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Muscarinic and nicotinic cholinergic receptor antagonists differentially mediate acquisition of fructose-conditioned flavor preference and quinine-conditioned flavor avoidance in rats

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ABSTRACT

Rats display both conditioned flavor preference (CFP) for fructose, and conditioned flavor avoidance (CFA) following sweet adulteration with quinine. Previous pharmacological analyses revealed that fructose-CFP expression was significantly reduced by dopamine (DA) D1 or D2 antagonists, but not NMDA or opioid antagonists. Fructose-CFP acquisition was significantly reduced by DA D1, DA D2 or NMDA antagonists, but not opioid antagonists. Quinine-CFA acquisition was significantly enhanced and prolonged by DA D1, NMDA or opioid, but not DA D2 antagonists. Cholinergic interneurons and projections interact with DA systems in the nucleus accumbens and ventral tegmental area. Further, both muscarinic and nicotinic cholinergic receptor signaling have been implicated in sweet intake and development of food-related preferences. Therefore, the present study examined whether systemic administration of muscarinic (scopolamine: SCOP) or nicotinic (mecamylamine: MEC) cholinergic receptor antagonists mediated fructose-CFP expression, fructose-CFP acquisition and quinine-CFA acquisition. For fructose-CFP expression, rats were trained over 10 sessions with a CS+ flavor in 8% fructose and 0.2% saccharin and a CS− flavor in 0.2% saccharin. Two-bottle choice tests with CS+ and CS− flavors mixed in 0.2% saccharin occurred following vehicle, SCOP (0.1–10 mg/kg) and MEC (1–8 mg/kg). For fructose-CFP acquisition, six groups of rats received vehicle, SCOP (1 or 2.5 mg/kg), MEC (4 or 6 mg/kg) or a limited intake vehicle control 0.5 h prior to 10 CS+ and CS− training sessions followed by six 2-bottle CS+ and CS− choice tests in 0.2% saccharin. For quinine-CFA acquisition, five groups of rats received vehicle, SCOP (1 or 2.5 mg/kg) or MEC (4 or 6 mg/kg) 0.5 h prior to 8 one-bottle CS− (8% fructose + 0.2% saccharin: FS) and CS+ (fructose + saccharin + quinine (0.030%: FSQ) training sessions followed by six 2-bottle CS− and CS+ choice tests in fructose–saccharin solutions. Fructose-CFP expression was significantly reduced by SCOP (2.5–10 mg/kg: 65–68%) and MEC (4–8 mg/kg: 67–73%) relative to vehicle (89–90%), that occurred only when antagonist doses reduced total saccharin intake but in which CS+ intake was still significantly higher than CS− intake. Fructose-CFP acquisition was eliminated by SCOP at doses of 1 (40–54%) and 2.5 (45–58%) mg/kg, and was accompanied by a failure to observe CS+ and CS− intake differences during testing relative to vehicle (85–92%) and limited control (74–88%) conditions. In contrast, MEC failed to alter fructose-CFP acquisition. Quinine-CFA acquisition was significantly enhanced and prolonged by MEC at 4 (18–24%) and 6 (11–13%) mg/kg relative to vehicle (34–48%). In contrast, SCOP failed to alter quinine-CFA acquisition. These data implicate the cholinergic receptor system in mediating acquisition (learning) of sugar-induced preferences and quinine-induced aversions with muscarinic receptor signaling controlling the former and nicotinic receptor signaling controlling the latter.

1. Introduction

Rats use flavor cues (taste, odor, texture) to guide their selection of nutritious foods (Capaldi, 1996). Sugar-induced conditioned flavor preferences (CFP) occur when a novel flavor (CS+) is paired

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with a more-preferred sucrose (16%) or fructose (8%) + saccharin (0.2%) solution relative to a flavor (CS−) paired with a less-preferred saccharin (0.2%) solution. These sugar-CFPs are based on learned associations between food flavor elements (flavor–flavor conditioning) as well as between flavor and post-ingestive consequences (flavor–nutrient conditioning) (Sclafani, 1995). Flavor–flavor conditioning has been studied for sucrose in sham-feeding rats (Yu, Sclafani, Delamater, & Bodnar, 1999; Yu, Silva, Sclafani, Delamater, & Bodnar, 2000a, 2000b), and for fructose in real-feeding rats (Baker, Li, Lee, Sclafani, & Bodnar, 2004; Baker, Shah, Sclafani, & Bodnar, 2003), given the inability of fructose to condition preferences after intragastric (IG) administration (Sclafani & Ackroff, 1994; Sclafani, Cardieri, Tucker, Blusk, & Ackroff, 1993; Sclafani, Fanizza, & Azzara, 1999). In contrast, glucose is capable of producing CFP following oral and IG administration (Dela Cruz, Coke, Icaza-Cukali, Kalifa, & Bodnar, 2014; Sclafani & Ackroff, 1994; Sclafani et al., 1993, 1999). Previous pharmacological analyses have evaluated the neurochemical substrates of the acquisition (learning) and expression (maintenance) of the flavor–flavor component of sugar-CFP. Systemic administration of either dopamine (DA) D1 (SCH23390) or D2 (raclopride) receptor antagonists eliminated both acquisition and expression of fructose-CFP in real-feeding, food-restricted rats and sucrose-CFP in sham-feeding, food-restricted rats (Baker et al., 2003; Hsiao & Smith, 1995; Yu et al., 2000a, 2000b). Central DA receptor mediation of the acquisition and expression of fructose-CFP is differentially controlled by the nucleus accumbens (NAC), amygdala, medial prefrontal cortex, medial orbital frontal cortex, and lateral hypothalamus (Amador et al., 2014; Bernal et al., 2008, 2009; Malkusz et al., 2012, 2015). Systemic administration of NMDA receptor antagonists (MK-801) eliminated the acquisition, but not the expression of fructose-CFP (Golden & Houpt, 2007). Further, systemic administration of cannabinoid (CB1) receptor inverse agonists (AM251) reduced the expression, but not the acquisition of fructose-CFP (Miner et al., 2008). In contrast, systemic and NAC administration of naltrexone, a general opioid receptor antagonist, reduced sweet intake, but failed to alter flavor–flavor-mediated sugar-CFP (Baker et al., 2004; Bernal et al., 2010; Yu et al., 1999). Therefore, DA D1, DA D2, NMDA and CB1, but not opioid receptor signaling is required for the full learning (acquisition) and maintenance (expression) of fructose-CFP, apparently in limbic sites associated with reward.

Conditioned flavor avoidances (CFA) can be induced by either ingested toxins that induce gastrointestinal distress (flavor–toxin learning; see review: Freeman & Riley, 2009) or by an aversive taste (flavor–taste learning; e.g., Dwyer, 2011; Fanselow & Birk, 1982). Pharmacological analyses have examined DA D1, DA D2, NMDA and opioid antagonists in flavor–toxin CFA learning. DA D1, but not D2 antagonism disrupted the acquisition of a lithium-chloride (LiCl)-induced CFA following systemic administration, and following central administration into the lateral hypothalamus or NAC shell (Caulliez, Meile, & Nicolaidis, 1996; Fenu, Bassareo, & Di Chiara, 2001; Fenu, Rivas, & Di Chiara, 2005, 2009). Blockade of NMDA, AMPA and metabotropic glutamate receptors in the amygdala disrupted LiCl-induced CFA (Yasoshima, Morimoto, & Yamamoto, 2000). Naloxone enhanced taste aversions elicited by LiCl (Davis et al., 2009; Miceli, Marfaing-Jallat, & Le Magnen, 1979; Smurthwaite, Kautz, Geter, & Riley, 1992). Our laboratory (Rotella et al., 2014) previously examined the pharmacological substrates of flavor–taste CFA learning using a design to match that used in our flavor–flavor CFP studies. In this case, food-restricted rats were trained with two differently flavored fructose + saccharin (FS) solutions with one adulterated with quinine (0.03%: FSQ). In contrast to the greater persistence of fructose-CFP over a week or more of testing (Baker et al., 2003, 2004), quinine (0.03%)-CFA typically lasts for one pair of sessions. However, the persistence of quinine-CFA was significantly enhanced by systemic administration of DA D1, NMDA and opioid, but not DA D2 receptor antagonists administered during training (Rotella et al., 2014). Thus, whereas DA D1, DA D2 and NMDA, but not opioid receptor antagonism blocks the acquisition of sweet taste-based CFP, DA D1, NMDA and opioid, but not DA D2 receptor antagonism enhanced the duration of a bitter taste-based CFA.

Avena and Rada (2012) have implicated acetylcholine (Ach) in the mediation of food intake, particularly the "addictive" aspects of excessive sugar intake, by its interactions with brain DA systems. One Ach–DA neuroanatomical interaction presumably occurs through Ach inputs from the pedunculopontine and laterodorsal tegmental (PPT/LDT) nuclei to identified DA cells in the ventral tegmental area (VTA) (Holmstrand & Sesack, 2011; Maskos, 2008; Omelchenko & Sesack, 2005; Woolf, Harrison, & Buchwald, 1990). The second Ach–DA interaction presumably occurs through DA terminal innervation of Ach-containing interneurons in the NAC (de Rover, Lodder, Kits, Schoffelmeer, & Brussaard, 2002; Witten et al., 2010; Zhou, Wilson, & Dani, 2002), although cholinergic PPT/LDT innervation is localized there as well (Dautan et al., 2014). NAC cholinergic–DA interactions act through local DA D2 receptors (Alcantara, Chen, Herring, Mendenhall, & Berlanga, 2003), mediate accumbal DA release that also involves glutamate signaling (Cachope et al., 2012; Chuma, Mingote, Moore, & Rayport, 2014; Threlfell & Cragg, 2011), and provide feedback control of VTA DA release (Rahman & McBride, 2002). These interactions are integral in the formulation of central mechanisms involved in food reward (see reviews: Avena & Rada, 2012; Kelley, Baldo, & Pratt, 2005; Laurent, Bertran-Gonzalez, Chieng, & Balleine, 2014; Mark, Shabani, Dobbs, & Hansen, 2011; McFadden, Cornier, & Tregellas, 2014; Nunes, Randall, Podurgiel, Correa, & Salamone, 2013), and suggest that cholinergic receptor mechanisms may also play a role in acquisition and expression of fructose-CFP mediated by systemic (Baker et al., 2003; Yu et al., 2000a, 2000b) and accumbal (Bernal et al., 2008; Malkusz et al., 2012) DA. Further direct evidence includes the observation that NAC cholinergic interneurons play a role in regulation of body weight and metabolism (Hajnal, Szekely, Galosi, & Lenard, 2000). Food intake increases acetylcholine (Ach) release in the amygdala (Hajnal, Pothos, Lenard, & Hoebel, 1998) and NAC (Mark, Rada, Pothos, & Hoebel, 1992; Mark, Weinberg, Rada, & Hoebel, 1995). Sugar intake under bingeing conditions potently increases NAC Ach release that is mediated by deprivation, sham intake and weight of the animals (Avena, Rada, Moise, & Hoebel, 2006; Avena, Bocarsly, Rada, Kim, & Hoebel, 2008; Avena, Rada, & Hoebel, 2008a, 2008b). Further, VTA Ach and NAC DA are concomitantly released by the orexigenic peptide, ghrelin (Jerlhag, Janson, Waters, & Engel, 2012), and activity of dorsomedial hypothalamic cholinergic neurons increases following overnight food deprivation (Groessl, Jeong, Talmage, Role, & Jo, 2013). Although food intake was significantly reduced by chronic nicotine (Dandekar, Nakhate, Kokare, & Subhedar, 2011), the nicotinic cholinergic receptor antagonist, mecamylamine (MEC) suppressed ghrelin-induced food intake (Dickson et al., 2010), and chronic 18-methoxycoronaridine reduced long-term sucrose intake (Taraschenko, Maisonneuve, & Glick, 2011). Pilocarpine, a muscarinic cholinergic receptor agonist, administered into the NAC core increased chow intake (Nunes et al., 2013). Muscarinic receptor antagonism with scopolamine (SCOP) in the NAC reduced both deprivation-induced feeding (Pratt & Blackstone, 2009) and NAC DAMGO-induced feeding (Perry, Baldo, Andrzejewski, & Kelley, 2009), and NAC sites at which SCOP suppressed feeding and DAMGO induced feeding overlapped (Perry, Pratt, & Baldo, 2014). DAMGO-induced increases in high-fat feeding were blocked by naltrexone and SCOP, but not by antagonists of DA, glutamate or nicotinic receptors (Will, Pratt, & Kelley,