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Differential effects of nicotine against stress-induced changes in dopaminergic system in rat striatum and hippocampus

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Abstract

A number of studies have shown an increase in nicotine self-administration among smokers when exposed to stress. Since it is well known that nicotine or stress alter the dopaminergic system, we examined the effect of chronic nicotine administration on the dopamine level and its metabolism in the striatum and the hippocampus during stressful conditions in rats. Nicotine (0.4 mg/kg, i.p. for 14 days) increased the dopamine level in the striatum ($P < 0.05$) and decreased it in the hippocampus ($P < 0.05$) in comparison with the effect of saline. Three hours of water-immersion restraint stress sharply elevated the dopamine level ($P < 0.05$) and reduced the 3-methoxytyramine level (P ranged from 0.05 to 0.001 depending on the area and time point) in both brain regions studied, while dihydroxyphenylacetic acid and homovanilic acid levels were not altered. Nicotine pretreatment attenuated some of these changes in a region- and time-dependent manner. However, stress induced a decrease in dopamine turnover in the hippocampus ($P < 0.05$) but not in the striatum, and nicotine failed to prevent this effect. Stress-induced alterations gradually returned toward normal during the 48-h observation period, and in some cases this was facilitated by nicotine. Thus, we demonstrated differential, region- and time-dependent protective effects of chronic nicotine administration against stress-induced changes in dopamine levels and release in brain regions critically affected by stress.

Keywords: Stress; Nicotine; Dopamine; Striatum; Hippocampus; (Rat)

1. Introduction

There is general agreement that both stress (Herman and Cullinan, 1997) and nicotine (Murray, 1991) increase central nervous system activity and alter brain peptidergic, catecholaminergic, opioid and steroid systems. It is well established, for example, that exposure to various stressors or to nicotine results in the release of dopamine (Di Chiara and Imperato, 1988; Roth et al., 1988; Imperato et al., 1992; Jedema and Moghaddam, 1994), norepinephrine (Thierry et al., 1968; Sharp and Matta, 1993) and serotonin (Takada et al., 1995) in some brain areas. However, a number of studies have shown an increase in nicotine self-administration among smokers when exposed to stress (McKennell, 1970; Frith, 1971) in order to attenuate the subjective feeling of stress-related tension (O'Neill and Parrott, 1992; Parrott, 1993). Although many attempts have been made, these paradoxical stress-reducing properties of nicotine are still not fully understood. Several lines of evidence point at the role of the dopaminergic system in mediating the central effects of stressors and nicotine. First, similarly to the other drugs of abuse, the addictive properties of nicotine are thought to be mediated by dopamine (Di Chiara and Imperato, 1988; Shoaib, 1998). Second, nicotine is known to promote dopamine synthesis and release (Di Chiara and Imperato, 1988; Marshall et al., 1997) and stress also increases the release of dopamine (Imperato et al., 1992). We have demonstrated recently that stress enhances the nicotine-induced increase in dopamine release in rat striatum but not in the nucleus accumbens (Takahashi et al., 1998a). Thus, it appears that the effect of stress and nicotine on dopamine release is additive in some brain regions, while in others it is not.

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However, all the above effects are time-dependent, vary among different brain areas studied and may differ from one stressor to another (Cabib et al., 1988; Mitchell et al., 1989; Carlson et al., 1991). Thus, it is not surprising that there are only a few studies on the role of the brain dopaminergic system in the interaction between stress and nicotine. Moreover, recent observations suggest that various stressors (defined either as systemic or processive) activate different regulatory pathways. Processive stressors (i.e., not life-threatening) require interpretation by the limbic structures, while systemic stressors (i.e., involving the threat of immediate survival value, like respiratory, cardiovascular or immune stressors) are limbic-insensitive and are related directly to the paraventricular nucleus of the hypothalamus (see Herman and Cullinan, 1997 for review). Thus, we decided to investigate the influence of nicotine on time-dependent and region-dependent changes in the dopaminergic system in the striatum and the hippocampus following water immersion restraint stress, which is reported to be a processive stressor (Herman and Cullinan, 1997; Senba and Ueyama, 1997).

2. Material and methods

2.1. Experimental protocol

The study was performed with 9-week-old male Wistar rats. The experimental animals had free access to standard laboratory chow and tap water. After a 2-week adaptation period in a temperature-controlled room (24 ± 1°C) maintained on a 12:12-h light/dark cycle, the rats were randomly divided into groups to receive either nicotine ((−)-nicotine di-(+)-tartrate salt, Sigma, USA; 0.4 mg of the salt/kg, i.p., once daily at 1000 h) or saline (the same volume and route) for 2 weeks. The dose of nicotine injected is similar to the amount that habitual smokers may absorb in a day from twenty cigarettes smoked (Plowchalk and deBethizy, 1992). Immediately after the last injection, a single session of water immersion restraint stress or no stress was applied to both nicotine-treated and control animals, in groups as follows: (1) saline ($n = 18$), (2) saline + stress ($n = 18$), (3) nicotine ($n = 19$), (4) nicotine + stress ($n = 18$). The animals were killed by decapitation after pentobarbital (45 mg/kg, i.p.) anesthesia either immediately after stress (i.e., 3 h after nicotine injection) or 24 and 48 h later (6 animals/group).

2.2. Water immersion restraint stress

Water immersion restraint stress was performed as described previously (Takada et al., 1995). Briefly, the rats were placed in water maintained at 23 ± 1°C for 3 h. Animals were held on the board in an upright position by fixing the four legs using threads and immersed up to the neck in the water.

2.3. Brain samples

The brains were removed and immediately chilled on ice. Hippocampus and striatum was dissected according to Glowinski and Iversen (1966). Thereafter, the samples were immediately frozen. The weight of each region was relatively reproducible from animal to animal. Then, frozen brain tissues were homogenized in 0.4 N perchloric acid and centrifuged at $30{,}000 \times g$ for 10 min at 4°C. The supernatants were passed through a Millipore filter (0.45 μm) and stored at −80°C until assayed.

2.4. High-pressure liquid chromatography (HPLC) procedures

Dopamine and its metabolites, dihydroxyphenylacetic acid, homovanilic acid and 3-methoxytyramine, were measured by HPLC with electrochemical detection. The electrochemical apparatus consisted of a reverse-phase HPLC column (MA-5ODS, Eicom, Kyoto, Japan) using a mobile phase composed of 0.1 M sodium acetate, 0.1 M citric acid, 15% methanol, 0.023% 1-octane sulfonate and 0.0005% EDTA, pH 3.5. The mobile phase was delivered by a pump at a flow rate of 0.3 ml/min. The column temperature was kept at 25°C. The graphite electrode (WE-3G, Eicom) was set at 0.8V (an Ag/AgCl reference electrode). The sample in a volume of 10 μl was injected into the chromatograph. The detection limit for dopamine was 1 pg.

2.5. Statistical analysis

The statistical comparison between experimental groups and/or time points was performed by two-tailed Mann–Whitney *U*-test. Data are expressed as means ± S.E.M. $P < 0.05$ was considered to be statistically significant.

2.6. Ethics

The study was submitted for approval to the Ethics Committee of our University. The committee judged the experimental design and approved the experiments after careful examination.

3. Results

3.1. Time-dependent changes in dopaminergic system in striatum of rats exposed to stress and/or administered with nicotine

The results of this part of the study are summarized in Figs. 1–4. In the non-stressed animals, 2-week treatment with nicotine significantly increased the dopamine level in the striatum ($P < 0.05$). No changes in dihydroxyphenylacetic acid, homovanilic acid and 3-methoxytyramine lev-

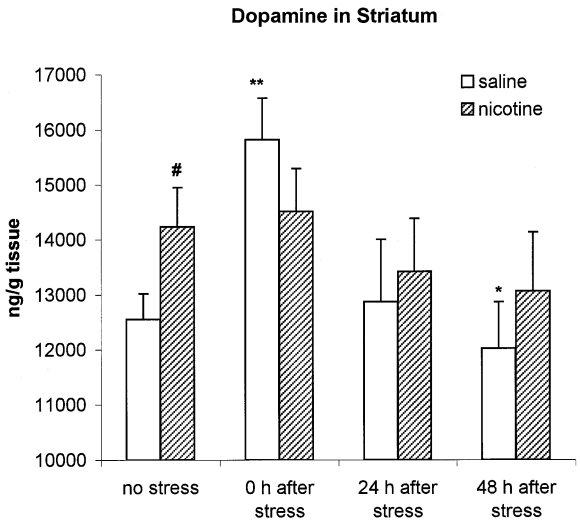

Fig. 1. The effect of stress and/or nicotine administration on dopamine level in the striatum. Data are expressed as means ± S.E.M. $^{\#}P < 0.05$ vs. saline; $^{*}P < 0.05$; $^{**}P < 0.01$ vs. non-stressed control.

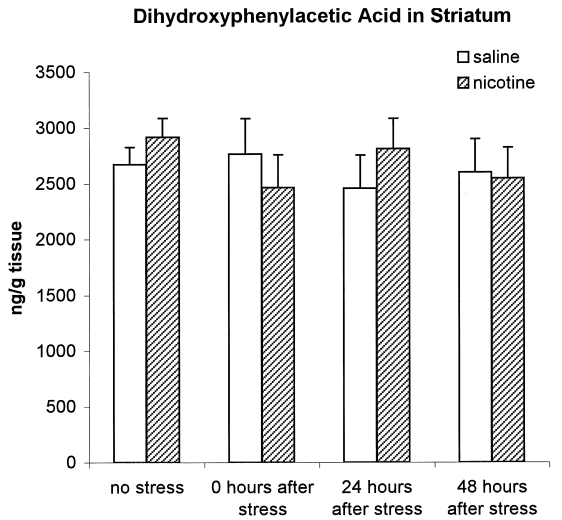

Fig. 3. The effect of stress and/or nicotine administration on dihydroxyphenylacetic acid level in the striatum. Data are expressed as means ± S.E.M.

els were observed at this time point in the nicotine-treated rats in comparison with the control group.

Three hours of water-immersion restraint stress alone produced a sharp increase in dopamine level ($P < 0.01$ vs. respective not-stressed control group), which returned to the normal range 24 h later and then declined below the control level 48 h after restraint ($P < 0.05$). The stress-induced increase in dopamine level immediately after stress was accompanied by a simultaneous sharp decrease in 3-methoxytyramine level ($P < 0.001$) in the studied area, which normalized 24 h later and then remained unaltered until the end of experimental period. No change in dopamine level was observed in the nicotine-treated animals after stress at any time point, but similarly to the nicotine-naive rats a dramatic decline in 3-methoxytyramine level could be detected immediately after water immersion and restraint ($P < 0.001$).

No statistically significant change in dihydroxyphenylacetic acid level was observed in any group of animals at any time point. The homovanilic acid level was parallel to that of dihydroxyphenylacetic acid and was not significantly altered (data not shown). Similarly, the dihydroxyphenylacetic acid + homovanilic acid/dopamine ratio was not altered by any conditions.

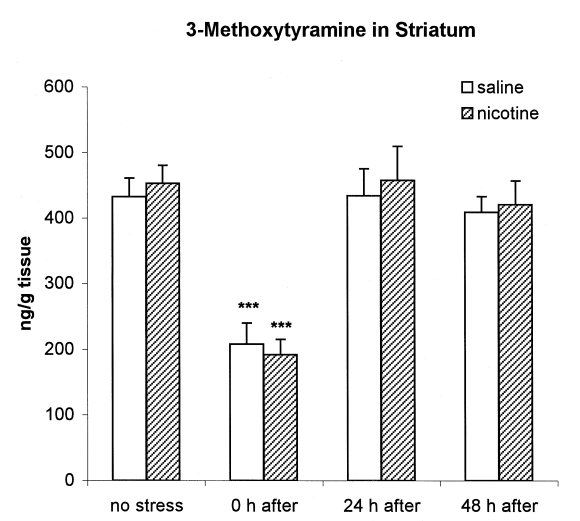

Fig. 2. The effect of stress and/or nicotine administration on 3-methoxytyramine level in the striatum. Data are expressed as means ± S.E.M. $^{***}P < 0.001$ vs. non-stressed control.

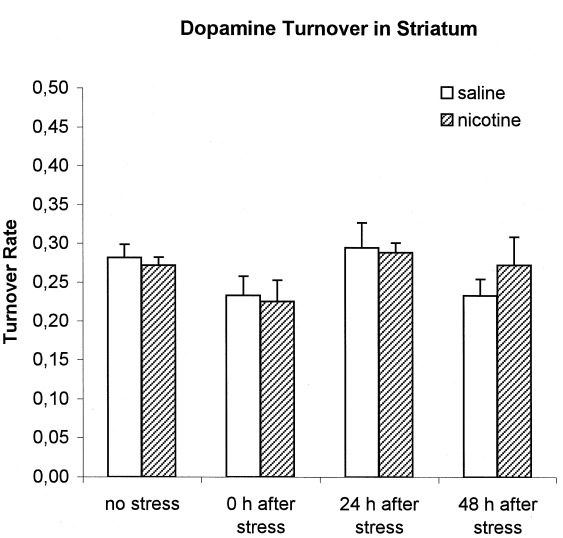

Fig. 4. The effect of stress and/or nicotine administration on the dihydroxyphenylacetic acid + homovanilic acid/dopamine ratio in the striatum. Data are expressed as means ± S.E.M.

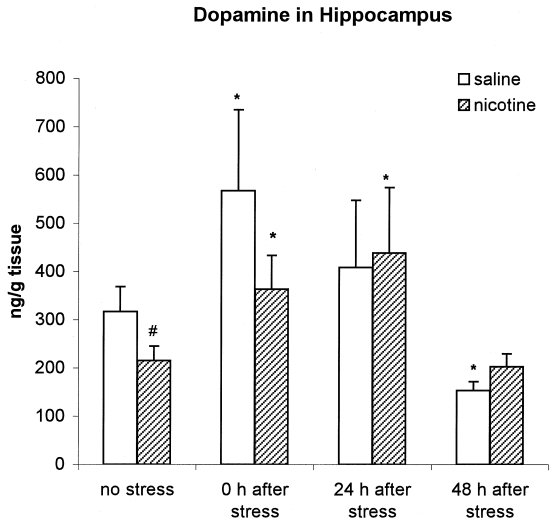

Fig. 5. The effect of stress and/or nicotine administration on dopamine level in the hippocampus. Data are expressed as means ± S.E.M. $^{\#}P < 0.05$ vs. saline; $^{*}P < 0.05$ vs. non-stressed control.

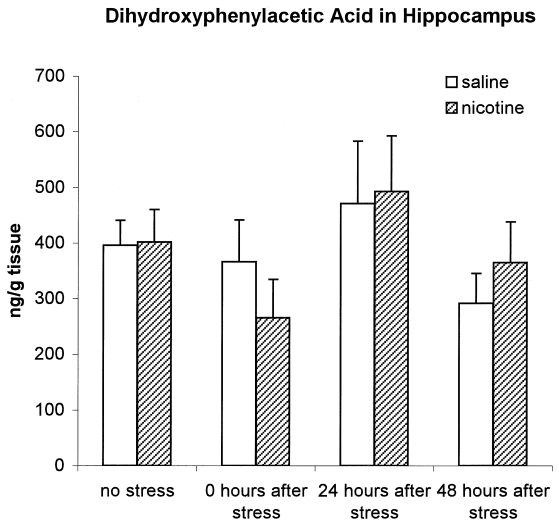

Fig. 7. The effect of stress and/or nicotine administration on dihydroxyphenylacetic acid level in the hippocampus. Data are expressed as means ± S.E.M.

3.2. Time-dependent changes in dopaminergic system in hippocampus of rats exposed to stress and/or administered with nicotine

The results of this part of the study are summarized in Figs. 5–8. In the non-stressed animals, the 2-week treatment with nicotine significantly decreased the dopamine level in the hippocampus ($P < 0.05$). Similarly to the striatum, no significant changes in dihydroxyphenylacetic acid, homovanilic acid and 3-methoxytyramine levels were observed at this time point in the nicotine-treated rats in comparison with the control group. However in this region, unlike in the striatum, the dihydroxyphenylacetic acid + homovanilic acid/dopamine ratio was significantly increased by nicotine ($P < 0.05$).

Three hours after stress a sharp increase in dopamine level was noted ($P < 0.05$ vs. respective not-stressed control group), which was normalized 24 h later and then declined below the control level 48 h after stress ($P < 0.05$). The stress-induced increase in dopamine immediately after restraint was accompanied with a simultaneous sharp decrease in the 3-methoxytyramine level ($P < 0.05$) in the studied area, which increased 24 h later ($P < 0.01$) and remained below control values 48 h after stress ($P < 0.05$). The dihydroxyphenylacetic acid + homovanilic acid/dopamine ratio was dramatically reduced immedi-

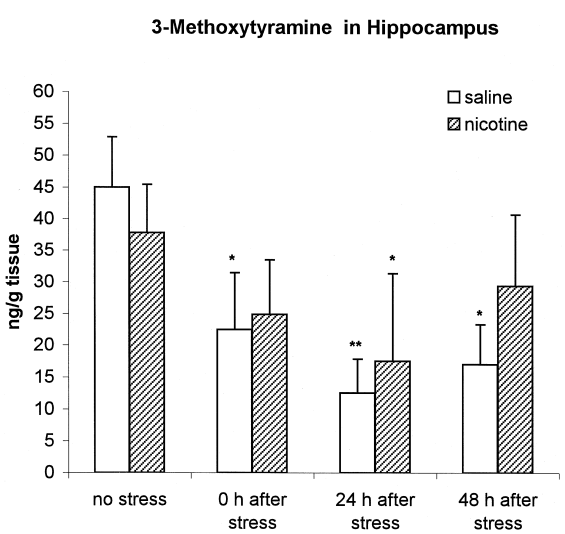

Fig. 6. The effect of stress and/or nicotine administration on 3-methoxytyramine level in the hippocampus. Data are expressed as means ± S.E.M. $^{*}P < 0.05$; $^{**}P < 0.01$ vs. non-stressed control.

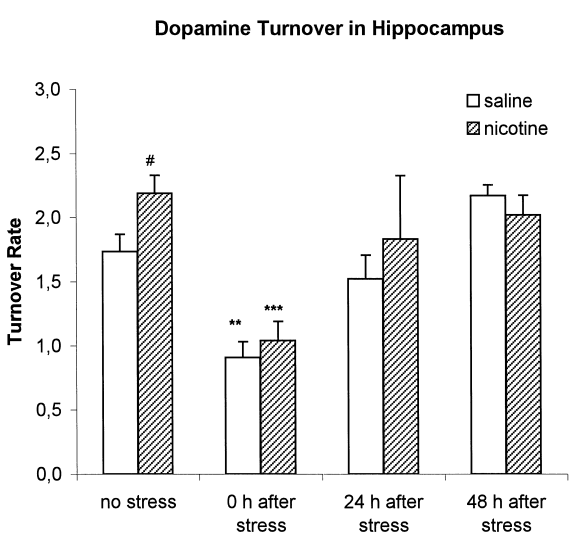

Fig. 8. The effect of stress and/or nicotine administration on the dihydroxyphenylacetic acid + homovanilic acid/dopamine ratio in the hippocampus. Data are expressed as means ± S.E.M. $^{\#}P < 0.05$ vs. saline; $^{**}P < 0.01$, $^{***}P < 0.001$ vs. non-stressed control.

ately after stress ($P < 0.01$) and returned to the normal range after 24 h. Nicotine pretreatment failed to prevent the stress-induced increase in dopamine in the hippocampus immediately after ($P < 0.05$) and 24 h after stress ($P < 0.05$), but prevented the decrease in this amine 48 h after water immersion and restraint when compared with that of respective non-stressed rats. Similarly, the stress-induced drop in the dihydroxyphenylacetic acid + homovanilic acid/dopamine ratio was not prevented by nicotine ($P < 0.001$). In contrast to the nicotine-naive rats, in the nicotine-treated rats, the stress-induced drop in 3-methoxytyramine level was significant only 24 h after stress ($P < 0.05$) and then returned to normal range.

As in the striatum, no statistically significant changes in dihydroxyphenylacetic acid level were observed in hippocampi of any experimental group at any time point. The homovanilic acid level was parallel to the dihydroxyphenylacetic acid level and was not significantly altered (data not shown).

4. Discussion

In the present study, we focused on changes in the dopaminergic system of the striatum (the terminal region of the dopaminergic nigrostriatal pathway; Moore and Bloom, 1978) and the hippocampus (which receives dopaminergic innervation from raphe nuclei and/or ventral tegmental area; Swanson, 1982) following stress and/or nicotine administration. Both of the above regions were previously demonstrated to possess dopaminergic receptors (Happe et al., 1994). The hippocampus is one of the anatomical substrates involved in emotions, cognitive functions and motivated behavior, including the circuitry for the stress response and reward-related events (see Herman and Cullinan, 1997), while the striatum is implicated in locomotor responses which may be altered by stress (Takahashi et al., 1998b) or nicotine (Fung and Lau, 1988).

The idea for the study was based on the fact that among the variety of brain neurotransmitters dopamine is considered to be responsible for the rewarding properties of nicotine (Di Chiara and Imperato, 1988; Shoaib, 1998) and this amine was also demonstrated to be altered by various stressors (Cabib et al., 1988; Carlson et al., 1991; Imperato et al., 1992). Since smokers increase their nicotine self-administration when exposed to stress (McKennell, 1970; Frith, 1971), we speculated that nicotine may alter dopaminergic functions during stress. This hypothesis was strongly supported by recent results from our laboratory, which demonstrated differential changes in dopamine release from the striatum and the nucleus accumbens after stress and/or nicotine administration (Takahashi et al., 1998a). To our knowledge, the role of the dopaminergic system in the hippocampus during stress after chronic administration of nicotine has not been studied so far.

In the present study, 2 weeks of nicotine administration resulted in a significant increase in the total dopamine level in the striatum accompanied by a simultaneous decrease in the dopamine level in the hippocampus. There seems to be general agreement about the increase in striatal dopamine elicited by nicotine (Yu and Wecker, 1994; Whiteaker et al., 1995) or cotinine (Dwoskin et al., 1999) but hippocampal changes in this amine are less clear. In our previous report in which we used the microdialysis technique (Takahashi et al., 1998a) we observed a decrease in the extracellular dopamine level in the nucleus accumbens (another component of the limbic system) following the same schedule of nicotine administration. Brazell et al. (1991) demonstrated a lack of change in dopamine content in the hippocampus after administration of nicotine in the same dose as used in our study and an increase in dopamine content following the higher dose; however, in their study, nicotine was injected in an acute manner. Similarly, Kubo et al. (1989) concluded that a high (1 mg/kg, s.c.), single dose of nicotine was able to increase dopamine in eight brain regions studied including the hippocampus. Thus, taken together, their and our data are in support of the concept that the acute and chronic effects of nicotine in the brain are at least different if not the opposite.

It seems unlikely that the increase in striatal dopamine following nicotine administration is related to the hypothermic effect of the drug, since nicotine, when administered to mice in doses similar to those used by us (0.3 mg/kg), failed to cause any changes in striatal dopamine, dihydroxyphenylacetic acid and homovanilic acid concentrations, although it produced hypothermia (Haikala et al., 1986). The observed effect of nicotine on the dopamine level in the striatum also cannot be explained by changes in the metabolism of this amine. Thus, it might simply have been caused by alterations in tyrosine hydroxylase activity. Indeed, it has been demonstrated that this enzyme, which serves as the rate-limiting step in dopamine synthesis, can be upregulated by nicotine (Hiremagalur et al., 1993) or stress (McMahon et al., 1992) in some tissues including brain (Masserano et al., 1981; Rusnak et al., 1998). The most striking feature of this part of the study, however, is that nicotine may differentially regulate dopamine levels in areas related to the limbic system (i.e., hippocampus) and those related to locomotion (i.e., striatum).

We demonstrated that water-immersion and restraint alone sharply elevated the level of dopamine in both the hippocampus and the striatum when measured immediately after stress, an effect which gradually returned toward normal within 24–48 h. Other studies which assessed the effect of restraint or other stress stimuli on dopaminergic systems demonstrated time, region and strain dependency of such an effect (Cabib et al., 1988; Abercrombie et al., 1989; Carlson et al., 1991; Inoue et al., 1994). Carlson et al. (1991) have shown an increase in striatal dopamine

15 min after restraint (but without water-immersion) followed by a decrease when the duration of stress was prolonged to 30 or 60 min. Thus, it appears that rearrangements in the dopaminergic system are not only region- and time-dependent but also may vary depending upon different kinds of stressors.

The stress-induced increase in dopamine in the striatum was attenuated by nicotine. It is known that nicotinic acetylcholine receptors exist on striatal dopaminergic neurons (Happe et al., 1994) and that nicotine induces the expression of tyrosine hydroxylase (Hiremagalur et al., 1993). Therefore, one plausible explanation is that repeated nicotine injections increased the striatal dopamine level to the maximum, which could not be further increased by stress.

Similar but less pronounced changes (significant only 48 h after stress) were observed in the hippocampus. In our previous study (Takahashi et al., 1998a), we showed that the extracellular dopamine level in the striatum following electric footshock increased only in nicotine-administered animals but not in saline-treated animals. In contrast, in that study (Takahashi et al., 1998a), footshock-induced increase in dopamine level in the nucleus accumbens was blunted by nicotine pretreatment. Thus, it once again appears that nicotine differentially modulates the dopaminergic system in the striatum and the limbic areas. Moreover, dopaminergic responses may vary depending probably on whether stressor conditions involve immobilization or not.

3-Methoxytyramine is the metabolite of dopamine produced by catechol-o-methyltransferase exclusively upon its release into the synaptic cleft (for review, see Wood and Altar, 1988). Thus, 3-methoxytyramine serves as an indirect indicator of dopamine release from nerve terminals. In this study, we showed that 3-methoxytyramine levels decreased dramatically both in the striatum (transient effect) and in the hippocampus (prolonged effect) after water-immersion restraint stress. Thus, it can be concluded that stress inhibits the release of dopamine into the synaptic cleft in these regions. Although nicotine alone did not alter 3-methoxytyramine levels in the regions studied, it attenuated stress-induced changes in 3-methoxytyramine in the hippocampus, but failed to do so in the striatum. Indeed, it has been shown previously that acute nicotine releases dopamine into the synaptic cleft under normal conditions (Yu and Wecker, 1994; Whiteaker et al., 1995), but to our knowledge, there is no study on such an effect after chronic administration of nicotine and/or during stress.

Dihydroxyphenylacetic acid is the main metabolite of dopamine in the rat brain (see Elsworth and Roth, 1997) and is considered an accurate index of intraneuronal dopamine degradation by monoamine oxidase (Wood and Altar, 1988). In this study, dihydroxyphenylacetic acid and homovanilic acid (its secondary metabolite) levels remained unchanged, although a nonsignificant tendency toward a decrease was observed immediately after stress. Thus, the decrease in the dopamine turnover ratio in the hippocampus after stress reflected both an increase in the level of dopamine and a decrease in the levels of its metabolites. Such changes are typical for inhibition of monoamine oxidase. There is a striking coincidence between these data and the finding that the levels of the endogenous monoamine oxidase inhibitor tribulin increases after stress (Bhattacharya et al., 1988) and the level of its constituent isatin is higher in the hippocampus than in other brain areas (Glover, 1998).

In summary, in this study, we have shown time- and region-dependent changes in the dopaminergic system following stress and/or nicotine administration. We demonstrated the protective effect of chronic nicotine administration against stress-induced changes in dopamine level and its release in the regions critically involved in locomotion (striatum) and emotions (hippocampus), which are altered by stress.

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