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Research report

Neuronal activity and the expression of hypothalamic oxytocin and vasopressin in social versus cocaine conditioning

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HIGHLIGHTS

- ICR mice produced CPP when conditioned with unfamiliar conspecific or cocaine alone.
- Subject mice reduced preference for conspecific in conspecific versus cocaine conditioning.
- The expression of c-Fos-IR neurons in conspecific or cocaine conditioning alone differed from that in conspecific versus cocaine conditioning.
- The subject mice undergoing different conditioning showed differential expression of OT and AVP in the PVN and SON.

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ABSTRACT

Although drug rewards and natural rewards share neural substrates, the neuronal activation patterns and mechanisms behind the interaction between cocaine and social reward are poorly understood. Here, we investigated the conditioned place preference (CPP) in social (conspecific) vs cocaine conditioning, and the expression of central c-Fos, hypothalamic oxytocin (OT) and vasopressin (AVP) in ICR mice. We found that the mice produced CPP when conditioned with unfamiliar conspecific or cocaine alone. However, the mice failed to produce CPP when the two stimuli were concurrently conditioned. Compared to conditioning with conspecific alone, the mice decreased preference for conspecific when conditioning with social vs cocaine. We observed differential expression of c-Fos-immunoreactive neurons in the ventral anterior cingulate cortex, posterior cingulate cortex, accumbens (shell and core), medial nucleus of the amygdale and the ventral pallidum when comparing the control (CK), social (SC) or cocaine conditioning (CC) group, and social vs cocaine conditioning (SCC) group. Compared to the CK group, the SC or CC group had higher OT expression in the paraventricular nucleus (PVN) and lower AVP expression in the PVN and supraoptic nucleus. The SCC group showed lower OT expression compared to the SC group, and higher OT and AVP expression in the PVN compared to the CC group. These results indicate that cocaine impairs social preference through competing with social reward. The differential activations of neurons within specific reward areas, and differential expression of OT and AVP are likely to play an important role in mediating the interaction between social and cocaine rewards.

1. Introduction

A great deal of research has showed negative consequences of drug abuse on social behaviors, such as social investigation, contact behavior, aggression and social bonding [1–3]. On the other hand, it is also known that dyadic social interaction (DSI) is a substantial natural reward. The mice with high levels of sociability spend more time in a compartment containing an unfamiliar mouse compared to an empty compartment or a compartment containing a familiar conspecific [4]. Social interaction influences the effective valence of drug abuse. For example, social interaction with a conspecific can influence the general responsiveness and sensitivity to alcohol, and prevent reinstatement of cocaine-induced conditioned place preference (CPP) [5–8]; the exposure to different peers can alter the abuse potential of opioids [9]. These findings highlight a growing interest in the synergistic interactions between social and drug rewards. Therefore, investigating how the two rewards interact would provide insights for treatment of drug addiction.

CPP is a widely used paradigm in studying the behavioral and neural processes involved in drugs and social rewards [10–12]. Social reward-CPP is established via Pavlovian association between the environment and rewarding effects of social interaction, similar

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to that of drug-CPP [8,11,13]. A wealth of data has demonstrated that social reward arising from social interaction modulates drug-CPP [6–8,14]. An ongoing assumption in the field is that the abuse of drugs activates neural pathways underlying natural rewards. Both social and drug rewards converge on the mesolimbic pathway and activate common mechanism of neural plasticity [15,16]. Prast et al. have demonstrated in rats that the neurons in accumbens corridor medial of the anterior commissure are differentially mediated by cocaine reward vs DSI reward; the time spent in the cocaine associated compartment is strongly correlated with the degree of activation, i.e., expression of the immediate early genes (IEGs) c-Fos and Early Growth Related Protein 1 (EGR1) in the accumbens corridor [17,18]. However, it is not well known about the extent to which there is overlap or differences in the other neurocircuitry and mechanisms that process social reward versus cocaine reward.

Oxytocin (OT) and arginine vasopressin (AVP) are two well-known neuropeptides produced by the hypothalamic paraventricular nucleus (PVN) and supraoptic nucleus (SON). OT and AVP can facilitate close social attachment and enhance the reward value by co-activating the dopaminergic circuits that are involved in motivation and reward [19–21]. Previous studies have demonstrated that OT may play a role in opposite-sex mate or same-sex partner preference formation [22,23]. In addition, OT and AVP are correlated with cocaine abuse. OT is involved in modulating acute and long-term drug effects and inhibiting addiction-relevant behaviors, such as cocaine-induced exploratory activity, locomotor hyperactivity, and stereotyped behavior [24,25]. AVP was previously implicated in acquisition of cocaine seeking behavior [26–28] and cocaine induced locomotion [27]. Thus, OT and AVP are important neuroendocrine factors regulating social facilitation and drug inhibition and it is possible that they are involved in the interaction between social reward and drugs reward. c-Fos is a non-specific marker of neuronal activity and there is a correlation between the cocaine CPP and the density of c-Fos-immunopositive neurons in accumbens corridor medial to the anterior commissure [18]. To identify neuronal activation patterns and the role of OT and AVP in the interaction between social and cocaine rewards, we investigated the expression of central c-Fos, hypothalamic OT and AVP in social versus cocaine conditioning.

2. Methods

2.1. Subjects

Male ICR mice (20–22 g) were purchased from Ningxia Medical University Laboratory Animal Center (Yinchuan, China). The animals were housed in groups of four in standard transparent polycarbonate (Makrolon) cages (32 × 21.5 × 17 cm). The colony room was illuminated with a 12:12 light-dark cycle (lights on 20:00 h), and the temperature was maintained at 23 ± 2 °C. Food and water was available ad libitum. All animals were treated humanely according to guidelines approved by the Animal Care and Use Committee of Beifang University of Nationalities.

2.2. CPP test

The place preference apparatus consisted of two large compartments (34 cm × 25 cm × 32 cm, length × width × height) with different visual cues (one had gray walls and the other had white-black striped walls) separated by a small middle compartment (11 cm × 25 cm × 32 cm, length × width × height). The middle compartment served as the acclimation compartment with a door (7 cm × 9 cm, height × width) in the center of the base.

2.2.1. Pre-test

On the day prior to conditioning, all animals were tested to determine whether there were any innate individual preferences to either of the large lateral compartments. The mice (n = 12) were given free access to each cue-decorated compartment. The time spent in two lateral compartments was recorded for 15 min by a camera (Sony, HDR-XR260E) mounted 70 cm above the arena. After each trial, the compartment was thoroughly cleaned using 70% ethanol.

2.2.2. Conditioning with unfamiliar conspecifics (social conditioning, SC)

The mice showed no inherent preference for either compartment. The subjects were conditioned in an alternate half of day design. In the morning, the subjects (n = 10) cohabited with an unfamiliar conspecific for 1 h in one of the outer compartments; in the afternoon, they were placed alone in the opposite compartment. Subjects underwent four consecutive days of conditioning, in which they were alternately reinforced with an unfamiliar conspecific or no conspecific for 1 h in the morning or afternoon. The post-test was performed 24 h after the last conditioning trial by placing the subject in the middle (neutral) compartment of the CPP apparatus, and allowing the mice to move freely between the three compartments. Subjects were given a 15 min post-test without the presence of conspecific.

2.2.3. Conditioning with cocaine (cocaine conditioning, CC)

Cocaine hydrochloride (Northwest Pharmaceutical, Sinopharm, Xian, China) was dissolved in sterile 0.9% physiological saline. Conditioning sessions and post-test procedure were similar to the social conditioning described above. The mice (n = 10) were conditioned by receiving 20 mg/kg intraperitoneally (i.p.) injections of cocaine or saline (4 ml/kg). Subjects were conditioned for 1 h per session. The morning session and the afternoon session were at least 6 h apart to allow time for cocaine clearance [10]. Thus, we provided four associative pairings with cocaine and saline: two stimuli per day in an alternating counterbalanced sequence for 4 days. On the fifth day, post-test was performed in a drug- and saline- free state for 15 min.

2.2.4. Conditioning with conspecifics versus cocaine (social vs cocaine conditioning, SCC)

Since the subjects established a preference for conspecific or cocaine, we compared the relative reinforcing strengths of conspecific and cocaine. An unfamiliar conspecific and a 20 mg/kg i.p. injection of cocaine were alternately presented in different compartments for 1 h. Thus, the subjects experienced opposing reinforcing stimuli to determine which is more rewarding. Conditioning sessions and post-test procedures were similar to that described above.

2.3. Tissue collection and immunochemistry

We used a different subset of mice conditioning for the c-Fos, OT and AVP immunoreactive (IR) neurons test. Subject mice were assigned to one of four treatment groups: SC group (n = 6), CC group (n = 6), SCC group (n = 6), and the control (CK) group (n = 6), which received no unconditioned stimulus-cue conditioning, only being exposed to cues that served as the conditioned stimuli for the experimental group. Animals were exposed to each cue-decorated compartment for 1 h in an alternating sequence, matching the parameters for the treatment of the experimental group [29].

Fifty min after the start of CPP test, animals were deeply anesthetized and perfused with 0.1 M phosphate buffer solution (PBS, pH 7.4) and 4% paraformaldehyde in 0.1 M PBS. The brain was