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Double dissociation of the anterior and posterior dorsomedial caudate-putamen in the acquisition and expression of associative learning with the nicotine stimulus

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ABSTRACT

Tobacco use is the leading cause of preventable deaths worldwide. This habit is not only debilitating to individual users but also to those around them (second-hand smoking). Nicotine is the main addictive component of tobacco products and is a moderate stimulant and a mild reinforcer. Importantly, besides its unconditional effects, nicotine also has conditioned stimulus effects that may contribute to the tenacity of the smoking habit. Because the neurobiological substrates underlying these processes are virtually unexplored, the present study investigated the functional involvement of the dorsomedial caudate putamen (dmCPu) in learning processes with nicotine as an interoceptive stimulus. Rats were trained using the discriminated goal-tracking task where nicotine injections (0.4 mg/kg; SC), on some days, were paired with intermittent (36 per session) sucrose deliveries; sucrose was not available on interspersed saline days. Pre-training excitotoxic or post-training transient lesions of anterior or posterior dmCPu were used to elucidate the role of these areas in acquisition or expression of associative learning with nicotine stimulus. Pre-training lesion of p-dmCPu inhibited acquisition while post-training lesions of p-dmCPu attenuated the expression of associative learning with the nicotine stimulus. On the other hand, post-training lesions of a-dmCPu evoked nicotine-like responding following saline treatment indicating the role of this area in disinhibition of learned motor behaviors. These results, for the first time, show functionally distinct involvement of a- and p-dmCPu in various stages of associative learning using nicotine stimulus and provide an initial account of neural plasticity underlying these learning processes.

1. Introduction

In the United States alone, tobacco consumption is responsible for a fifth of all deaths (480,000 deaths per year) and more than $300 billion a year in expenditures related to health care and productivity loss (USDHHS, 2014). Nicotine is the primary addictive component of tobacco and is a mild stimulant and a relatively weak reinforcer (Chaudhri et al., 2006; Palmatier et al., 2007; Perkins, 1999). Previous research has been instrumental in advancing our understanding of nicotine's primary reinforcing and behavioral or psychological effects that include reward, analgesia, and psychomotor activation among many others (Balfour, 2004; Damaj et al., 1998; Markou, 2008). Although studying nicotine's primary reinforcing properties and their behavioral and neurobiological effects is of great importance to understanding tobacco addiction, learning processes involving nicotine are likely to be more complex and there is a need to study this complexity.

Researchers are increasingly aware that certain forms of the associative learning, including both Pavlovian and instrumental conditioning, contribute to the tenacity of tobacco use and nicotine dependence (Bevins and Besheer, 2014). For example, nicotine's pharmacological effects originating inside the body, and which comprise a complex multimodal internal or interoceptive stimulus, can come into association with such reinforcers as peer interaction, food, alcohol, and work breaks, to name a few. Hence, the

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interoceptive effects of nicotine can acquire some additional motivation or appetitive effects by association with other stimuli in the environment; such conditioning can exert a profound influence on behavior. This coupling of the interoceptive effects of nicotine with non-nicotine rewards co-occurring in the environment can be modeled in rodents. For example, when nicotine in a controlled manner is repeatedly paired with access to sucrose, it acquires the ability to evoke an anticipatory food-seeking response in rats (goal-tracking). Although there has been significant progress in understanding the behavioral aspects of learning with nicotine as an interoceptive stimulus (for review see Bevins and Murray, 2011), there remains a significant gap in understanding neural mechanisms underlying this type of learning (Charntikov et al., 2012).

We recently began elucidating the neurobiological loci involved in learning with the nicotine stimulus (Charntikov et al., 2012). This research used a discriminated goal-tracking (DGT) task where on some days rats received nicotine paired with access to sucrose; on separate interspersed saline days, sucrose was not available. Across sessions, nicotine comes to evoke a goal-tracking response in the form of increased snout entries into the receptacle where sucrose has been delivered in the past (Besheer et al., 2004; Murray and Bevins, 2007). Behaviorally, this learning follows many of the postulates of Pavlovian conditioning (Bevins and Murray, 2011; Murray et al., 2009) and likely simulates learning process in human smokers (Glautier et al., 1996). Using this model, we found that rats that had a reliable history of nicotine-sucrose association had significantly higher nicotine induced c-Fos expression in the dmCPu when compared to controls (Charntikov et al., 2012). Importantly, this effect was evident in the presence of two carefully designed conditions that served as controls. One control condition had equal exposure to nicotine and sucrose, but nicotine was not reliably paired with the sucrose presentation (only half of nicotine sessions paired with the sucrose). The second control condition had exposure to nicotine in a manner identical to the other two conditions; however, sucrose was never available for this subset of rats. Following training, rats in all conditions were challenged with either nicotine or saline and assessed in the absence of sucrose reward for their goal-tracking behavior and the immediate neuronal activation. Results of this preliminary study provide a first account of possible neurobiological loci involved in conditioning processes with interoceptive effects of drugs.

Although our previous report showed the involvement of dmCPu in learning with the nicotine stimulus (Charntikov et al., 2012), this correlational increase in c-Fos activity does not inform us about the functional involvement of dmCPu in these learning processes. In addition, because the anatomical connections within anterior-posterior axis of rat dorsal striatum are not homogeneous (Kelley et al., 1982) and can differ in their control of learning processes (Hikosaka et al., 1999; Jeanblanc et al., 2003; Yin et al., 2005; Murray et al., 2012), it is unclear whether anterior (a-dmCPu) or posterior (p-dmCPu) regions are differentially involved in learning with the nicotine stimulus. For example, Yin et al. (2005) showed that only lesion to p-dmCPu and not a-dmCPu disrupted instrumental learning during acquisition and expression learning phases (lever pressing for food reinforcer). On the other hand, Murray et al. (2012) showed that lesions to p-dmCPu disrupted instrumental learning (cocaine seeking) only during early learning stage while lesions to a-dmCPu and not p-dmCPu disrupted instrumental performance after extensive period of learning. Because our previous aforementioned study showed that the history of learning with nicotine as a conditioned stimulus for an appetitive reward, and not the nicotine or sucrose alone, evoked higher neural activation in dmCPu (Charntikov et al., 2012), the goal of this study was to systematically assess the role of a- and p-dmCPu in the acquisition or expression of learning with the nicotine stimulus. Based on previous reports we hypothesized that lesions to p-dmCPu would decrease acquisition of learning with nicotine stimulus while lesions to a-dmCPu would decrease the expression of learning with nicotine stimulus.

2. Materials and methods

2.1. Animals

Subjects were experimentally naive male Sprague-Dawley rats (total n = 79 purchased from Harlan Industries (275–290 g; Indianapolis, IN, USA). Rats were housed individually in a temperature- and humidity-controlled colony (12:12 light:dark cycle; lights on at 6 a.m.). Water was freely available; access to chow (Harlan Teklad Rodent Diet; Harlan, Indianapolis, IN, USA) was restricted to maintain rats at 85% of their free-feeding body weight. This 85% target weight was increased by 2 g every four weeks from beginning of the study. The night before and for two days following surgery, food was freely available. Experimental protocols were approved by the University of Nebraska-Lincoln Institutional Animal Care and Use Committee.

2.2. Apparatus

Behavioral testing was conducted in commercially available chambers (ENV-008CT; Med Associates, Inc., St. Albans, VT, USA) enclosed in sound- and light-attenuating cubicles equipped with an exhaust fan. Each conditioning chamber had aluminum sidewalls, metal rod floors with polycarbonate front, back, and ceiling. A recessed receptacle ($5.2 \times 5.2 \times 3.8$ cm; $l \times w \times d$) was centered on one of the sidewalls. A dipper arm, when raised, provided access to 0.1 ml of 26% (w/v) sucrose solution in the receptacle. Access to the dipper was monitored by an infrared beam mounted 1.2 cm into the receptacle and 3 cm above the chamber floor. Beam breaks for dipper entries were monitored using Med Associates interface and software (Med-PC for Windows, version IV).

2.3. Drugs

Nicotine hydrogen tartrate, buprenorphine hydrochloride, and sodium pentobarbital (Sigma; St. Louis, MO, USA) were dissolved in 0.9% saline. NMDA and lidocaine hydrochloride (Sigma) were dissolved in sterile distilled water and pH was adjusted to 7.0 ± 0.2 with a dilute NaOH solution. Nicotine dose (0.4 mg/kg; reported as base) and the 5 min injection-to-placement interval was selected based on previous research (Charntikov et al., 2012).

2.4. Discriminated goal-tracking task

Rats were subcutaneously (SC) injected with 0.4 mg/kg nicotine for three consecutive days before training to attenuate the initial locomotor suppressant effects of nicotine (Charntikov et al., 2012). For each daily training session, all rats were injected with either nicotine (0.4 mg/kg; SC) or saline 5 min before placement in the conditioning chamber for a 20-min session. During training, each rat received equal number of nicotine and saline sessions. Sessions were assigned using a unique pseudorandom order of nicotine and saline sessions for each rat with the condition that no more than two of the same session type occur in a row. On nicotine sessions, the interoceptive stimulus effects of nicotine were paired with intermittent access to sucrose. Access to sucrose was initiated between 124 and 152 s from the start of the session with 4 possible onset times randomized throughout the training phase. There were 36 separate 4-sec deliveries of sucrose per nicotine session. Time between sucrose deliveries ranged from 4 to 80 s ($\bar{x} = 25$ s). For