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Cocaine decreases saccharin preference without altering sweet taste sensitivity

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ABSTRACT

In rodents, saccharin consumption is suppressed when the sweet taste stimulus is paired with moderate doses of cocaine. Several hypotheses have been used to explain the seemingly contradictory effect of decreased consumption of a normally preferred substance following a highly rewarding drug. A common theme across these hypotheses is that saccharin is interpreted as less rewarding after cocaine pairing. We considered the alternative possibility that suppression is caused not by a change in reward circuitry, but rather by a change in taste detection, for instance by altering the afferent taste response and decreasing sensitivity to sweet taste stimuli. To evaluate this possibility, we measured saccharin taste sensitivity of mice before and after a standard cocaine-pairing paradigm. We measured taste sensitivity using a brief-access lickometer equipped with multiple concentrations of saccharin solution and established concentration–response curves before and after saccharin–cocaine pairing. Our results indicate that the EC_{50} for saccharin was unaltered following pairing. Instead, the avidity of licking saccharin, an indicator of motivation, was depressed. Latency to first-lick, a negative indicator of motivation, was also dramatically increased. Thus, our findings are consistent with the interpretation that saccharin–cocaine pairing results in devaluing of the sweet taste reward.

1. Introduction

Cocaine exposure and consumption of sweet tasting solutions both cause increased dopamine signaling in the nucleus accumbens, leading to pleasurable or rewarding sensations (Avena et al., 2008; Mark et al., 1991; Rada et al., 2005). These two stimuli enhance dopamine signaling through separate mechanisms. Cocaine directly inhibits the dopamine transporter, thereby elevating synaptic dopamine levels. In contrast, sucrose elicits neural circuit activity that indirectly increases dopamine release in the nucleus accumbens (Avena et al., 2008; Norgren et al., 2006; Rada et al., 2005). There also are notable differences in the reward value and specific pathways for sweet stimuli and cocaine. For example, dopamine firing patterns in the nucleus accumbens are usually blunted after repeated access to sweet rewards, but not cocaine (Di Chiara et al., 2004; Rada et al., 2005). In addition, lesion studies have shown that taste circuits in the thalamus and projections from the parabrachial nucleus are essential for sweet- but not cocaine-elicited reward (Grigson et al., 2000; Norgren et al., 2006; Nyland et al., 2012).

It has been known for many years that rodents will avoid intake of a palatable taste cue when it is repeatedly presented prior to an injection of cocaine (Ferrari et al., 1991; Glowa et al., 1994; Grigson, 1997). This appears to cause a paradox where a reinforcing drug of abuse causes avoidance rather than enhanced pursuit of the conditioned stimuli. There are several behavioral hypotheses that seek to explain this observation. For instance, changes in homeostasis following drug injection may cause a 'taste shyness' around the conditioned tastant (Hunt and Amit, 1987). Alternatively, anticipation of the future high drug reward may dampen the value of the less rewarding natural stimulus (Grigson, 1997). Other hypotheses include the idea that the drug is aversive to the mice and induces conditioned taste aversion (Lin et al., 2014) or conditioned disgust (Parker et al., 2008).

Another possibility is that there may be an afferent, taste-driven explanation for the decreased consumption. For example, decreased ability to taste the cue (saccharin) may result in decreased consumption following cocaine exposure and conditioning. Such a mechanism may be quite independent of hedonic value and motivation. It is known that cocaine inhibits several transporter proteins, thus blocking transport, not only of dopamine, but also of the other monoamines, serotonin and norepinephrine (Amara and Sonders, 1998; Mateo et al., 2004). Peripheral taste cells employ both serotonin and norepinephrine as neurotransmitters (Huang et al., 2005, 2007) and the transporters for norepinephrine and serotonin are present and functional on cells of taste buds (Chaudhari and Roper, 2010; Dvoryanchikov et al., 2007). It also has been shown that knockout of both dopamine and serotonin

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transporters are required to abolish cocaine conditioned place preference, even though dopamine remains the primary neurotransmitter underlying the rewarding effects of cocaine (Sora et al., 2001). Similarly, mice with genetic deletion of transporters for serotonin or norepinephrine show altered responses to taste-selective behavior (Jones et al., 2010). Cocaine also has been shown to alter many aspects of appetite and ingestion (Cui and Lutter, 2013; Vicentic and Jones, 2007). Cocaine dependence in humans causes profound changes in diet, specifically by increasing consumption of fats and carbohydrates, but decreasing sugar intake (Ersche et al., 2013).

If cocaine acutely alters signaling in taste buds, repeated exposures may well result in chronically altered gene expression. Cocaine has been shown to lead to long-term transcriptional alterations through CREB expression (Xu et al., 2013) and chromatin remodeling (Taniguchi et al., 2012). Cocaine could alter taste sensitivity by modifying gene expression in existing and particularly in newly formed taste bud cells, which are replaced every few days (Beidler and Smallman, 1965). In support of this, the time-frame for cocaine-induced is similar to that of taste bud cell turnover. Thus, we considered whether long-term exposure to cocaine might change chemosensory detection and neural signals from the taste periphery.

The goal of the present study was to apply a model commonly used in taste studies but not commonly used in drug studies to measure rodent taste sensitivity before and after saccharin is paired with cocaine to determine if the pairing paradigm causes taste sensitivity to be dampened. We used a brief-access lickometer assay, as it is commonly used to identify taste quality and to separate orosensory-mediated responses from higher order responses (Loney et al., 2012; Mantella and Youngentob, 2014; McCaughey and Glendinning, 2013). This assay has been used to quantify differences of taste sensitivity in mice with mutations in taste-related genes (Tordoff and Ellis, 2013; Treesukosol et al., 2009) and to compare orosensory ability and drug preference for both nicotine (Glatt et al., 2009) and alcohol (Brasser et al., 2012). Brief-access lickometry has been optimized to elicit concentration-dependent licking for different taste stimuli and to effectively separate mice with altered taste function (Glendinning et al., 2002; Sinclair et al., 2014). A brief-access lickometer assay generates a concentration–response curve of the acceptance of a taste stimulus. Importantly, voluntary consumption, preference in a 2-bottle assay, and brief-access lick-rate all are dependent on similar concentrations of the stimulus and display parallel responses (Inoue et al., 2007). A substantial difference between the brief-access lickometer assay and the commonly used two-bottle preference test is that licking responses reflect taste-dependent acceptance or rejection that is minimally influenced by post-ingestive effects. Thus, we used a Davis rig lickometer to determine if detection of a sweet taste stimulus is altered when mice are exposed to a standard saccharin–cocaine pairing paradigm. We administered this brief-access test both before and after cocaine exposure (pre-test vs. post-test, respectively).

2. Materials and methods

2.1. Animals

Sixteen male C57BL/6 mice between 2 and 4 months of age were individually housed on a 12-h light/dark cycle with food and water available. All mice were handled according the 2010 NIH guide for the Care and Use of Laboratory Animals, 8th ed. and all procedures were approved by the University of Miami Institutional Animal Care and Use Committee (IACUC). Male mice were used exclusively to match conditions used in previous studies.

2.2. Drugs and dosage

Cocaine was obtained from NIDA (Rockville, MD, USA) and was dissolved in 0.9% NaCl. Cocaine (30 mg/kg) was injected i.p. for experimental animals while an equal volume (0.01 ml/g) of normal saline was injected for controls. Dosage and procedures for pairing saccharin and cocaine in C57BL/6J mice were followed exactly as described in Freet et al. (2013). Saccharin solutions were made by dissolving saccharin sodium salt hydrate (Sigma #S1002) in deionized autoclaved water.

2.3. Water and Food deprivation

Glendinning et al. (2002) devised a mild water- and food-restriction paradigm that motivates mice to lick in a Davis Rig Lickometer and optimizes the concentration-dependence of the response (Glendinning et al., 2002). Prior to Lickometer Training Sessions 1 and 2, mice were fully deprived of water for 23.5 h. This familiarizes the animals to the drinking spout. For all subsequent sessions, mice were subjected to a limited water and food restriction: 1 g LabDiet 5001 mouse chow plus 3 ml of water for the 23.5 h prior to testing (Glendinning et al., 2002). All animals were weighed and examined daily for weight loss or behavioral changes associated with dehydration. None of the animals showed a >20% weight drop or sudden increase in lethargy during food or water restriction.

2.4. Lickometer Sessions

Each mouse was placed in a Davis MS-160 “lickometer” (DiLog Instruments Tallahassee, FL) during seven separate sessions. On the first training day, mice were water deprived for 23.5 h prior to the experiment and placed individually in the lickometer cage for 1 h to familiarize them with the novel environment. A stationary drinking spout was present and the mouse was free to drink water ad libitum. Mice were given 1 h following training to recover in their home cage with full access to food and water before being water deprived for the next session.

On Training Day 2, the mouse was placed in the lickometer cage for 30 min and was introduced to a non-stationary drinking tube. During this training session, a bottle of water was presented and the mouse was allowed to drink for five seconds before a shutter prevented further drinking. After a 15 second wait, a new bottle of water was presented.

Training Day 3 serves to familiarize mice with repeated presentations of varying concentrations of saccharin, representing a novel taste (Sinclair et al., 2014). On Training Day 3 and on all test days, seven bottles were filled with either water or a solution of sodium saccharin (0.9 mM, 2 mM, 7 mM, 9 mM, 18 mM, or 45 mM corresponding to 0.018%, 0.041%, 0.18%, 0.37%, 0.92% g/ml, respectively) and were presented in computer-generated random order. Concentrations of saccharin were chosen to span the preferred concentration range in C57BL/6 mice (Bachmanov et al., 2001; Fuller, 1974; Inoue et al., 2007). In all tests, water and saccharin solutions were presented one at a time over a total of 30 min. or for a maximum of 49 presentations, whichever came first. Each presentation comprised of the shutter opening to reveal a drinking spout, a variable latency before the mouse began drinking, and 5 s of drinking time. Mice were given one day of rest with full hydration after each testing session. Every mouse was tested for all concentrations of saccharin twice prior to cocaine (or saline) exposure (Pre-test 1,2) and twice post-cocaine (or saline) exposure (Post-test 1,2). The post-tests were conducted at least 27.5 h after the last cocaine injection. Thus, mice were never tested in the lickometer while under the influence of cocaine. The time course of experiments is outlined in Fig. 1.

2.5. Data analysis: maximal lick rate and the Standardized Lick Ratio

For every lickometer presentation, we recorded the inter-lick interval (in msec), the total number of licks, the identity of the solution, and the latency interval before the mouse started to drink in each trial. First, we calculated the maximum lick rate for each mouse as