylene (PE 20) tubing (Becton Dickinson and Company, Sparks, Maryland) at a rate of .5 μL/min for 2 min. Because PACAP has long-lasting effects on acoustic startle (9), separate cohorts of rats were used for each dose. Antalarmin (ANT; Sigma-Aldrich, St. Louis, Missouri) was dissolved in .5% carboxymethylcellulose (pH 5.5; Sigma-Aldrich) and injected intraperitoneally (ip) at 20 mg/kg, a dose that blocks the anxiogenic effects of CRF without producing toxicity (28). JDTic (RTI International, Research Triangle Park, North Carolina) was dissolved in .9% sterile saline and injected at 10 mg/kg (ip), a dose that produces anxiolytic-like effects in rats (29). Cocaine HCl (Sigma-Aldrich) was dissolved in sterile saline and administered at 5.0 mg/kg (ip), a dose that produces moderate effects on ICSS (30).

Surgery

All rats tested with PACAP or VEH were anesthetized with pentobarbital (65 mg/kg, ip) and implanted with an intracerebroventricular (icv) stainless steel guide cannula (23-gauge; Plastics One, Roanoke, Virginia) with an obturator extending 1.5 mm beyond the cannula tip aimed at the right lateral ventricle as described previously (31) (from bregma, −.8 mm anterior, +1.3 mm lateral, −3.6 mm ventral to dura). Rats in the ICSS experiment were simultaneously implanted with a unilateral monopolar electrode (.25 mm diameter; Plastics One) aimed at the right medial forebrain bundle as described (31) (from bregma, −2.8 mm anterior, −1.6 mm lateral, −7.8 mm ventral from dura). Rats were individually housed after surgery and allowed 1 week of recovery.

Behavioral Testing

The ICSS test was performed as described previously (32). The ICSS thresholds were calculated using a least-squares line of best-fit analysis (33). After stable baseline thresholds were established (±10% for 3 consecutive days), rats received an infusion of VEH to ensure the infusion procedure did not affect performance. The following day, rats were infused with VEH or PACAP (.25–1.0 μg). Testing (90 min) began immediately after infusions. Rats were tested for 7 days postinfusion to assess long-term effects of PACAP. Thresholds and maximum response rates were expressed as % mean baseline established on the 3 days that fulfilled stability criteria. We also examined if PACAP altered the reward-related effects of a cocaine challenge on day 8 after PACAP treatment. For this test, responding was first evaluated for 60 min for each rat, which served as the daily baseline. All rats then received cocaine (5.0 mg/kg, ip) and were tested immediately for an additional 60 min. Data are expressed as % mean daily baselines.

Social behavior was measured using a modified version of the SI test (34). Rats were habituated for 10 min to the interaction arena (60 cm × 60 cm × 35 cm) 1 day before testing. On the test day, rats were infused with PACAP (.25–1.0 μg) or VEH and placed in the interaction arena 60 min later with a naïve weight-matched partner rat. Partner rats were housed under identical conditions to, and had no previous contact with, the treated rat. Social behavior was videotaped for 5 min in red light, and an observer blind to the treatment conditions quantified the following metrics: time spent interacting (active social interaction, e.g., sniffing, grooming, and play initiated or reciprocated by treated rat), time spent fleeing (social avoidance), time spent in the arena corners (anxiety-like behavior), and locomotor activity. Active SI was also quantified for the partner rat to assess whether its behavior was affected by the dose of PACAP administered to the treated rat. Rats were retested in the SI test with a novel (unfamiliar) partner rat 7 days later. A separate cohort of rats was tested only at the 1-week post-treatment time point to control for repeated presentation effects.

The 5CSRTT was performed as described previously (35). Sessions ended after 90 trials or 30 min, whichever came first. The following performance measures, as defined previously (34), were analyzed on each day: % correct responses, % omissions, accuracy, premature responses, correct response latency, reward latency, and latency to complete the task. We also examined % correct responses posterror (% correct/total trials following an incorrect response) and % correct responses postcorrect (% correct/total trials following a correct response) because these are affected in psychiatric illness (36). Rats were required to perform at criteria (>60% correct responses and <20% omissions, ±10% for 3