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Neuro-anatomic mapping of dopamine D_1 receptor involvement in nicotine self-administration in rats

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ABSTRACT

Dopaminergic signaling has long been known to be a critical factor in nicotine addiction, as well as other drugs of abuse. Dopaminergic projections from the VTA to the nucleus accumbens and prefrontal cortex have been well established to be critical to the reinforcing effects of these drugs. However, other projections of dopamine neurons are likely to have significant roles in this process. Also, the relative contributions of D_1 and D_2 dopamine receptors in drug addiction and its treatment remain to be fully understood. In this study, we examined the effects of blocking D_1 and D_2 receptors in the nucleus accumbens shell (AcS), anterior cingulate cortex (ACC), and parietal association cortex (PtA) on nicotine self-administration in rats. Female Sprague–Dawley rats were fitted with jugular catheters and allowed to self-administer nicotine (0.03 mg/kg/infusion) on an FR1 schedule. Rats were fitted with bilateral infusion cannulae to allow infusion of D_1 or D_2 antagonists (SCH-23390 or haloperidol) into each targeted brain area. Acute local infusions of SCH-23390 (1–4 μg/side) into the AcS and PtA significantly reduced nicotine self-administration by up to 75%. SCH-23390 infusion into the ACC was less effective with only suggestive non-significant reductions of nicotine self-administration. Acute, local infusions of haloperidol (0.5–2 μg/side) in any of the brain regions targeted did not have significant effects on nicotine self-administration. These results demonstrate a more significant role for D_1 receptor mechanisms in the process of nicotine reinforcement and help provide a more detailed neuroanatomic map of nicotine dependence in the brain.

1. Introduction

Dopaminergic activity in the brain is inextricably linked to tobacco addiction. Indeed, nicotine from tobacco has been shown to promote dopamine release in the brain via activation of nicotinic acetylcholine receptors (nAChRs), and elevations in dopamine (DA) levels have been shown contribute to the reinforcing effects of nicotine (for review, see Di Chiara, 2000). Dopamine signaling in the nucleus accumbens is known to attribute incentive salience to factors in the environment that are associated with previous drug use (Day and Carelli, 2007; Day et al., 2007; Schultz, 1998; Schultz et al., 1992). Previous studies have demonstrated that systemic injections of dopaminergic antagonists reduce nicotine self-administration as well as nicotine-induced elevations in locomotor activity in rats (Corrigall and Coen, 1991; O'Neill et al., 1991). Lower DA receptor expression levels in striatal areas have been implicated in nicotine dependence and susceptibility to addiction to tobacco (Fehr et al., 2008). Furthermore, altered D_1 and D_2 DA receptor signaling is known to contribute to the negative effects of nicotine withdrawal (Grieder et al., 2010; Laviolette et al., 2008). The dopaminergic projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) and prefrontal cortex (PFc) have been well established as critical to the reinforcing effects of nicotine and other drugs of abuse. However, there are dopaminergic projections in other areas of the brain that likely contribute significantly to these processes as we have previously shown (Kutlu et al., 2013), and the specific roles of D_1 vs. D_2 DA receptors in the mesolimbic system in nicotine addiction remain to be fully understood.

The anterior cingulate cortex (ACC) is a transitory region between the cortical and limbic systems that is involved in error detection, attentional selectivity, cost/benefit analysis, discrimination learning, and several other executive functions (Dalley et al.,

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2004; Delatour and Gisquet-Verrier, 2001; Schweimer and Hauber, 2006; Walton et al., 2009; Williams et al., 2004). The region is especially important for the apportionment of behavioral effort when performing problem-solving tasks, particularly if the task is reward-related (Niki and Watanabe, 1979; Shima and Tanji, 1998). It has been speculated that the ACC is involved in the manifestation of impulsive behavior, although its exact role is not well understood (Cardinal et al., 2001; Muir et al., 1996). There is ample evidence that the ACC plays a role in the process of drug addiction. Human imaging studies have repeatedly implicated the ACC in the processing of visual stimuli associated with tobacco use; activity that has shown to positively correlate with cigarette cravings in smokers (Brody et al., 2004, 2002; Canterberry et al., 2013; McClernon et al., 2005; Zubieta et al., 2005). Pharmacological inactivation of the ACC has been shown to reduce cue-induced reinstatement to cocaine in rats (McLaughlin and See, 2003), and reduce contextual coding during extinction training (Torregrossa et al., 2013). When presented with cues associated with previous cocaine use, activity in the ACC has been shown to increase (Thomas et al., 2003). The ACC is heavily innervated with DA neurons, even in comparison to other cortical areas of the brain (Gaspar et al., 1989). Although it has been shown that D1 DA receptors in the ACC are involved in effort-based decision making (Schweimer and Hauber, 2006), the roles for D1 and D2 receptors in this region in the process of nicotine addiction are not as well characterized.

The posterior parietal cortex in humans (parietal association cortex in rats, or PtA) is a region that processes visuospatial attention and cognitive information (Torrealba and Valdes, 2008). The PtA receives projections from the hippocampus and has a role in memory formation and consolidation. There is also evidence that the PtA is involved in the process of nicotine addiction. The PtA has been shown to be involved in processing visual stimuli associated with previous nicotine use, implicating the region in the process of reward-related learning (Due et al., 2002; Smolka et al., 2006). Indeed, there appear to be neural circuits connecting regions of the PfC, the PtA, and the hippocampus that become active in response to drug-related cues, providing a neural link between memory and attentional processes and drug cravings (Daglish et al., 2003). The PtA receives DA input, albeit at much lower levels compared to PfC areas (Brown et al., 1979). All of this evidence makes the PtA a particularly relevant brain region for nicotine addiction studies. However, like the ACC, the contributions of DA receptors in the PtA to the onset and maintenance of nicotine addiction have not been sufficiently investigated, and the region is often overlooked in preclinical addiction studies.

The present studies were performed to determine the relative roles of D1 and D2 DA receptors in the ACC, PtA, and nucleus accumbens shell (AcS), in nicotine addiction using a rat model of nicotine self-administration. Utilizing the dopaminergic receptor-selective antagonists SCH-23390 (D1 receptors (Hyttel, 1983)) and haloperidol (D2 receptors (Seeman and Tallerico, 1998)), it was hypothesized that antagonizing D1 and D2 receptors in these brain regions would produce differential effects on nicotine self-administration. Specifically, drawing on conclusions from our previous work in the insular cortex (Kutlu et al., 2013), it was hypothesized that antagonism of D1 receptors would reduce nicotine self-administration and antagonism of D2 receptors would be without significant effect.

2. Materials and methods

2.1. Subjects

All testing procedures in this study were approved by the Duke University Animal Care and Use Committee and conducted according to AAALAC guidelines. Young adult female Sprague–Dawley rats (postnatal day 60 at the start of behavioral testing) were purchased from Taconic Laboratories (Germantown, NY, USA), and used in the local infusion experiments. Animals were individually housed in a temperature-controlled vivarium at Duke University adjacent to the testing room under standard laboratory conditions. Single housing the animals was necessary to prevent catheter damage from cagemates. All animals were kept on a 12:12 reverse light/dark cycle, and behavioral testing was performed during the animals' active phase of the cycle. All animals were allowed unrestricted access to water while in their home cages. Food was initially given ad libitum; once behavioral training commenced the rats were kept on a restricted diet of standard rat chow after completing each testing session. The animals' weights were maintained at approximately 85% of free-feeding levels, and throughout the study, all animals progressively gained weight.

2.2. Drugs

Nicotine hydrogen tartrate, haloperidol, and R-(±) SCH-23390 were purchased from Sigma–Aldrich (St. Louis, MO, USA). The nicotine and SCH-23390 for systemic administration was dissolved in 0.9% sterile saline (Hospira Inc, Lake Forest, IL, USA). Haloperidol and SCH-23390 for local infusion were dissolved in artificial cerebrospinal fluid (aCSF), which served as the vehicle for both compounds.

2.3. Catheterization surgery

A combination of ketamine (60 mg/kg i.p.) and dexmedetomidine (0.15 mg/kg i.p.) was used to anesthetize each animal. A sterile catheter (SAI Infusion Technologies, Libertyville, IL, USA) was surgically implanted into the jugular vein of each animal using aseptic technique. Once the animal was sufficiently anesthetized, an incision slightly lateral to the midline was made, and the jugular vein exposed via blunt dissection. The area of the jugular vein distal to the desired nick incision was tied off to prevent bleeding, and a small incision was made in the vein to allow the insertion of the catheter. The catheter was then inserted into the vein until the tip was just outside the heart. Once in place the catheter was then sutured to deep muscle, and the remaining portion was routed subcutaneously around the back of the animal to emerge between the scapulae. The catheter was then attached to an infusion harness (SAI Infusion Technologies, Libertyville, IL, USA) that was fitted around the animal. Each animal was given ketoprofen (5 mg/kg, s.c.) for post-operative pain; all surgical wounds were sutured using polypropylene and treated with the topical anesthetic bupivacaine. After surgery, and for the remainder of the studies, all animals' catheters were flushed daily with a solution containing sterile saline and heparin (0.25 ml/day). After each self-administration testing session, the nicotine solution contained in the animals' harness ports was removed and replaced with a sterile lock solution that contained heparinized saline and the antibiotic gentamicin (8 mg/ml, Butler Schein Animal Health, Dublin, OH, USA). Upon completion of self-administration sessions, animals were tested for jugular-catheter patency and sacrificed. Only those with verified patent catheters were included in the data analysis.

2.4. Cannulation surgery

Each rat tested in the local infusion studies underwent surgery for the implantation of a bilateral brain cannula. After the completion of five consecutive baseline nicotine self-administration sessions, each rat had a bilateral local infusion cannula implanted via stereotaxic surgery (David Kopf Instruments, Tujunga, CA, USA). There were three brain regions selected for local infusion of dopaminergic receptor antagonists: nucleus accumbens shell (AcS), anterior cingulate cortex (ACC) and parietal association cortex (PtA). Rats were anesthetized as described above, and placed on the stereotaxic instrument. The stereotaxic coordinates for each brain region, relative to bregma, were taken from Paxinos and Watson, 2007 (Paxinos et al., 2007). For the ACC, the coordinates used were anteroposterior +2.70 mm, lateral ±0.75 mm, dorsoventral −2.70 mm. For the AcS the coordinates were anteroposterior +2.70 mm, lateral ±1.20 mm, dorsoventral −5.80 mm. Finally, for the PAC, the coordinates were anteroposterior −4.16 mm, lateral ±2.50 mm, dorsoventral −1.50 mm. A screw and wire structure was used to secure the cannula, along with a mixture of carboxylate cement (Durelon™, 3 M, St. Paul, MN, USA) that covered the site. Animals that received brain cannulae were perfused and the brains were removed and placed in a formalin solution. Each brain was then sliced on a cryostat and examined for proper placement of the infusion cannula. Only those animals with patent jugular catheters and the correct histological localization of the bilateral cannulae for the respective targeted brain region were considered for statistical analysis (Fig. 1).

2.5. Nicotine self-administration

Each rat was trained to self-administer nicotine under an FR1 schedule of reinforcement via lever response. Rats were initially trained to respond on a lever for a 45 mg food pellet reward. Once acceptable training criteria was met (3 consecutive 30 min training sessions with ≥50 lever responses per session), rats underwent catheterization surgery (see above) and nicotine self-administration sessions were begun. The nicotine self-administration sessions were conducted in operant chambers (30.5 × 24.1 × 21.0 cm, Med Associates, St. Albans, VT, USA) containing a house light, tone generator, two response levers, and cue-lights placed above each lever. During all sessions, an illuminated cue-light indicated an active lever.

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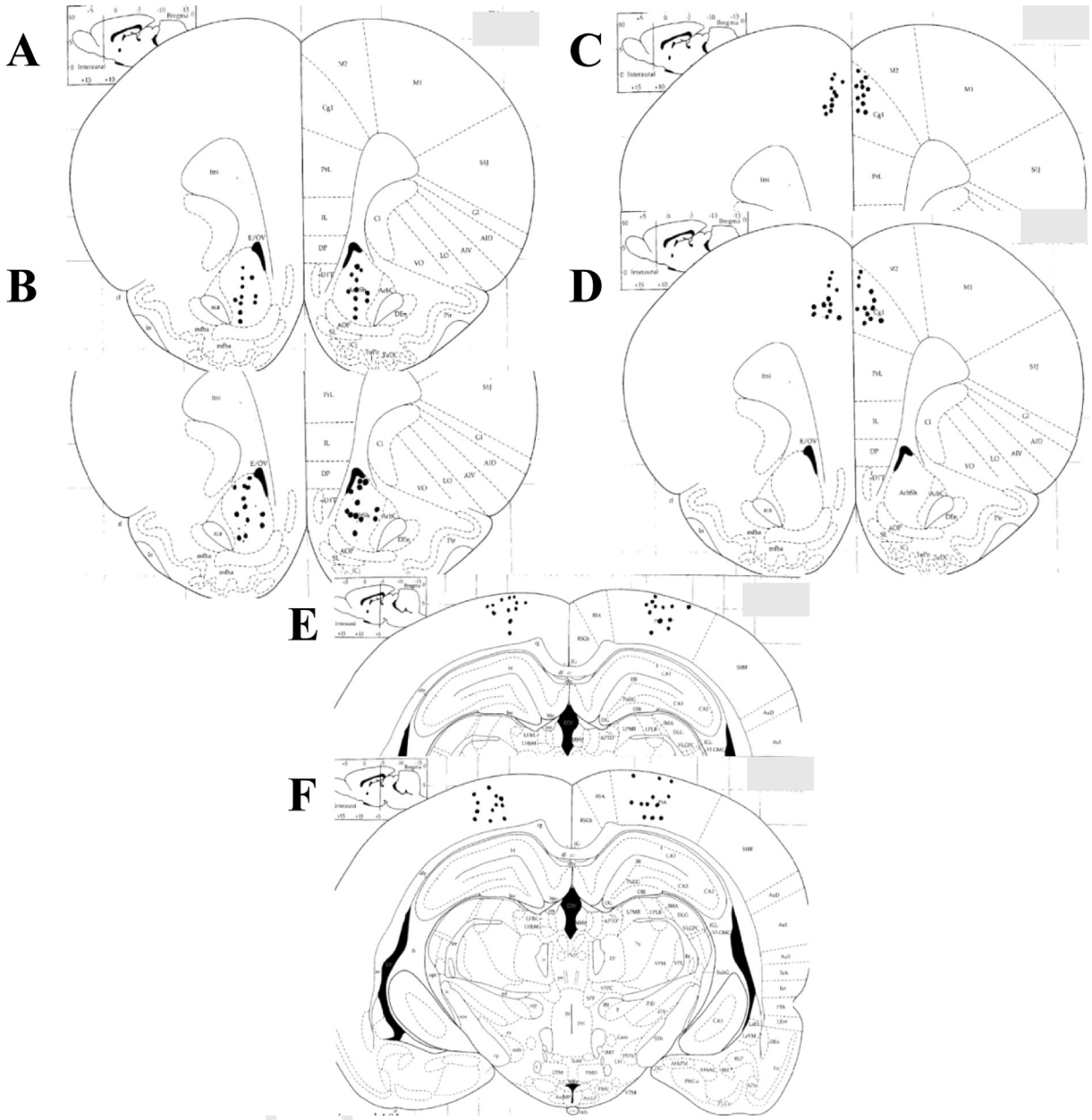

Fig. 1. Representative placements of the bilateral infusion cannulae for each group of animals tested in the study. A) Infusion of SCH-22390 into the AcS; B) Infusion of Haloperidol into the AcS; C) Infusion of SCH-22390 into the ACC; D) Infusion of Haloperidol into the ACC; E) Infusion of SCH-22390 into the PtA; F) Infusion of Haloperidol into the PtA. Q3

Responding on the active lever resulted in an infusion of 50 μL of nicotine (0.03 mg/kg) delivered over less than 1 s, and the activation of the tone generator for 0.5 s. Responding on the inactive lever carried no result. Each nicotine infusion was followed by a 1 min timeout period in which the cue-light was extinguished and lever responses were still recorded but no infusions were delivered. All self-administration sessions lasted 45 min. Rats underwent 5 baseline responding sessions before receiving test injections or infusions of SCH-23390 or haloperidol.

2.6. Acute systemic injections of SCH-23390

An initial cohort of animals was used to examine the effects of systemic injections of SCH-23390 on food-motivated lever responding and nicotine self-administration. To test for SCH-23390 effects on food-motivated lever responding, doses of SCH-23390 (0.02, 0.04, 0.08 and 0.016 mg/kg) and saline vehicle were given subcutaneously (s.c.) 20 min before sessions in a randomized order for each animal. Upon completion of all of these test sessions, each rat underwent catheterization surgery and after recovery began nicotine self-administration sessions. Each dose of SCH-23390 (0.02, 0.04 and 0.08 mg/kg) and the saline vehicle control was administered 20 min before nicotine self-administration sessions in a repeated-measures, counterbalanced design two times.

2.7. Local brain infusions of SCH-23390 and haloperidol

Separate cohorts of animals were used to determine the effects local infusions of either SCH-23390 or haloperidol into specific brain areas on nicotine self-administration. After 5 baseline nicotine self-administration sessions and 5 days recovery from brain cannulation surgery (see above), animals began nicotine self-administration sessions preceded by local infusions of drug (SCH-23390 or haloperidol) into the respective brain region targeted (AcS, ACC, or PtA). Infusions were performed via two plastic tubes connected to Hamilton microsyringes that were mounted on an infusion pump. The rate of infusion for SCH-23390 was 0.250 μg/min for 2 min, and 0.333 μg/min for 3 min for haloperidol. The doses and infusion rates chosen for each drug were based on previously published literature (Di Pietro et al., 2008; Kutlu et al., 2013) and were as follows: SCH-23390: 0, 1, 2, and 4 μg/side; haloperidol: 0, 0.5, 1, and 2 μg/side. After the infusion was complete, rats were placed in their home cages for a period of 5 min before test sessions to allow for diffusion of drug. Each dose was given in a randomized, repeated measures-counterbalanced

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design two times, for a total of 8 test sessions. There were six separate groups of animals in the infusion studies, i.e., each group only received infusions of one of the two test drugs into the respective targeted brain region.

2.8. Statistical analysis

Averaged data sets are presented as mean ± S.E.M. A repeated measures (RM) ANOVA was used to analyze the data from each experiment (Supernova/Statview software, SAS, Cary, NC, USA). An α level of $p < 0.05$ (two-tailed) was considered statistically significant for all data sets. Planned comparisons were made between each dose of SCH-23390 and haloperidol with saline or ACSF vehicle.

3. Results

3.1. Acute systemic injections of SCH-23390

Effects of acute systemic injections of SCH-23390 on food-motivated responding and nicotine self-administration were examined in an initial cohort of rats. The effects on food-motivated responding are presented in Fig. 2. There was a significant main effect of dose ($F4, 60 = 16.48$, $p < 0.0005$; $n = 16$) of SCH-23390 on food-motivated lever pressing. Planned comparisons revealed significant reductions in responding at the higher doses of 0.08 and 0.16 mg/kg ($p < 0.0005$) compared with vehicle injections, with more modest reductions at 0.04 mg/kg ($p < 0.05$). No effect was observed at the 0.02 mg/kg dose. Fig. 3 shows the results of acute systemic injections of SCH-23390 on nicotine self-administration. Analysis of variance revealed a significant main effect of dose of SCH-23390 ($F3, 39 = 21.57$, $p < 0.0005$, $n = 14$) on average nicotine infusions per session. Planned comparisons showed significant differences between each dose of SCH-23390 administered compared to vehicle control (0.04 and 0.08 mg/kg $p < 0.0005$; 0.02 mg/kg $p < 0.01$).

3.2. Local infusions of SCH-23390 and haloperidol into the nucleus accumbens shell

The results of acute, local infusions of the D1 antagonist SCH23390 into the AcS are presented in Fig. 4. Analysis of variance revealed a significant main effect of dose ($F3, 30 = 4.301$, $p < 0.05$; $n = 11$). At each dose tested in the study (1, 2 and 4 μg/side), infusions of SCH-23390 into the AcS resulted in significant reductions in nicotine self-administration compared to infusions of aCSF vehicle; the highest dose of 4 μg/side produced a nearly 75% reduction in average nicotine infusions per session compared to control. Fig. 5 shows the results of local infusions of haloperidol into the AcS. There was no significant difference observed on nicotine self-administration after infusions of haloperidol compared to aCSF control ($n = 12$).

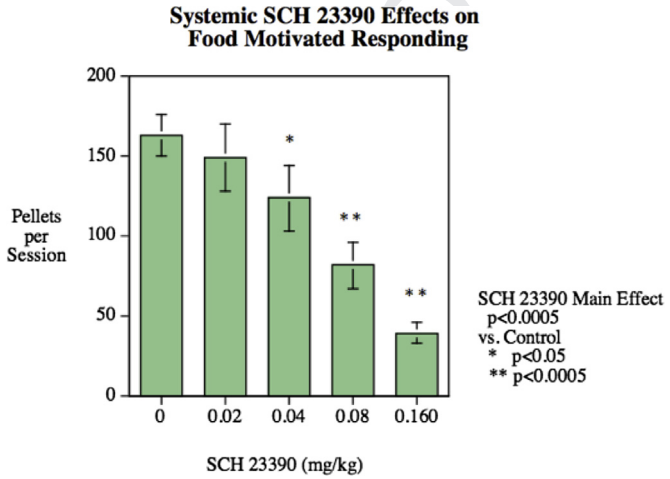

Fig. 2. Systemic SCH-23390 injection effects on food self-administration (mean ± sem). Planned comparisons revealed significant differences in the average number pellets obtained per session compared to vehicle as a result of pretreatment with SCH-23390 ($n = 16$).

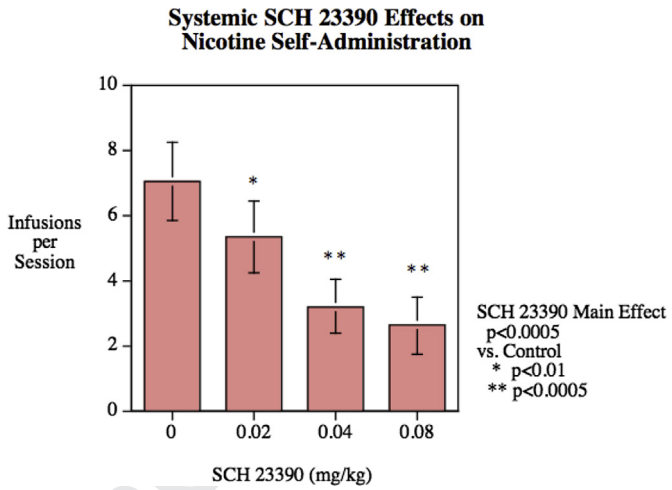

Fig. 3. Systemic SCH-23390 injection effects on nicotine self-administration (mean ± sem). RM ANOVA revealed significant effects of dose of SCH-23390 on nicotine infusions per session ($n = 14$).

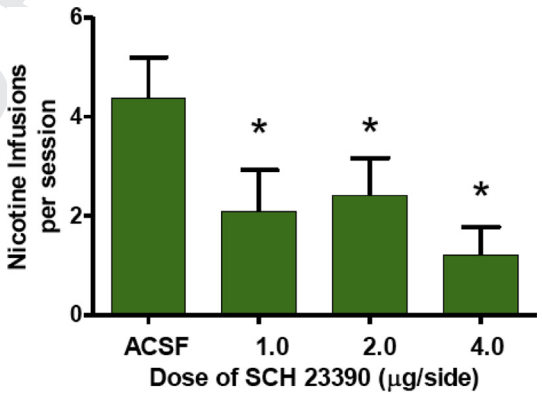

Fig. 4. Local infusion of SCH-23390 into the nucleus accumbens shell: Effects on nicotine self-administration (mean ± sem). Planned comparisons revealed significant differences in average nicotine infusions per session compared to aCSF vehicle as a result of the dose of SCH-23390 infused into the AcS (*$p < 0.05$, $n = 11$).

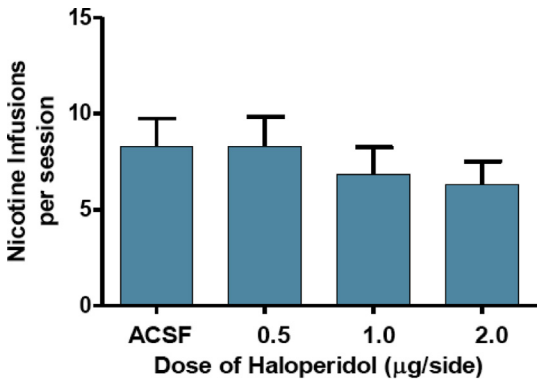

Fig. 5. Local infusion of haloperidol into the nucleus accumbens shell: Effects on nicotine self-administration (mean ± sem). No significant differences were observed in average nicotine infusions per session as a result of haloperidol infusions into the AcS ($n = 12$).

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3.3. Local infusions of SCH-23390 and haloperidol into the anterior cingulate cortex

Fig. 6 shows the results of infusions of SCH-23390 into the ACC. There was no main effect of dose of SCH23390 on nicotine infusions per session, although infusions of the highest dose of 4 μg/side resulted in a slight reduction compared to infusions of aCSF vehicle that did not quite reach the level of significance (n = 11). Acute, local infusions of haloperidol into the ACC did not significantly affect nicotine self-administration (Fig. 7, n = 12).

3.4. Local infusions of SCH-23390 and haloperidol into the parietal association cortex

Significant effects on nicotine self-administration were observed as a result of local infusions of SCH-23390 into the PtA (Fig. 8). Analysis of variance revealed a significant main effect of dose of SCH-23390 on nicotine infusions per session ($F_{3, 33} = 4.437$, $p < 0.05$, n = 12). Acute, bilateral infusions of SCH-23390 into the PtA produced a dose-dependent reduction of nicotine self-administration, with reductions of 38% with infusions of 2.0 μg/side and 45% with infusions of 4.0 μg/side compared to aCSF vehicle. Infusions of haloperidol into the PtA had no significant effect on nicotine self-administration (Fig. 9, n = 12).

4. Discussion

The link between dopamine and drug reinforcement has been well documented in humans and in animal models. This is particularly true with regard to nicotine and tobacco addiction. However, a complete understanding of the interactions between DA receptor subtypes, DA activity, and striato-cortical neurocircuitry has remained elusive. Although it has been known for quite some time that systemic administration of DA receptor antagonists can reduce nicotine self-administration in the rat model (Corrigall and Coen, 1991), the question of what effects these receptors have in specific brain regions has remained largely unanswered. The current studies were designed to shed light on the relative roles of D1 and D2 DA receptors on nicotine self-administration in areas of the brain that have been previously shown to be relevant to the process of tobacco addiction. Our results from this study would indicate that in each brain region that was targeted, D1 receptors had a more significant role in nicotine self-administration and reinforcement (Figs. 4, 6 and 8) than D2 receptors (Figs. 5, 7 and 9). Combined with our previous work examining these receptors in the insular cortex (Kutlu et al., 2013), these results would indicate a greater overall role for D1 receptors in nicotine reinforcement.

Our previous work indicated that the threshold for significant effects of infusions of SCH-23390 into the insular cortex on nicotine self-administration was between 1 and 2 μg/side. The results from the current study obtained in the AcS and PtA are consistent with these findings. Our highest dose of 4 μg/side SCH-23390 also

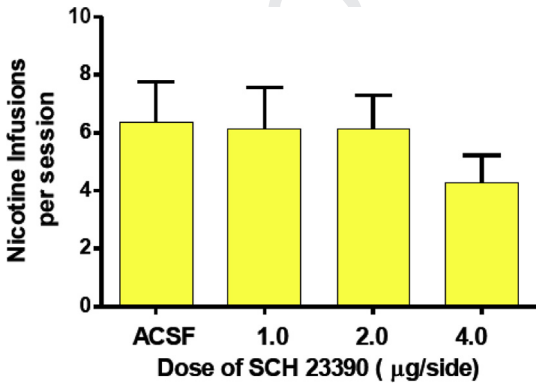

Fig. 6. Local infusion of SCH-23390 into the anterior cingulate cortex: Effects on nicotine self-administration (mean ± sem). Significant differences were observed in average nicotine infusions per session compared to aCSF vehicle as a result of the dose of SCH-23390 infused into the ACC (*p < 0.05, n = 11).

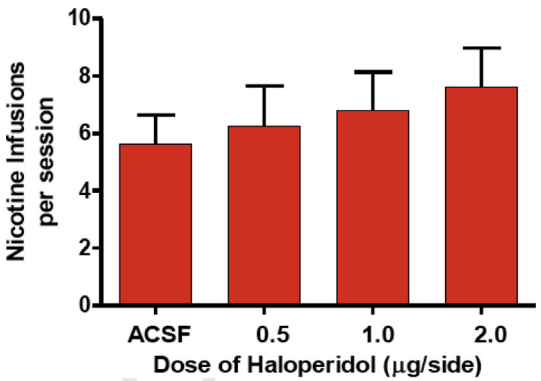

Fig. 7. Local infusion of haloperidol into the anterior cingulate cortex: Effects on nicotine self-administration (mean ± sem). No significant differences were observed in average nicotine infusions per session as a result of haloperidol infusions into the ACC (n = 12).

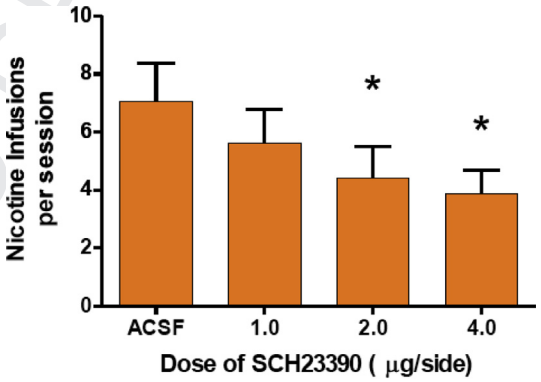

Fig. 8. Local infusion of SCH-23390 into the parietal association cortex: Effects on nicotine self-administration (mean ± sem). Significant differences were observed in average nicotine infusions per session compared to aCSF vehicle as a result of the dose of SCH-23390 infused into the PtA (*p < 0.05, n = 12).

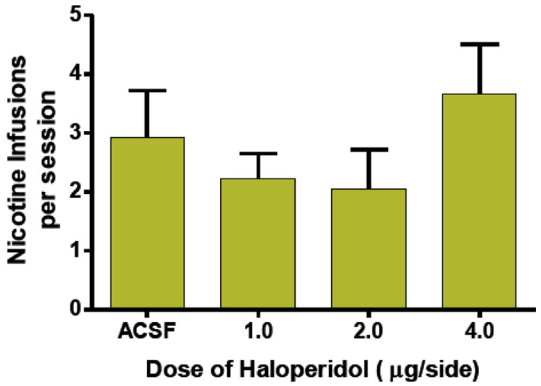

Fig. 9. Local infusion of haloperidol into the parietal association cortex: Effects on nicotine self-administration (mean ± sem). There were no significant differences observed in average nicotine infusions per session as a result of haloperidol infusions into the PtA (n = 12).

resulted in significant reductions in nicotine self-administration when infused in these areas (Figs. 4 and 8). However, it should be noted that this dose has been previously shown to attenuate food-motivated responding when infused into the agranular insular cortex, indicating possible non-specific effects on motivational behavior (Di Pietro et al., 2008). Indeed, the threshold for non-specific effects on behavior for SCH-23390 appears to be from 3 to 4 μg/side, as previous work from Bachtell et al. found that a dose of 3 μg/side infused into the nucleus accumbens did not alter responding for 50 mg sucrose pellets (Bachtell et al., 2005). This was also reflected in our results obtained after infusions of SCH-23390 into the ACC. Doses of 1 and 2 μg/side had no significant effect on nicotine self-administration when infused into the ACC in our study (Fig. 6). However, there was a slight reduction of nicotine infusions per session at the dose of 4 μg/side that did not reach the level of statistical significance. This would further suggest non-specific effects of SCH-23390 at our highest dose. It is known that at higher doses SCH-23390 can have off-target actions at 5HT receptors. Specifically, it is known that the compound can act as an agonist at 5HT2c receptors at higher doses. We have previously shown that the 5HT2c agonist loraserin can significantly decrease nicotine self-administration in the rat model (Levin et al., 2011).

The reductions in nicotine self-administration observed after local infusions of SCH-23390 in our study are in line with previous work demonstrating an important role for D1 receptors in the manifestation of risky, or risk-taking, behaviors, a category to which drug abuse certainly belongs. Adolescents are known to engage in heightened risk-taking behavior, and there is evidence that adolescents have elevated D1 receptor levels on projections from the prefrontal cortex to the NAc compared with adults (Brenhouse et al., 2008). These projections are thought to be critical to the processing of environmental cues that predict drug availability. Indeed, elevated D1 receptor activity in cortical areas appears to enhance risky behaviors. Lentiviral-mediated overexpression of D1 receptors in the PFc has been shown to increase high-risk behaviors in male adult rats, including increases in impulsive behavior, novelty seeking, elevated plus−maze activity, and reactivity to drug related cues, including nicotine (Sonntag et al., 2014). In light of this evidence, when combined with the results of our current study, a convincing case could be made that reduced D1 receptor activity in the brain confers a lower risk for drug-taking and drug-seeking behavior, and that D1 receptor mechanisms offer an intriguing target for further research and development of therapeutics.

Local regional blockade of D2 DA receptors with haloperidol did not result in any statistically significant effects on nicotine self-administration in our study, regardless of brain the region targeted (Figs. 5, 7 and 9). It is interesting to note the discrepancy between this finding and the results of previous work that showing that D2 antagonists reduce nicotine self-administration when administered systemically (Corrigall and Coen, 1991). There has also been work showing that systemic injections of haloperidol block nicotine's effects on brain stimulation reward thresholds (Ivanova and Greenshaw, 1997), although similar studies using different D2 antagonists have reported negative results (Harrison et al., 2002). The initial conclusion would be that the contributions of D2 receptors to nicotine's effects lie outside of the specific brain regions targeting in this study. One intriguing brain region for further study of D2 effects on nicotine reinforcement would be the ventral tegmental area (VTA). The VTA has long been thought of as a having one of the most significant roles in the reinforcing properties of drugs of abuse, including nicotine. However, even in the VTA, previous work investigating D2 receptor effects on nicotine reinforcement have been difficult to adequately quantify. Administration of the D2 antagonist quinpirole into the posterior VTA has been demonstrated to decrease nicotine self-administration (Ikemoto et al., 2006), although there is also evidence that D2 receptor activity in the anterior VTA is unaltered by chronic administration of nicotine (Bruijnzeel and Markou, 2005). It is clear that more work is needed to clarify what specific role D2 DA receptors have in nicotine reinforcement and addiction to tobacco.

In summary, the results from this study suggest that D1 dopamine receptors have a larger role in nicotine reinforcement than D2 receptors in the AcS and PtA. Our results provide further evidence that decreased D1 receptor mechanisms in the brain are a key factor in reducing drug-taking and drug-seeking activity as well as other forms of risk-taking behaviors. Although our results showed no involvement of D2 receptors in nicotine reinforcement in the brain regions targeted, there is clearly a role for these receptors in drug addiction and more work examining these receptors is needed. Future studies using agonists at dopamine receptors may possibly reveal contributions of D2 receptors to this process.

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References

Bachtell, R.K., Whisler, K., Karanian, D., Self, D.W., 2005. Effects of intra-nucleus accumbens shell administration of dopamine agonists and antagonists on cocaine-taking and cocaine-seeking behaviors in the rat. Psychopharmacology (Berl) 183, 41–53.

Brenhouse, H.C., Sonntag, K.C., Andersen, S.L., 2008. Transient D1 dopamine receptor expression on prefrontal cortex projection neurons: relationship to enhanced motivational salience of drug cues in adolescence. J. Neurosci. 28, 2375–2382.

Brody, A.L., Mandelkern, M.A., Lee, G., Smith, E., Sadeghi, M., Saxena, S., Jarvik, M.E., London, E.D., 2004. Attenuation of cue-induced cigarette craving and anterior cingulate cortex activation in bupropion-treated smokers: a preliminary study. Psychiatry Res. 130, 269–281.

Brody, A.L., Mandelkern, M.A., London, E.D., Childress, A.R., Lee, G.S., Bota, R.G., Ho, M.L., Saxena, S., Baxter Jr., L.R., Madsen, D., Jarvik, M.E., 2002. Brain metabolic changes during cigarette craving. Arch. Gen. Psychiatry 59, 1162–1172.

Brown, R.M., Crane, A.M., Goldman, P.S., 1979. Regional distribution of monoamines in the cerebral cortex and subcortical structures of the rhesus monkey: concentrations and in vivo synthesis rates. Brain Res. 168, 133–150.

Bruijnzeel, A.W., Markou, A., 2005. Decreased sensitivity to the effects of dopamine D1-like, but not D2-like, receptor antagonism in the posterior hypothalamic region/anterior ventral tegmental area on brain reward function during chronic exposure to nicotine in rats. Brain Res. 1058, 91–100.

Canterberry, M., Hanlon, C.A., Hartwell, K.J., Li, X., Owens, M., LeMatty, T., Prisciandaro, J.J., Borckardt, J., Saladin, M.E., Brady, K.T., George, M.S., 2013. Sustained reduction of nicotine craving with real-time neurofeedback: exploring the role of severity of dependence. Nicotine Tob. Res. 15, 2120–2124.

Cardinal, R.N., Pennicott, D.R., Sugathapala, C.L., Robbins, T.W., Everitt, B.J., 2001. Impulsive choice induced in rats by lesions of the nucleus accumbens core. Science 292, 2499–2501.

Corrigall, W.A., Coen, K.M., 1991. Selective dopamine antagonists reduce nicotine self-administration. Psychopharmacology (Berl) 104, 171–176.

Daglish, M.R., Weinstein, A., Malizia, A.L., Wilson, S., Melichar, J.K., Lingford-Hughes, A., Myles, J.S., Grasby, P., Nutt, D.J., 2003. Functional connectivity analysis of the neural circuits of opiate craving: “more” rather than “different”? Neuroimage 20, 1964–1970.

Dalley, J.W., Cardinal, R.N., Robbins, T.W., 2004. Prefrontal executive and cognitive functions in rodents: neural and neurochemical substrates. Neurosci. Biobehav. Rev. 28, 771–784.

Day, J.J., Carelli, R.M., 2007. The nucleus accumbens and Pavlovian reward learning. Neuroscientist 13, 148–159.

Day, J.J., Roitman, M.F., Wightman, R.M., Carelli, R.M., 2007. Associative learning mediates dynamic shifts in dopamine signaling in the nucleus accumbens. Nat. Neurosci. 10, 1020–1028.

Delatour, B., Gisquet-Verrier, P., 2001. Involvement of the dorsal anterior cingulate cortex in temporal behavioral sequencing: subregional analysis of the medial prefrontal cortex in rat. Behav. Brain Res. 126, 105–114.

Di Chiara, G., 2000. Role of dopamine in the behavioural actions of nicotine related to addiction. Eur. J. Pharmacol. 393, 295–314.

Di Pietro, N.C., Mashhoon, Y., Heaney, C., Yager, L.M., Kantak, K.M., 2008. Role of dopamine D1 receptors in the prefrontal dorsal agranular insular cortex in mediating cocaine self-administration in rats. Psychopharmacology (Berl) 200, 81–91.

Due, D.L., Huettel, S.A., Hall, W.G., Rubin, D.C., 2002. Activation in mesolimbic and visuospatial neural circuits elicited by smoking cues: evidence from functional magnetic resonance imaging. Am. J. Psychiatry 159, 954–960.

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Fehr, C., Yakushev, I., Hohmann, N., Buchholz, H.G., Landvogt, C., Deckers, H., Eberhardt, A., Klager, M., Smolka, M.N., Scheurich, A., Dielentheis, T., Schmidt, L.G., Rosch, F., Bartenstein, P., Grunder, G., Schreckenberger, M., 2008. Association of low striatal dopamine d2 receptor availability with nicotine dependence similar to that seen with other drugs of abuse. Am. J. Psychiatry 165, 507–514.

Gaspar, P., Berger, B., Febvret, A., Vigny, A., Henry, J.P., 1989. Catecholamine innervation of the human cerebral cortex as revealed by comparative immunohistochemistry of tyrosine hydroxylase and dopamine-beta-hydroxylase. J. Comp. Neurol. 279, 249–271.

Grieder, T.E., Sellings, L.H., Vargas-Perez, H., Ting, A.K.R., Siu, E.C., Tyndale, R.F., van der Kooy, D., 2010. Dopaminergic signaling mediates the motivational response underlying the opponent process to chronic but not acute nicotine. Neuropsychopharmacology 35, 943–954.

Harrison, A.A., Gasparini, F., Markou, A., 2002. Nicotine potentiation of brain stimulation reward reversed by DH beta E and SCH 23390, but not by eticlopride, LY 314582 or MPEP in rats. Psychopharmacology (Berl) 160, 56–66.

Hyttel, J., 1983. SCH 23390-the first selective dopamine D-1 antagonist. Eur. J. Pharmacol. 91, 153–154.

Ikemoto, S., Qin, M., Liu, Z.H., 2006. Primary reinforcing effects of nicotine are triggered from multiple regions both inside and outside the ventral tegmental area. J. Neurosci. 26, 723–730.

Ivanova, S., Greenshaw, A.J., 1997. Nicotine-induced decreases in VTA electrical self-stimulation thresholds: blockade by haloperidol and mecamylamine but not scopolamine or ondansetron. Psychopharmacology (Berl) 134, 187–192.

Kutlu, M.G., Burke, D., Slade, S., Hall, B.J., Rose, J.E., Levin, E.D., 2013. Role of insular cortex D and D dopamine receptors in nicotine self-administration in rats. Behav. Brain Res. 256C, 273–278.

Laviolette, S.R., Lauzon, N.M., Bishop, S.F., Sun, N., Tan, H., 2008. Dopamine signaling through D1-like versus D2-like receptors in the nucleus accumbens core versus shell differentially modulates nicotine reward sensitivity. J. Neurosci. 28, 8025–8033.

Levin, E.D., Johnson, J.E., Slade, S., Wells, C., Cauley, M., Petro, A., Rose, J.E., 2011. Lorcaserin, a 5-HT2C agonist, decreases nicotine self-administration in female rats. J. Pharmacol. Exp. Ther. 338, 890–896.

McClernon, F.J., Hiott, F.B., Huettel, S.A., Rose, J.E., 2005. Abstinence-induced changes in self-report craving correlate with event-related FMRI responses to smoking cues. Neuropsychopharmacology 30, 1940–1947.

McLaughlin, J., See, R.E., 2003. Selective inactivation of the dorsomedial prefrontal cortex and the basolateral amygdala attenuates conditioned-cued reinstatement of extinguished cocaine-seeking behavior in rats. Psychopharmacology (Berl) 168, 57–65.

Muir, J.L., Everitt, B.J., Robbins, T.W., 1996. The cerebral cortex of the rat and visual attentional function: dissociable effects of mediofrontal, cingulate, anterior dorsolateral, and parietal cortex lesions on a five-choice serial reaction time task. Cereb. Cortex 6, 470–481.

Niki, H., Watanabe, M., 1979. Prefrontal and cingulate unit activity during timing behavior in the monkey. Brain Res. 171, 213–224.

O'Neill, M.F., Dourish, C.T., Iversen, S.D., 1991. Evidence for an involvement of D1 and D2 dopamine receptors in mediating nicotine-induced hyperactivity in rats. Psychopharmacology (Berl) 104, 343–350.

Paxinos, G., Watson, C., ebrary Inc, 2007. The Rat Brain in Stereotaxic Coordinates. Elsevier, Amsterdam, Boston, p. 1 v.

Schultz, W., 1998. Predictive reward signal of dopamine neurons. J. Neurophysiol. 80, 1–27.

Schultz, W., Apicella, P., Scarnati, E., Ljungberg, T., 1992. Neuronal activity in monkey ventral striatum related to the expectation of reward. J. Neurosci. 12, 4595–4610.

Schweimer, J., Hauber, W., 2006. Dopamine D1 receptors in the anterior cingulate cortex regulate effort-based decision making. Learn. Mem. 13, 777–782.

Seeman, P., Tallerico, T., 1998. Antipsychotic drugs which elicit little or no parkinsonism bind more loosely than dopamine to brain D2 receptors, yet occupy high levels of these receptors. Mol. Psychiatry 3, 123–134.

Shima, K., Tanji, J., 1998. Role for cingulate motor area cells in voluntary movement selection based on reward. Science 282, 1335–1338.

Smolka, M.N., Buhler, M., Klein, S., Zimmermann, U., Mann, K., Heinz, A., Braus, D.F., 2006. Severity of nicotine dependence modulates cue-induced brain activity in regions involved in motor preparation and imagery. Psychopharmacology (Berl) 184, 577–588.

Sonntag, K.C., Brenhouse, H.C., Freund, N., Thompson, B.S., Puhl, M., Andersen, S.L., 2014. Viral over-expression of D1 dopamine receptors in the prefrontal cortex increase high-risk behaviors in adults: comparison with adolescents. Psychopharmacology (Berl) 231, 1615–1626.

Thomas, K.L., Arroyo, M., Everitt, B.J., 2003. Induction of the learning and plasticity-associated gene Zif268 following exposure to a discrete cocaine-associated stimulus. Eur. J. Neurosci. 17, 1964–1972.

Torrealba, F., Valdes, J.L., 2008. The parietal association cortex of the rat. Biol. Res. 41, 369–377.

Torregrossa, M.M., Gordon, J., Taylor, J.R., 2013. Double dissociation between the anterior cingulate cortex and nucleus accumbens core in encoding the context versus the content of pavlovian cocaine cue extinction. J. Neurosci. 33, 8370–8377.

Walton, M.E., Groves, J., Jennings, K.A., Croxson, P.L., Sharp, T., Rushworth, M.F., Bannerman, D.M., 2009. Comparing the role of the anterior cingulate cortex and 6-hydroxydopamine nucleus accumbens lesions on operant effort-based decision making. Eur. J. Neurosci. 29, 1678–1691.

Williams, Z.M., Bush, G., Rauch, S.L., Cosgrove, G.R., Eskandar, E.N., 2004. Human anterior cingulate neurons and the integration of monetary reward with motor responses. Nat. Neurosci. 7, 1370–1375.

Zubieta, J.K., Heitzeg, M.M., Xu, Y., Koeppe, R.A., Ni, L., Guthrie, S., Domino, E.F., 2005. Regional cerebral blood flow responses to smoking in tobacco smokers after overnight abstinence. Am. J. Psychiatry 162, 567–577.

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