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Effects of donepezil on DOI-induced head twitch response in mice: implications for Tourette syndrome

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Abstract

Tourette syndrome (TS) is a neurological disorder characterized by persistent motor and phonic tics. Administration of the selective 5-$HT_{2A/2C}$ agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) induces head twitches in mice that have been proposed to model tics seen in TS. Previous studies have demonstrated that nicotine markedly attenuates DOI-induced head twitch response (HTR). This and the reports that nicotine may have clinical efficacy in reducing symptoms of TS suggest possible involvement of the nicotinic cholinergic system in this disorder. Donepezil is an acetylcholinesterase inhibitor approved for use in mild to moderate Alzheimer's disease. The purpose of this study was to investigate whether donepezil might also reduce DOI-induced HTR, and whether its combination with nicotine might result in an additive or synergistic effect. Moreover, to elucidate the possible role of nicotinic receptors in this paradigm, the effects of mecamylamine, a nicotinic antagonist, were also evaluated. Acute and chronic administration of donepezil (0.1 mg/kg) or nicotine (0.5 mg/kg base) significantly reduced DOI-induced HTR. No additive or synergistic effects of donepezil and nicotine were observed. Acute mecamylamine administration (0.5–5.0 mg/kg) dose dependently inhibited DOI-induced HTR. None of the mecamylamine doses blocked the inhibitory effects of donepezil or nicotine on DOI-induced HTR. These results suggest that donepezil may have therapeutic potential in treating motor tic symptoms of TS. Moreover, the action of donepezil and nicotine may be mediated through the same mechanism.

Keywords: Donepezil; Aricept; Nicotine; Mecamylamine; DOI; Head twitch; Tourette syndrome

1. Introduction

Tourette syndrome (TS) is a neurological disorder in humans characterized by persistent motor and phonic tics and occurs in patients before the age of 18 years. Tics range in severity and are coupled with sensory urges (Leckman, 2002). The disorder affects approximately 0.1–1% of the population and males are affected 3–4 times more than females (Peterson and Leckman, 1998). In addition, behavioral disorders such as obsessive–compulsive disorder and attention deficit–hyperactivity disorder are sometimes linked with TS (Dure and Tucker, 1997).

The etiology of TS is unknown; however, a genetic component and abnormalities of neurotransmitter systems are suggested. Twin and family studies indicate that TS has strong genetic determinants (Price et al., 1985; Pauls et al., 1991). Furthermore, an imbalance among neurotransmitter systems including the catecholamines and acetylcholine may contribute to the symptoms of the disorder (Baker et al., 1995). It is also postulated that a developmental abnormality in cortico–striato–thalamo–cortical circuits is responsible for tic symptoms (Leckman et al., 1997; Singer, 1997).

Pharmacological treatment of TS utilizes neuroleptics such as haloperidol, pimozide, risperidone, and ziprasidone whose actions include blockade of dopamine receptors. Although these agents have shown efficacy in treating symptoms of TS, severe side effects such as drowsiness, muscle rigidity, and movement disorders may limit their use and long-term effectiveness. The alpha-2 adrenergic agonists, clonidine and guanfacine, are also used, but these agents possess sedative properties as well (Leckman, 2002). Nicotine, in the form of a gum (McConville et al., 1991) or transdermal patch (Dursun et al., 1994; Shytle et al., 1996; Sanberg et al., 1997), has shown clinical efficacy in treating tic symptoms. In addition, combination of nicotine and a neuroleptic may further reduce the tic

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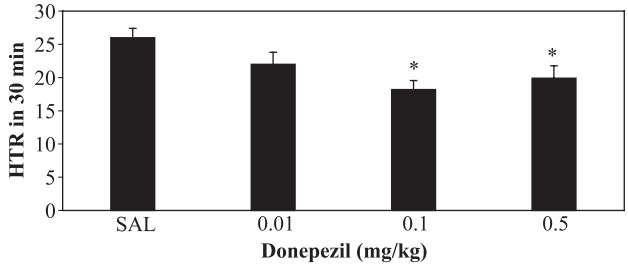

Fig. 1. Effects of acute donepezil administration on DOI (1.0 mg/kg)-induced HTR; $n = 8$/group. * $P < .05$ compared to saline group (SAL).

severity (Sanberg et al., 1989; McConville et al., 1991; Shytle et al., 1996; Silver et al., 1996, 2001).

It has been proposed that shakes or twitches of the head in mice or shakes in the shoulders in rats following administration of the selective serotonin 5-$HT_{2A/2C}$ agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) can serve as an animal model of tics seen in TS (Handley and Dursun, 1992; Gaynor and Handley, 2001). In addition, the neuroleptic haloperidol significantly reduces DOI-induced head shakes in mice (Dursun and Handley, 1996).

Previous studies have demonstrated that acute nicotine administration markedly attenuates the DOI-induced head shakes (Gaynor and Handley, 2001) or head twitch response (HTR) in mice (Tizabi et al., 2001), suggesting possible involvement of the nicotinic cholinergic system in this behavior. Donepezil (Aricept) is a reversible noncompetitive acetylcholinesterase inhibitor approved for use in mild to moderate Alzheimer's disease. It is believed that increases in acetylcholine concentrations is a major contributory factor to therapeutic efficacy of donepezil. However, specific acetylcholinesterase inhibitors may also interact directly with nicotinic receptors (Storch et al., 1995). The purpose of this study was to investigate whether donepezil might also be effective in reducing the DOI-induced HTR, and whether its combination with nicotine would have an additive or synergistic effect. Moreover, to elucidate possible involvement of nicotinic receptors in this paradigm, the effects of mecamylamine, a nicotinic antagonist, were also evaluated.

2. Methods

2.1. Animals

Adult male albino ICR mice, weighing 22–25 g at the beginning of the experiments, were used. The animals were housed four to six per cage and kept on a 12:12-h light/dark cycle (lights on at 7:00 a.m.) in a temperature-controlled room (24–26 °C). The animals had ad libitum access to food and water except during experiments. All behavioral experiments were performed during the light hours. Experimental procedures were conducted in compliance with the National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No. 85–23, revised 1985).

2.2. Drugs

Donepezil HCl was supplied by Eisai Pharmaceutical (Ibaraki, Japan). Nicotine hydrogen tartrate salt, mecamylamine HCl, and DOI HCl were purchased from Sigma-Aldrich (St. Louis, MO). All drugs were dissolved in saline and were injected intraperitoneally in a volume of 10 ml/kg. Nicotine dose was calculated as the base weight. Control animals were injected with saline.

2.3. Behavioral experiments

To induce HTR, a dose of 1 mg/kg of DOI was used throughout the study. This dose has been shown to produce robust frequencies of HTR in mice (Darmani and Gerdes, 1995; Darmani et al., 1996; Tizabi et al., 2001). The HTR is a very distinctive behavior that rarely occurs spontaneously and usually cannot be mistaken for spontaneous behaviors such as head shakes (lateral movements of the head from side to side) or head jerks (up and down jerks). Mice were randomly assigned to various treatment groups (7–8 mice/group). Each mouse was tested in a clear plastic cage lined with bedding. Animals were allowed to habituate to the test environment for 30 min prior to experiments. The test was carried out immediately after DOI injection and lasted for 30 min, during which the number of head twitches was recorded.

2.4. Acute studies

For acute studies, the effects of various doses of donepezil (0.01, 0.1, or 0.5 mg/kg), nicotine (0.2 or 0.5 mg/kg, base), or mecamylamine (0.2, 0.5, 1.0, 2.0, or 5.0 mg/kg) on DOI-induced HTR were evaluated. These drugs

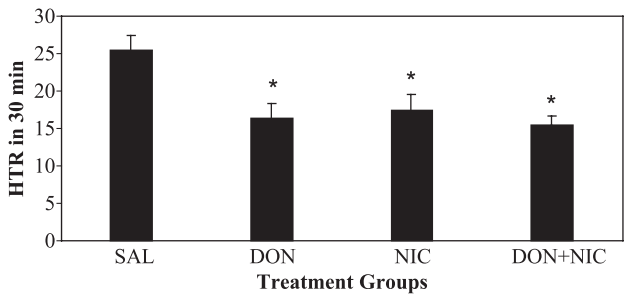

Fig. 2. Effects of acute administration of donepezil (DON, 0.1 mg/kg), nicotine (NIC, 0.5 mg/kg), and their combination (DON + NIC) on DOI (1.0 mg/kg)-induced HTR; $n = 7–8$/group. * $P < .05$ compared to saline group (SAL).

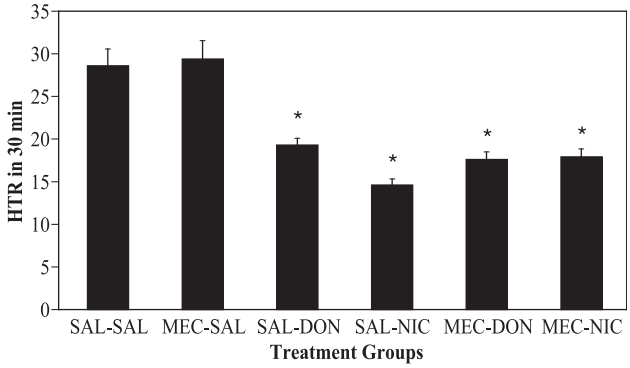

Fig. 3. Effects of mecamylamine (MEC, 0.5 mg/kg) pretreatment on acute administration of donepezil (DON, 0.1 mg/kg) and nicotine (NIC, 0.5 mg/kg) prior to DOI (1.0 mg/kg)-induced HTR; $n = 8$/group. $^{*}P < .05$ compared to saline group (SAL–SAL).

were injected 10 min prior to DOI administration. To determine the effects of the combination of donepezil and nicotine, donepezil was injected 10 min before administration of nicotine, which was followed 10 min later by injection of DOI. To investigate whether mecamylamine could block the effects of donepezil or nicotine, groups of mice were injected with various doses of mecamylamine 10 min prior to donepezil or nicotine administration. Ten minutes later, mice were injected with DOI and were monitored for HTR.

2.5. Chronic studies

To evaluate the effects of chronic donepezil, nicotine, or their combination on DOI-induced HTR, groups of mice were treated once or twice daily (first injection before 11:00 a.m. and second injection after 4 p.m.) for 7 or 14 days and were tested 18–20 h after the last injection. The doses of the drugs used in chronic studies were derived from the doses that produced maximal effects in acute studies. On the test day, the mice were injected with DOI (1.0 mg/kg), and the HTR frequency was recorded for 30 min.

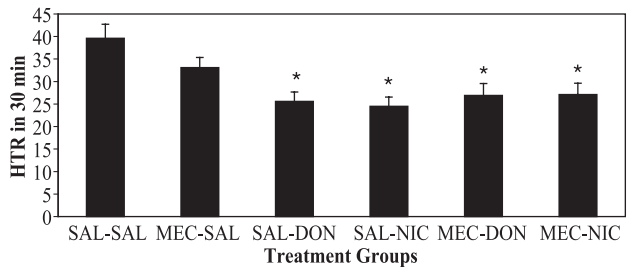

Fig. 4. Effects of mecamylamine (MEC, 1 mg/kg) pretreatment on acute administration of donepezil (DON, 0.1 mg/kg) and nicotine (NIC, 0.5 mg/kg) prior to DOI (1.0 mg/kg)-induced HTR; $n = 8$/group. $^{*}P < .05$ compared to saline group (SAL–SAL).

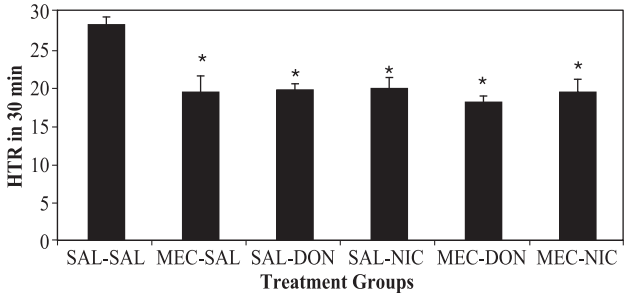

Fig. 5. Effects of mecamylamine (MEC, 2 mg/kg) pretreatment on acute administration of donepezil (DON, 0.1 mg/kg) and nicotine (NIC, 0.5 mg/kg) prior to DOI (1.0 mg/kg)-induced HTR; $n = 8$/group. $^{*}P < .05$ compared to saline group (SAL–SAL).

2.6. Statistical analysis

All data were analyzed using one-way ANOVA, followed by Tukey's post hoc test. Significance was set a priori at $P < .05$.

3. Results

3.1. Acute studies

3.1.1. Effects of donepezil on DOI-induced HTR

Fig. 1 depicts the effects of acute administration of various doses of donepezil on DOI-induced HTR. Maximal reduction of DOI-induced HTR was obtained at 0.1 mg/kg dose (approximately 30%) [$F(3,28) = 9.71$, $P < .05$]. Increasing the dose to 0.5 mg/kg did not have any additional effect, suggesting a ceiling effect of donepezil at 0.1 mg/kg. Therefore, the 0.1 mg/kg dose was chosen for chronic studies.

3.1.2. Effects of nicotine on DOI-induced HTR

Acute administration of 0.2 mg/kg of nicotine did not exhibit any effect on DOI-induced HTR. The dose of 0.5

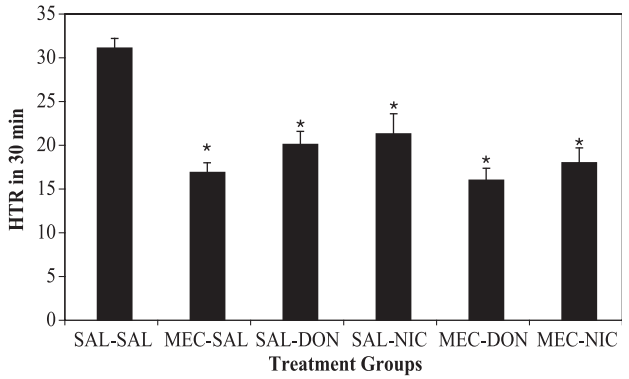

Fig. 6. Effects of mecamylamine (MEC, 5 mg/kg) pretreatment on acute administration of donepezil (DON, 0.1 mg/kg) and nicotine (NIC, 0.5 mg/kg) prior to DOI (1.0 mg/kg)-induced HTR; $n = 8$/group. $^{*}P < .05$ compared to saline group (SAL–SAL).

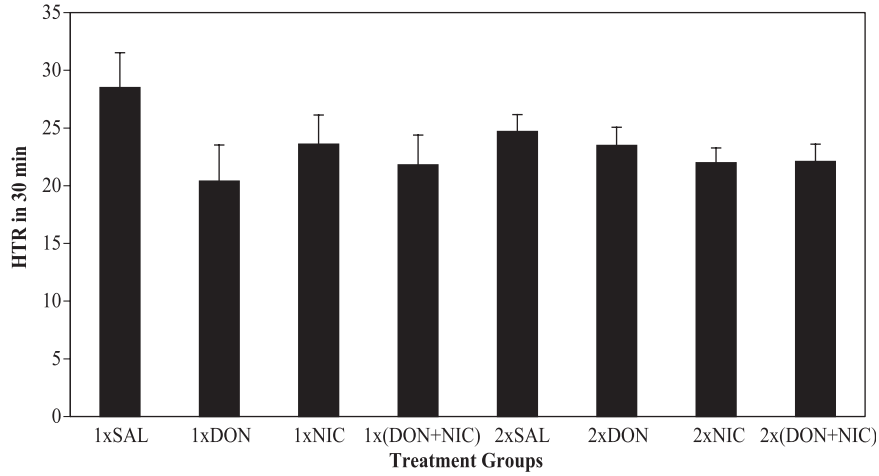

Fig. 7. Effects of chronic administration of donepezil (DON, 0.1 mg/kg), nicotine (NIC, 0.5 mg/kg), and the combination of donepezil and nicotine (DON + NIC) on DOI (1.0 mg/kg)-induced HTR. Mice were treated once (1 ×) or twice (2 ×) daily for 7 days and were tested on Day 8 with DOI (1.0 mg/kg); $n = 8$/group.

mg/kg, however, produced a significant reduction of DOI-induced HTR (approximately 32%) [$F(3,26) = 6.11$, $P < .05$]. Therefore, the 0.5 mg/kg dose of nicotine was used in chronic studies.

3.1.3. Effects of donepezil and nicotine on DOI-induced HTR

Acute administration of the combination of submaximal doses of donepezil (0.05 mg/kg) and nicotine (0.2 mg/kg) did not exhibit any detectable effect on DOI-induced HTR. Acute administration of the combination of donepezil (0.1 mg/kg) and nicotine (0.5 mg/kg), as depicted in Fig. 2, significantly decreased DOI-induced HTR (approximately 39%) [$F(3,26) = 6.11$, $P < .05$]. However, the reduction was not significantly different from either donepezil alone (approximately 35%) or nicotine alone (approximately 32%), indicating lack of an additive or synergistic effect between donepezil and nicotine.

3.1.4. Effects of mecamylamine pretreatment on DOI-induced HTR

Acute mecamylamine administration at 0.2–1 mg/kg did not significantly affect DOI-induced HTR. However, at 2 and 5 mg/kg, mecamylamine significantly reduced the DOI-induced HTR (approximately 31% and 44%, respectively) [$F(4,36) = 4.20$, $P < .05$]. These results are in agreement with previous studies where higher mecamylamine doses attenuated DOI-induced HTR (Tizabi et al., 2001). To investigate whether nicotinic receptors mediate the actions of donepezil or nicotine on DOI-induced HTR, animals

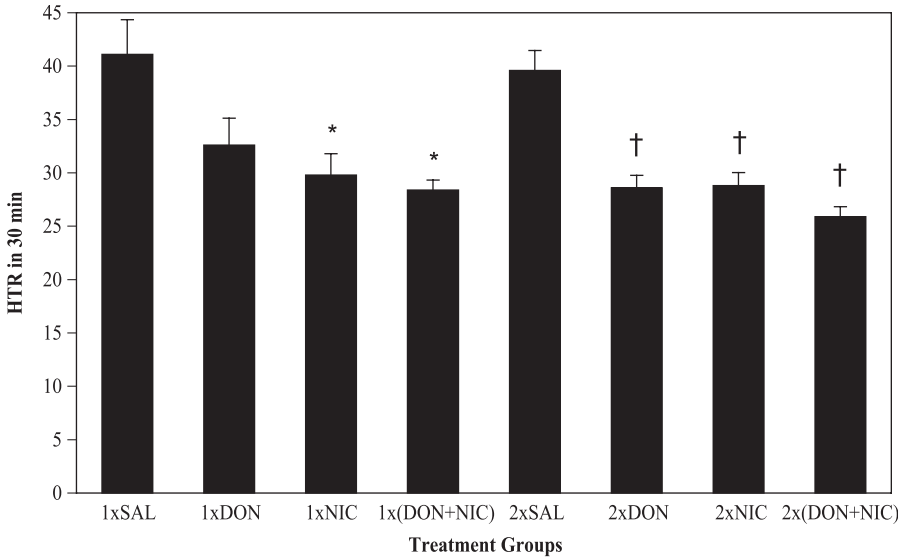

Fig. 8. Effects of chronic administration of donepezil (DON, 0.1 mg/kg), nicotine (NIC, 0.5 mg/kg), and the combination of donepezil and nicotine (DON + NIC) on DOI (1.0 mg/kg)-induced HTR. Mice were treated once (1 ×) or twice (2 ×) daily for 14 days and were tested on Day 15 with DOI (1.0 mg/kg); $n = 8$/group. * $P < .05$ compared to once-daily saline group (1 × SAL). † $P < .05$ compared to twice-daily saline group (2 × SAL).

were treated with various doses of mecamylamine prior to donepezil or nicotine administration. As depicted in Figs. 3–6, pretreatment with a single dose of mecamylamine (0.5–5.0 mg/kg) did not modify the effects of either drug on DOI-induced HTR.

3.2. Chronic studies

Administration of once or twice daily of 0.1 mg/kg donepezil, 0.5 mg/kg nicotine, or their combination for 1 week did not significantly affect DOI-induced HTR (Fig. 7). However, as depicted in Fig. 8, administration of once- or twice-daily donepezil, nicotine, or their combination for 2 weeks resulted in a reduction of DOI-induced HTR. Administration of donepezil once daily for 2 weeks resulted in approximately 21% reduction, although this decrease did not achieve statistical significance. Two weeks of twice-daily treatment with donepezil resulted in approximately 28% reduction in DOI-induced HTR [$F(3,34)=5.43$, $P<.05$]. Once- or twice-daily treatment with nicotine for 2 weeks resulted in approximately 27% reduction in DOI-induced HTR in both cases, for once-daily [$F(3,28)=5.09$, $P<.05$] and for twice-daily [$F(3,34)=5.43$, $P<.05$] injection. Administration of a combination of donepezil and nicotine once or twice daily for 2 weeks resulted in approximately 31% [$F(3,28)=5.09$, $P<.05$ for once daily] and 35% [$F(3,34)=5.43$, $P<.05$ for twice daily] reduction in DOI-induced HTR. In all cases, the combination treatment was not significantly different from single drug treatment, indicating lack of an additive or synergistic effect between donepezil and nicotine in reducing DOI-induced HTR.

4. Discussion

Acute and chronic donepezil administration significantly attenuated DOI-induced HTR. These results suggest possible therapeutic efficacy of an acetylcholinesterase inhibitor in treating motor tic symptoms of TS. This finding is in line with recent suggestion of potential applicability of cholinesterase inhibitors in treatment of various neuropsychiatric disorders including motor tics (Burt, 2000). Interestingly, a case report on effectiveness of donepezil in treating TS has appeared (Hoopes, 1999).

Our results indicate that multiple daily dosing of donepezil at 0.1 mg/kg for at least 14 days was required to achieve an inhibitory effect on DOI-induced HTR. Similarly, 2 weeks of chronic nicotine treatment was required to produce significant reduction in DOI-induced HTR. Relatively long-term dosing of donepezil or nicotine to exhibit an inhibitory response on DOI-induced HTR may be the result of neurochemical adaptations that require prolonged and sustained increases in acetylcholine concentrations or stimulation of central nicotinic receptors. Alternatively, pharmacokinetic parameters or prolonged inactivation of nicotinic receptors due to chronic intermittent exposure to donepezil or nicotine may be important contributory mechanisms in observed behavioral effects (Quick and Lester, 2002; Gentry et al., 2003). In this regard, receptor desensitization following chronic exposure to nicotine (Marks et al., 1993; Fenster et al., 1999) or a cholinesterase inhibitor (Zhou et al., 2001) have been reported. Cholinesterase inhibitors may interact directly with nicotinic receptors (Storch et al., 1995) or indirectly through elevation of acetylcholine levels (Giacobini et al., 1996; Zhou et al., 2001).

Due to complex diversity of nicotinic receptors and indication of both functional desensitization (Quick and Lester, 2002; Gentry et al., 2003), as well as sensitization (Buisson and Bertrand, 2002) following chronic exposure to nicotine, it seems reasonable to assume that a combination of these two phenomena may be responsible for the final pharmacological effects of nicotinic agents. Thus, a balance between desensitization or inactivation of specific nicotinic receptors in certain areas and sensitization or activation in other areas of the brain may be the final determinant of the pharmacological outcome. Further investigation is necessary to determine the exact mechanism of donepezil and nicotine in reducing DOI-induced HTR.

Acute and chronic administration of nicotine significantly reduced DOI-induced HTR, consistent with a previous report (Tizabi et al., 2001). It is interesting to note that multiple daily doses of nicotine (0.5 mg/kg) for 14 days did not produce a greater reduction in DOI-induced HTR compared to once-daily administration of the same dose of nicotine for 14 days, suggesting a possible ceiling effect of nicotine dosing.

Acute and chronic administration of the combination of donepezil and nicotine significantly decreased DOI-induced HTR. However, these reductions were not additive or synergistic compared to either agent administered alone. These data suggest that the actions of donepezil and nicotine may be mediated through the same mechanism.

Pretreatment with various doses of the nicotinic receptor antagonist, mecamylamine, did not alter the acute inhibitory effects of donepezil or nicotine in this model. These findings are consistent with a previous report indicating that mecamylamine did not block the inhibitory effect of nicotine on DOI-induced HTR (Tizabi et al., 2001). Indeed, mecamylamine by itself caused a dose-dependent decrease in DOI-induce HTR. Gaynor and Handley (2001) did observe a block of nicotine effect on DOI-induced head shakes by mecamylamine. The discrepancy between these studies may be due to differences in nicotine doses and/or differences in strains of mice. The ICR mice used in our studies exhibited an insignificant amount of spontaneous head twitches during the 30-min test period, whereas the strain used by Gaynor and Handley (2001) had a significant number of spontaneous head shakes. Lack of mecamylamine effect in our studies does not support a nicotinic receptor-mediated action for acute donepezil or nicotine on DOI-induced HTR.

Interactions between nicotine and nonnicotinic receptors (e.g., NMDA) are widely recognized (Court et al., 1990;

Aizenman et al., 1991; Zhang et al., 1994; Tizabi et al., 1998). Nicotine may also block behavioral effects of quinpirole, a dopamine D_2/D_3 agonist (Tizabi et al., 1999, 2002). Some of quinpirole effects may be reflective of symptoms associated with TS or obsessive–compulsive disorder (Tizabi et al., 1999, 2002). Interaction between nicotine and the serotonergic system has also been documented. Specifically, $5\text{-}HT_{2c}$ receptors have been implicated in the locomotor and rewarding effects of nicotine (Grottick et al., 2001). In this regard, it would be of considerable interest to determine whether the same receptors may also be involved in actions of donepezil or nicotine in attenuating the DOI-induced HTR.

In summary, acute and chronic administration of donepezil reduced DOI-induced HTR in mice, suggesting possible therapeutic potential of donepezil in treating motor tics. Combination of nicotine and donepezil did not result in any further effect. Mecamylamine at higher doses attenuated DOI-induced HTR but did not block the effects of donepezil or nicotine. Further investigation of possible involvement of nicotinic receptors in TS as well as direct interaction between donepezil or nicotine with $5HT_{2A/2C}$ receptors is warranted.

Acknowledgements

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References

Aizenman E, Tang L, Reynolds IJ. Effects of nicotinic agonists on the NMDA receptor. Brain Res 1991;551:355–7.

Baker GB, Chokka PR, Bornstein RA. Neurochemical and some related psychopharmacological aspects of Tourette's syndrome: an update. J Psychopharmacol 1995;9:273–80.

Buisson B, Bertrand D. Nicotine addiction: the possible role of functional upregulation. Trends Pharmacol Sci 2002;23:130–6.

Burt T. Donepezil and related cholinesterase inhibitors as mood and behavioral controlling agents. Curr Psychiatry Rep 2000;2:473–8.

Court JA, Piggott MA, Perry EK. Nicotine reduces the binding of [3H]MK-801 to brain membranes but not via the stimulation of high affinity nicotinic receptors. Brain Res 1990;524:319–21.

Darmani NA, Gerdes CF. Temporal differential adaptation of head-twitch and ear-scratch responses following administration of challenge doses of DOI. Pharmacol Biochem Behav 1995;50:545–50.

Darmani NA, Shaddy J, Gerdes CF. Differential ontogenesis of the DOI-induced behavior in mice. Physiol Behav 1996;60:1495–500.

Dure LS, Tucker DM. Tourette syndrome. Curr Opin Neurol 1997;10:153–9.

Dursun SM, Handley SL. Similarities in the pharmacology of spontaneous and DOI-induced head shakes suggest 5-HT2A receptors are active under physiological conditions. Psychopharmacology 1996;128:198–205.

Dursun SM, Reveley MA, Bird R, Stirton RF. Long lasting improvement of Tourette's syndrome with transdermal nicotine. Lancet 1994;344:1577.

Fenster CP, Whitworth TL, Sheffield EB, Quick MW, Lester RA. Upregulation of surface alpah4beta2 nicotinic receptors is initiated by receptor desensitization after chronic exposure to nicotine. J Neurosci 1999;19:4804–14.

Gaynor CM, Handley SL. Effects of nicotine on head-shakes and tryptophan metabolites. Psychopharmacology 2001;153:327–33.

Gentry CL, Wilkins Jr LH, Lukas RJ. Effects of prolonged nicotinic ligand exposure on function of heterogeneously expressed, human alpha4-beta2- and alpha4beta4-nicotinic acetylcholine receptors. J Pharmacol Exp Ther 2003;304:206–16.

Giacobini E, Zhu XD, Williams E, Sherman KA. The effect of the selective reversible acetylcholinesterase inhibitor E2020 on intracellular acetylcholine and bioorganic amine levels in rat cortex. Neuropharmacology 1996;35:205–11.

Grottick AJ, Corrigall WA, Higgins GA. Activation of 5-HT(2C) receptors reduces the locomotor and rewarding effects of nicotine. Psychopharmacology 2001;157:292–8.

Handley SL, Dursun SM. Serotonin and Tourette's syndrome: movements such as head-shakes and wet-dog shakes may model human tics. Adv Biosci 1992;85:235–53.

Hoopes SP. Donepezil for Tourette's disorder and ADHD. J Clin Psychopharmacol 1999;19(4):381–2.

Leckman JF. Tourette's syndrome. Lancet 2002;360:1577–86.

Leckman JF, Peterson BS, Anderson GM, Arnsten AFT, Pauls DL, Cohen DJ. Pathogenesis of Tourette syndrome. J Child Psychol Psychiatry 1997;38:119–42.

Marks MJ, Grady SR, Collins AC. Downregulation of nicotinic receptor function after chronic nicotine infusion. J Pharmacol Exp Ther 1993;1268–76.

McConville BJ, Fogelson MH, Norman AB, Klyklo WM, Manderscheid PZ, Parker KW, et al. Nicotine potentiation of haloperidol in reducing tic frequency in Tourette's disorder. Am J Psychiatry 1991;148:793–4.

Pauls DL, Raymond CL, Stevenson JM, Leckman JF. A family study of Gilles de la Tourette syndrome. Am J Hum Genet 1991;48:154–63.

Peterson BS, Leckman JF. The temporal dynamics of tics in Gilles de la Tourette syndrome. Biol Psychiatry 1998;44:1337–48.

Price RA, Kidd KK, Cohen DJ, Pauls DL, Leckman JF. A twin study of Tourette syndrome. Arch Gen Psychiatry 1985;42:815–20.

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

Sanberg PR, McConville BJ, Fogelson HM, Manderscheid PZ, Parker KW, Blythe MM, Klykylo WM, Norman AB. Nicotine potentiates the effects of haloperidol in animals and in patients with Tourette syndrome. Biomed Pharmacother 1989;43:19–23.

Sanberg PR, Silver AA, Shytle RD, Philipp MK, Cagill DW, Fogelson HM, et al. Nicotine for the treatment of Tourette's syndrome. Pharmacol Ther 1997;74:21–5.

Shytle RD, Silver AA, Philipp MK, McConville BJ, Sanberg PR. Transdermal nicotine for Tourette's syndrome. Drug Dev Res 1996;38:290–8.

Silver AA, Shytle RD, Philipp MK, Sanberg PR. Case study: long-term potentiation of neuroleptics with transdermal nicotine in Tourette's syndrome. J Am Acad Child Adolesc Psych 1996;35:1631–6.

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

Singer HS. Neurobiology of Tourette syndrome. Neurol Clin N Am 1997;15:357–79.

Storch A, Schrattenholz A, Cooper JC, Abdel Ghani EM, Gutbrod O, Weber KH, et al. Physostigmine, galanthamine and codeine act as "non-competitive nicotinic receptor agonist" on clonal rat pheochromocytoma cells. Eur J Pharmacol 1995;290:207–19.

Tizabi Y, Mastropaolo J, Park CH, Riggs RL, Powell D, Rosse RB, et al. Both nicotine and mecamylamine block dizocilpine-induced explosive jumping behavior in mice: psychiatric implications. Psychopharmacology 1998;140:202–5.

Tizabi Y, Copeland RL, Brus R, Kostrzewa RM. Nicotine blocks quinpirole-induced behavior in rats: psychiatric implications. Psychopharmacology 1999;145:433–41.

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.

Tizabi Y, Louis VA, Taylor CT, Waxman D, Culver KE, Szechtman H. Effect of nicotine on quinpirole-induced checking behavior in rats: implications for obsessive–compulsive disorder. Biol Psychiatry 2002;51:164–71.

Zhang X, Gong ZH, Nordberg A. Effects of chronic treatment with (+)- and (−)-nicotine on nicotinic acetylcholine receptors and *N*-methyl-D-aspartate receptors in rat brain. Brain Res 1994;644:32–9.

Zhou FM, Liang Y, Dani JA. Endogenous nicotinic cholinergic activity regulates dopamine release in the striatum. Nat Neurosci 2001;4: 1224–9.