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Invited review

When a good taste turns bad: Neural mechanisms underlying the emergence of negative affect and associated natural reward devaluation by cocaine

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ABSTRACT

An important feature of cocaine addiction in humans is the emergence of negative affect (e.g., dysphoria, irritability, anhedonia), postulated to play a key role in craving and relapse. Indeed, the DSM-IV recognizes that social, occupational and/or recreational activities become reduced as a consequence of repeated drug use where previously rewarding experiences (e.g., food, job, family) become devalued as the addict continues to seek and use drug despite serious negative consequences. Here, research in the Carelli laboratory is reviewed that examined neurobiological mechanisms that may underlie these processes using a novel animal model. Oromotor responses (taste reactivity) were examined as rats learned that intraoral infusion of a sweet (e.g., saccharin) predicts impending but delayed access to cocaine self-administration. We showed that rats exhibit aversive taste reactivity (i.e., gapes/rejection responses) during infusion of the sweet paired with impending cocaine, similar to aversive responses observed during infusion of quinine, a bitter tastant. Critically, the expression of this pronounced aversion to the sweet predicted the subsequent motivation to self-administer cocaine. Electrophysiology studies show that this shift in palatability corresponds to an alteration in nucleus accumbens (NAc) cell firing; neurons that previously responded with inhibition during infusion of the palatable sweet shifted to excitatory activity during infusion of the cocaine-devalued tastant. This excitatory response profile is typically observed during infusion of quinine, indicating that the once palatable sweet becomes aversive following its association with impending but delayed cocaine, and NAc neurons encode this aversive state. We also review electrochemical studies showing a shift (from increase to decrease) in rapid NAc dopamine release during infusion of the cocaine-paired tastant as the aversive state developed, again, resulting in responses similar to quinine infusion. Collectively, our findings suggest that cocaine-conditioned cues elicit a cocaine-need state that is aversive, is encoded by a distinct subset of NAc neurons and rapid dopamine signaling, and promotes cocaine-seeking behavior. Finally, we present data showing that experimentally induced abstinence (30 days) exacerbates this natural reward devaluation by cocaine, and this effect is correlated with a greater motivation to lever press during extinction. Dissecting the neural mechanisms underlying these detrimental consequences of addiction is critical since it may lead to novel treatments that ameliorate negative affective states associated with drug use and decrease the drive (craving) for the drug.

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1. Introduction

Cocaine addiction is a complex disease characterized by cycles of drug consumption and abstinence followed by craving and relapse (Kalivas and Volkow, 2005; Koob and Volkow, 2010). Embedded in the addiction cycle is the well-established finding that natural rewards become devalued as a consequence of repeated drug use (American Psychiatric Association, 1993; Volkow et al., 2004). For example, friends, family, jobs and recreational activities become much less important to the addict in comparison to the drug. This occurs despite devastating consequences of continued drug use including alienation of friends and family, loss of employment and negative health consequences. Understanding the neurobiological

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mechanisms underlying natural reward devaluation by cocaine may be critically important when developing new behavioral and pharmacological treatments for addiction (Volkow et al., 2004).

A primary focus of research in the Carelli lab has been to understand neurobiological mechanisms mediating goal-directed actions for natural rewards (e.g., food/water) versus cocaine. We have directed our work at the nucleus accumbens (NAc) and its dopaminergic input given the unique anatomical arrangement of this structure and its role in 'limbic-motor integration' (Carelli and Wightman, 2004; Mogenson et al., 1980; Pennartz et al., 1994). Using electrophysiological recording procedures in behaving rats, we have shown that distinct subsets of NAc neurons selectively encode important features of goal-directed behaviors for cocaine versus natural rewards (Carelli and Deadwyler, 1994; Carelli et al., 2000, 1993; Carelli and Wightman, 2004; Carelli and Wondolowski, 2003, 2006). Further, NAc neural activity, as well as rapid dopamine signaling in this structure, are highly dynamic and profoundly altered by a variety of factors including learning about stimuli associated with cocaine (Carelli, 2000, 2004), operant conditioning contingences (Carelli and Deadwyler, 1996; Carelli and Ijames, 2000, 2001; Carelli et al., 1993; Hollander et al., 2002), as well as decision-making related to effort, delay (Day et al., 2011, 2010) and risk-taking (Sugam and Carelli, 2013; Sugam et al., 2012). Additionally, neural activity in the NAc is dramatically altered by experimenter-controlled cocaine abstinence (Cameron and Carelli, 2012; Hollander and Carelli, 2005, 2007).

The dynamic nature of NAc signaling is also evident in our work that examined the role of the NAc in natural reward devaluation by cocaine. This interest was sparked by our early observations of behavioral profiles during tasks involving lever pressing for a natural reward (water or food) versus self-administered cocaine in a multiple schedule design. We noted that rats would stop lever pressing for the natural reward when that lever consistently preceded the drug lever (unpublished finding). This was a fascinating observation given the work by Grigson and others that showed that animals will respond less for a previously palatable natural reward when it comes to predict an abused drug (Grigson, 1997, 2000, 2008; Grigson and Twining, 2002; Wise et al., 1976). Here, we review our work that examined a role of the NAc in natural reward devaluation by cocaine using a novel behavioral model in combination with electrophysiological and electrochemical approaches.

2. An animal model of natural reward devaluation by cocaine

In our initial study (Wheeler et al., 2008), rats were implanted with intraoral cannulae (for tastant infusion directly into their mouths), an intrajugular catheter for self-administration, and microelectrode arrays bilaterally positioned in the NAc core and shell. Our model was based on the finding that rats exhibit stereotyped oromotor responses, termed 'taste reactivity', to taste stimuli infused directly into the oral cavity that correspond to hedonic aspects of the stimulus (Grill and Norgren, 1978). Specifically, rats exhibit appetitive taste reactivity (e.g., licks) during infusion of a sweet tastant such as saccharin, and aversive taste reactivity (e.g., gapes) during intraoral infusion of a bitter tastant such as quinine. In our study, rats were given daily conditioning sessions completed in 2 phases. In the first phase, rats were intraorally infused with a distinctly flavored (e.g., orange) saccharin solution delivered over 3.5 s per trial every minute for 30 trials. In Phase 2, animals were trained to self-administer cocaine during daily 2-hour sessions using established procedures. Lever depression on an FR1 schedule resulted in intravenous cocaine delivery (0.33 mg/inf, 6 s) that was signaled by termination of the cue light and simultaneous onset of a tone-houselight stimulus complex (20 s). The next day, the same rats underwent the same procedure with two changes: 1) the flavor of the saccharin solution was changed (e.g., from orange to grape) and 2) phase 2 involved self-administration of saline. This procedure was repeated for 14 days (7 of each pairing).

Using this design rats learned that an infusion of a distinctly flavored tastant during phase 1 predicted the ability to self-administer cocaine in phase 2. Inherent in this design however is that rats had to wait an extended period of time (30 min) to gain access to the drug. We hypothesized that the "drug waiting" period in phase 1 allowed for a strong association to develop between the tastant paired with delayed cocaine, and enabled the emergence of a negative affective state as measured by taste reactivity. In support, rats developed a strong aversion to the tastant that predicted cocaine (but not saline), reflected by changes in the oro-facial expression during tastant delivery. That is, the flavored saccharin solution paired with saline elicited classic appetitive taste reactivity (licking, lateral tongue protrusions; Fig. 1A (Wheeler et al., 2008). In contrast, the cocaine-paired tastant elicited aversive taste reactivity (gapes, Fig. 1B). This behavioral response profile was also reflected in EMG recordings of the anterior digastric muscle, a muscle coupled to licking (Fig. 1C & D).

Critically, the negative affective state that developed in phase 1 increased motivation to consume cocaine, once the drug was available in phase 2. Specifically, aversive taste reactivity (gapes) was significantly correlated with cocaine loading responses (presses during the first 5 min of the session) and latency to the first press during cocaine self-administration. That is, rats that exhibited the most gapes in phase 1 showed the greatest number of load up responses and the fastest latency to initiate responding for cocaine once the self-administration phase began (Fig. 1E). Following the final training day, rats were given a test session in which the unpaired (saline associated) then the paired (cocaine associated) tastants were intraorally infused. During the test session, rats exhibited primarily appetitive taste reactivity to the tastant associated with saline (unpaired) but aversive taste reactivity during infusion of the tastant predictive of cocaine (paired) (Fig. 1F). Further, rats preferred the tastant paired with saline over the one associated with cocaine in a two bottle test given following the test session. These findings are consistent with the view that a robust reversal of palatability occurs (from rewarding to aversive) for a tastant that predicts delayed cocaine availability, and that motivation for the drug increases following this shift.

3. NAc neurons track the learned aversion to the sweet

Under normal conditions, NAc neurons exhibit differential activity during direct application of palatable and unpalatable taste stimuli (Roitman et al., 2005; Wheeler and Carelli, 2009). Specifically, intraoral infusions of a palatable sucrose solution are associated, predominantly, with transiently reduced firing rates for NAc neurons. This response profile is illustrated in the perievent histogram (PEH) and raster display for one NAc neuron in Fig. 2A. In contrast, NAc neurons exhibit predominantly excitatory responses during infusion of an aversive tastant, such as a bitter quinine solution, illustrated for another neuron in Fig. 2B. This differential pattern of neural activity cannot be attributed to goal-seeking (since the tastants were infused directly into the oral cavity), and therefore likely reflects the hedonic properties of the solutions.

Importantly, the aversive state that develops in our model of natural reward devaluation by cocaine is reflected in a shift in the activity of populations of NAc neurons. As noted above and illustrated in the pie charts in Fig. 3, under normal conditions the predominant response (approximately 75%) of all phasically active NAc neurons to the application of a palatable taste stimulus is a reduction (inhibition) in firing rate (top left). Not surprisingly, a similar response profile was observed during infusion of the tastant