Available online at www.sciencedirect.com

SCIENCE DIRECT®

Pharmacology, Biochemistry and Behavior 81 (2005) 551 – 558

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

www.elsevier.com/locate/pharmbiochembeh

Nicotine pretreatment diminished physostigmine-induced tremor in rats

Adenilson de Souza da Fonseca, Ricardo Santos*

Departamento de Farmacologia e Psicobiologia, Instituto de Biologia, Universidade do Estado do Rio de Janeiro, Av. 28 de Setembro, 87-Fundos, 20551-030, Rio de Janeiro, Brasil

Received 22 October 2004; received in revised form 15 April 2005; accepted 26 April 2005
Available online 20 June 2005

Abstract

The aim of this work was evaluate the effects of acute and chronic nicotine pretreatment in the physostigmine-induced tremor in rats. Wistar male rats (3–4 months) were pretreated acutely with different nicotine doses (0, 0.1, 0.5 or 1.0 mg/kg) 10 min before physostigmine (0 and 0.5 mg/kg) treatment and then the tremor was registered by computerized system for 10 min. In another group, rats were pretreated acutely with 0.1 mg/kg of nicotine, recovered at different times (30 or 70 min), and were registered for physostigmine-induced tremor. Nicotine was also used chronically with equal doses for 8 days and recovered at 2, 7 or 21 days before registration of physostigmine-induced tremor. Tremor spectral analysis was performed for amplitude and frequency quantification. Our data show that the acute and chronic nicotine pretreatments alter physostigmine spectrum profile. Nicotine decreased physostigmine-induced tremor amplitude ($p<0.05$), without changing its tremor frequency. In acutely pretreated rats, recovery experiments showed return of physostigmine-induced tremor for control levels after 70 min, but after 8 days of chronic nicotine pretreatment recovery was delayed 3 weeks. The data analysis shows that acute or chronic nicotine administration can alleviate the physostigmine-induced tremor. Chronic nicotine pretreatment has a long tremor alleviation effect of physostigmine-induced tremor. Possible mechanisms involving the nicotine effects on the physostigmine-induced tremor are discussed.

Keywords: Nicotine; Physostigmine; Spectral analysis; Tremor

1. Introduction

Nicotine is a toxic component of the tobacco producing a wide array of alterations in the body (Balfour and Fagerstrom, 1996; Morgan et al., 2004; Valenca et al., 2004), with psychoactive actions and addictive properties on the central nervous system. (Balfour, 2002; Van Den Eijnden et al., 2003).

Despite negative effects, nicotine increases arousal and attention in humans (Wesnes and Warburton, 1984; Conners et al., 1996) and more than 14 independent important epidemiological studies show that smokers present a lower risk of developing Parkinson's disease (PD) (Fratiglioni and Wang, 2000; Quik, 2004). This finding could provide clues for therapies treating PD (Balfour and Fagerstrom, 1996; Quik, 2004) and Alzheimer's disease (Maelicke et al., 2000). In addition, positive effects on Tourette's syndrome have been suggested (Silver et al., 2001; Tizabi et al., 2001; Howson et al., 2004).

Pathophysiology in PD is based on the degenerative process of dopamine neurons of substantia nigra (SN), dopamine deficiency and reduced activation of dopamine receptors (Obeso et al., 2000). Replacement therapy with the dopamine precursor L-DOPA is the most effective pharmacotherapy (Graybiel et al., 2000). The basal ganglia motor circuit is directly related to PD in a classical pathophysiological model. However, new models explaining pathophysiology of PD and new strategies for treatment are in progress (Obeso et al., 2000; Bjarkam and Sorensen, 2004; Quik, 2004).

There are dense dopaminergic and cholinergic neurons with different dopamine, nicotinic and muscarinic receptors

* Corresponding author. Tel./fax: +55 51 21 2587 6808.
E-mail address: rsantos@uerj.br (R. Santos).

0091-3057/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2005.04.011

in the striatum, which is involved in motor coordination, PD and other functions and disorders, (Zhou et al., 2003). A well-coordinated dopamine/acetylcholine balance is suggested as being important in striatum functions (Zhou et al., 2003). On the other hand, the loss of this coordination can cause several PD symptoms (Zhou et al., 2003). Undoubtedly, neuroleptics induce movement disorders where D2 receptor antagonism simulates parkinsonism (Owens, 1999). Similarly, stimulating muscarinic receptors by direct or indirect agonists in experimental animals (Salamone et al., 2001) or in patients therapy with acetylcholinesterase (AchE) inhibitors can present as side effects similar movement disorders symptoms (Aarsland et al., 2004). Muscarinic antagonists, actually used as secondary treatments for PD (Carlsson, 2002; Aarsland et al., 2004), can relieve motor side effects induced by neuroleptics (Owens, 1999). Thus, the knowledge about the cholinergic system, and the possible interactions with other neurotransmitters systems in experimental models of tremor, is of great importance in understanding PD pathology as well as for developing new pharmacological agents.

Nicotine, the most important candidate of chemicals of tobacco to explain lower risk of PD in smokers, stimulates different nicotinic cholinergic receptors in the brain and in the nigrostriatal pathway (Quik, 2004). Nicotine increases the release of some neurotransmitters in the brain (Gallardo and Leslie, 1998; Zhu and Chiappinelli, 1999), especially dopamine (Salminen and Ahtee, 2000). The dopamine decrease leads to PD pathophysiology with the appropriate replacement therapy.

Physostigmine, a reversible AchE inhibitor, causes an increase of acetylcholine at the synaptic cleft that in turn acts on nicotinic and muscarinic receptors (Kandel et al., 2000). This drug has also been described as a weaker allosteric potentiator on the nicotinic receptor (Maelicke et al., 2000). The tremorigenic effect of physostigmine involves the whole body in small laboratory animals and has been used as an experimental model of tremor (Santos and Carlini, 1988; Mehta et al., 2001; Fonseca et al., 2002).

Few studies have evaluated the influence of nicotine on pathological tremor (Ishikawa and Miyatake, 1993; Fagerstrom et al., 1994; Nishimura et al., 1997; Vieregge et al., 2001) or experimental tremor (Wang et al., 1996). Moreover, tremor data were accessed by tremor rating scales that, despite their usefulness (Santos and Carlini, 1988; Almeida and Santos, 1993), do not measure tremor "intensity" (degrees) and frequency. Therefore, to better quantify drug-induced tremor, a new technique was developed and validated, where tremor amplitude and frequency were accessed (Pereira and Santos, 1998; Fonseca et al., 2002). However, the effect of nicotine on physostigmine-induced tremor has not been evaluated until now.

The aim of this work was to evaluate the influence of the acute and chronic nicotine pretreatment, as well as its discontinuation, on the physostigmine-induced tremor in rats.

2. Materials and methods

2.1. Animals

Adult male Wistar naive rats (250–350 g, 3–4 months of age) from our own colony were used for this study. They were housed, six per cage, in a room under controlled environment: normal light/dark cycle conditions (12-h light/12-h dark; lights on at 6:00 a.m.). Animals had free access to water and food and ambient temperature was kept at 23±2 °C. Experiments were conducted in accordance with the Department Committee of Animal Care.

2.2. Drugs

Physostigmine (HCl) and (−)-nicotine ([-]-1-methyl-2-[3-pyridyl]-pyrrolidine) was purchased from Sigma, USA. Water was used as vehicle and solutions were prepared immediately before intraperitoneal administrations in 0.1 ml/100 g of body weight.

2.3. Nicotine pretreatment and recovery

For the acute pretreatment the nicotine was administered in different doses (0, 0.1, 0.5 or 1.0 mg/kg, i.p.) 10 min before physostigmine (0.5 mg/kg, i.p.) administration and tremor registration procedure. Also, recovery of this acute nicotine pretreatment was performed for 0.1 mg/kg of nicotine dose at different periods (10, 30 or 70 min). After these periods physostigmine (0.5 mg/kg, i.p.) was administered and tremor was registered.

For the chronic pretreatment nicotine was administered once a day in different doses (0, 0.1, 0.5 or 1.0 mg/kg, i.p.) for 8 days, then the day after (24 h), physostigmine (0.5 mg/kg, i.p.) was administered and tremor was registered. Recovery of this chronic nicotine pretreatment, was also performed for 0.1 mg/kg of nicotine dose at different periods (0, 2, 7 or 21 days). After these periods physostigmine (0.5 mg/kg, i.p.) was administered and tremor was registered.

As control groups, rats were pretreated and treated respectively with: vehicle+vehicle (C1), nicotine+vehicle (C2) and vehicle+physostigmine (C3).

2.4. Tremor registration and spectral analysis procedures

After nicotine pretreatment and physostigmine administration (0.50 mg/kg, i.p.), tremor was registered during 10 min by computerized system and spectral analysis was performed for tremor amplitude and frequency quantification as described (Pereira and Santos, 1998; Fonseca et al., 2002).

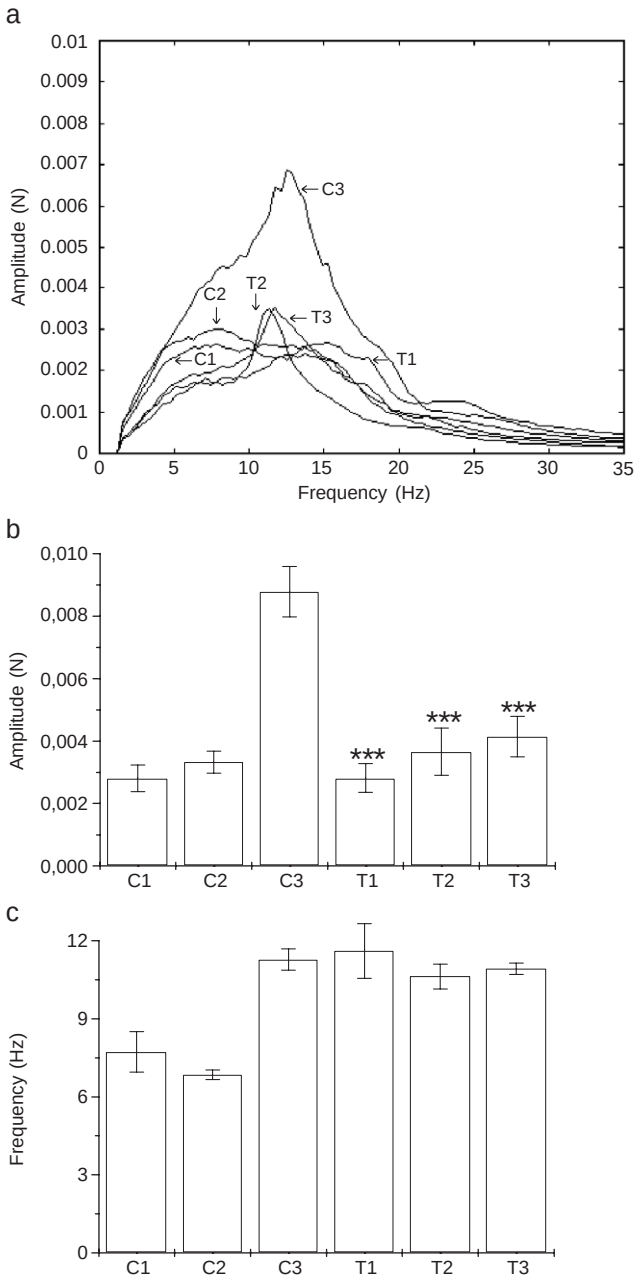

Fig. 1. Average spectrum (a) and graphs of the amplitude (b) and frequency (c) of physostigmine-induced tremor in rats submitted to acute nicotine pretreatment. Rats ($n=6$; each group) were pretreated with different nicotine doses and treated 10 min after with physostigmine (0.5 mg/kg) i.p. and tremor was registered. Control groups were: (C1) vehicle+vehicle; (C2) nicotine−vehicle; (C3) vehicle−physostigmine. Nicotine pretreated groups were: (T1) nicotine(0.1 mg/kg)+physostigmine; (T2) nicotine(0.5 mg/kg)+physostigmine; (T3) nicotine(1.0 mg/kg)+physostigmine. Statistical significance: ***$p \leq 0.001$, when compared to control C3.

2.5. Statistical analysis

The data obtained for tremor amplitude and frequency under different conditions of nicotine pretreatment were analyzed by one-way ANOVA, followed by Bonfferoni post hoc test. Statistical significance was chosen at $p<0.05$.

3. Results

Our data show that acute nicotine pretreatment (0.1 to 1.0 mg/kg) modified spectrum profile of physostigmine-induced tremor (Fig. 1a) when compared with rats pretreated with vehicle (C3 group). Fig. 1b shows a significant ($p<0.05$)

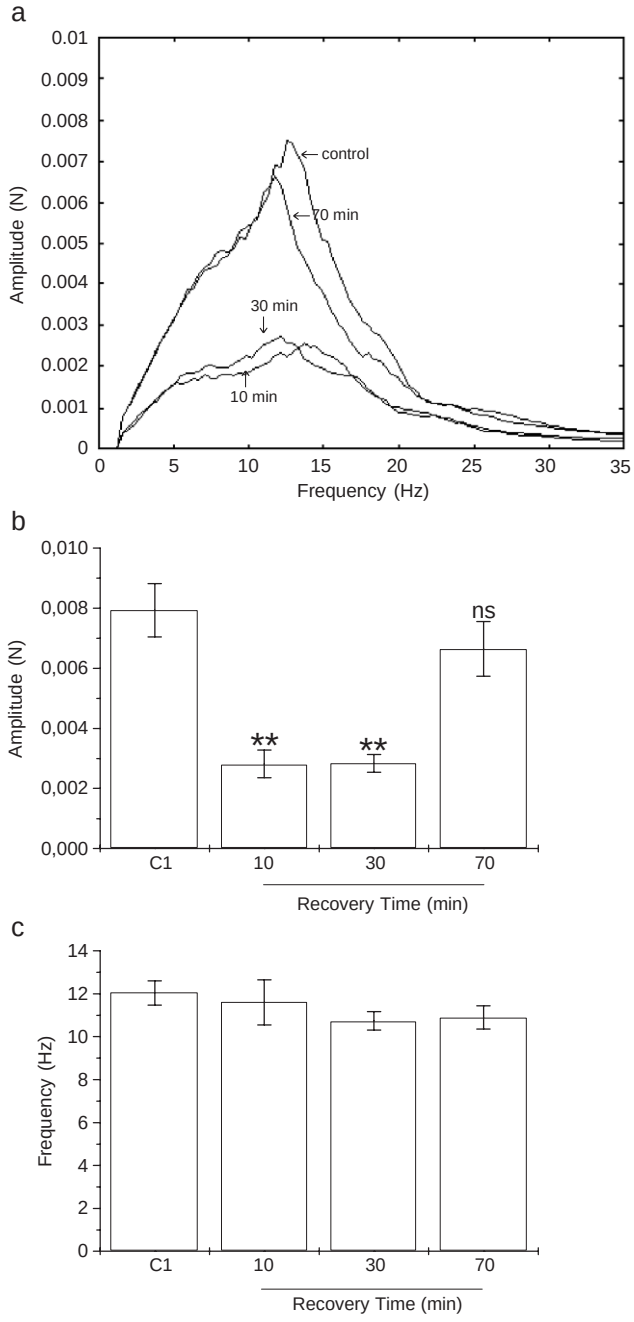

Fig. 2. Average spectrum (a) and graphs of the amplitude (b) and frequency (c) of physostigmine-induced tremor in rats after different times of the acute nicotine pretreatment. Rats ($n=6$; each group) were pretreated with nicotine (0.1 mg/kg) and recovered at different periods (10, 30 or 70 min). After these periods physostigmine (0.5 mg/kg) was administered i.p. and tremor was registered. Rats pretreated with vehicle before physostigmine administration were used as control. Statistical significance: **$p \leq 0.01$, when compared to control group.

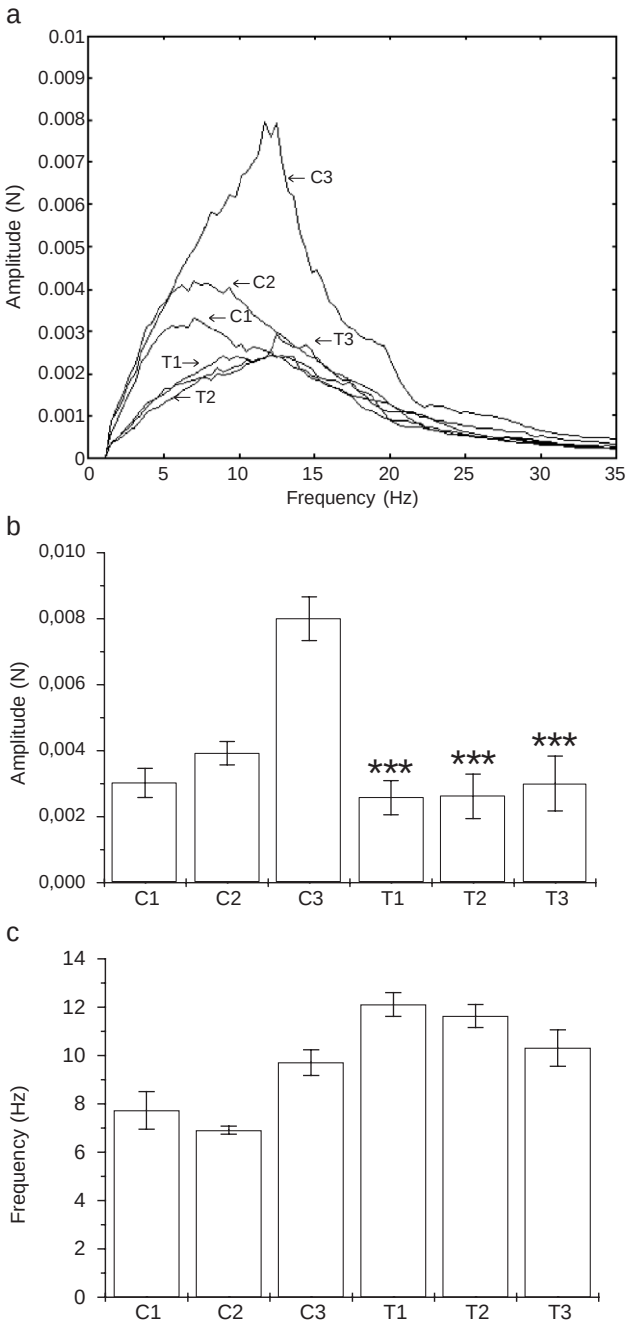

Fig. 3. Average spectrum (a) and graphs of the amplitude (b) and frequency (c) of physostigmine-induced tremor in rats submitted to chronic nicotine pretreatment. Rats ($n=6$; each group) were treated with different nicotine doses during 8 days; after this period, physostigmine (0.5 mg/kg) was administered i.p. and tremor was registered. Controls groups were: (C1) vehicle+vehicle; (C2) nicotine−vehicle; (C3) vehicle+physostigmine. Nicotine pretreated groups were: (T1) nicotine(0.1 mg/kg)+physostigmine; (T2) nicotine(0.5 mg/kg)+physostigmine; (T3) nicotine(1.0 mg/kg)+physostigmine. Statistical significance: ***$p \leq 0.001$, when compared to control C3.

decrease of the amplitude of physostigmine-induced tremor after acute nicotine pretreatment. The frequency of tremor did not change in the same experiment (Fig. 1c). Rats of C1 and C2 groups presented a typical spectra of alleviatory movement and did not show significant differences in amplitude or frequency when similarly compared. No important difference was observed between spectra of rats pretreated acutely with different nicotine doses and pretreated with vehicle (data not shown).

Tremor spectra (Fig. 2a) of rats pretreated with nicotine 30 min before physostigmine show a similar modified

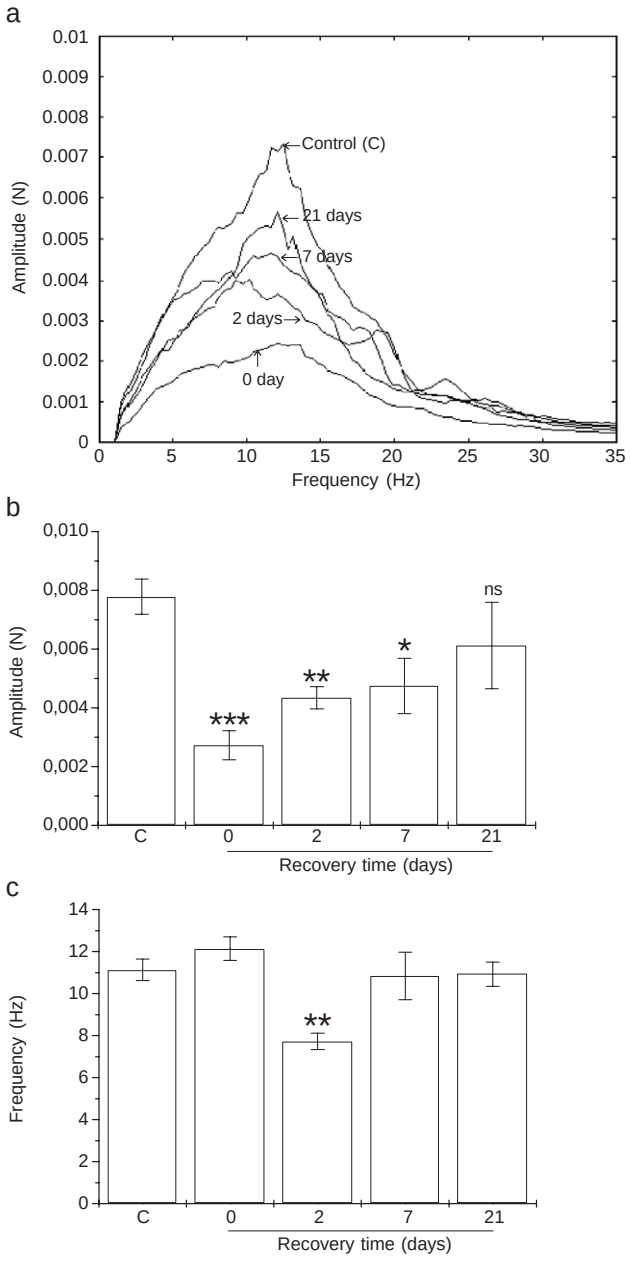

Fig. 4. Average spectrum (a) and graphs of the amplitude (b) and frequency (c) of physostigmine-induced tremor in rats after different times of the chronic nicotine pretreatment. Rats ($n=6$; each group) were pretreated with nicotine (0.1 mg/kg) during 8 days and recovered at different times (0, 2, 7 or 21 days). After these periods physostigmine (0.5 mg/kg) was administered i.p. and tremor was registered. Rats pretreated with vehicle before physostigmine administration were used as control. Statistical significance: *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$, when compared to control group.

spectrum profile of the rats which received nicotine only 10 min before physostigmine. Otherwise, after 70 min of nicotine pretreatment the effect on physostigmine-induced tremor disappeared as shown by a spectrum profile similar to control group (C group). Thus, compared with control (Fig. 2b), the amplitude of physostigmine-induced tremor was significantly decreased when nicotine was administered 10 or 30 min before, but not after a pretreatment period of 70 min, when it remained at control tremor levels. Frequency analysis showed no significant differences among the groups (Fig. 2c).

Chronic nicotine pretreatment also altered the spectrum profile of physostigmine-induced tremor (Fig. 3a) when compared with vehicle pretreated group (C3). Fig. 3b shows a significant ($p<0.01$) decrease of tremor amplitude induced by physostigmine, after chronic nicotine pretreatment. There was no significant difference in tremor frequency among the groups (Fig. 3c). Rats of C1 and C2 groups presented a typical spectra of alleatory movement and showed no significant differences in amplitude or frequency when similarly compared (Fig. 3a–c). No important difference was observed between spectra of rats pretreated chronically with different nicotine doses and pretreated with vehicle (data not shown).

Fig. 4a shows the spectra of physostigmine-induced tremor at different times after discontinuation of chronic nicotine pretreatment. Two and seven days after chronic nicotine pretreatment discontinuation, amplitude of physostigmine-induced tremor remains significantly decreased ($p<0.05$; Fig. 2b) and then increased (control level) only after 21 days. Frequency analyses indicate no differences between the groups (Fig. 4c).

4. Discussion

There was significantly decreased amplitude of physostigmine-induced tremor without altering its frequency (Figs. 1a–c and 3a–c) when using all doses in acute and chronic nicotine pretreatments. However, in acute experiments this effect partially or totally disappeared after a short period of time (70 min) when pretreated with nicotine (Fig. 2a,b), while in chronic experiments amplitude reduction of physostigmine-induced tremor remained at least 7 days after nicotine discontinuation (Fig. 4a,b). Nevertheless, acute and chronic nicotine (all doses used), per se, had no effect on the spectra profiles of the respective control groups (C1 and C2; Figs. 1a and 3a). There was no important alteration in tremor frequency after discontinuation of chronic nicotine pretreatment in rats (Fig. 4c).

Nicotine half-life in plasma is approximately 2 h (Benowitz et al., 1991) but its concentration in the brain decreases by half 30 min after nicotine administration (Sziráki et al., 1998). Thus, the brain nicotine kinetic could explain the recovery time (Fig. 2b) after acute nicotine pretreatment.

Our results with acute nicotine are not in agreement with previous data which described increased incidence of oxotremorine-induced tremor in mice after two nicotine treatments at 5-min intervals (Wang et al., 1996). Others results in our laboratory also showed that acute nicotine pretreatment decreased oxotremorine-induced tremor (not published). However, this discordance may be explained by difference in schedules of nicotine pretreatment and the use of subjective methods (percentage incidence) to evaluate tremor. Therefore, other data have shown that nicotine effects depend on the administration schedule (Rowell and Duggan, 1998).

Our results showing that nicotine decreased amplitude of physostigmine-induced tremor could be explained by the effect of increased release of dopamine in striatum (Salminen and Ahtee, 2000; Sziráki et al., 1998) and striatal synaptosomes (Rowell, 1995). This acute effect of nicotine on dopaminergic system has been described as a rapid effect (Sziráki et al., 1998). Other studies show that nicotine action at presynaptic receptors stimulates striatal glutamate release, which in turn stimulates glutamate receptors at dopaminergic terminals (Kaiser and Wonnacott, 2000; Machová et al., 2003). Also, it was verified that nicotine action on striatal neurons decreased during dopamine blockade (Zarrindast et al., 1998) and haloperidol blocks, while apomorphine mimicked the effect of nicotine on the blink reflex (Evinger et al., 1993). These data suggest that nicotine can act directly on dopamine release through presynaptic nAChRs on dopaminergic neurons or indirectly by stimulation of glutamatergic and dopaminergic nerve terminals leading to dopamine enhancement, which in turn may decrease the firing rate of cholinergic interneurons.

Chronic nicotine or tobacco smoke alters the functioning of dopaminergic system by: (i) releasing dopamine (Gaddnas et al., 2002); (ii) increasing dopaminergic receptor binding in striatum (Fung et al., 1996; Wiener et al., 1989); (iii) increasing tyrosine hydroxylase activity (Smith et al., 1991); (iv) decreasing dopamine metabolite dihydroxyphenyl-acetic acid in striatum (Kirch et al., 1987); and (v) altering behavioral responses to dopaminergic drugs (Sershen et al., 1991; Suemaru et al., 1993).

These observations suggest that acute and chronic nicotine pretreatment may be involved in decreasing physostigmine-induced tremor amplitude by increasing striatal dopaminergic activity.

Physostigmine could be a weaker allosteric potentiator on nicotinic receptor (Maelicke et al., 2000). Others studies using acetylcholinesterase inhibitors not having this direct action on nicotinic receptors are useful in making comparison with our data and may contribute to understanding the mechanisms involved in physostigmine-induced tremor.

Chronic nicotine decreases muscarinic receptor function in the striatum but also increases in the hippocampus without altering in the cortex (Li et al., 1992). In the cortex and brainstem there is a decrease and an increase, respectively, of muscarinic receptor affinity after chronic nicotine pretreat-

ment (Yamanaka et al., 1985, 1987) but binding studies did not show any modification in hippocampus and thalamus (Marks and Collins, 1985; Yamanaka et al., 1987). However, chronic nicotinic antagonist pretreatment produces supersensitivity to hypothermic effects of oxotremorine (Dilsaver et al., 1991). Thus, our data suggest that a decreased function of striatal muscarinic receptors after acute and chronic nicotine pretreatment could also explain a decreased amplitude of physostigmine-induced tremor.

Another important aspect of the present results is the long-lasting effect after discontinuation of chronic nicotine pretreatment (at least 7 days). There are no other experimental or clinical studies reporting similar nicotine long-lasting effect on tremor. This long-lasting effect shown in our results are in accordance with similar nicotine long-lasting effect observed with motor symptoms in Tourette's syndrome (Dursun et al., 1994; Howson et al., 2004; Silver et al., 2001). An explanation for our data with tremor can be a long-lasting neuroadaptation in the basal ganglia circuit as a result of chronic nicotine exposure involving possible genetic expression. In fact, studies show an increased number of nicotinic binding sites in smokers (Breese et al., 1997; Court et al., 1998). Similarly, chronic nicotine pretreatment results in an increase of nAChRs in experimental animals (Meyer et al., 2001; Zhang et al., 2001). In addition, nicotine increases the mRNA expression of some genes in various brain regions (Kane et al., 2000; Konu et al., 2001).

However, chronic nicotine pretreatment causes desensitization of nAChRs (Benwell and Balfour, 1997; Dwoskin et al., 2001; Quick and Lester, 2002). The return of desensitized receptors to normal function, as well as their regulation, after interruption of prolonged stimulus appears to be subtype-specific and brain-region-dependent (Olale et al., 1997; Jacobs et al., 2002) and the nicotine effects on specific behavior can vary. So, despite several studies indicating that nicotinic mechanisms are important in regulating dopamine release, desensitization of nAChRs, which potently decrease dopamine release (Zhou et al., 2003), also has to be taken into consideration.

Nicotine action in decreasing physostigmine-induced tremor appears to have complex mechanisms, despite other possible neurotransmitters being involved in nicotine action. Nicotine also increases release of GABA, serotonin, epinephrine and norepinephrine in some brain areas (Toth et al., 1992; Ribeiro et al., 1993; Gallardo and Leslie, 1998; Zhu and Chiappinelli, 1999).

In conclusion, our results suggest that the balance between dopaminergic and muscarinic receptors can be altered after acute and chronic nicotine pretreatment. Nicotine effect can be mediated by release of dopamine and/or an induction of decrease in muscarinic receptor function. Chronic pretreatment and discontinuation of nicotine suggest a neuroadaptation process between nicotinic, muscarinic and/or dopaminergic receptors. In addition, our data suggest that no continuous treatment with nicotinic agonists was necessary to alleviate this experimental tremor. However, further studies are being undertaken by us to elucidate further knowledge in this field. Other studies are necessary to find which mechanisms or neurotransmitters systems are involved in the nicotinic effects on dopamine/acetylcholine balance in this experimental model of tremor.

Acknowledgment

The authors wish to thank Prof. Paul Dykstra for checking the manuscript. This research was partially supported by University of State of Rio de Janeiro (UERJ) and Centro de Estudos em Psicofarmacologia Jayme Grabois (CEJAG). It is a requirement for Doctorate thesis of A.S. Fonseca which will be submitted to the Universidade do Estado do Rio de Janeiro. Preliminary accounts of the results have been already presented at the XVII Annual Meeting of FESBE, Caxambú, MG, 2001.

References

Aarsland D, Mosimann UP, McKeith IG. Role of cholinesterase inhibitors in Parkinson's disease and dementia with Lewy bodies. J Geriatr Psychiatry Neurol 2004;17:164–71.

Almeida OMS, Santos R. Triiodothyronine (T3) modifies cholinergic-induced hypothermia and tremor in rats. Pharmacol Biochem Behav 1993;46:729–32.

Balfour DJ. The neurobiology of tobacco dependence: a commentary. Respiration 2002;69:7–11.

Balfour DJ, Fagerstrom KO. Pharmacology of nicotine and its therapeutic use in smoking cessation and neurodegenerative disorders. Pharmacol Ther 1996;72:51–81.

Benowitz NL, Jacob P III, Denaro C, Jenkins R. Stable isotope studies of nicotine kinetics and bioavailability. Clin Pharmacol Ther 1991;49:270–7.

Benwell EM, Balfour DJK. Regional variation in the effects of nicotine on catecholamine overflow in rat brain. Eur J Pharmacol 1997;325:13–20.

Bjarkam CR, Sorensen JC. Therapeutic strategies for neurodegenerative disorders: emerging clues from Parkinson's disease. Biol Psychiatry 2004;56:213–6.

Breese CR, Marks MJ, Logel J, Adams CE, Sullivan B, Collins AC, et al. Effect of smoking history on [3H]nicotine binding in human post-mortem brain. J Pharmacol Exp Ther 1997;282:7–13.

Carlsson A. Treatment of Parkinson's with L-DOPA The early discovery phase, and a comment on current problems. J Neural Transm 2002;109:777–87.

Conners CK, Levin ED, Sparrow E, Hinton SC, Erhardt D, Meck WH, et al. Nicotine and attention in adult attention deficit hyperactivity disorder (ADHD). Psychopharmacol Bull 1996;32:67–73.

Court JA, Lloyd S, Thomas N, Piggot MA, Marshall EF, Morris CM, et al. Dopamine and nicotinic receptor binding and the levels of dopamine and homovallinic acid in human brain related to tobacco use. Neuroscience 1998;87:63–78.

Dilsaver SC, Majchrzak MJ, Snider RM, Davidson RK. A nicotinic receptor antagonist enhances the hypothermic response to a muscarinic agonist. Prog Neuropsychopharmacol Biol Psychiatry 1991;15:539–49.

Dursun SM, Reveley MA, Bird R, Stirton F. Longlasting improvement of Tourette's syndrome with transdermal nicotine. Lancet 1994;344(8936):1577.

Dwoskin LP, Teng LH, Crooks PA. Nornicotine, a nicotine metabolite and tobacco alkaloid: desensitization of nicotinic receptor-stimulated dopamine release from rat striatum. Eur J Pharmacol 2001;428:69–79.

Evinger C, Basso MA, Manning KA, Sibony PA, Pellegrini JJ, Horn AK. A role for the basal ganglia in nicotinic modulation of the blink reflex. Exp Brain Res 1993;92:507–15.

Fagerström KO, Pomerleau O, Giordani B, Stelson F. Nicotine may relieve symptoms of Parkinson's disease. Psychopharmacology 1994; 116:117–9.

Fonseca AS, Pereira FR, Santos R. Validation study of a new computerized system for registration and analysis of tremor in rats. J Pharmacol Toxicol Methods 2002;46:137–43.

Fratiglioni L, Wang H. Smoking and Parkinson's and Alzheimer's disease: review of the epidemiological studies. Behav Brain Res 2000;113:117–20.

Fung YK, Schmid MJ, Anderson TM, Lau YS. Effects of nicotine withdrawal on central dopaminergic systems. Pharmacol Biochem Behav 1996;53:635–40.

Gaddnas H, Piepponen TP, Ahtee L. Mecamylamine decreases accumbal dopamine output in mice treated chronically with nicotine. Neurosci Lett 2002;330:219–22.

Gallardo KA, Leslie FM. Nicotine-stimulated release of [3H]norepinephrine from fetal rat locus coeruleus cells in culture. J Neurochem 1998;70: 663–70.

Graybiel AM, Canales JJ, Capper-Loup C. Levodopa-induced dyskinesias and dopamine-dependent stereotypies: a new hypothesis. Trends Neurosci 2000;23:S71–7.

Howson AL, Batth S, Ilivitsky V, Boisjoli A, Jaworski M, Mahoney C, et al. Clinical and attentional effects of acute nicotine treatment in Tourette's syndrome. Eur Psychiatry 2004;19:102–12.

Ishikawa A, Miyatake T. Effects of smoking in patients with early-onset Parkinson's disease. J Neurol Sci 1993;117:28–32.

Jacobs I, Anderson DJ, Surowy CS, Puttfarcken PS. Differential regulation of nicotinic receptor-mediated neurotransmitter release following chronic (−)- nicotine administration. Neuropharmacology 2002;43: 847–56.

Kaiser S, Wonnacott S. α-Bungarotoxin-sensitive nicotinic receptors indirectly modulate [3H]dopamine release in rat striatal slices via glutamate release. Mol Pharmacol 2000;58:312–8.

Kandel ER, Schwartz JH, Jessell TM. Principles of neural science. 4th ed. New York: McGraw-Hill; 2000.

Kane JK, Parker SL, Matta SG, Fu Y, Sharp BM, Li MD. Nicotine up-regulates expression of orexin and its receptors in rat brain. Endocrinology 2000;141:3623–9.

Kirch DG, Gerhardt GA, Shelton RC, Freedman R, Wyatt RJ. Effect of chronic nicotine administration on monoamine and monoamine metabolite concentrations in rat brain. Clin Neuropharmacol 1987; 10:376–83.

Konu O, Kane JK, Barrett T, Vawter MP, Chang R, Ma JZ, et al. Region-specific transcriptional response to chronic nicotine in rat brain. Brain Res 2001;909:194–203.

Li R, Wing LL, Kirch DG, Wyatt RJ, Chuang DM. Effects of chronic nicotine and haloperidol administration on muscarinic receptor-mediated phosphoinositide turnover in rat brain slices. Psychopharmacology 1992;109:248–50.

Machová E, Zemlicková VV, Dolezal V. Nicotine indirectly increases acetylcholine release in rat striatum. J Neurochem 2003;85(Suppl. 2): 16.

Maelicke A, Schrattenholz A, Samochocki M, Radina M, Albuquerque EX. Allosterically potentiating ligands of nicotinic receptors as a treatment strategy for Alzheimer's disease. Behav Brain Res 2000;113(1–2): 199–206.

Marks MJ, Collins AC. Tolerance, cross-tolerance, and receptors after chronic nicotine or oxotremorine. Pharmacol Biochem Behav 1985;22: 283–91.

Mehta H, Thomas B, Mohanakumar KP. Effects of *p*-chlophenylalanine on striatal acetylcholinesterase activity and on biogenic amine levels in nuclei raphe and caudate–putamen during physostigmine-induced tremor in rats. Neurosci Lett 2001;299:105–8.

Meyer EL, Xiao Y, Kellar KJ. Agonist regulation of rat α3β4 nicotinic acetylcholine receptors stably expressed in human embryonic kidney 293 cells. Mol Pharmacol 2001;60:568–76.

Morgan TM, Crawford L, Stoller A, Toth D, Yeo KT, Baron JA. Acute effects of nicotine on serum glucose insulin growth hormone and cortisol in healthy smokers. Metabolism 2004;53:578–82.

Nishimura H, Tachibana H, Okuda B, Sugita M. Transient worsening of Parkinson's disease after cigarette smoking. Intern Med 1997;36:651–3.

Obeso JA, Rodriguez-Oroz MC, Rodriguez M, Lanciego JL, Artieda J, Gonzalo N, et al. Pathophysiology of the basal ganglia in Parkinson's disease. Trends Neurosci 2000;23:S8–19.

Olale F, Gerzanich V, Kuryatov A, Wang F, Lindstrom J. Chronic nicotine exposure differentially affects the function of human α3, α4 and α7 neuronal nicotinic receptor subtypes. J Pharmacol Exp Ther 1997;283: 675–83.

Owens DGC. A guide to the extrapyramidal side-effects of antipsychotic drugs. Cambridge, UK: Cambridge University Press; 1999.

Pereira FR, Santos R. A system for spectral analysis of drug-induced tremors in rats. Rev Bras Eng 1998;14:65–73.

Quick MW, Lester RAJ. Desensitization of neuronal nicotinic receptors. J Neurobiol 2002;53:457–78.

Quik M. Smoking, nicotine and Parkinson's disease. Trends Neurosci 2004; 27:561–8.

Ribeiro EB, Bettiker RL, Bogdanov M, Wurtman RJ. Effects of systemic nicotine on serotonin release in rat brain. Brain Res 1993;621:311–8.

Rowell PP. Nanomolar concentration of nicotine increase the release of [^{3}H]dopamine from rat striatal synaptosomes. Neurosci Lett 1995;189: 171–5.

Rowell PP, Duggan DS. Long-lasting inactivation of nicotinic receptor function in vitro by treatment with high concentrations of nicotine. Neuropharmacology 1998;37:102–11.

Salminen O, Ahtee L. The effects of acute nicotine on the body temperature and striatal dopamine matabolism of mice during chronic nicotine infusion. Neurosci Lett 2000;284:37–40.

Salamone JD, Correa M, Carlson BB, Wisniecki A, Mayorga AJ, Nisenbaum E, et al. Neostriatal muscarinic receptor subtypes involved in the generation of tremulous jaw movements in rodents implications for cholinergic involvement in parkinsonism. Life Sci 2001;68:2579–84.

Santos R, Carlini EA. Central responses to cholinergic drugs of REM sleep deprived rats. Pharmacol Biochem Behav 1988;29:217–21.

Sershen H, Hashim A, Harsing L, Lajtha A. Chronic nicotine-induced changes in dopaminergic system: effect on behavioral response to dopamine agonist. Pharmacol Biochem Behav 1991;39:545–7.

Silver AA, Shytle RD, Philipp MK, Wilkinson BJ, McConville B, Sanderg PR. Transdermal nicotine and haloperidol in Tourette's disorder: a double-blind placebo-controlled study. J Clin Psychiatry 2001;62:707–14.

Smith KM, Mitchell SN, Joseph MH. Effects of chronic and subchronic nicotine on tyrosine hydroxylase activity in noradrenergic and dopaminergic neurones in the rat brain. J Neurochem 1991;57:1750–6.

Suemaru K, Gomita Y, Furuno K, Araki Y. Chronic nicotine treatment potentiates behavioral responses to dopaminergic drugs in rats. Pharmacol Biochem Behav 1993;46:135–9.

Sziráki I, Serschen H, Benuck M, Hashim A, Lajtha A. Receptor systems participating in nicotine-specific effects. Neurochem Int 1998;33: 445–57.

Tizabi Y, Russell LT, Johnson M, Darmani NA. Nicotine attenuates DOI-induced head-twitch response in mice: implications for Tourette syndrome. Prog Neuropsychopharmacol Biol Psychiatry 2001;25: 1445–57.

Toth E, Sershen H, Hashim A, Vizi ES, Lajtha A. Effect of nicotine on extracellular levels of neurotransmitters assessed by microdialysis in various brain regions: role of glutamic acid. Neurochem Res 1992;17: 265–71.

Valenca SS, de Souza da Fonseca A, da Hora K, Santos R, Porto LC. Lung morphometry and MMP-12 expression in rats treated with intraperitoneal nicotine. Exp Toxicol Pathol 2004;55:393–400.

Van Den Eijnden R, Spijkerman R, Fekkes D. Craving for cigarettes among low and high dependent smokers: impact of norharman. Addict Biol 2003;8:463–72.

Vieregge A, Sieberer M, Jacobs H, Hagenah JM, Vieregge P. Transdermal nicotine in PD: a randomized, double-blind, placebo-controlled study. Neurology 2001;57:1032–5.

Wang H, Cui W, Liu C. Regulatory effects of acutely repeated nicotine treatment towards central muscarinic receptors. Life Sci 1996;17: 1415–21.

Wesnes K, Warburton DM. Effects of scopolamine and nicotine on human rapid information processing performance. Psychopharmacology (Berl) 1984;82:147–50.

Wiener HL, Lajtha A, Sershen H. Dopamine D1 receptor and dopamine D2 receptor binding activity changes during chronic administration of nicotine in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated mice. Neuropharmacology 1989;28:535–7.

Yamanaka K, Masafumi O, Muramatsu I. Alteration of alpha and muscarinic receptors in rat brain and heart following chronic nicotine treatment. Brain Res 1985;348:241–8.

Yamanaka K, Muramatsu I, Kigoshi S. Muscarinic agonist binding in rat brain following chronic nicotine treatment. Brain Res 1987;409:395–7.

Zarrindast MR, Haeri-Zadeh F, Zarghi A, Lahiji P. Nicotine potentiates sulpiride-induced catalepsy in mice. J Psychopharmacol 1998;12: 279–82.

Zhang X, Petterson D, James R, Gong Z, Liu C, Rosecrans J, et al. Rats exhibiting acute behavioural tolerance to nicotine have more [^{125}I]α-bungarotoxin binding sites in brain than rats not exhibiting tolerance. Behav Brain Res 2001;113:105–15.

Zhou FM, Wilson C, Dani JA. Muscarinic and nicotinic cholinergic mechanisms in the mesostriatal dopamine systems. Neuroscientist 2003; 9:23–36.

Zhu PJ, Chiappinelli VA. Nicotine modulates evoked GABAergic transmission in the brain. J Neurophysiol 1999;82:3041–5.