



Neuropharmacology and Analgesia

Nicotine sensitization of monkey striatal dopamine release[☆]Edward F. Domino^{*}, Hideo Tsukada

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ABSTRACT

This study with monkeys was designed to answer two questions. 1) Does acute nicotine preferentially release more dopamine in the striatum than in the prefrontal cortex? 2) Do repeated doses of nicotine produce sensitization of striatal dopamine release? Microdialysis techniques were used to measure extracellular dopamine in both brain regions in two separate groups of conscious animals. The acute nicotine i.v. dose schedule was a bolus of 32 µg/kg plus an infusion of ± 0.8 µg/kg/min and a 100 µg/kg bolus plus an infusion of ± 2.53 µg/kg/min for 30 min to mimic human tobacco smoking arterial plasma nicotine concentrations. Acute nicotine given i.v. released more dopamine in the striatum than in the prefrontal cortex. In the second experiment, for convenience, daily nicotine was given i.m. and not i.v. bid in doses of 32 or 100 µg/kg for nine days. Dopamine release was measured after overnight nicotine abstinence using the i.v. dose schedule from the first experiment. Baseline dopamine release was significantly reduced (77.6% of control, $P < 0.05$). With a lowered baseline, a greater facilitation of dopamine release was produced by nicotine compared to that obtained under control conditions when the baseline was higher. The impaired dopamine release with overnight nicotine abstinence was transiently enhanced in a dose dependent manner. These data regarding the striatum are consistent with previous findings in rodents of nicotine sensitization of dopamine release especially in nucleus accumbens following repeated administration.

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1. Introduction

Nicotine has been studied extensively as another important drug of abuse. Tolerance to nicotine is well known in both animals and humans. For example, tolerance to the daily nicotine effects on rat bar pressing for water reinforcement is marked (Domino and Lutz, 1973). On the other hand, locomotor behavioral sensitization is described by many (Morrison and Stephenson, 1972; Clarke and Kumar, 1983a,b; Ksir et al., 1985, 1987; Hakan and Ksir, 1988, 1991; Johnson, 1995; Johnson et al., 1994, 1995; Domino, 2001). Balfour et al. (1998) reviewed the literature to that date. They proposed that the sensitized mesoaccumbens dopamine response to nicotine is closely related with nicotine dependence. Research by Shim et al. (2001) strongly suggests that both striatum and the shell of nucleus accumbens play a major role in nicotine induced behavioral sensitization in rodents. The earlier report of Shoaib et al. (1994) indicates involvement of glutamatergic NMDA receptors in nicotine induced sensitization similar to other drugs of abuse (Vanderschuren and Kalivas, 2000). Obviously, a great deal of basic research using rodents indicates that repeated exposure to drugs of abuse produce behavioral sensitization.

Nicotine sensitization in primates including humans has not been described. In 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced hemiparkinsonian monkeys, daily nicotine produces negligible evidence of sensitization (Domino et al., 1999). McCallum et al. (2006c) reported that after nigrostriatal damage with MPTP in squirrel monkeys presynaptic dopamine compensation occurs with near control levels of K⁺ evoked release. Vezina et al. (1994) injected 6-hydroxydopamine into the ventral tegmental area which destroyed mesolimbic dopamine neurons but spared the locomotor activating effects of nicotine, indicating a dissociation. The proposals by Robinson and Berridge (1993) and Berridge and Robinson (2003) that behavioral sensitization in rodents to many drugs of abuse is a major model of human drug dependence are widely accepted. Evidence that behavioral sensitization occurs with nicotine in primates is important to note. The present study using monkeys indicates that nicotine sensitization to striatal dopamine release, while not large under the conditions used, does occur when baseline dopamine release is reduced after daily overnight nicotine abstinence.

2. Methods

2.1. Animals and drugs

Two separate groups of young adult male rhesus monkeys (*Macaca mulatta*) weighing from 5.5 to 7.9 kg were used in these studies. Ten Group 1 monkeys were used for experiment 1 to measure release of

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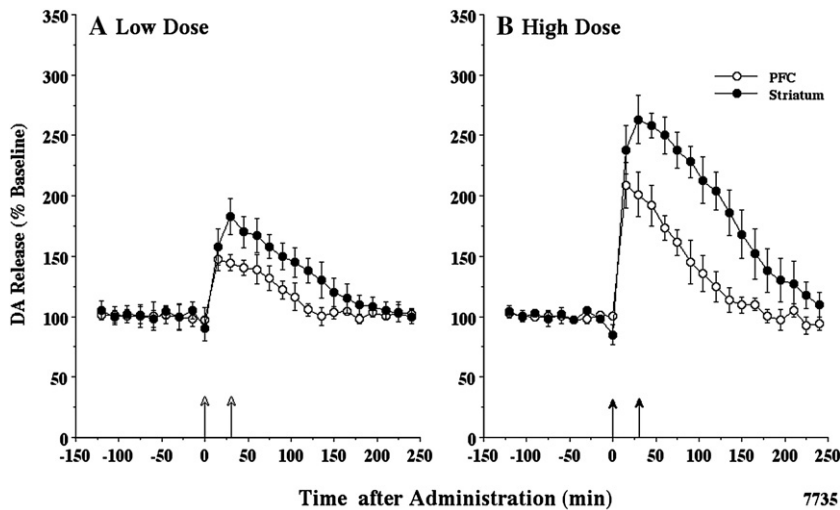


Fig. 1. Greater acute nicotine induced dopamine release in monkey striatum than prefrontal cortex. Note that as a percent of baseline control, nicotine in two different doses releases more dopamine in the striatum than in the prefrontal cortex. In this and the subsequent figure, the low dose of nicotine bolus plus infusion for 30 min is $32 + 0.8 \mu\text{g}/\text{kg}/\text{min}$, and the high dose of nicotine is $100 + 2.53 \mu\text{g}/\text{kg}/\text{min}$ given i.v. as illustrated between the arrows.

dopamine from prefrontal cortex following acute nicotine. They subsequently were involved in a different study described by Tsukada et al. (2005b). Eight Group 2 monkeys were used for experiment 2 to measure release of dopamine from the striatum following acute as well as chronic nicotine. All monkeys were maintained and handled in accordance with the recommendations of the U.S. National Institutes of Health and guidelines of the Central Research Laboratory, Hamamatsu Photonics. Nicotine bitartrate was purchased from Karito Chemical Co (Tokyo, Japan). It was given i.v. in a bolus plus infusion dose of $32 \mu\text{g}/\text{kg} + 0.8 \mu\text{g}/\text{kg}/\text{min}$ or $100 \mu\text{g}/\text{kg} + 2.53 \mu\text{g}/\text{kg}/\text{min}$ for 30 min under both acute as well as chronic bid 32 and $100 \mu\text{g}/\text{kg}$ i.m. conditions. These doses were chosen because preliminary data indicated arterial plasma levels of nicotine were obtained in the smoking range of humans from 18.1 to $86.7 \text{ ng}/\text{ml}$ (Tsukada et al., 2002). In experiment 2, monkeys received 32 or $100 \mu\text{g}/\text{kg}$ bid i.m. nicotine daily for nine days. Measurements of dopamine microdialysis levels after i.v. nicotine were taken after overnight abstinence on the morning of the 10th day.

2.2. Microdialysis procedures

The microdialysis procedures used have been described in detail by Tsukada et al. (2005a,b). Briefly, the monkeys were given isoflurane/oxygen general anesthesia for surgical procedures. A guide cannula was previously implanted according to individual magnetic resonance images (MRI). One indwelling microdialysis probe with a membrane region $250 \mu\text{m}$ in diameter and 3 mm in length (Eicom A-I-8-03, Eicom, Kyoto, Japan) was inserted into the prefrontal cortex of the monkey brain (3.0 mm below the dura matter), and the other in the head of the caudate in the left brain hemisphere via a guide cannula. When the animals recovered, the probe was initially perfused with a modified Ringer solution (147 mM NaCl , 4 mM KCl , 2.3 mM CaCl_2 , Otsuka Pharmaceutical, Tokyo Japan) at a rate of $10 \mu\text{l}/\text{min}$ to remove overflow of neurotransmitters from the damaged tissue. The perfusion rate was decreased to $5 \mu\text{l}/\text{min}$ 2 h after insertion of the probes. The $75 \mu\text{l}$ samples were collected every 15 min. The dopamine concentration was measured by HPLC (HTEC-500 and DTA-300, Eicom, Kyoto, Japan). These

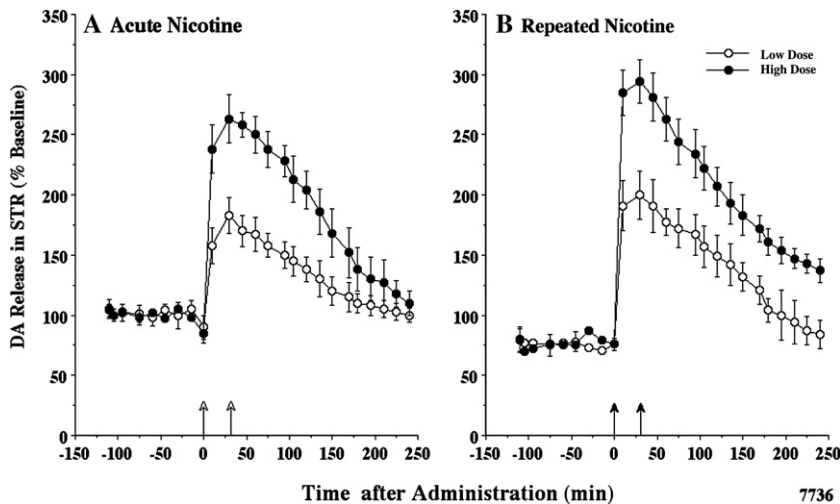


Fig. 2. Nicotine sensitization of monkey striatal dopamine release after overnight abstinence. A. Dopamine release following acute nicotine to naive animals is dose related and lasts about 250 min with a 30 min bolus + infusion. B. After overnight abstinence following 9 days of bid i.m. nicotine, baseline control levels of dopamine release are about 23% lower than control. After nicotine, dopamine levels are enhanced and last much longer than after the same doses in naive animals. For comparison purposes, dopamine release is expressed as a percentage of control. As described in Results, control levels of dopamine release were $11.49 \text{ fmol}/\mu\text{l}$ and $8.91 \text{ fmol}/\mu\text{l}$ after overnight abstinence from repeated bid nicotine administration.

methods have been described by Tsukada et al. (2000a,b). Both group and paired Student “t” test statistics were used as appropriate for the data from the two experimental groups.

3. Results

In the acute nicotine condition (experiment 1), there was a dose-related significantly greater ($P < 0.05$) percent of dopamine release following nicotine in monkey striatum (Group 2) than in prefrontal cortex (Group 1, see Fig. 1). Basal dopamine release in the prefrontal cortex was very small with 0.61 fmol/ μ l, and large with 11.49 fmol/ μ l in the dorsal striatum ($P < 0.05$). In view of these results from experiment 1, it was decided to examine nicotine induced sensitization in the striatum in relationship to the published sensitization effects in rodents.

For experiment 2, the monkeys were given nine days of bid nicotine. After overnight abstinence, basal levels of dopamine were about 77.6% of normal prenicotine treatment (8.91 fmol/ μ l vs 11.49 fmol/ μ l, respectively). Even with the lower baseline dopamine release after nine days of nicotine, single doses of nicotine clearly enhanced striatal dopamine release (Fig. 2B). The area under the dopamine curve was significantly greater for both doses of nicotine after chronic nicotine administration than that given to nicotine naive monkeys ($P < 0.05$).

4. Discussion

The functional importance of dopamine in the prefrontal cortex has been well described (Brozoski et al., 1979; Goldman-Rakic and Brown, 1981; Goldman-Rakic, 1987; Sawaguchi and Goldman-Rakic, 1991; Tsukada et al., 2005a,b). As demonstrated by the present study, compared to monkey striatum the basal/prefrontal cortex dopamine released extracellularly is only 5%. Nevertheless, acute nicotine in a dose related manner produces about 150 and 210% increase of dopamine release compared to baseline levels in the prefrontal cortex, whereas similar doses of nicotine produced about 175 and 275% increases in the striatum. These findings indicate that acute nicotine produces impressive percent increased release of dopamine in both brain structures irrespective of basal control levels.

As described in Introduction, there are many reports of nicotine induced rodent locomotor sensitization. Nicotine locomotor sensitization is especially enhanced when the agent is given to conscious female animals placed in a different environment than their home cage (Becker, 1999). In the present study, the male monkeys were injected with nicotine in their home cages for 9 days but studied before and after overnight abstinence from nicotine in a laboratory experimental unit for the microdialysis studies. Obviously, this nicotine treatment design is less than ideal. A group of chronic 0.9% NaCl animals was not run. Nevertheless, the results obtained indicate that nicotine sensitization to dopamine release occurs in the dorsal striatum. Similar sensitization studies to dopamine release should be done in the ventral striatum. As described in Introduction, it has been difficult to observe any nicotine behavioral sensitization in hemiparkinsonian monkeys (Domino et al., 1999). However, nicotine even produces sensitization of dopamine release *in vitro* in neuroblastoma cells (Kantor et al., 2002; Park et al., 2002, 2003).

It is of interest that several drugs of abuse such as alcohol, cocaine, and opiates, given chronically produce upregulation of cAMP in rodent nucleus accumbens (Nestler et al., 2001). These investigators related these cellular adaptations to “emotional-motivational dependence.” Nicotine should be studied and probably added to this list. Whether $\alpha 4\beta$ or $\alpha 3/\alpha 6$ nicotinic receptors are involved is also of importance to study further. McCallum et al. (2006a,b) reported that squirrel monkeys given chronic oral nicotine have an increase in $\alpha 4$ nicotinic acetylcholine receptor (nAChR)-evoked [3]dopamine release in striatal subregions. An overall increase in the striatum was seen when normalized to uptake. In contrast, $\alpha 3/\alpha 6$ nAChRs and function were decreased or unchanged.

Many investigators have reported that nicotine stimulates rodent dopaminergic neurons and releases dopamine primarily in nucleus accumbens (Singer et al., 1982; Imperato et al., 1986; Grenhoff et al., 1986; Mereau et al., 1987; Rowell et al., 1987; Clarke et al., 1988; Di Chiara and Imperato, 1988; Fuxe et al., 1988; Grenhoff and Svensson, 1988; Damsma et al., 1989; Lapin et al., 1989; Brazell et al., 1990; Corrigan and Coen, 1991; Corrigan et al., 1992, 1994; Nisell et al., 1994a,b; Marshall et al., 1997; Pontieri et al., 1996; Gardner, 1997; Gerasimov et al., 2000; Di Chiara, 2002). As described in Introduction, in most rat strains, single doses of nicotine produce marked depression, but repeated daily or intermittent doses produce stimulation and sensitization. Clarke and Kumar (1983b) observed that behavioral sensitization occurs even in nicotine tolerant rats. Damsma et al. (1989) noted nicotine induced dopamine release in nucleus accumbens in rats that were not tolerant to nicotine. However, constant infusion of nicotine in doses that produce plasma levels similar to tobacco smokers attenuates or abolishes dopamine release in nucleus accumbens (Balfour and Benwell, 1995). Balfour and Benwell concluded that the dopamine overflow in nucleus accumbens hypothesis of nicotine addiction should be viewed with caution. Cadoni and Di Chiara (1999) noted differential changes in dopamine release in rat nucleus accumbens shell and core with nicotine administration after behavioral sensitization. Shim et al. (2001) found that the striatum as well as nucleus accumbens plays a major role in nicotine-induced behavioral sensitization in rodents. Whether sensitization to nicotine/tobacco smoking occurs in humans is not certain. Any research design using nicotine-naive human volunteers to study nicotine behavioral sensitization is unethical. Therefore, further nicotine sensitization studies using subhuman primates are needed to support the findings of rodent research to tobacco smoking humans.

An important finding of this subprimate study is that after overnight abstinence the baseline levels of striatal extracellular dopamine are reduced below control levels. Only after nicotine is given are the levels transiently elevated toward normal and above (see Fig. 2B). One is reminded of an analogy to nicotine dependent smokers who upon awakening in the morning smoke a cigarette before getting out of bed. It is alleged to be the best cigarette of the day. Perhaps, like dependent monkeys given nicotine, smokers in the morning transiently normalize and slightly enhance their levels of released brain dopamine before they begin their daily activities. Only later throughout the day do they need to smoke additional cigarettes to maintain their released levels of dopamine at normal levels. A working hypothesis that needs further research is that the turnover of brain dopamine is reduced after nicotine abstinence, resulting in lower levels of dopamine release following overnight abstinence.

There are at least two major limitations to this study. One issue in interpreting the findings is the fact that the pharmacokinetics of nicotine may be different following acute vs repeated bid nicotine administration. However, the peaks of dopamine release did not differ, indicating nicotine kinetics probably did not differ greatly. Another limitation of the study is that the effects of repeated nicotine on dopamine release were not determined during the nine day period of bid nicotine administration. This makes it impossible to conclude that the reduction in basal dopamine after the last i.m. dose is related to overnight abstinence as opposed to a gradual decline in dopamine release over the nine day period.

In summary: 1) In species, age, and gender matched monkeys, single doses of nicotine produce greater release of dopamine in the striatum than in prefrontal cortex as measured by microdialysis. 2) Basal striatal dopamine release is reduced from control levels after overnight abstinence from nine days of bid nicotine. 3) Daily nicotine induces sensitization of striatal dopamine release.

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