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Dopamine D4 receptors inhibit depolarization-induced [^{3}H]GABA release in the rat subthalamic nucleus

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Abstract

We explored the role of dopamine D4 receptors on [^{3}H]GABA release in the subthalamic nucleus. [^{3}H]GABA release was evoked by high K^+ in slices of the nucleus. The selective dopamine D4 receptor agonist PD168,077 (*N*-[[4-(2-cyanophenyl)-1-piperazynil]methyl]-3-methyl-benzamide) inhibited GABA release with greater potency (EC_{50}=3.2 nM) than quinpirole (EC_{50}=200 nM). SKF 21297 (6-chloro-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrobromide), a dopamine D1-like receptor agonist, had no effect. L-745,870 (3-{[4-(4-chlorophenyl)piperazin-1-yl]methyl}-1-1*H*-pyrollo[2,3-b] pyridine), a selective dopamine D4 receptor antagonist, reverted the quinpirole inhibition with greater potency (IC_{50}=8.7 nM) than that of the dopamine D2/D3 receptor antagonist sulpiride and raclopride (IC_{50}=4804 and 788 nM, respectively). Both methylphenidate and methamphetamine, dopamine reuptake blockers, inhibited by 30% high K^+-evoked GABA release; the inhibition was blocked by L-745,870. These results show that dopamine D4 receptors modulate GABA release in the subthalamic nucleus. The results would explain how agents that increase interstitial dopamine like methylphenidate and amphethamine might control locomotor hyperactivity seen in disorders of dopamine D4 receptors.

Keywords: Dopamine receptor; GABA transmission; Hyperactivity disorder

1. Introduction

Subthalamic neurons modulate locomotion and muscle tone by providing excitatory projections to the major output structures of the basal ganglia, the substantia nigra pars reticulata and the entopeduncular nucleus (DeLong, 1990; Hemsley et al., 2002). The subthalamic nucleus receives dopaminergic innervation in the rat (Hassani et al., 1997; Gauthier et al., 1999), monkey (Francois et al., 2000) and human (Cossette et al., 1999; Hedreen, 1999; Augood et al., 2000) brain. Moreover, subthalamic neurons express D1-like, D2 and D3 dopamine receptors but there are only binding sites but no mRNA for D4 receptors in the nucleus (Flores et al., 1999). It is therefore of interest to determine how each type of dopamine receptor modulates the activity of subthalamic neurons. The role of dopamine D4 receptors could be especially interesting because their abnormalities may be important in generating the symptoms of attention deficit hyperactivity disorder (ADHD) (Faraone et al., 2001), however, the location of the dopamine D4 receptors involved is not known. Because of its critical role in determining locomotor activity, the subthalamic nucleus could be in one location.

Dopamine modulates GABA release in multiple brain regions including the subthalamic nucleus (Floran et al., 1990; Shen and Johnson, 2000; Seamans et al., 2001). GABAergic projections from the dorsal and ventral pallidum innervate the subthalamic nucleus (Bevan et al., 1997). Since neurons of the globus pallidus express dopamine D4 receptors (Mrzljak et al., 1996; Ariano et al., 1997), it is likely that the receptors are transported to the

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axon terminals in the subthalamic nucleus. The location of dopamine D4 receptors in afferents but not in neurons of the STN (Flores et al., 1999) is in agreement with this possibility. We examined the presence of the receptors in the GABAergic terminals by comparing the dose dependence of agonists and antagonists with different affinities for subtypes of dopamine D2 receptors on K^+-evoked [^{3}H]GABA release in slices of the subthalamic nucleus.

2. Materials and methods

2.1. Preparation, labeling and superfusion of slices

Slices microdissected (Aceves and Cuello, 1981) from the STN were obtained from Wistar male rats (180–200 g weight) maintained and handled according to the guidelines of the CINVESTAV-IPN Animal Care Committee, taking all efforts to minimize suffering and the number of animals used. After rapid sacrifice of the rat, the brain was immersed in oxygenated ice-cool Krebs solution, and sagittal brain slices (300-μm thick) were obtained with a vibratome. Usually four slices were obtained from each rat. Once microdissected, the slices were incubated for 30 min at room temperature in a Krebs-Henseleit (K-H) solution (composition in mM: NaCl 118, KCl 1.75, $MgSO_4$ 1, KH_2PO_4 1.25, $NaHCO_3$ 25, $CaCl_2$ 2, and D-glucose 10), gassed continuously with O_2/CO_2 (95:5, v/v). The slices were incubated for 30 min with 8 nM [^{3}H]GABA in 2-ml K-H solution containing 10 μM aminooxyacetic acid (to prevent degradation of [^{3}H]GABA). At the end of this period, excess radiolabel was removed by washing twice with K-H solution containing 10 μM aminooxyacetic acid and 10 μM nipecotic acid (to prevent the reuptake of the label). Both compounds were present in the superfusion medium throughout the experiment.

2.2. K^+-evoked release and basal efflux of radioactivity

The slices were apportioned randomly between 20 parallel chambers (usually four slices per chamber) of a homemade superfusion system (the design of the superfusion chambers was essentially as described by Aceves and Cuello, 1981) and superfused with K-H solution at a rate of 0.5 ml/min for 1 h. Basal release of [^{3}H]GABA was measured by collecting four fractions of superfusate at 4-min intervals (each fraction 2 ml) before stimulation of release by changing to a solution containing 20 mM K^+(composition in mM: NaCl 101.25, KCl 18.75, $MgSO_4$ 1, KH_2PO_4 1.25, $NaHCO_3$ 25 $CaCl_2$ 2 and D-glucose 10). Six more fractions were collected in the high K^+ medium. To determine the total amount of tritium remaining in the tissue, the slices of each chamber were collected, treated with 1 ml of 1 M HCl and allowed to stand for 1 h before addition of the scintillator (composition: 2,5-diphenyloxazole, 4 g and 1,4-bis-2-(5-phenyloxazolyl)-benzene, 0.2 g dissolved in 1 l toluene/Triton X-100, 2:1, v/v). The scintillator counter used was a Beckman model LS6500.

2.3. Data analysis

[^{3}H]GABA release was expressed initially as a fraction of the total amount of tritium remaining in the tissue. Basal release per 2-ml superfusate fraction was normally in the range of 0.006 to 0.0161. The within-treatments variability in an experiment was greatly reduced by expressing the amount of tritium in each fraction as a ratio of the amount of tritium present in the fraction collected immediately before the change to the high K^+ medium (i.e., the release in fraction 4 was set as unity).

The effect of drugs on basal release of [^{3}H]GABA was assessed by comparing the fractional release in fraction 1, immediately before exposure to the drug, and fraction 4 (immediately prior to exposure to 20 mM K^+), using paired *t*-test.

A measure of the degree of change in the release of [^{3}H]GABA was estimated by comparing the areas (obtained by subtracting the release of slices not exposed to high K^+ from the release of the corresponding slices exposed to the high K^+ medium) under the appropriate release curves between fractions 5 and 10 (the first and last fractions collected after the change to high K^+). The significance of the differences was assessed by one-way analysis of variance followed by Tukey–Kramer multiple comparison post hoc test using Prism GraphPad Software 4.0, (GraphPad Software, San Diego CA, USA).

Dose–response curves were obtained plotting the area under the curve (determined by the trapezoid rule) of different doses of agonists or antagonists. The dose–response curves were analyzed by nonlinear regression (Prism GraphPad Software 4.0, San Diego, CA, USA), which provided estimations of the EC_{50} or IC_{50} values and the confidence intervals (CI).

2.4. Reserpinization

Rats were pretreated with reserpine (10 mg kg^{-1}, i.p.) 18 h before preparation of slices. Control animals were treated with the same volume (1 ml kg^{-1}) of vehicle (7% w/v lactic acid).

3. Results

We first assessed whether activation of dopamine receptors modifies [^{3}H]GABA release. Fig. 1A illustrates the effect of the D2-like agonist quinpirole and of the D1-like agonist SKF 21297 (6-chloro-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrobromide) on basal and high K^+-evoked [^{3}H]GABA release. Quinpirole (10 μM) inhibited evoked, but not basal, release. By contrast, SKF 21297 (1 μM) did not affect the release.

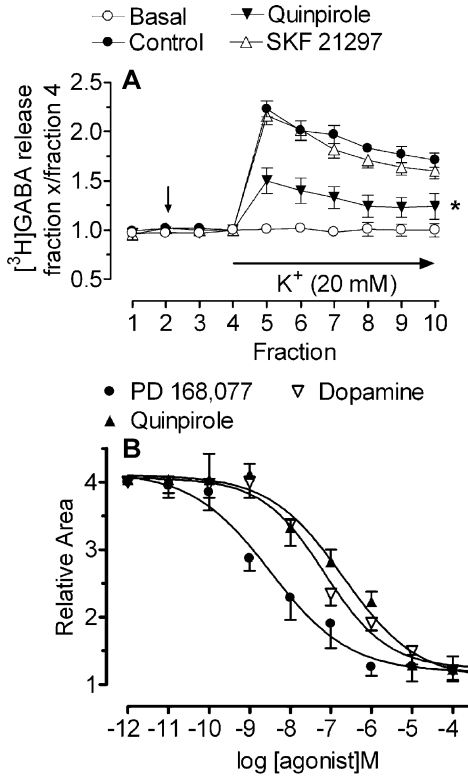

Fig. 1. Effect of dopamine receptors agonists on [^{3}H]GABA release from slices of the subthalamic nucleus. (A) Effect of quinpirole (10 μM) and SKF 21297 (1 μM) on release from slices isolated from normal rats. Dopamine agonists were added at the moment indicated by the arrow (after the collection of the second fraction). [K^+] was increased (horizontal bar) after the collection of the fourth fraction. Basal indicates the release from slices not exposed to high [K^+]. Control indicates the release from slices exposed to high [K^+] but not to drugs. The four conditions were run in parallel. (B) Dose dependence of effects of quinpirole, dopamine and the selective D4 agonist PD 168,077 on K^+-induced release from slices isolated from reserpinized rats. Release is expressed as the area under the curve of the different doses of the agonists. Points are the mean±S.E.M. of three independent experiments (three replicates in each experiment). *Significantly (P<0.001) different from control.

The D2-like dopamine receptors include D2, D3 and D4 types (Missale et al., 1998). The dopamine D2 receptor involved in a given effect can be identified by comparing agonists and antagonists with different affinities for each receptor type. To avoid the effects of endogenous dopamine on dose–response curves of agonists or antagonists, the experiments were done in slices from reserpine-treated rats. The EC_{50} for the quinpirole inhibition was 200 nM (CI, 64–631) (Fig. 1B). The maximum inhibition was 55±5% and it was seen at a concentration of 10^{-5} M. Dopamine inhibited the release with an EC_{50} of 69 (CI, 31–152) nM (Fig. 1B). The selective D4 agonist PD 168,077 (*N*-[[4-(2-cyanophenyl)-1-piperazynil]methyl]-3-methyl-benzamide) also inhibited depolarization-induced [^{3}H]GABA release (Fig. 1B). Its potency (EC_{50}=3.2 nM (CI, 1–10)) was about 65 times higher than that of quinpirole. The maximum PD 168,077 inhibition was 59±3% and was reached at a concentration of 10^{-6}M. This maximum inhibition was not significantly different from that of quinpirole or dopamine. Basal release was not affected by any of the compounds.

The experiments in which the antagonism of the inhibitory effects of quinpirole by D2-like receptor antagonists was evaluated are shown in Fig 2. Quinpirole has much higher affinity for dopamine D2-like than for D1 receptors whereas dopamine has similar affinities for both families of receptors (see Vallone et al., 2000); for this reason and because we had estimated the EC_{50} of quinpirole to inhibit [^{3}H]GABA release in the present conditions, we chose to comparatively study the reversal of its inhibitory effect to estimate the IC_{50} of the dopamine antagonists. Fig. 2A shows a typical experiment in which the antagonism of the quinpirole-induced inhibition by 0.1 μM of sulpiride and 0.1 μM L-745,870 (3-{[4-(4-chlorophenyl)piperazin-1-yl] methyl}-1-1*H*-pyrollo[2,3-b] pyridine) are compared. The

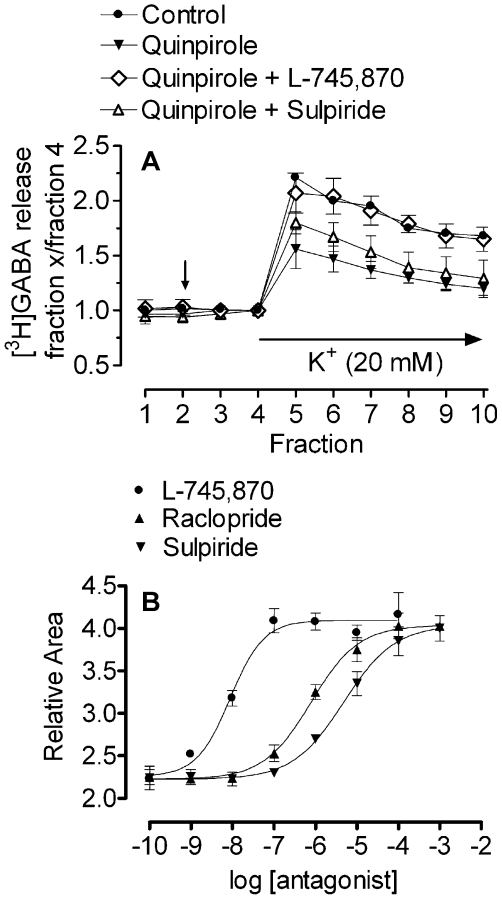

Fig. 2. Effect of D2-like antagonists on the quinpirole (1 μM)-induced inhibition of [^{3}H]GABA release. (A) Comparative effect of the selective D4 antagonist L-745,780 (0.1 μM) and of the D2/D3 antagonist sulpiride (0.1 μM) upon the quinpirole (0.1 μM) inhibition. (B) Dose dependency of the antagonism of quinpirole action of L-745,870, sulpiride and raclopride. Slices were obtained from reserpinized rats. The points are the mean±S.E.M. of at least three replicates per each concentration. Data were obtained from three independent experiments. In A, the difference between quinpirole alone and quinpirole plus sulpiride was not significantly different (P>0.05) whereas the difference between quinpirole and quinpirole plus L745,780 was highly significant (P<0.01) at these concentrations.

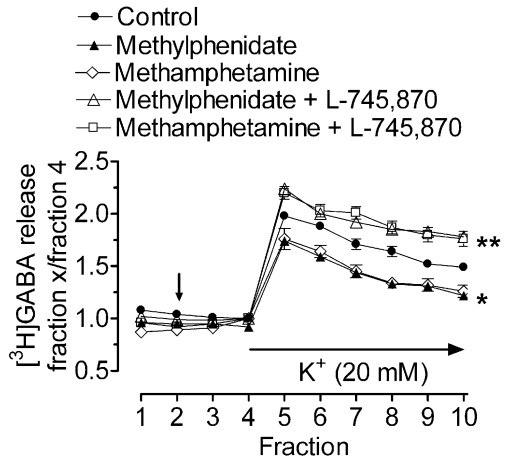

Fig. 3. Blockade of the inhibitory effect of methamphetamine (100 μM) and methylphenidate (100 μM) on [^{3}H] GABA release by L-745,780 (0.1 μM). Vertical arrow indicates addition of the compounds to the superfusion medium. Horizontal bar indicates period in which [K^+] was elevated. The selective D4 antagonist L-745,870 (0.1 μM) was added concurrently with either methamphetamine or methylphenidate. Points are the mean±S.E.M. of three independent experiments (four replicates in each experiments). The five conditions were run in parallel, *Significantly ($P<0.05$) different as compared to control. **Significantly ($P<0.001$) different from methylphenidate and methamphetamine but not from control ($P>0.05$).

dose dependency of the effects of these compounds and of raclopride is shown in Fig 2B. The selective D4 antagonist L-745,870 reverted the inhibitory effect of quinpirole with an IC_{50} of 8.8 (CI, 4–18) nM. The D2-like receptor antagonists raclopride and sulpiride antagonized the inhibitory effect of quinpirole with IC_{50} values of 788 (CI, 584–1051) and 4804 (CI, 3544–6514) nM, respectively. These values are 89 and 545 times higher than that of L-745,870.

We blocked dopamine uptake with methamphetamine or methylphenidate to test whether GABA release is controlled by endogenous dopamine in the subthalamic nucleus. In slices from normal rats, methamphetamine (100 μM) inhibited evoked [^{3}H]GABA release by 29±3% (Fig. 3). The blocking of D4 receptors with L-745,870 (100 nM) completely prevented the methamphetamine-induced inhibition. As methamphetamine, methylphenidate (100 μM) inhibited (28±5%) the evoked release. The blockade of D4 receptors with L-745,870 (100 nM) also abolished the methylphenidate inhibition (Fig. 3). The concurrent addition of L-745,870 with methamphetamine or methylphenidate increased the release above that of control slices (Fig. 3), however, the change was not statistically significant. This tendency suggests possible occupancy of D4 receptors by endogenous dopamine released by depolarization. Neither methamphetamine nor methylphenidate affected basal release.

4. Discussion

We have found that activation of dopamine receptors decreases GABA release in the subthalamic nucleus. Activation of D1-like receptors with SKF 21297 was without effect while both agonists and antagonists of D2-like receptors markedly modified depolarization-induced GABA release. Pharmacological analysis showed that the subtype of D2 receptor involved in this effect is likely to be the dopamine D4 receptor. The EC_{50} and IC_{50} both for the D4 agonist (PD 168,077) and antagonist (L-745,870) are in remarkable agreement with the affinities reported for both compounds in binding studies in D4 receptors expressed in cultured cells: 3.2 vs. 8.7 nM for PD 168,077 (Glase et al., 1997) and 8.8 vs. 1.5 nM for L-745,870 (Patel et al., 1997). The relatively low potency of quinpirole (IC_{50}=200 nM) as well as the low potency for raclopride (IC_{50}=788 nM) (see Vallone et al., 2000) and the very low potency for sulpiride (IC_{50}=4804 nM) further reinforce the suggestion that D4 receptors mediate dopamine modulation of GABA release in the subthalamic nucleus. Shen and Johnson (2000) found that dopamine inhibited GABAergic inhibitory postsynaptic currents (IPSCs) in the subthalamic nucleus through presynaptic receptors. The inhibition appeared to be mediated by dopamine D2-like receptors because it was mimicked by quinpirole. Since dopamine D2-like receptors include D2, D3 and D4 types (Missale et al., 1998), it is likely that the D2-like effects seen by Shen and Johnson (2000) correspond to those described here and therefore were mediated by D4 receptors.

Immunocytochemical (Mrzljak et al., 1996; Ariano et al., 1997) as well as electrophysiological studies in transgenic mice with deletion of dopamine D2 receptors (Shin et al., 2003) have revealed dopamine D4 receptors in neurons of the globus pallidus. Flores et al. (1999) found that subthalamic neurons do not express mRNA for D4 receptors although dopamine D4 receptors were detected in this structure with binding techniques. These results suggest that the receptors are located in afferents to the subthalamic nucleus. The only known GABAergic inputs to the subthalamic nucleus are the projections from the dorsal and ventral pallidum (Bevan et al., 1997); accordingly, the dopamine D4 receptors characterized here are probably located on terminals from the globus pallidus.

The inhibition caused by either amphetamine or methylphenidate was fully blocked with L-745,870, a highly selective dopamine D4 receptor agonist (Patel et al., 1997). Such an effect suggests that the effects of dopamine on GABA release may be mediated solely by dopamine D4 receptors. The other types of dopamine receptors present in the subthalamic nucleus (Flores et al., 1999) possibly modulate postsynaptic membrane function or the release of other transmitters.

By reducing the amount of GABA released in the subthalamic nucleus, one would expect that activation of D4 receptors by dopamine would disinhibit subthalamic neurons and increase their firing rate, thereby increasing the excitatory input to neurons of substantia nigra pars reticulata and entopeduncular nucleus, which on their turn, would increase the inhibition of premotor thalamic nuclei thereby

decreasing locomotor activity (DeLong, 1990). The expected increase in the activity of subthalamic neurons brought about by increased dopamine action in the subthalamic nucleus is in line with electrophysiological studies showing that activation of dopamine D2-like receptors increased the firing of subthalamic neurons in normal (Zhu et al., 2002) and 6-hydroxydopamine-lesioned rats (Hassani and Feger, 1999). Moreover, Trinh et al. (2003) found that both amphetamine and methylphenidate increased Fos-like immunoreactivity in the subthalamic nucleus, indicating activation of some population of subthalamic neurons by the increase in dopamine levels. The present results show that both methylphenidate and methamphetamine inhibited GABA release. The inhibition was blocked by the selective dopamine D4 receptor antagonist, L-745,870, indicating that the effect was mediated by dopamine D4 receptors.

The present results and the abovementioned findings are contrary to the model of basal ganglia function (DeLong, 1990). In this model, dopamine would inhibit the firing of subthalamic neurons. The reduced firing of the subthalamic neurons would result, in turn, in a reduction of the inhibitory output from the basal ganglia thus increasing locomotor activity. However, the final effect of dopamine on the firing of subthalamic neurons may vary under different conditions. In addition to the increase in firing by inhibition of GABA release mediated by dopamine D4 receptors, dopamine may affect the firing of the neurons activating dopamine D1, D2 and D3 receptors present on subthalamic neurons (Flores et al., 1999).

If dopamine increases neuronal firing of the subthalamic nucleus via activation of dopamine D4 receptors, then abnormalities (hypofunctionality) of D4 receptors may lead to reduced firing rates, which would be associated with locomotor hyperactivity (see Davids et al., 2003). Methylphenidate and amphetamine, by increasing dopamine levels in the subthalamic nucleus, may activate dopamine D4 receptors, thereby controlling increased locomotor activity disorders (Castellanos and Tannock, 2002). Juvenile rats with neonatal lesions of the dopaminergic innervation are widely used to model ADHD and its treatment. Methylphenidate reduces the hyperactivity of these animals (Davids et al., 2002). The effect might be mediated by increased firing of subthalamic neurons via a reduced inhibitory input from the globus pallidus. In support of this suggestion is the fact that methylphenidate inhibited GABA release via D4 receptors (Fig. 3).

In conclusion, the present results show that dopamine D4 receptors appear to inhibit the GABA input from the globus pallidus to the subthalamic nucleus, which may increase the firing of subthalamic neurons. The inhibitory effect of amphetamine and methylphenidate upon locomotor hyperactivity disorders may be mediated in part by activation of dopamine D4 receptors by endogenous dopamine in the subthalamic nucleus.

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References

Aceves, J., Cuello, A.C., 1981. Dopamine release induced by electrical stimulation of microdissected caudate-putamen and substantia nigra of the rat brain. Neuroscience 6, 2069–2075.

Ariano, M.A., Wang, J., Noblett, K.L., Larson, E.R., Sibley, D.R., 1997. Cellular distribution of the rat D4 dopamine receptor protein in the CNS using anti-receptor antisera. Brain Res. 752, 26–34.

Augood, S.H., Hollingsworth, Z.R., Standaert, D.G., Emson, P.C., Penney Jr., J.B., 2000. Localization of dopaminergic markers in the human subthalmic nucleus. J. Comp. Neurol. 421, 247–255.

Bevan, M.D., Clark, N.P., Bolam, J.P., 1997. Synaptic integration of functionally pallidal information in the entopeduncular nucleus and subthalamic nucleus in the rat. J. Neurosci. 17, 308–324.

Castellanos, F.X., Tannock, R., 2002. Neuroscience of the attention deficit / hyperactivity disorder: the search for endophenotypes. Nat. Rev., Neurosci. 3, 617–628.

Cossette, M., Levesque, M., Parent, A., 1999. Extrastriatal dopaminergic innervation of human basal ganglia. Neurosci. Res. 34, 51–54.

Davids, E., Zhang, F.I., Baldessarini, R.J., 2002. Stereoselective effects of methylphenidate on motor hyperactivity in juvenile rats induced by neonatal 6-hydroxydopamine lesioning. Psychopharmacology 160, 92–98.

Davids, E., Zhang, K., Tarazi, F.I., Baldessarini, R.J., 2003. Animal models of attention-deficit hyperactivity disorder. Brain Res. Rev., 1–121.

DeLong, M.R., 1990. Primate models of movement disorders of basal ganglia origin. Trends Neurosci. 13, 281–285.

Faraone, S.V., Doyle, A.E., Mick, E., Biederman, J., 2001. Meta-analysis of the association between the 7-repeated allele of the dopamine D4 receptor gene and attention deficit hyperactivity disorder. Am. J. Psychiatry 158, 1052–1057.

Floran, B., Aceves, J., Sierra, J., Martinez-Fong, D., 1990. Activation of D1 dopamine receptors stimulates the release of GABA in the basal ganglia of the rat. Neurosci. Lett. 116, 136–140.

Flores, G., Liang, J.J., Sierra, A., Martinez-Fong, D., Quirion, R., Aceves, J., Srivastava, L.K., 1999. Expression of dopamine receptors in the subthalamic nucleus of the rat: characterization using reverse transcriptase-polymerase chain reaction and autoradiography. Neuroscience 91, 549–556.

Francois, C., Savy, C., Jan, C., Tande, D., Hirsch, E.C., Yelnik, J., 2000. Dopaminergic innervation of the subthalamic nucleus in the normal state, in MPTP-treated monkeys, and in Parkinson's disease patients. J. Comp. Neurol. 425, 121–129.

Gauthier, J., Parent, M., Levesque, M., Parent, A., 1999. The axonal arborization of single nigrostriatal neurons in rats. Brain Res. 834, 228–232.

Glase, S.A., Akunne, H.C., Georgic, L.M., Heffner, T.G., MacKenzie, R.G., Manley, P.J., Pugsley, T.A., Wise, L.D., 1997. Substituted [(4-phenylpiperazinyl)-methyl]benzamides: selective D4 agonists. J. Med. Chem. 40, 1771–1772.

Hassani, O.K., Feger, J., 1999. Effects of intrasubthalamic injection of dopamine receptor agonists on subthalamic neurons in normal and 6-hydroxydopamine-lesioned rats: an electrophysiological and c-Fos study. Neuroscience 92, 533–543.

Hassani, O.K., Francois, C., Yelnik, J., Feger, J., 1997. Evidence for a dopaminergic innervation of the subthalamic nucleus in the rat. Brain Res. 749, 88–94.

Hedreen, J.C., 1999. Tyrosine hydroxylase-inmunoreactive elements in the human globus pallidus and subthalamic nucleus. J. Comp. Neurol. 409, 400–410.

Hemsley, K.M., Farrall, E.J., Crocker, A.D., 2002. Dopamine receptors in the subthalamic nucleus are involved in the regulation of muscle tone in the rat. Neurosci. Lett. 317, 123–126.

Missale, C., Nash, R., Robinson, S.W., Jaber, M., Caron, M.G., 1996. Dopamine receptors: from structure to function. Physiol. Rev. 78, 189–225.Mrzljak, L., Bergson, C., Pappy, M., Huff, R., Levenson, R., Goldman-Rakic, P.S., 1998. Localization of dopamine D4 receptors in GABAergic neurons of the primate brain. Nature 381, 245–248.

Patel, S., Freedman, S., Chapman, K.L., Emms, F., Fletcher, A.E., Knowles, M., Marwood, R., Mcallister, G., Myers, J., Curtis, N., Kulagowski, J.J., Leeson, P.D., Ridgill, M., Graham, M., Matheson, S., Rathbone, D., Watt, A.P., Bristow, L.J., Rupniak, N.M., Baskin, E., Lynch, J.J., Ragan, C.I., 1997. Biological profile of L-745,870, a selective antagonist with high affinity for the dopamine D4 receptor. J. Pharmacol. Exp. Ther. 283, 636–647.

Seamans, J.K., Gorelova, N., Durstewitz, D., Yang, C.R., 2001. Bidirectional dopamine modulation of GABAergic inhibition in prefrontal cortical pyramidal neurons. J. Neurosci. 21, 3628–3638.

Shen, K.Z., Johnson, S.W., 2000. Presynaptic dopamine D2 and muscarine M3 receptors inhibit excitatory and inhibitory transmission to rat subthalamic neurones in vitro. J. Physiol. 525 (Pt2), 331–341.

Shin, R.M., Masuda, M., Suzuki, T., Miura, M., Sano, H., Shirasawa, T., Song, W.-J., Kobayashi, K., Aosaki, T., 2003. Dopamine D4 receptor-induced postsynaptic inhibition of GABAergic currents in mouse globus pallidus neurons. J. Neurosci. 17, 11662–11672.

Trinh, J.V., Nehrenberg, D.L., Jacobsen, J.P., Caron, M.G., Wetsel, W.C., 2003. Differential psychostimulant-induced activation of neural circuits in dopamine transporter knockout and wild type mice. Neuroscience 118, 297–310.

Vallone, D., Picetti, R., Borrelli, E., 2000. Structure and function of dopamine receptors. Neurosci. Biobehav. Rev. 24, 125–132.Zhu, Z., Bartol, M., Shen, K., Johnson, S.W., 2002. Excitatory effects of dopamine on subthalamic nucleus neurons: in vitro study of rats pretreated with 6-hydroxydopamine and levodopa. Brain Res. 945, 31–40.