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Research Report

Effect of dopamine D_1 and D_2 receptor antagonism in the lateral hypothalamus on the expression and acquisition of fructose-conditioned flavor preference in rats

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ABSTRACT

The attraction to sugar-rich foods is influenced by conditioned flavor preferences (CFP) produced by the sweet taste of sugar (flavor–flavor learning) and the sugar's post-oral actions (flavor–nutrient) learning. Brain dopamine (DA) circuits are involved in both types of flavor learning, but to different degrees. This study investigated the role of DA receptors in the lateral hypothalamus (LH) on the flavor–flavor learning produced the sweet taste of fructose. In an acquisition study, food-restricted rats received bilateral LH injections of a DA D_1 receptor antagonist (SCH23390), a D_2 antagonist (RAC, raclopride) or vehicle prior to 1-bottle training sessions with a flavored 8% fructose+0.2% saccharin solution (CS+/F) and a less-preferred flavored 0.2% saccharin solution (CS−). Drug-free 2-bottle tests were then conducted with the CS+ and CS− flavors presented in saccharin. The fructose-CFP did not differ among groups given vehicle (76%), 12 nmol SCH (78%), 24 nmol (82%) or 24 nmol RAC (90%) during training. In an expression study with rats trained drug-free, LH injections of 12 or 24 nmol SCH or 12–48 nmol RAC prior to 2-bottle tests did not alter CS+ preferences (77–90%) relative to vehicle injection (86%). Only a 48 nmol SCH dose suppressed the CS+ preference (61%). The minimal effect of LH DA receptor antagonism upon fructose flavor–flavor conditioning differs with the ability of LH SCH injections to block the acquisition of glucose flavor–nutrient learning.

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1. Introduction

Learning plays an important role in the development of food and fluid preferences. Preferences for novel flavors can be learned based on associations between that flavor and an already preferred flavor (e.g., sweet taste of sugar) and/or the post-oral reinforcing properties of a nutrient (e.g., glucose). These processes are respectively referred to as flavor–flavor and flavor–nutrient conditioning (Sclafani, 1995). We have studied flavor–flavor conditioning, the subject of the present study, by training food-restricted rats to drink a flavor (the CS+, e.g., grape) mixed into a preferred sugar solution and an alternative flavor (the CS−, e.g., cherry) mixed into a less preferred saccharin solution during daily one-bottle sessions, and then assessing preferences in two-bottle choice tests with the CS+ and CS− flavors presented in a saccharin solution. In initial studies, flavor–flavor conditioning was produced using sucrose in a sham-feeding procedure to minimize the post-oral nutrient reinforcement (Yu et al., 2000a, 2000b). Subsequent studies used fructose in a real-feeding procedure (Baker et al., 2003) based on the finding that fructose does not support post-oral flavor conditioning in rats with short training sessions (Sclafani and Ackroff, 1994; Sclafani et al., 1993, 1999). Parallel flavor–nutrient conditioning studies were conducted with a CS+ flavor paired with paired with an intragastric (IG) infusion of sucrose or glucose and a CS− flavor paired with an IG water infusion (see reviews: Sclafani et al., 2011; Touzani et al., 2010b).

Brain dopamine (DA) systems are differentially implicated in the acquisition and expression of flavor–flavor and flavor–nutrient preferences. In particular, systemic administration of DA D_1-like (SCH23390, SCH) or D_2-like (raclopride, RAC) receptor antagonists reduced the acquisition and expression of flavor–flavor conditioning by sucrose and fructose (Baker et al., 2003; Yu et al., 2000a, 2000b). In contrast, only systemic SCH blocked IG sucrose-conditioned flavor–nutrient preferences and SCH and RAC had minimal or no effects of the expression of the learned preferences (Azzara et al., 2001). Subsequent studies revealed selective effects on flavor–flavor and flavor nutrient conditioning of drug microinfusions into the nucleus accumbens (NAc), amygdala (AMY) and medial prefrontal cortex (mPFC) which receive DA projections from the ventral tegmental area (VTA) (e.g., Swanson, 1982). Whereas SCH or RAC administered into the NacS significantly reduced expression of fructose-CFP, NAcS administration of SCH or RAC during training failed to prevent initial acquisition of a fructose-CFP, but elicited more rapid extinction (Bernal et al., 2008; Malkusz et al., 2012). Correspondingly, AMY administration of SCH and RAC significantly reduced expression of fructose-CFP, whereas AMY administration of RAC, but not SCH blocked fructose-CFP acquisition (Bernal et al., 2009b; Malkusz et al., 2012). Administration of SCH or RAC into the mPFC blocked acquisition, but not expression of fructose-CFP (Malkusz et al., 2012). In flavor–nutrient conditioning, the acquisition of IG glucose-CFP was blocked by SCH (12 nmol) administration during training into the NacS (Touzani et al., 2008), AMY (Touzani et al., 2009a) and mPFC (Touzani et al., 2010a).

Whereas the NacS, AMY and mPFC receive DA projections from the ventral tegmental area (VTA) (e.g., Swanson, 1982), DA D_1 and D_2 receptors in the LH (e.g., Bubser et al., 2005; Mansour et al., 1990, 1992; Wamsley et al., 1989, 1992) receive DA innervation from the A13 DA-containing cells in the neighboring zona incerta (e.g., Eaton et al., 1994; Wagner et al., 1995). The LH plays a crucial role in the modulation of feeding and food-related learning and aversions (see reviews: Bures et al., 1998; Scalera, 2002). Classic studies demonstrated that LH neurons of monkeys trained to lick sweet solutions are activated by the sight of food (Rolls et al., 1976) that are modulated by learning (Mora et al., 1976) and hunger (Burton et al., 1976), and actually precede the animal's response to the sweet stimulus (Rolls et al., 1979). Specific roles for the LH itself and LH DA signaling have been demonstrated for flavor–nutrient CFP learning such that both LH lesions and DA D_1-like receptor antagonism within this area attenuated flavor preference learning induced by the post-oral reinforcing actions of nutrients (Touzani and Sclafani, 2001, 2002; Touzani et al., 2009b). These findings make the LH another important brain site to analyze in establishing the location at which DA receptor antagonists affect the expression and acquisition of fructose-CFP. To this end, SCH and RAC were administered into LH sites either during acquisition training or expression testing sessions.

2. Results

2.1. *Histological verification*

Fig. 1 is a schematic representation (Paxinos and Watson, 2009) of the bilateral cannula placements ($n=106$) of all 53 animals in the acquisition and expression studies. All cannulae were localized within the mid-caudal LH at the levels of the hypothalamic ventromedial and dorsomedial nuclei and the levels of the median eminence and arcuate nuclei. The distributions of cannulae of animals in the acquisition studies administered vehicle ($n=18$), SCH12 ($n=20$), SCH24 ($n=22$) or RAC24 ($n=22$) and in the expression studies administered SCH ($n=12$) or RAC ($n=12$) displayed considerable overlap with respect to one another within the mid-caudal LH. Moreover, these cannula placements displayed considerable overlap with those in the study (Touzani et al., 2009b) evaluating D_1 antagonist effects upon IG glucose flavor–nutrient CFP.

2.2. *LH D_1 and D_2 Antagonists and acquisition of fructose-CFP*

Training intakes were limited to 16 ml/session to minimize the difference between CS+/F and CS− intakes as described previously (see reviews: Sclafani et al., 2011; Touzani et al., 2010b). In the 1-bottle training sessions, overall, CS+/F intake (13.3 g/1 h) exceeded CS− intake (10.0 g/1 h, $F(1,10)=47.94$, $p<0.0001$). Significant differences in training intakes failed to be observed among groups ($F(3,30)=0.71$, ns) or for the interactions between groups and CS intakes ($F(3,30)=1.81$, ns). Small, but significant differences were observed for CS+/F intake over CS− intake in the Veh (12.4 (±0.6) vs. 9.8 (±0.9) g/1 h) and RAC24 (14.9 (±0.3) vs. 9.8 (±0.8) g/1 h) groups, but not in the SCH12 (13.0 (±1.2)