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Basolateral amygdalar D_2 receptor activation is required for the companions-exerted suppressive effect on the cocaine conditioning

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ABSTRACT

The presence of companions renders decreases in cocaine-stimulated dopamine release in the nucleus accumbens and cocaine-induced conditioned place preference (CPP) magnitude. Limbic systems are widely believed to underlie the modulation of accumbal dopamine release and cocaine conditioning. Thus, this study aimed to assess whether intact basolateral nucleus of amygdala (BLA), dorsal hippocampus (DH), and dorsolateral striatum (DLS) is required for the companions-exerted suppressive effect on the cocaine-induced CPP. Three cage mates, serving as companions, were arranged to house with the experimental mice in the cocaine conditioning compartment throughout the cocaine conditioning sessions. Approximately 1 week before the conditioning procedure, intracranial ibotenic acid infusions were done in an attempt to cause excitotoxic lesions targeting bilateral BLA, DH and DLS. Albeit their BLA, DH, and DLS lesions, the lesioned mice exhibited comparable cocaine-induced CPP magnitudes compared to the intact and sham lesion controls. Bilateral BLA, but not DH or DLS, lesions abolished the companions-exerted suppressive effect on the cocaine-induced CPP. Intact mice receiving intra-BLA infusion of raclopride, a selective D2 antagonist, 30 min prior to the cocaine conditioning did not exhibit the companions-exerted suppressive effect on the cocaine-induced CPP. Intra-BLA infusion of Sch23390, a selective D1 antagonist, did not affect the companions-exerted suppressive effect on the CPP. These results, taken together, prompt us to conclude that the intactness of BLA is required for the companions-exerted suppressive effect on the cocaine-induced CPP. Importantly, activation of D2 receptor in the BLA is required for such suppressive effect on the CPP.

1. Introduction

A hypothetical rewarding effect has been proposed for the presence of a mate and/or the opportunity of interacting with a mate in social species such as rats and mice (Fritz et al., 2011; Thiel, Okun, & Neisewander, 2008; Thiel, Sanabria, & Neisewander, 2009; Watanabe, 2011, 2013). Moreover, the presence of cage mates may prevent stress-induced decrease in the rewarding effect of cocaine (Tzeng et al., 2013). However, we have lately reported that three age-matched cage mates, serving as companions, housing with the experimental mice throughout the cocaine-place conditioning sessions may paradoxically attenuate, rather than enhance, cocaine-induced CPP (Tzeng, Cherng, Wang, & Yu, 2016). Cocaine is known to exert its rewarding effect, in part, by increasing extracellular dopamine level in the nucleus accumbens (Carboni et al., 2001; Hernandez & Hoebel, 1988), thus may support the establishment of the cocaine conditioning. We have found that the presence of three companions rapidly diminishes the cocaine-stimulated synaptic dopamine increase in the nucleus accumbens (Tzeng et al., 2016), suggesting that the presence of companions may decrease the cocaine-induced CPP, at least in part, by attenuating cocaine-produced rewarding effect.

Amygdala is known for its role in modulating dopamine release in the nucleus accumbens and cocaine conditioned behavior (Chuang, Lin, Cherng, & Yu, 2012; Heldt et al., 2014; Tzeng, Chang, Lin, Cherng, & Yu, 2012; Lai et al., 2008). A recent study has shown that the number of neurons in the basolateral nuclei of amygdala (BLA) is positively correlated with the magnitude of cocaine-induced CPP in male C57BL/6J mice (de Guevara-Miranda et al., 2016). Moreover, the presence of a discriminative stimulus previously predicting sucrose reinforcement contingent upon a lever press would evoke dopamine release in the nucleus

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accumbens and conditioned lever-approaching behavior in a rat model (Jones et al., 2010). Importantly, inactivation of amygdala attenuates such discriminative stimulus-evoked accumbal dopamine release and lever approaches (Jones et al., 2010). Furthermore, dopamine D1 and D2 receptor activation in the amygdala may modulate the activity of amygdalar inhibitory projections onto the nucleus accumbens and thus augment salient environmental cues-induced affective responses (Rosenkranz & Grace, 1999). Finally, immediate-early gene expression in the amygdala is enhanced by the cocaine conditioning and the presence of the conditioned cues, whereas reversed by social interaction-produced extinction of the cocaine conditioning (Fritz et al., 2011). An implication of these findings is that the amygdala may play a critical role in facilitating conditioned stimuli-stimulated dopamine release in the nucleus accumbens and the conditioned behavior, whereas decreasing such dopamine release and behavior by sending the social interaction-activated inhibitory projections onto the nucleus accumbens. Thus, we hypothesized that the presence of companions may attenuate cocaine-induced CPP magnitude by attenuating the amygdalar neuronal activity and/or enhancing its inhibitory efferent activity. Accordingly, we predicted that irreversible BLA lesions may abolish three companions-exerted suppressive effects on the cocaine-induced CPP magnitude. Moreover, we predicted that using selective D1 and D2 antagonists (SCH 23390 and raclopride) to prevent the binding of dopamine with local D1 and D2 receptor in the BLA may also prevent such companions-exerted suppressive effects on the CPP magnitude.

Hippocampus and striatum are another two neural substrates for their likely involvement in mediating the cocaine-induced synaptic plasticity and behavioral changes. For instance, intra-hippocampal NMDA infusion may regulate the dopamine release in the nucleus accumbens in a region-specific manner (Peleg-Raibstein & Feldon, 2006). A hippocampal extracellular matrix component has been demonstrated to limit the time-dependent enhancement of cocaine-induced CPP, serving as an index in modeling the incubation of cocaine craving (Lubbers et al., 2015). Hippocampal oxidative stress, inflammation, and apoptosis, in together, may play complex roles in modulating the anxiety-like behaviors in cocaine withdrawn animals (Hu et al., 2016). Most importantly, dorsal hippocampus seems to be required for the consolidation of cocaine-induced CPP (Kramar, Barbano, & Medina, 2014; Raybuck & Lattal, 2014). Likewise, the presentation of cocaine conditioned environmental cues may increase striatal pERK and FosB protein levels (Nygard, Klambatsen, Balouch, Quinones-Jenab, Jenab, 2015). Acute cocaine exposure induces protein kinase D1 activation in rat striatum, and knockdown of protein kinase D1 in dorsal striatum may attenuate the cocaine-induced locomotor hyperactivity (Wang et al., 2014). Thus, ibotenic acid-induced excitotoxic lesions were done in bilateral BLA, dorsal hippocampus (DH) and dorsolateral striatum (DLS) to test whether these brain regions may be involved in the companions-exerted suppressive effects on the cocaine-induced CPP magnitude.

Using our experimental protocol, companions housing with the experimental mice in the cocaine-conditioned place would not be present in the CPP test. Based upon the prediction provided by compound-stimulus conditioning (Baker, 1968) or its mirror procedure, stimulus compounding (Weiss, 1972), two conditioned stimuli (place and companions) together may share the associative strength for the presence of unconditioned stimulus (cocaine) in the conditioning. Thus, companions produced suppressive effect on the cocaine-induced CPP could be due to the fact that the absence of the companions may diminish the associative strength for the cocaine conditioned stimuli in the CPP test. In an attempt to test this possibility, we decided to substitute inanimate objects, wood blocks, for the companions in the cocaine conditioning.

2. Materials and methods

2.1. Animals

After weaning, male C57BL/6N mice were group housed (4 per cage) in plastic cages (28 × 17 × 12 cm) 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* throughout each experiment. All experiments started when mice reached 8 weeks of age. Three cage mates or wooden blocks (Tzeng, Chen, Cherng, Tsai, & Yu, 2014) living with the respective experimental mice were regarded as companions in this study. 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.

2.2. Cocaine-induced CPP

Pretest, conditioning sessions, and the cocaine-induced CPP test were conducted in commercial chambers (43 × 13 × 13 cm) designed for mice (MedAssociates Inc., Georgia, VT, USA). Each chamber consisted of a center (9 × 13 × 13 cm) and two side compartments (17 × 13 × 13 cm). The side compartments provided three sets of distinctive cues: medium vs. dim light illumination, black vs. white walls and ceilings, and steel grid bar vs. wire-mesh floors. The center compartment was bright-lit with gray walls, ceiling and a gray platform floor. Passages between the center and the side compartments were controlled by automatic guillotine doors. Mouse location in chambers was monitored by photocell detectors aligned 1.5 cm above the floor across the three compartments, each 3 cm apart and connected via interface cards to IBM-compatible PCs. The time spent in each compartment was recorded and analyzed by MED-PC for Windows. Chambers were deodorized by a thorough cleaning with an isopropyl alcohol (70%)-rinsed paper towel wiping and followed by a period of drying before each round of pretest, conditioning sessions and test. One day before the beginning of the conditioning session, experimental mice were placed in the center of any randomly chosen chamber and the time spent in each compartment was measured for 15 min as the pretest for their unconditioned preference. Mice spending over 40% of the time in any one compartment for a chamber in the pretest were excluded for further study. Cocaine-induced CPP conditioning sessions consisted of 3 saline and cocaine conditioning sessions in 3 consecutive days (Liao et al., 2016; Lin et al., 2011; Lu, Lu, Hong, Yang, & Yu, 2013; Tzeng et al., 2012, 2013; Yang et al., 2013). On the first day of the conditioning sessions, experimental mice receiving an intra-peritoneal (i.p.) saline injection were immediately confined in their preferred compartment individually for 30 min in the morning (08:00–09:00). Approximately eight hours later, experimental mice receiving a cocaine hydrochloride (20 mg/kg) injection were confined in their non-preferred compartment individually, with the respective companions or wooden blocks from their home cages (Tzeng et al., 2014) for 30 min. It was of importance to note that the wooden blocks were in the cages with the mice for, at least, two weeks. These wooden blocks were taped to the upper wall of the cocaine conditioned compartment (4 cm above the floor, thus accessible by the experimental mice for exploration) in the cocaine conditioning to avoid interruption of photocell detection. The conditioning procedures were repeated for the following two days. Since companions' pharmacological conditions do not affect their suppressive effect on the cocaine-induced CPP (Tzeng et al., 2016), saline-treated