Psychopharmacology (1999) 145:433–441

ORIGINAL INVESTIGATION

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Nicotine blocks quinpirole-induced behavior in rats: psychiatric implications

Received: 1 January 1999 / Final version: 25 March 1999

Abstract *Rationale and objectives:* Because of known and imputed roles of dopaminergic and nicotinic cholinergic systems in a variety of neurological and neuropsychiatric disorders, combined neurochemical and behavioral methods assessments were made to study the intermodulatory roles of these neurochemical systems. *Methods:* Rats were treated daily during postnatal ontogeny with the dopamine D_2/D_3 agonist, quinpirole (QNP) HCl (1.0 mg/kg/day), for the first 3 weeks from birth. This priming process replicated previous findings of behavioral sensitization, manifested as hyperlocomotion, increased paw treading with jumping, and increased yawning. *Results:* All effects were partially or totally blocked by acute treatment with nicotine (0.3 mg/kg, i.p.). The effects of nicotine, in turn, were partially or totally blocked by the nicotinic antagonist, mecamylamine (1.0 mg/kg, i.p.). In concert with these behavioral actions, QNP-primed rats displayed greater binding of [^{3}H]cytisine in midbrain and cerebellum and greater [^{125}I]α-bungarotoxin binding in hippocampus and striatum. *Conclusions:* Accordingly, these selective ligands for $\alpha_4\beta_2$ and α_7 nicotinic receptors, respectively, demonstrate that nicotinic receptors are altered by dopamine D_2/D_3 agonist treatment of rats with primed dopamine receptors. We propose that nicotinic agonists may have a therapeutic benefit in behavioral disorders brought about by central dopaminergic imbalance.

Key words Nicotine · Nicotinic receptor · Quinpirole · Animal model · Psychiatric disorder

Introduction

Central dopaminergic dysfunction has been implicated in a variety of neurological and neuropsychiatric disorders, including schizophrenia and Tourette syndrome (TS). It has been proposed that dopaminergic hypoactivity in the frontal cortex and dopaminergic hyperactivity in the subcortical regions are major contributing factors in the symptomatology of schizophrenia (see recent reviews by Haber and Fudge 1997; Lidow et al. 1998; O'Donnell and Grace 1998; Wilson et al. 1998). Similarly, a frontal-subcortical circuit dysfunction involving dopaminergic neurotransmission has been hypothesized in symptom manifestations of TS (see review by Singer 1997). Moreover, haloperidol, a neuroleptic which blocks dopamine D_2 receptors is effective in both schizophrenia and TS. However, the side effects associated with haloperidol limit its long-term therapeutic applicability (Sanberg et al. 1997; Wilson et al. 1998).

Involvement of other neurotransmitter systems in schizophrenia and TS, either directly or through the dopaminergic system, is now well accepted (Deutsch et al. 1989; Meltzer 1994; Strous and Javitt 1996; Freedman et al. 1997; Willner 1997; Singer 1997; Csernansky and Bardgett 1998). Indeed, it has been proposed that the primary abnormality in schizophrenia might be in the systems that have an intimate interaction with the dopamine system (Willner 1997).

Central interaction between nicotinic cholinergic and dopaminergic systems is amply documented (see reviews by Clarke 1995; Levin and Rose 1995; Nisell et al. 1995; Stolerman et al. 1995; Dani and Heinemann 1996; Wonnacott 1997; Balfour et al. 1998). Moreover, possible therapeutic benefits of nicotine in both schizophrenia

This work was supported in part by Departments of Pharmacology at Howard University, Silesian Academy of Medicine and East Tennessee State University

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and TS have been suggested (Adler et al. 1993, 1998; Freedman et al. 1997; Sanberg et al. 1997).

Chronic treatment of rat pups with quinpirole (QNP), an agonist at the D_2/D_3 receptors results in behavioral sensitization manifested in hyperlocomotion, increased yawning, paw treading and jumping behavior (Kostrzewa et al. 1990, 1993a, 1993b; Kostrzewa and Brus 1991; Kostrzewa 1995). Because these QNP-induced behaviors can be prevented by administration of neuroleptics, including haloperidol (reviewed in Kostrzewa 1995), they may be a suitable model for screening drugs that may be effective in specific psychiatric disorders. As mentioned above, nicotinic agonists may have therapeutic potentials in various psychiatric disorders (Freedman et al. 1997; Sanberg et al. 1997; see also Tizabi et al. 1998, 1999). Thus, this study was designed to investigate whether QNP-induced behaviors might also be antagonized by administration of nicotine. Moreover, to further delineate possible involvement of central nicotinic receptors, the effects of mecamylamine, a nicotinic antagonist, and the effects of QNP-induced sensitization on the density and affinity of nicotinic receptors in discrete brain regions were also evaluated.

Materials and methods

Drugs

QNP HCl, (–)-nicotine bitartrate and mecamylamine HCl were purchased from Research Biochemicals Inc. (Natick, Mass.). The QNP dose refers to the salt form, while all other substances are given as base.

Treatment

In this study, rats were behaviorally sensitized to QNP (primed) by daily treatments for the first 3 weeks of postnatal ontogeny with QNP HCl (1.0 mg/kg/day). In previous studies, rats were similarly sensitized, but with a higher dose of QNP HCl (3.0 mg/kg/day) for 28 days (Kostrzewa et al. 1990, 1991, 1993b; Kostrzewa and Brus 1991) or lower dose of QNP HCl, either 200 µg/kg/day (Brus et al. 1998a) or 50 µg/kg/day (Brus et al. 1998b; Kostrzewa et al. 1993a). The dose of QNP in the current study was selected to be approximately midway between these previously observed dose boundaries, on a logarithmic scale, and for a duration approximately midway between an 11-day and 28- to 32-day treatment duration of those studies. Control rats (non-primed) received saline instead of QNP for the same time period.

Behavioral evaluation

Between day 23 and day 29, rats were treated i.p. with one or a combination of the following: vehicle (saline), QNP HCl (1.0 mg/kg), nicotine (0.3 mg/kg) or mecamylamine (1.0 mg/kg). In combination treatments, mecamylamine preceded nicotine which preceded QNP. Each treatment preceded the next by 10 min. It was shown previously that the animals maintain sensitization within this time span (Kostrzewa et al. 1993a, 1993b). Furthermore, this procedure allowed for tests to be conducted within a certain time period of the day (1100–1400 hours). All treated animals were matched with their proper control at each test session. The doses of nicotine and mecamylamine were selected on the basis of numerous studies evaluating the behavioral effects of these drugs (Tizabi et al 1998, 1999). Immediately after the last injection, each rat was placed in individual clear plastic cages (48×26×36 cm) in a quiet, well-ventilated and well-lit room, while a camcorder recorded locomotor activity and other behaviors (paw treading and jumping), 5 min after being placed in the cage. Paw treading represents the coordinated swim-like movements of rats while rearing. Jumping in this study was exclusively vertical jumping, occurring while the animal was rearing and involving hindlimbs, exclusively. Locomotor activity was taken as numbers of cage crossings from back-to-front or vice-versa (score of 1), or half crossings from side-to-side (score of 0.5) during a 10-min interval starting 20 min after placement in the cage. Paw treading and jumping were also recorded for the same time interval. The reason for selecting a 10-min time period was to allow for a simple and relatively quick evaluation of the effects of various pretreatments on QNP-induced effects. Each of the parameters was quantified from videotapes by an impartial observer who was not blinded to treatment groupings (Kostrzewa et al. 1993, 1993b, 1994). Each group consisted of four male and four female rats.

For evaluation of yawning behavior, male rats were challenged between day 30 and day 40 after birth with QNP HCl (50 µg/kg i.p.). In this study, each rat was placed individually in a clear plastic cage, as described above, and was observed for 60 min. The number of yawns was recorded for each rat for the entire session. The effects of nicotine, mecamylamine or their combination on QNP-induced yawning were also determined.

Tissue collection

On day 30, two groups of rats (eight rats per group, four male and four female in each group) that were treated for the first 21 days after birth with vehicle or QNP were decapitated between 1100 hours and 1300 hours. Brains were rapidly removed, frozen on dry ice, and stored at –80°C until dissected and assayed for receptor density and binding affinity.

Brain dissection and determination of nicotinic receptors

Brain dissection and determination of [^{3}H]cytisine and [^{125}I]α-bungarotoxin binding were carried out as described previously in detail (Tizabi et al. 1999). Briefly, frontal cortex (up to the genu of corpus callosum and excluding the olfactory bulb and olfactory tubercle), cerebral cortex (the rest of the cortex, left and right hemisphere), striatum (bilateral), hippocampus (bilateral), midbrain (containing the thalamus), colliculi (superior and inferior) and cerebellum were obtained. Tissue was homogenized in ice-cold 50 mM Tris-HCl buffer (pH 7.0 at room temperature). Following various washes and centrifugation, the final homogenate equivalent to approximately 10–20 mg tissue were divided into two sets of tubes for determination of [^{3}H]cytisine and [^{125}I]α-bungarotoxin binding. These ligands bind specifically to the $\alpha_4\beta_2$ and α_7 nicotinic receptor subtypes, respectively (Flores et al. 1992; Barrantes et al. 1995). For binding affinity measurements in cortex, eight concentrations of [^{3}H]cytisine (0.3–12 nM) or eight concentrations of [^{125}I]α-bungarotoxin (0.1–10 nM) were utilized. Scatchard plots (for determination of B_{max} and K_d) were generated using a radioligand binding analysis program. Protein concentration in the final homogenate was determined by the method of Bradford (1976).

Statistical analysis

Data were analyzed by means of one-way analysis of variance (ANOVA), followed by a Newman-Keuls post-hoc test when significant main effects were indicated. All analyses were two-tailed and used a P value of 0.05 or less to determine significance.

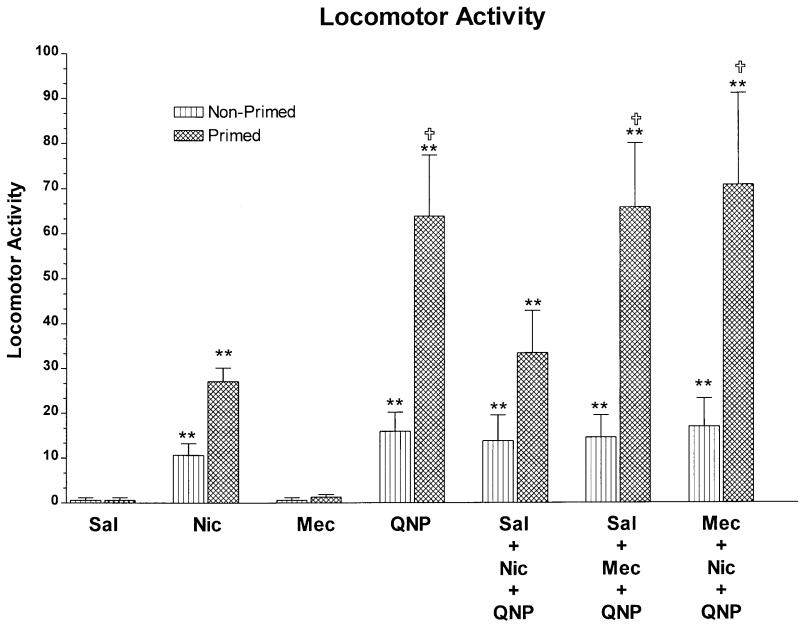

Fig. 1 Effects of nicotine (Nic), mecamylamine (Mec) and their combination on locomotor activity in male and female rats that were primed in postnatal ontogeny by quinpirole (QNP, 1.0 mg/kg/day for 21 days after birth). Non-primed rats received saline for the same time period. Locomotor activity, assessed from 23 days until 29 days after birth, represents numbers of cage crossings or half-cage crossings from front to back or side to side. Values are expressed as mean ± SEM, n=8/group. **P<0.01 compared with saline-treated group in the same category [note, this group is treated chronically with vehicle or QNP prior to acute administration of saline (Sal)]; †P<0.05 compared with Sal + Nic + QNP in the same category

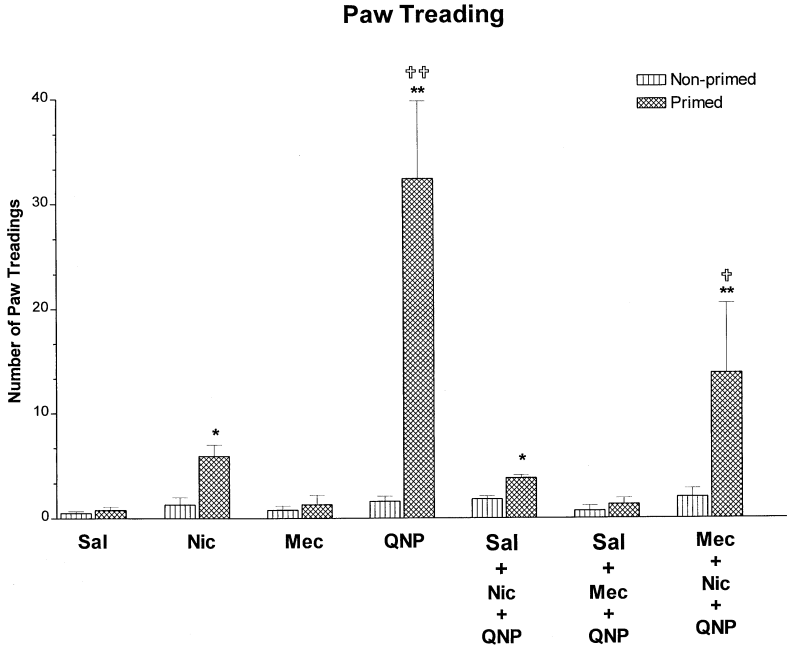

Fig. 2 Effects of nicotine (Nic), mecamylamine (Mec) and their combination on paw treading in male and female rats that were primed in postnatal ontogeny by quinpirole (QNP) (see legend in Fig. 1 for details). Paw treading was assessed from 23 days until 29 days after birth. Values are expressed as mean ± SEM, n=8/group. *P<0.05 compared with saline-treated group in the same category; **P<0.01 compared with saline-treated group in the same category; †P<0.05 compared with Sal + Nic + QNP in the same category; ††P<0.01 compared with Sal + Nic + QNP in the same category

Results

Effects on locomotor activity

Figure 1 presents the results with respect to locomotor activity. There was a significant main effect of treatments (F7,56=9.26, P<0.001). Sensitization to QNP pretreatment was evident by more than a fourfold increase in locomotion in the primed rats compared with non-primed rats. Nicotine alone caused a moderate increase in this behavior in both primed and non-primed rats (P<0.01). Mecamylamine alone had no significant effect on locomotor activity in either group. QNP-induced locomotor activity following nicotine pretreatment was indistinguishable from the effect of nicotine by itself, implying complete block of QNP effect by nicotine. While mecamylamine had no effect on QNP-induced locomotor activity, it completely blocked the effects of nicotine on QNP-induced locomotion in both primed and non-primed rats (P<0.05).

Effects on paw treading

Figure 2 presents the results with respect to paw-treading behavior. There was a significant main effect of treatments (F7,56=8.94, P<0.001). Only the primed rats exhibited a dramatic increase in paw treading following

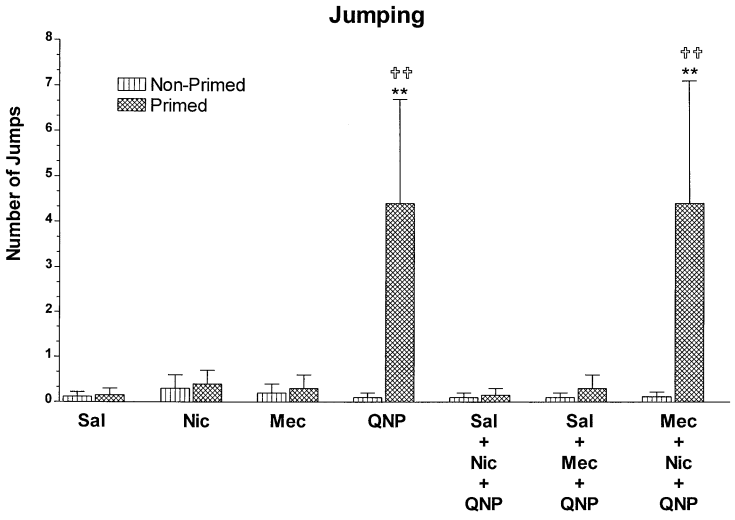

Fig. 3 Effects of nicotine (Nic), mecamylamine (Mec) and their combination on jumping behavior in male and female rats that were primed in postnatal ontogeny by quinpirole (QNP) (see legend in Fig. 1 for details). Jumping was assessed from 23 days until 29 days after birth. Values are expressed as mean ± SEM, *n*=8/group. ***P*<0.01 compared with saline-treated group in the same category; ††*P*<0.01 compared with Sal + Nic + QNP in the same category

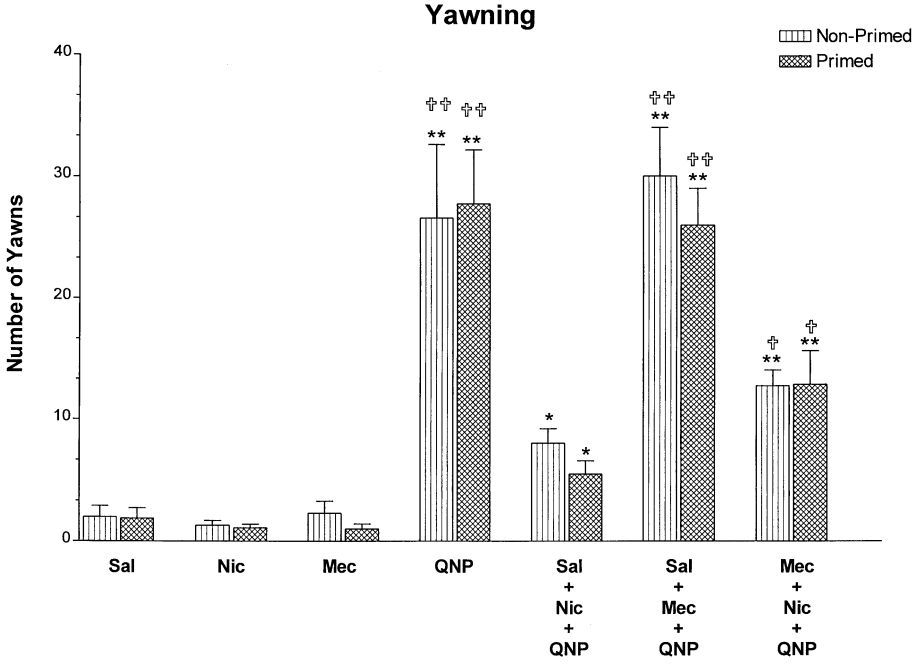

Fig. 4 Effects of nicotine (Nic), mecamylamine (Mec) and their combination on yawning behavior in male rats that were primed in postnatal ontogeny by quinpirole (QNP) (see legend in Fig. 1 for details). Yawning was assessed from 30 days until 40 days after birth. Values are expressed as mean ± SEM, *n*=8/group. **P*<0.05 compared with saline-treated group in the same category; **P<0.01 compared with saline-treated group in the same category; †*P*<0.05 compared with Sal + Nic + QNP in the same category; ††*P*<0.01 compared with Sal + Nic + QNP in the same category

acute challenge with QNP. Nicotine alone caused a slight increase in paw treading in primed rats only ($P<0.05$), while mecamylamine alone had no significant effect. QNP-induced paw treading following nicotine pretreatment was indistinguishable from the effect of nicotine by itself, implying complete block of QNP effect by nicotine. Mecamylamine also blocked QNP-induced effects on paw treading. However, combination pretreatment with both mecamylamine and nicotine resulted in partial block (approximately 69%) of QNP-induced effects on paw treading.

Effects on jumping

Figure 3 presents the results with respect to jumping behavior. There was a significant main effect of treatments ($F7,56=5.95$, $P<0.01$). Only the primed rats exhibited a significant increase in jumping behavior following acute challenge with QNP. Neither nicotine nor mecamylamine alone had any significant effect on this behavior. However, nicotine completely blocked the jumping induced by QNP ($P<0.01$). QNP-induced jumping was also totally blocked by mecamylamine. However, combination treatment with both mecamylamine and nicotine resulted in complete reversal of the effects of either drug alone ($P<0.01$). In a separate study, it was verified that pretreatment with the D_2 antagonist spiperone (0.3 mg/kg) (Kostrzewa et al. 1993b) or haloperidol (1 mg/kg) totally blocked QNP-induced jumping behavior.

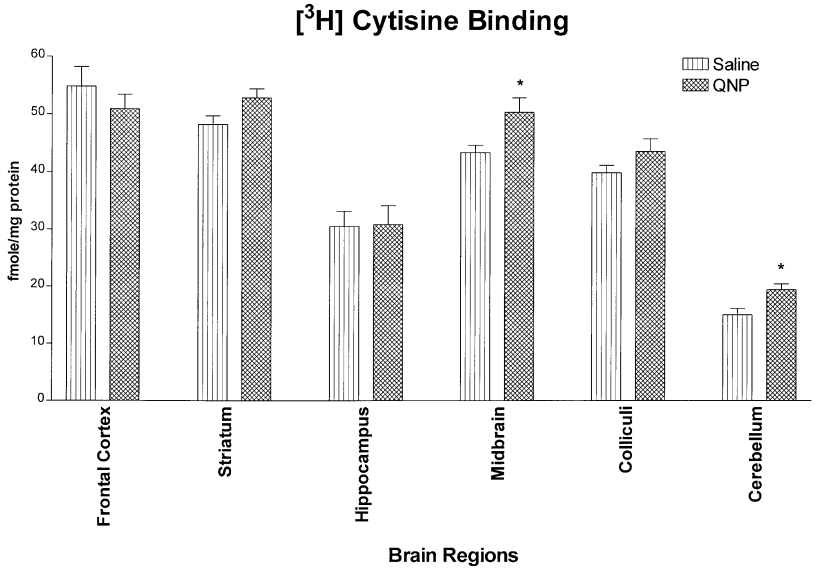

Fig. 5 Effects of ontogenetic quinpirole (QNP) priming (1.0 mg/kg/day for 21 days after birth) on [^{3}H]cytisine binding in various brain regions of rats. Brains were taken at 30 days after birth. Values are mean ± SEM, *n*=8/group. **P*<0.05 compared with saline-treated rats

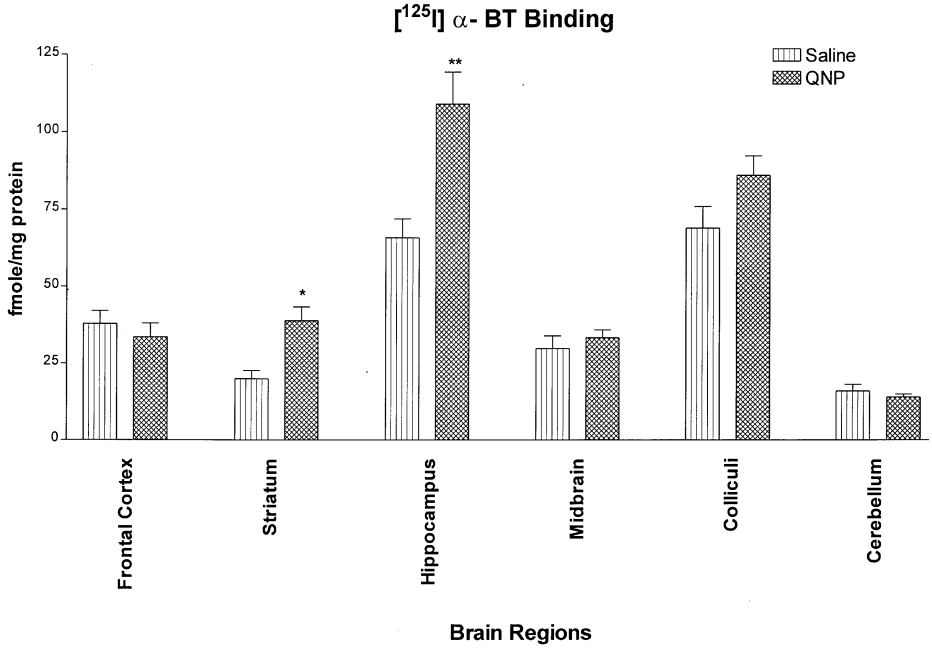

Fig. 6 Effects of ontogenetic quinpirole (QNP) priming (1.0 mg/kg/day for 21 days after birth) on [^{125}I]α-bungarotoxin binding in various brain regions of rats. Brains were taken at 30 days after birth. Values are mean ± SEM, n=7–8/group. **P*<0.05 compared with saline-treated rats; ***P*<0.01 compared with saline-treated rats

Effects on yawning

Figure 4 presents the results with respect to yawning behavior. There was a significant main effect of treatments ($F7,56=9.96$, $P<0.001$). Acute treatment of either primed or non-primed rats with QNP resulted in a significant increase in yawning episodes. Neither nicotine nor mecamylamine had any effects of their own on the yawning behavior in either primed or non-primed rats. Whereas nicotine reduced QNP-induced yawning by 70–80% in both groups ($P<0.01$), mecamylamine had no effect on QNP-induced yawning in either group. The effects of nicotine on QNP-induced yawning, however, was partially antagonized by mecamylamine pretreatment in primed (approximately 33%) and non-primed (approximately 25%) rats ($P<0.05$).

Effects of QNP on nicotinic receptors

Figure 5 presents the effects of chronic QNP treatment (QNP priming in rat pups) on [^{3}H]cytisine binding (specific for $\alpha_4\beta_2$ nicotinic receptor subtype) in discrete brain regions. QNP-treated rats had elevated [^{3}H]cytisine binding in midbrain (16%, $F1,14=6.21$, $P=0.03$) and cerebellum (29% $F1,14=8.0$, $P=0.02$). No significant effect was detected in any other area examined. Moreover, the binding affinity measured in the cortex did not differ be-

Table 1 Effects of ontogenetic QNP priming (1.0 mg/kg/day ×21 days, from birth) on [^{3}H]cytisine and [^{125}I]alpha-bungarotoxin (α-BT) binding parameters in the cortex at 30 days from birth

	[^{3}H] Cytisine binding		[^{125}I] α-BT binding	
	B_{max} (fmole/mg protein	Kd nM	B_{max} (fmole/mg protein)	Kd nM
Saline	41.3±3.1	1.14±0.1	54.8±2.9	1.1±0.22
QNP	42.4±2.8	1.25±0.1	54.4±2.6	1.3±0.28

Values are Mean±SEM, n=7–8/groups

tween QNP-treated and control rats (Table 1). In a separate study (data not shown), addition of QNP (0.01–100 μM) to incubation medium did not affect [^{3}H]cytisine binding in cortical tissue.

Figure 6 presents the effects of chronic QNP treatment on [^{125}I]α-bungarotoxin binding (specific for α_7 nicotinic receptor subtype) in discrete brain regions. QNP-treated rats exhibited elevated [^{125}I]α-bungarotoxin binding in hippocampus (65%, F1,13=6.07, P=0.03) and striatum (94%, F1,14=13.4, P=0.003). No significant effect was detected in any other area examined. The binding affinity measured in the cortex did not differ between QNP-treated and control rats (Table 1). In a separate study (data not shown), addition of QNP (0.01–100 μM) to incubation medium did not affect [^{125}I]α-bungarotoxin binding in cortical tissue.

Discussion

The results of this study indicate that assorted behaviors induced by acute dopamine D_2/D_3 agonist treatment of rats, D_2-primed in postnatal ontogeny, can be totally or partially blocked by acute nicotine pretreatment. The effects of nicotine, in turn, can be totally or partially blocked by pretreatment with mecamylamine, a nicotinic receptor antagonist. This, plus the finding that chronic QNP treatment resulted in increased nicotinic receptor binding in specific brain regions, suggests that at least some of the effects of QNP may be mediated by central nicotinic cholinergic systems.

Antagonism of QNP-induced behavior by nicotine could have significant implications in neuropsychiatric disorders that might be brought about by an imbalance in central dopaminergic systems. Indeed, the results suggest that nicotinic agonists may be of therapeutic benefit in such disorders. Dopaminergic imbalance has been hypothesized to be causally related to such disorders as schizophrenia and TS (Haber and Fudge 1997; Singer 1997; Lidow et al. 1998; O'Donnell and Grace 1998; Wilson et al. 1998). Haloperidol, a dopamine D_2 receptor antagonist is effective in both schizophrenia and TS (Sanberg et al. 1997; Wilson et al. 1998). It also blocks QNP-induced behaviors described in this study (Kostrzewa 1995). The similarity between nicotine and haloperidol in counteracting QNP-induced behaviors suggests a possible advantage in combining these two treatments for the above-mentioned disorders. Interestingly, preliminary clinical studies indicate advantageous combination of nicotine and haloperidol in the treatment of schizophrenia (Levin et al. 1996) and TS (Sanberg et al. 1997).

Actions of nicotine are presumably mediated by specific nicotinic cholinergic receptors, although interaction between nicotine and other ligand-gated ion-channel receptors, such as glutamatergic *N*-methyl-D-aspartate (NMDA) receptors, has also been documented (Court et al. 1990; Aizenman et al. 1991; Kiba and Jayaraman 1994; Zhang et al. 1994). Various subtypes of nicotinic receptors with distinct structural, physiological and pharmacological properties have been identified in the brain (see reviews by Lukas and Bencherif 1992; Albuquerque et al. 1995; Clarke 1995; Conti-Fine et al. 1995; Olale et al. 1997; Changeux et al. 1998). Activation of nicotinic receptors may influence the release of a number of neurotransmitters including dopamine (Wonnacott 1997). Our results indicate that the two prominent nicotinic receptor subtypes, $\alpha_4\beta_2$ and α_7, are both affected by QNP, although to different degrees and in different brain regions. Because we did not detect displacement of ligands specific for these receptor subtypes by QNP in in-vitro binding assays, it will be of interest to determine the mechanism of QNP-induced increases in nicotinic receptors. In addition, we did not detect any gender differences in either the behavioral or neurochemical parameters. However, further experiments specifically designed to address possible gender influences are required.

Although the significance of these receptor changes in relation to observed behavioral changes remains to be elucidated, it is of relevance to note that nicotinic interactions with dopaminergic neurotransmission in mesolimbic and nigrostriatal pathways may be responsible for the observed locomotor effects (Clarke 1990; Richardson and Tizabi 1994; Museo and Wise 1995). Alternatively, changes in locomotor activity could occur indirectly, as a result of changes in stereotypy that is also mediated by the same pathways (Lyon and Robbins 1975; Copeland et al. 1980). Thalamic nuclei are also rich in nicotinic receptors and their influence on thalamo-cortico-subcortical circuitry may have significant roles in modulation of the studied behaviors (Clarke 1995). However, nicotinic receptors in the hippocampus may be intimately involved in cognitive functions such as sensory gating and attentional processes (Freedman et al. 1997). Participation of cerebellar nicotinic receptors in motor coordination has been suggested by studies demonstrating that local injection of nicotine into cerebellum overcomes the ataxia induced by alcohol administration in mice (Dar et al. 1994).

The complexity of behavioral disorders such as schizophrenia or TS precludes, at least theoretically, the assignment of a single neurotransmitter system dysfunction, as the sole culprit. Indeed, ample evidence implicates other neurotransmitter systems as well (Deutsch et al. 1989; Meltzer 1994; Strous and Javitt 1996; Freedman et al. 1997; Wilner 1997; Singer 1997; Csernansky and Bardgett 1998). Thus, it is likely that each disorder may be a cluster of various subtype disorders with different neurochemical bases. Therefore, a drug that might interact in some specific ways with various transmitter systems, may have a unique advantage in treatment of such disorders. In this regard, it is of interest to note that nicotine may be of value in psychiatric disorders that may be brought about by glutamatergic imbalance (Tizabi et al. 1998). An important distinction of interactions of nicotine with glutamatergic versus the dopaminergic system, however, is that the effects of nicotine in the glutamatergic paradigm are not antagonized by mecamylamine, whereas, in this paradigm, the effects of nicotine are partially or totally antagonized by mecamylamine. Thus, depending on the etiology and/or underpinning neurotransmitter abnormality of the manifested symptoms, specific combination pharmacotherapy could prove more effective.

It should be noted that mecamylamine blockade of nicotine effects on some QNP-induced behaviors in our study might also involve interactions at peripheral (ganglionic) nicotinic receptors. This is because mecamylamine alone also blocked QNP-induced effects on paw treading and jumping behavior; however, the combination of mecamylamine and nicotine, partially or totally restored the QNP effects on these behaviors (Fig. 2 and Fig. 3). The extent of central versus peripheral nicotinic receptor participation in observed effects remains to be evaluated. Moreover, it remains to be determined whether any pharmacokinetic interactions between the administered drugs may be responsible for the observed effects.

Because administration of nicotine alone in primed rats resulted in similar, albeit smaller increases in locomotor activity and paw treading (Fig. 1 and Fig. 2), it could be argued that nicotinic antagonism of QNP effects on these behaviors might not represent a true pharmacological antagonism, i.e., both compounds acting at the same receptor site. Rather, nicotine may be affecting a circuit that does not allow full expression of QNP effects (presumably mediated by dopaminergic receptors). This mechanism of antagonism would further support the applicability of nicotinic agonists in disorders brought about by a dopaminergic imbalance. Clearly, more research utilizing various other paradigms and specific nicotinic agents is required to delineate the role of distinct nicotinic receptors in circuits controlling behavioral functions. Moreover, it would be of considerable clinical relevance to determine whether chronic nicotine administration would also exert similar effects and, if so, establish the dose–response and time-course relationships.

The results in non-primed rats show that yawning and, to some extent, locomotor activity were also manifested in this group following acute QNP administration (Fig. 1 and Fig. 4). Thus, it appears that, for some of the studied behaviors, ontogenic QNP treatment is not a requirement for the manifestation of acute QNP effects. In addition, blockade of QNP-induced yawning in non-primed rats by nicotine indicates that QNP sensitization is not a prerequisite for observation of nicotine effects in this behavior. Nonetheless, ontogenic QNP treatment and/or sensitization of dopaminergic receptors by chronic QNP administration offer suitable paradigms for investigation of biochemical causes of behavioral disorders and development of novel pharmacotherapies (Kostrzewa 1995; Szechtman et al. 1998).

It is of interest to note that postmortem studies indicate a decrease in hippocampal $\alpha 7$ nicotinic receptors in brains of schizophrenic patients, prompting the suggestion that the deficit of sensory gating in these patients might be due to a loss or a reduction of $\alpha 7$ nicotinic receptor function (Freedman et al. 1995, 1997). Interestingly, and seemingly paradoxical, it has been demonstrated that upregulation of nicotinic receptors might actually represent a functional downregulation of these receptors (Wonnacott 1990; see also Wang et al. 1998). Thus, if receptor upregulation in our paradigm is also associated with a functional decrease of nicotinic receptors, then a common basis for efficacy of nicotine in our model and schizophrenia might be suggested. Moreover, the high incidence of smoking in schizophrenic patients is consistent with the possibility of self medication by nicotine in these individuals (Goff et al. 1992). Therefore, development of a specific nicotinic agonist that might alleviate the psychotic symptoms may also have therapeutic applicability in smoking cessation in this population.

In summary, nicotine, like haloperidol, is capable of blocking behavioral effects induced by the dopamine D_2/D_3 agonist QNP. Mecamylamine, a nicotinic receptor antagonist may block the effects of nicotine. Moreover, chronic QNP treatment results in an increase in nicotinic receptor binding in discrete brain regions. These results strongly implicate nicotinic receptor in some behavioral effects of QNP and suggest a possible therapeutic benefit of nicotinic agonists in behavioral disorders that may be brought about by central dopaminergic imbalance.

Acknowledgements The authors wish to thank Mr. Vely A. Louis and Mr. David Neely for their excellent technical assistance.

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