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Drinking sucrose or saccharin enhances sensitivity of rats to quinpirole-induced yawning

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ABSTRACT

Diet can impact sensitivity of rats to some of the behavioral effects of drugs acting on dopamine systems. The current study tested whether continuous access to sucrose is necessary to increase yawning induced by the dopamine receptor agonist quinpirole, or if intermittent access is sufficient. These studies also tested whether sensitivity to quinpirole-induced yawning increases in rats drinking the non-caloric sweetener saccharin. Dose–response curves (0.0032–0.32 mg/kg) for quinpirole-induced yawning were determined once weekly in rats with free access to standard chow and either continuous access to water, 10% sucrose solution, or 0.1% saccharin solution, or intermittent access to sucrose or saccharin (i.e., 2 days per week with access to water on other days). Cumulative doses of quinpirole increased then decreased yawning, resulting in an inverted U-shaped dose–response curve. Continuous or intermittent access to sucrose enhanced sensitivity to quinpirole-induced yawning. Continuous, but not intermittent, access to saccharin also enhanced sensitivity to quinpirole-induced yawning. In all groups, pretreatment with the selective D_3 receptor antagonist PG01037 shifted the ascending limb of the quinpirole dose–response curve to the right, while pretreatment with the selective D_2 receptor antagonist L-741,626 shifted the descending limb to the right. These results suggest that even intermittent consumption of diets containing highly palatable substances (e.g. sucrose) alters sensitivity to drugs acting on dopamine systems in a manner that could be important in vulnerability to abuse drugs.

1. Introduction

Diet (e.g., type and amount of food consumed) can impact sensitivity to drugs acting on dopamine systems (Avena and Hoebel, 2003; Collins et al., 2008; Gosnell, 2005; Baladi et al., 2012a, 2011a; Puhl et al., 2011). For example, rats eating a high fat chow or drinking a 10% sucrose solution are more sensitive than rats eating standard chow and drinking water to the behavioral effects of direct- (i.e., quinpirole; Baladi et al., 2011a, b) and indirect-acting (i.e., cocaine; Baladi et al., 2012b) dopamine receptor agonists. Although consumption of foods high in fat or sugar contributes to the development of obesity, sensitivity changes to the behavioral effects of drugs acting on dopamine systems even in the absence of weight gain (Baladi et al., 2011a, b); specifically, consuming a high fat or high sugar diet can markedly affect drug sensitivity in the absence of accelerated body weight gain.

Rats drinking sucrose are more sensitive than rats drinking water to the behavioral effects of quinpirole (Baladi et al., 2011b). Like many other direct-acting dopamine receptor agonists, quinpirole dose-dependently increases then decreases yawning in rats (Collins et al., 2008; Baladi and France, 2010) resulting in an inverted U-shaped dose–response curve. Experiments using selective dopamine receptor antagonists have revealed that the ascending limb (initiation of yawning) is mediated by dopamine D_3 receptors, while the descending limb (inhibition of yawning) is mediated by dopamine D_2 receptors (Collins et al., 2008; Baladi et al., 2011a; though see Depoortere et al. (2009), Sanna et al. (2011, 2012)). The D_3 receptor-mediated ascending limb of the quinpirole dose–response curve is shifted to the left in rats drinking sucrose (Baladi et al., 2011b). When consumption of highly preferred substances (fat or sugar) is restricted or access is intermittent, animals often increase consumption which is accompanied by an enhanced sensitivity to drugs acting indirectly on dopamine systems (Avena and Hoebel, 2003; Gosnell, 2005; Puhl et al., 2011). However, intermittency of access varied markedly across these studies and it is not known whether intermittent access to sucrose enhances sensitivity of rats to the behavioral

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effects of the direct-acting dopamine receptor agonist quinpirole.

While the mechanism(s) underlying these changes in sensitivity is not known, consumption of a diet high in sucrose or fat also causes metabolic changes (e.g., insulin resistance) that could impact drug sensitivity. Changes in insulin signaling can impact dopamine neurotransmission (Daws et al., 2011); however, non-caloric sweeteners such as saccharin are also highly preferred (compared with water) by rats (Carroll et al., 2007, 2008) but do not cause insulin resistance. Animals that show the greatest preference for sweeteners often are also more sensitive to drugs acting on dopamine systems (Carroll et al., 2008). The current study examined the effects of continuous or intermittent access to sucrose or saccharin solutions on sensitivity of rats to quinpirole-induced yawning.

2. Materials and methods

2.1. Subjects

Male Sprague Dawley rats ($N=52$; Harlan, Indianapolis, IN, USA), weighing 250–300 g upon arrival, were housed individually in an environmentally controlled room (24 ± 1 °C, 50 ± 10% relative humidity) under a 12:12 h light/dark cycle (light period 0700–1900 h). All rats had free access to food and water in the home cage except as indicated below. Animals were maintained and experiments were conducted in accordance with the Institutional Animal Care and Use Committee, the University of Texas Health Science Center at San Antonio, and with the 2011 Guide for Care and Use of Laboratory Animals (Institute of Laboratory Animal Resources on Life Sciences, the National Research Council, and the National Academy of Sciences).

2.2. Drinking conditions

All 52 rats had free access to water in the home cage during the first week of the study when they were habituated to the facility and experimental procedures. The experiment was conducted at two different times in two separate cohorts. For cohort 1, beginning in week 2 and continuing for 16 weeks, 5 rats continued to have free access to water in the home cage, 5 had free access to a 10% sucrose in water solution, 5 had free access to a 0.1% saccharin solution, and two other groups of 5 rats each had free access to water 5 days per week and free access to sucrose or saccharin, respectively, for 2 days per week (intermittent access). Cohort 1 was tested with quinpirole once per week through week 12, and again in week 16. For cohort 2, beginning in week 2 and continuing for 16 weeks, 6 rats continued to have free access to water in the home cage, 6 had free access to 10% sucrose in water solution, 5 had access to a 0.1% saccharin solution, and two other groups of 5 rats each had free access to water 5 days per week and access to sucrose or saccharin, respectively, for 2 days per week. Cohort 2 was tested with quinpirole once per week through week 4, from weeks 8–12, and in week 16. Body weight, food and fluid intake were measured and recorded daily.

2.3. Yawning

Yawning was defined as an opening and closing of the mouth ($\sim$1 s) such that the lower incisors were completely visible (Baladi and France, 2010). On the day of testing, rats were transferred to test cages and allowed to habituate for 15 min. Yawning experiments were conducted at the same time each day (1400 h). Yawning was assessed after injection of vehicle followed by injection of increasing doses of quinpirole (0.0032–0.32 mg/kg, i.p.) administered every 30 min using a cumulative dosing procedure. Beginning 20 min after each injection, the total number of yawns observed for 10 min was recorded (resulting in 6 observation periods per test). The dopamine D_2 receptor selective antagonist L-741,626 (1.0 mg/kg) and the dopamine D_3 receptor selective antagonist PG01037 (56.0 mg/kg) were assessed for their ability to alter quinpirole-induced yawning. Antagonists were administered immediately after vehicle.

2.4. Body temperature

Body temperature was measured in a temperature controlled room (24 ± 1 °C and 50 ± 10% relative humidity) by inserting a lubricated thermal probe attached to a thermometer 3 cm into the rectum. Animals were adapted to the procedure by measuring body temperature on multiple occasions before assignment to an experimental condition. During yawning experiments, body temperature was measured upon completion of each 10-min yawning observation period and prior to the next injection. The dopamine D_2 receptor selective antagonist L-741,626 (1.0 mg/kg) and the dopamine D_3 receptor selective antagonist PG01037 (56.0 mg/kg) were assessed for their ability to alter quinpirole-induced hypothermia.

2.5. Data analyses

Quinpirole-induced yawning results are expressed as the average ($\pm$S.E.M.) number of yawns during each 10-min observation period plotted as a function of dose. With increasing cumulative doses, quinpirole increased then decreased yawning resulting in an inverted U-shaped dose–response curve (see Section 3). The ascending and descending limbs of the dose–response curve were analyzed separately as follows: (1) by expressing each dose–response curve in an individual rat as a percentage of the maximal effect observed in that individual; (2) by determining the linear portion of the ascending and descending limbs of the curve, which included doses that spanned the 50% level of effect and included not more than one dose producing greater than 75% effect and not more than one dose producing less than 25% effect; and (3) by using linear regression to estimate the log ED_{50} for the ascending and the descending limb of each individual dose–response curve. Differences in log ED_{50} values and in maximal effects were analyzed using repeated measures ANOVAs with Geisser Greenhouse adjustment and Dunnett's *post hoc* analyses with corrections for multiple comparisons by means of Graph Pad Prism (GraphPad, San Diego, California, USA) and NCSS Statistical Software (NCSS, LLC, Kaysville, Utah, USA). Similar ANOVAs and post hoc analyses were used to examine differences in body temperature, body weight, and in food and fluid consumption. Results are shown and analyzed for both cohorts of rats (combined) except during weeks 5–7 in which only one cohort was tested with quinpirole.

2.6. Drugs

Quinpirole dihydrochloride (Sigma-Aldrich, St. Louis, Missouri, USA) was dissolved in sterile 0.9% saline and administered i.p. in a volume of 1 ml/kg body weight. L-741,626 (Tocris, Ellisville, Missouri, USA) was dissolved in 5% ethanol with 1 M HCl, added by drops until the solution was clear, and injected s.c., typically in a volume of 1 ml/kg body weight (see Baladi et al. (2011a), Collins et al. (2005, 2007)). PG01037 hydrochloride, generously provided by Dr. Amy Newman, was synthesized by J. Cao in the Medicinal Chemistry Section, Intramural Research Program, National Institute on Drug Abuse (Baltimore, Maryland, USA) using previously published methods (Grundt et al., 2005); PG01037 was dissolved in 0.9% saline and administered s.c., typically in a volume of 1 ml/