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Dopamine receptor signaling in the medial orbital frontal cortex and the acquisition and expression of fructose-conditioned flavor preferences in rats

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ABSTRACT

Systemic dopamine (DA) D1 (SCH23390: SCH) and D2 (raclopride: RAC) antagonists blocked fructose-conditioned flavor preference (CFP) acquisition and expression. Fructose-CFP acquisition was eliminated by medial prefrontal cortex (mPFC) SCH and mPFC or amygdala (AMY) RAC. Fructose-CFP expression was reduced following SCH or RAC in AMY or nucleus accumbens (NAc). The present study examined fructose-CFP acquisition and expression following SCH and RAC in the medial orbital frontal cortex (MOFC), another ventral tegmental area DA target. For fructose-CFP acquisition, five groups of rats received vehicle, SCH (24 or 48 nmol) or RAC (24 or 48 nmol) in the MOFC 0.5 h prior to 8 training sessions with one flavor (CS+/Fs) mixed in 8% fructose and 0.2% saccharin, and another flavor (CS−/s) mixed in 0.2% saccharin. In six 2-bottle choice tests in 0.2% saccharin, similar fructose-CFP preferences occurred in groups trained with vehicle (76–77%), SCH24 (69–78%), SCH48 (70–74%) and RAC48 (85–92%). RAC24-trained rats displayed significant CS+ preferences during the first (79%) and third (71%), but not second (58%) test pair. For fructose-CFP expression, rats similarly trained with CS+/Fs and CS− solutions received 2-bottle choice tests following MOFC injections of SCH or RAC (12–48 nmol). CS+ preference expression was significantly reduced by RAC (48 nmol: 58%), but not SCH relative to vehicle (78%). A control group receiving RAC in the dorsolateral prefrontal cortex displayed fructose-CFP expression similar to vehicle. These data demonstrate differential frontal cortical DA mediation of fructose-CFP with mPFC D1 and D2 signaling exclusively mediating acquisition, and MOFC D2 signaling primarily mediating expression.

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1. Introduction

Flavor cues (taste, odor, texture) are used by animals to guide their selection of nutritious foods and avoidance of toxic substances, and this selection is shaped by learning (Capaldi, 1996). Flavor preferences conditioned by sugars have been studied to examine its pharmacological substrates (Sclafani, 1995). Sugar-conditioned flavor preferences (CFP) can be separated into the study of orosensory (flavor–flavor conditioning) factors through the use of one-bottle intakes of novel flavors mixed in oral fructose (CS+, e.g., cherry) and saccharin (CS−, e.g., grape) solutions during training followed by two-bottle choice testing of both flavors mixed in saccharin (Baker et al., 2003). The study of post-ingestive factors (flavor-nutrient conditioning) occurs through the use of one-bottle intakes of novel flavors in saccharin solutions paired with intragastric (IG) infusions of sucrose or glucose (CS+, e.g., cherry) relative to water (CS−, e.g., grape) followed by two-bottle choice testing of both flavored mixed in saccharin without infusions (Azzara et al., 2001; Touzani et al., 2008). Fructose, relative to sucrose or glucose elicits minimal post-oral flavor conditioning effects in short-term tests (Sclafani and Ackroff, 1994; Sclafani et al., 1993, 1999).

Sweet taste activates mesolimbic and mesocortical dopamine (DA) circuits involved in the mediation of natural as well as drug rewards (e.g., Genn et al., 2004; Hajnal et al., 2003), and DA receptor antagonism suppresses the intake of sweet solutions in rats (Geary and Smith, 1985; Muscat and Willner, 1989; Xenakis and Sclafani, 1981). Systemic administration of the DA D2 receptor antagonist, RAC reduced the preference for a flavor mixed into a sucrose solution (Hsiao and Smith, 1995). Subsequent studies examining flavor-nutrient processes revealed that systemic treatment with a DA D1 (SCH), but not a D2 (RAC) receptor antagonist blocked the acquisition (learning), but not the expression (maintenance) of IG sucrose-CFP (Azzara et al., 2001). Moreover, evaluation of central sites of action revealed that acquisition, but not expression of IG glucose-CFP was eliminated by bilateral SCH microinjections into the NAcS (Touzani et al., 2008), AMY (Touzani et al., 2009), or mPFC (Touzani et al., 2010) projection zones of mesocorticolimbic DA from the ventral tegmental area (VTA) (e.g., Swanson, 1982). Subsequent studies examining flavor–flavor processes revealed that systemic treatment with DA D1 or D2 receptor antagonists blocked the acquisition and expression of sucrose-CFP in sham-fed rats (Yu et al., 2000a, 2000b) and fructose-CFP in real-fed rats (Baker et al., 2003). Analysis of central sites of action revealed that the acquisition of fructose-CFP was blocked by DA D1 antagonists in the mPFC and by DA D2 antagonists in the mPFC and AMY. In contrast, expression of fructose-CFP was reduced by DA D1 or D2 antagonists in the NAcS or AMY, but not the mPFC (Bernal et al., 2008, 2009; Malkusz et al., 2012), and by DA D1 antagonism in the lateral hypothalamus (Amador et al., 2014).

The mPFC area tested in the previous studies (Malkusz et al., 2012; Touzani et al., 2010) was defined as the prelimbic and infralimbic cortex, and was chosen because it is intimately and reciprocally connected with the NAcS and AMY (e.g., Berendse et al., 1992; Brog et al., 1993; McDonald, 1991; McGeorge and Faull, 1989; Sesack et al., 1989). A role for the mPFC in food-related learning includes impairments in food consumption in response to conditioned cues following lesions placed in the mPFC, but not the posterior or lateral orbitofrontal cortex (Holland and Petrovich, 2005; Petrovich et al., 2007). DA mPFC involvement was also confirmed by increased DA release observed in food-deprived rats presented with food stimuli (Feenstra and Botterblom, 1996) as well as following feeding and food-related cues in Pavlovian and instrumental learning tasks (Bassareo et al., 2002; D'Angio and Scatton, 1989; Hernandez and Hoebel, 1990; Izaki et al., 1999). Further, DA D1 antagonism in the mPFC impaired bar pressing for sucrose reward (Baldwin et al., 2002).

Like the mPFC, the medial orbital frontal cortex (MOFC) also receives mesocortical DA afferents from the VTA (e.g., Swanson, 1982), has intrinsic DA D1 and D2 receptors (Gaspar et al., 1995; Lidow et al., 1989, 1991), and also has direct connections with the AMY, NAC and mPFC (e.g., Brog et al., 1993; Hoover and Vertes, 2011; Ishikawa and Nakamura, 2003; McGeorge and Faull, 1989). Both the mPFC and MOFC mediate reward learning (Andrzejewski et al., 2004; Baldwin et al., 2002; Cardinal et al., 2002; Samson and Chappell, 2003), and NAcS DA release facilitates firing of neurons elicited by mPFC and MOFC glutamatergic inputs (Ishikawa et al., 2008; Nicola, 2007). Lesions placed in the MOFC, but not mPFC impaired behavioral inhibition (Kheramin et al., 2005; Winter et al., 2009), whereas destruction of the mPFC and MOFC differentially altered perseverative and premature responses to stimuli (Chudasama et al., 2003). DA and serotononergic innervation of the MOFC and mPFC produce site-specific double dissociations in behavioral flexibility to changing reward value during tests of impulsive choice (Winstanley et al., 2004, 2006). Therefore, the present study examined the effects of DA D1 and D2 receptor antagonists administered into the MOFC on the acquisition and expression of fructose-CFP to determine potential similarities or differences with effects previously observed in the mPFC (Malkusz et al., 2012). Both fructose-CFP acquisition and expression studies were performed with equimolar dose–response curves of both antagonists in the MOFC. Further, to determine the specificity of MOFC DA D2 antagonist effects upon fructose-CFP expression, an additional group of rats was tested with the same fructose-CFP expression paradigm following DA D2 antagonists administered into the adjacent dorsolateral prefrontal cortex.

2. Results

2.1. *Histological verification*

Fig. 1 displays schematic representations (Paxinos and Watson, 2009) of the bilateral MOFC placements (circles) of the 68 animals tested in the acquisition and expression experiments, and of the bilateral dorsolateral prefrontal placements (squares) of the five site-specificity control animals tested with RAC in the expression experiment. All of the MOFC placements were found within the ventro-orbital and medial-orbital frontal cortices, and there was considerable overlap among rats receiving VEH, SCH24, SCH48, RAC24 or RAC48 in the acquisition paradigm, and SCH or RAC in the expression paradigm. Moreover, the