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DIFFERENCES IN BINGEING BEHAVIOR AND COCAINE REWARD FOLLOWING INTERMITTENT ACCESS TO SUCROSE, GLUCOSE OR FRUCTOSE SOLUTIONS

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Abstract—Daily intermittent access to sugar solutions results in intense bouts of sugar intake (i.e. bingeing) in rats. Bingeing on sucrose, a disaccharide of glucose and fructose, has been associated with a ''primed'' mesolimbic dopamine (DA) pathway. Recent studies suggest glucose and fructose engage brain reward and energy-sensing mechanisms in opposing ways and may drive sucrose intake through unique neuronal circuits. Here, we examined in male Sprague–Dawley rats whether or not (1) intermittent access to isocaloric solutions of sucrose, glucose or fructose results in distinctive sugar-bingeing profiles and (2) previous sugar bingeing alters cocaine locomotor activation and/or reward, as determined by conditioned place preference (CPP). To encourage bingeing, rats were given 24-h access to water and 12-h-intermittent access to chow plus an intermittent bottle that contained water (control) or 8% solutions of sucrose, glucose or fructose for 9 days, followed by *ad libitum* chow diet and a 10-day cocaine (15 mg/kg; i.p.) CPP paradigm. By day 4 of the sugar-bingeing diet, sugar bingeing in the fructose group surpassed the glucose group, with the sucrose group being intermediate. All three sugar groups had similar chow and water intake throughout the diet. In contrast, controls exhibited chow bingeing by day 5 without altering water intake. Similar magnitudes of cocaine CPP were observed in rats with a history of sucrose, fructose or chow (control) bingeing. Notably, the glucose-bingeing rats did not demonstrate a significant cocaine CPP despite showing similar cocaine-induced locomotor activity as the other diet groups. Overall, these results show that fructose and glucose, the monosaccharide components of sucrose, produce divergent degrees of bingeing and cocaine reward.

Key words: sugar bingeing, cocaine-conditioned place preference, sucrose, glucose, fructose.

INTRODUCTION

In the United States sugar consumption exceeds the dietary guidelines more than any other macronutrient, with added sugar intake comprising over 15% of daily calories (USDA, 2011). Added sugar calories are commonly derived from sucrose, a glucose–fructose disaccharide, and high fructose corn syrup, a mixture of free sugars, most often containing 55% fructose, 42% glucose and 3% polycose, a glucose polymer. Although glucose and fructose are commonly consumed together, it is now appreciated that glucose and fructose utilize different mechanisms for absorption, cellular transport and metabolism and that they stimulate opposing endocrine and hypothalamic responses (Teff et al., 2004; Cha et al., 2008; Stanhope et al., 2008; Tappy and Le, 2010; Page et al., 2013). A human imaging study found ingestion of glucose, but not fructose, increases the functional connectivity between the hypothalamus and the striatum, areas critical for energy-sensing and reward processing, respectively (Page et al., 2013). In a follow-up study, drinking a fructose-sweetened drink, as compared to a glucose-sweetened drink, was linked with greater hunger ratings and willingness to give up monetary reward in exchange for palatable food (Luo et al., 2015). In combination, these studies suggest that glucose and fructose may contribute to sucrose intake and reward through unique mechanisms and these diverging processes ultimately affect feeding behavior. Understanding the rewarding properties produced by these monosaccharides, as well as the individual mechanisms underlying these properties, may help to identify therapies to curb excessive consumption of complex sugars (i.e. sucrose and high-fructose corn syrup).

Previous work has shown that rats given repeated intermittent access to highly palatable food (foods high in sugar, fat or both) develop bingeing behavior and behavioral and neurochemical signs of dysfunction in their stress and reward circuitry (Bello et al., 2002, 2003; Avena and Hoebel, 2003; Gosnell, 2005; Rada

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Abbreviations: ANOVA, analysis of variance; CPP, conditioned place preference; DA, dopamine; NAc, nucleus accumbens; R, receptor; RMANOVA, repeated measures analysis of variance; SEM, standard error of the mean.

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et al., 2005; Avena et al., 2006b; Wojnicki et al., 2007, 2008; Cottone et al., 2008; Corwin and Wojnicki, 2009; Hoebel et al., 2009; Johnson and Kenny, 2010; Lê et al., 2011; Cifani et al., 2012; Iemolo et al., 2012; Micioni Di Bonaventura et al., 2014). The various bingeing models differ in the macronutrient composition, whether chow is offered concurrently and at onset and duration of palatable food access; but all models robustly increase palatable food intake at the onset of food access, which is termed a "binge". Here we used a sugar-bingeing model developed by Drs. Hoebel, Avena and colleagues that fosters bingeing behavior by cycling rats between 12 h of food deprivation and 12 h of sugar and chow access, coupled with delaying food access until 4 h into the dark cycle (Reviewed here Hoebel et al., 2009). Within several days of this diet, rats shift to consuming a large sugar meal within the 1st h of food presentation, i.e. a sugar binge, while water and chow intake remains unchanged (Rada et al., 2005; Avena et al., 2006b; Rorabaugh et al., 2014). The majority of sugar-bingeing papers has used a 10% sucrose solution, although 25% glucose and 8–12% fructose solutions also produce bingeing behavior (Colantuoni et al., 2001; Avena and Hoebel, 2003; Gosnell, 2005; Rada et al., 2005; Avena et al., 2006a; Wojnicki et al., 2007; Rorabaugh et al., 2014). However, the wide range of sugar concentrations with varying caloric densities used in the different bingeing studies confound any direct comparisons between these three sugars.

Previous studies have found sucrose bingeing enhances the locomotor responses to cocaine and amphetamine (Avena and Hoebel, 2003; Gosnell, 2005). This cross-sensitization is thought to reflect hypersensitivity in dopamine (DA) systems, also known as "priming" (Reviewed here Robinson and Berridge, 2008). Likewise, sucrose-bingeing rats show some of the neurochemical signs of DA hypersensitivity including elevated extracellular DA levels in response to sucrose intake, decreased DA D2 receptor (D2R) levels and increased DA transporter levels within the nucleus accumbens (NAc) (Bello et al., 2002, 2003; Rada et al., 2005; Avena et al., 2006b). Glucose-bingeing, but not fructose-bingeing, rats also display reduced D2R levels within the NAc (Colantuoni et al., 2001; Rorabaugh et al., 2014). A history of sucrose bingeing enhances locomotor responses to cocaine; however, whether bingeing on sucrose, or its components glucose and fructose, similarly alters the rewarding properties of cocaine has not been investigated. Here, we used the sugar-bingeing model to assess whether isocaloric 8% sucrose, glucose and fructose solutions result in similar or distinct bingeing profiles and whether previous sugar bingeing alters cocaine-induced locomotion and reward, as determined by the development of conditioned place preference (CPP).

EXPERIMENTAL PROCEDURES

Sugar-bingeing model

The University of Colorado Denver IACUC approved all animal procedures. This research program operates in accordance with the National Institutes of Health's and National Research Council's guidelines (Guide for Care and Use of Animals, 8th Edition, 2011). A total of 40, outbred male Sprague–Dawley rats (Charles Rivers Laboratories, Wilmington, MA, USA), weighing 200–220 g on arrival, were used. A 12-h light–dark cycle was used throughout testing (lights on 0300–1500). Rats were singly housed with food (Teklad 2020X chow: 3.1 kcal/g, 24% protein, 16% fat, 60% carbohydrate; Harlan Laboratories, Denver, CO, USA) and water available *ad libitum* for 5 days prior to commencing experiments. Rats were subsequently tested using the sugar-bingeing model, as previously described (Avena et al., 2006a; Rorabaugh et al., 2014). At the onset of the experiment, rats continued to have 24-h access to an *ad libitum* water bottle but were cycled between 12 h of food deprivation and 12 h of access to chow and a second intermittent bottle that contained water (control; $n = 10$), 8% sucrose, 8% glucose, or 8% fructose solution (0.29 kcal/mL; $n = 10$/group). Food access was shifted 4 h into the dark cycle (1900-0700). Sugar, chow and water intake was recorded daily following 1 and 12 h of food access for each rat. Rats were also weighed daily. The sugar-bingeing diet was maintained for 9 days; this diet length corresponds to the period during which we observed maximal 8% fructose bingeing in previous cohorts (three published, one unpublished) (Rorabaugh et al., 2014). An 8% sugar concentration was chosen because (1) it is in the range of sugar concentrations that produce fructose (8–12%) and sucrose (10%) bingeing, (2) it is the most preferred sucrose concentration in a 2-bottle choice test and (3) it is a similar concentration as in most sodas and fruit juices (Smith and Sclafani, 2002; Rada et al., 2005; Avena et al., 2006a; Rorabaugh et al., 2014). All sugars were purchased from Fisher Scientific (Waltham, MA, USA). Consistent with the model, all results are expressed in raw intake values (mL or kcal) (Colantuoni et al., 2001; Rada et al., 2005; Avena et al., 2006a; Rorabaugh et al., 2014).

Cocaine CPP paradigm

After 9 days of the intermittent sugar diet, rats were switched to an *ad libitum* chow diet without any sugar for the remainder of the study. Rats were given a day to adjust to *ad libitum* feeding prior to CPP conditioning/testing, which occurred during the animals' light cycle between 0700 and 1300. The CPP boxes (Med Associates Inc., St. Albans, VT, USA) were housed in sound-attenuating cabinets and had three distinct chambers equipped with photobeams: two larger conditioning chambers ($10.5'' \times 8'' \times 8''$) connected by a smaller neutral chamber ($4.5'' \times 8'' \times 8''$). The chambers were separated by doors and had distinct visual, tactile and bedding odor cues. On day 1 of the CPP procedure, rats were placed in the neutral chamber and allowed free access to all three chambers for 15 min to measure any preconditioning chamber preferences. Over the next 8 days, animals underwent a single, daily 30-min conditioning session in which rats were injected on alternate days with either saline (1 mL/kg; i.p.) or cocaine (15 mg/kg; i.p.) and then confined to the respective saline- or cocaine-paired chamber. If