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Dopaminergic involvement in effort-based but not impulsive reward processing in smokers

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ABSTRACT

Background: A reduction in reward responsivity and an increase in temporal discounting of rewards are both evident in smokers during acute abstinence compared to satiation. However, it is not yet known whether these processes can be modulated pharmacologically in smokers, other than with nicotine or tobacco.
Methods: A double-blind placebo controlled crossover design assessed the effects of 0.5 mg pramipexole, a dopamine D_2/D_3 agonist, in smokers following 2 h of abstinence. Reward responsivity was measured using an effort-based card sorting task. Temporal discounting of monetary reward was assessed using Area Under the Curve (AUC) analysis, and affective and subjective effects were indexed.
Results: On placebo, smokers showed an equivalent speed of card sorting when a financial incentive was provided compared to when it was not. Conversely, more cards were sorted under rewarded compared to non-rewarded trials after pramipexole, indicating an improvement in reward responsivity. Temporal discounting of monetary reward was not affected by pramipexole. Drug treatment also decreased positive affect and increased drowsiness.
Conclusions: A single dose of pramipexole can enhance effort-based reward responsivity, but does not alter temporal discounting in smokers. These findings highlight pharmacological correlates of reward processing deficits in nicotine dependence and offer potential targets for their treatment.

1. Introduction

Accumulating evidence suggests that tobacco smokers show abnormal processing of non-drug rewards, such as money (Chiu et al., 2008; Martin-Sölch et al., 2001; Luo et al., 2011). Although addiction research often focuses on the rewarding aspects of the drug, 'alternative' reward processing may also have important consequences for drug dependent individuals. For example, smokers with elevated anhedonia, experiencing little pleasure from everyday activities, show a faster latency to relapse (Cook et al., 2010) and experience stronger appetitive urges for cigarettes during smoking abstinence (Leventhal et al., 2009). Moreover, the extent to which smokers discount rewards which are temporally delayed can predict their likelihood of smoking during a cessation attempt (Krishnan-Sarin et al., 2007) and when abstinence is financially rewarded in a laboratory setting (Dallery and Raiff, 2007).

Dysregulation of brain reward processes are thought to play a central role in the development and maintenance of drug addiction (Koob and Le Moal, 2001) and targeting non-drug reward processes is an important treatment strategy (Volkow et al., 2004). Varenicline and bupropion are effective smoking cessation pharmacotherapies (Gonzales et al., 2006; Jorenby et al., 2006) and, in addition to their interactive effects with nicotine, they also act independently on non-drug reward (Cryan et al., 2003; Levin et al., 2012; Palmatier et al., 2009). These compounds have diverse pharmacological profiles but they both act upon the dopamine system, in common with nicotine itself (Benowitz, 2008). Although nicotine has been shown to moderate the expression of certain reward processes in smokers (e.g., reward responsivity and temporal discounting), the extent to which they can be modulated using alternative mechanisms is not well understood. If the expression of specific reward processes can precipitate relapse, a better understanding of their psychopharmacology could refine treatment. This may be particularly relevant for specific groups of smokers for whom tobacco dependence and non-drug reward dysfunction are correlated (Ahnallen et al., 2012).

Reward responsivity, or the effect of a reward-based incentive on behaviour, can be indexed in smokers using a simple psychomotor card sorting task (Powell et al., 1996). Results have shown that reward responsivity is impaired during abstinence from tobacco (Al-Adawi and Powell, 1997; Powell et al., 2002) and might

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therefore be amenable to pharmacological treatment. Performance on this task can be improved with nicotine administered under double blind conditions (Dawkins et al., 2006), which enhances striatal dopamine release in smokers (Takahashi et al., 2008). Further support for the role of dopamine on this task comes from evidence that extended treatment with the D_2 agonist bromocriptine can elevate reward responsivity in brain injured patients with severe motivational impairments (Powell et al., 1996). Moreover, d-amphetamine has been shown to increase willingness to exert effort on another reward-based task amongst healthy volunteers (Wardle et al., 2011). However, to the best of our knowledge, the role of dopamine in reward responsivity has not yet been explored amongst smokers.

Temporal discounting refers to the behaviourally impulsive tendency for rewards to lose subjective value as their delivery is delayed in time. Current and dependent smokers are distinguished from non-dependent, ex- and non-smokers in showing elevated temporal discounting of monetary reward (Bickel et al., 1999; Sweitzer et al., 2008) and discounting of cigarettes and/or money can be exacerbated during tobacco abstinence (Field et al., 2006; Mitchell, 2004; Yi and Landes, 2012). Temporal discounting of reward co-varies with dopamine agonist medication status in Parkinson's disease patients with impulse control disorders (Voon et al., 2009), suggesting it may be influenced by dopaminergic function. Moreover, in healthy volunteers, a single dose of the D_2/D_3 agonist pramipexole can increase risky decision making (Riba et al., 2008). However, although DA is thought to play a role in temporal discounting of reward, dopaminergic drugs, including bupropion, have produced mixed effects to date (Acheson and de Wit, 2008; Pine et al., 2010; de Wit et al., 2002), and a previous study found no effect of acute pramipexole on temporal discounting or any other indices of behavioural impulsivity in healthy volunteers (Hamidovic et al., 2008).

This study aimed to investigate the effects of the D_2/D_3 agonist pramipexole on reward processes in smokers during a brief period (~2 h) of tobacco abstinence. Whilst a role for nicotine and tobacco in acutely modulating non-drug reward function has been established (Al-Adawi and Powell, 1997; Dawkins et al., 2006; Field et al., 2006; Mitchell, 2004; Powell et al., 2002; Yi and Landes, 2012), the extent to which these effects can be achieved using non nicotine-based approaches has not yet been established. Based on evidence for enhanced reward responsivity in brain injured volunteers following bromocriptine (Powell et al., 1996), we predicted that the D_2/D_3 agonist pramipexole would enhance reward responsivity in smokers. However, given that pramipexole did not impact on temporal discounting or other indices of impulsivity in healthy volunteers (Hamidovic et al., 2008) we predicted that temporal discounting of reward would be unaffected by pramipexole.

2. Methods

2.1. Design and participants

A randomized double-blind placebo controlled crossover design was used to asses the effects of 0.5 mg pramipexole in 16 non treatment-seeking smokers (8 male) recruited from the community. Inclusion criteria were age 18–40, smoking ≥10 cigarettes per day for at ≥1 year, smoking a first cigarette ≤1 h after waking, normal or corrected to normal vision, and fluent spoken English. Exclusion criteria were current use of nicotine replacement therapy or any other smoking cessation pharmacotherapy, a learning, mental health or substance abuse problem, tumours of the pituitary or adrenal gland, reduced liver or kidney function, pregnancy or breast feeding. Participants were paid £7.50 per hour for their time and were informed that they would be given the opportunity to win additional money during the experiment. Participants provided written, witnessed, informed consent. This study was approved by the UCL Graduate School Ethics Committee and was conducted in accordance with the Declaration of Helsinki.

Following screening, participants attended two three-hour laboratory sessions separated by a washout period lasting between 5 and 9 days. Both sessions followed the same protocol (see Fig. 1). Participants were asked to fast for an hour before attendance, to refrain from caffeine consumption on the day of testing and to avoid driving or using machinery for the remainder of day. After smoking a cigarette, a carbon monoxide (CO) reading (Bedfont Micro Smokerlyzer, UK) and baseline assessments (Positive and Negative Affect Schedule, subjective effects) were taken. This was followed by drug administration, which was either 0.5 mg pramipexole (peak plasma levels at 1–3 h, half life elimination 8–12 h; Wright et al., 1997) or matched placebo administered in a gelatin capsule. The peripheral D_2 antagonist domperidone (30 mg) was co-administered on both days in a gelatin capsule in order to reduce unwanted side effects of dopamine agonist treatment, such as nausea and vomiting (Parkes, 1986). Smoking was not permitted for the remainder of each test day. After drug administration, participants were given trait questionnaires regarding mood and smoking behaviour (0–15 min post drug) which were split across the two laboratory visits and included the Fagerström Test of Nicotine Dependence and Barratt Impulsiveness Scale. Next, participants were encouraged to read magazines or books provided (15–90 min post drug) before testing began. The test battery was administered in a fixed order, with the Card Arranging Reward Responsivity Object Test administered at 120 min post drug and temporal discounting at 165 min post drug. Subjective effects were taken before drug administration and 150 min post drug. These tasks formed part of a wider battery of assessments that will be reported elsewhere.

2.2. Materials

2.2.1. Card Arranging Reward Responsivity Object Test (CARROT; Powell et al., 1996). This task was used to measure individuals' responsivity to financial reward. Each card has five digits marked on its face and one (but only one) of these digits is always a 1, a 2 or a 3. Participants are required sort cards into three piles based on the corresponding digit (1, 2 or 3) as quickly as possible in a series of four trials. Trial one is a baseline trial in which 60 cards are sorted. The speed at which these cards are sorted is used as the baseline time limit for the remaining experimental trials, in which a maximum of 100 cards can be sorted. Trial two and four proceed in the same way as trial one. In trial three, participants are paid 10p for every 5 correctly sorted cards. During the trial, 10p pieces earned are cumulatively placed in front of the participant and they are paid in full at the end of the testing session. This reward-based incentive allowed individuals to earn more money depending on their performance, in addition to receiving a standard payment of £7.50 per hour for the entire duration of the study. The extent to which card sorting differs in the rewarded trial compared to non-rewarded performance (mean of trials two and four) was used as an index of reward responsivity.

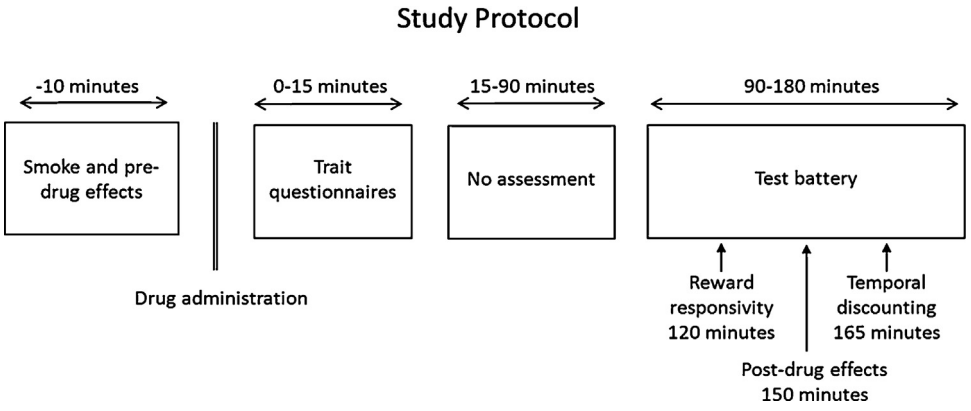

Fig. 1. Study protocol. A crossover design was used to compare the effects of 0.5 mg pramipexole with placebo. The same protocol was used on both testing days.