Pharmacology, Biochemistry and Behavior 96 (2010) 136–140

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Autoradiographic and pharmacological studies on the role of dopamine D3 receptors in genetically dystonic (dt^{sz}) hamsters

Svenja E. Sander [a], Roger Raymond [b], José N. Nobrega [b], Angelika Richter [a,*]

[a] Institute of Pharmacology and Toxicology, Faculty of Veterinary Medicine, Freie Universität Berlin, Koserstr. 20, 14195 Berlin, Germany
[b] Neuroimaging Research Section, Centre for Addiction and Mental Health, Toronto, Ontario, Canada M5T 1R8

ARTICLE INFO

Article history:
Received 27 October 2009
Received in revised form 15 April 2010
Accepted 28 April 2010
Available online 6 May 2010

Keywords:
Dopamine
Dystonia
Dystonic Choreoathetosis
Dyskinesia
Movement disorders

ABSTRACT

Previous examinations demonstrated periodic increases in striatal extracellular dopamine levels during dystonic attacks and changes in dopamine D1 and D2 receptor binding in the dt^{sz} mutant hamster, an animal model of paroxysmal non-kinesiogenic dyskinesia in which dystonic episodes can be induced by stress. Since dopamine D3 receptors are involved in the regulation of striatal dopamine release, D3 receptor function was investigated by autoradiographic and pharmacological examinations in mutant hamsters in the present study. [^{125}I]7-[[(E)-3-iodoprop-2-enyl]-propylamino]-5,6,7,8-tetrahydronaphthalen-2-ol ([^{125}I]7-OH-PIPAT) binding was not significantly altered in the striatum, n. accumbens, ventral pallidum or cerebellum in dt^{sz} hamsters in comparison to non-dystonic control hamsters. In line with the unaltered D3 receptor binding, the preferential dopamine D3 versus D2 receptor antagonist U-99194 (5,6-dimethoxy-*N*,*N*-dipropyl-2,3-dihydro-1H-inden-2-amine hydrochloride) did not exert significant effects on the severity of dystonia in dt^{sz} hamsters at doses of 10 to 40 mg/kg which induced hyperlocomotion. These results suggest that periodic elevations of dopamine levels in these animals are not related to D3 receptor dysfunctions.

1. Introduction

Dystonia is a syndrome of involuntary muscle contractions causing twisting movements and abnormal postures. This common movement disorder shows a heterogeneous etiology and a wide clinical spectrum (Breakefield et al., 2008; Fahn et al., 1998). The pathophysiology is not well understood, but changes in striatal dopaminergic transmission have been suggested to be involved in various types of dystonias and in dystonia-associated dyskinesias (Breakefield et al., 2008; Wichmann, 2008). In the dt^{sz} mutant hamster, an animal model of paroxysmal dystonia (Richter, 2005), previous studies have shown abnormalities in dopaminergic transmission, such as episodic increases in extracellular dopamine levels in the dorsal striatum during the manifestation of dystonic attacks and regional changes in dopamine D1 and D2 receptor binding (Hamann and Richter, 2004; Nobrega et al., 1996; Rehders et al., 2000). However, the role of dopamine D3 receptors in primary dystonias, both in patients and in animal models, is unknown.

Among the five subtypes of dopamine receptors (D1–D5), D1 and D5 show a D1-like pharmacological profile, while D2, D3, and D4 receptors have a D2-like pharmacology. Dopamine has a 70-fold higher affinity for the dopamine D3 receptor than for D1 or D2 receptors. Post- and presynaptic dopamine D3 receptors are particularly expressed in brain regions which regulate limbic and motor functions (Joyce, 2001; Schwartz et al., 1993, 2000). In the human striatum, D2 receptors are expressed in the dorsal striatum and the nucleus accumbens, while D3 receptors are primarily localized in the accumbens and the ventral side of the putamen (Meador-Woodruff et al., 1996).

Interestingly, levodopa-induced dyskinesias were found to be accompanied by enhanced expression of dopamine D3 receptors on striatonigral neurons of the dorsal striatum in a rat model (Schwartz et al., 1998). This observation indicates that D3 receptors deserve attention in dystonias, because levodopa-induced dyskinesias can be associated with dystonic symptoms. Mice with a genetic deletion of the dopamine D3 receptor exhibit hyperlocomotion. In these mice, significantly elevated extracellular dopamine levels in the striatum (Joseph et al., 2002) suggest an important role of the D3 receptor in the regulation of dopaminergic activity. The dopamine D3 autoreceptor seems to control the phasic, but not tonic activity of dopamine neurons (Sokoloff et al., 2006). Thus, the previous finding of periodic elevations of striatal dopamine levels in dystonic hamsters might be related to altered dopamine D3 receptor function.

In the present study we therefore examined the pathophysiological role of dopamine D3 receptors in dystonia by autoradiographic analyses in the dt^{sz} mutant. In addition, the effects of the preferential dopamine D3 versus D2 receptor antagonist 5,6-dimethoxy-N,N-dipropyl-2,3-dihydro-1H-inden-2-amine hydrochloride (U-99194) on the severity of dystonia were examined. The high degree of homology between the binding sites of the D2 and D3 dopamine

* Corresponding author. Tel.: +49 30 83854317; fax: +49 30 83853112.
E-mail address: richtera@zedat.fu-berlin.de (A. Richter).

0091-3057/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2010.04.021

receptor subtypes hampered the development of D3 receptor subtype selective compounds. Systemically active and highly selective dopamine D3 receptor agonists and antagonists are not available, but U-99194 exhibits a 30-fold preference for the D3 receptor compared to the D2 receptors and has a 60-fold preference for D3 than for D4 receptors (Audinot et al., 1998; Hackling and Stark, 2002).

2. Material and methods

2.1. Animals

The study was carried out in groups of male and female dt^{sz} mutant Syrian golden hamsters (inbred line) and age- and sex-matched non-dystonic control hamsters, which were obtained by selective breeding as described previously (Richter and Löscher, 1998). All dystonic and control hamsters were born and kept under the same controlled environmental conditions. All experiments were done in compliance with the German Animal Welfare Act (G0160/05).

2.2. Severity-score of dystonia and induction of dystonic episodes

As reported previously in detail, motor impairments in dt^{sz} hamsters are transmitted by a recessive gene and show several features in common with human primary paroxysmal non-kinesiogenic dystonia (paroxysmal dystonic choreoathetosis), characterized by long-lasting dystonic attacks (Richter, 2005). In mutant hamsters, dystonic attacks can be reproducibly induced by a triple stimulation technique (Richter and Löscher, 1998), i.e., stressful stimuli consisting of (1) taking the animal from its home cage and placing it on a balance, (2) intraperitoneal (i.p.) injection of saline (or of U-99194, see below), and (3) placement of the animal in a new plastic cage. After this procedure, dt^{sz} hamsters develop a sequence of abnormal movements and postures. Therefore, the severity of dystonia can be rated by the following score system (Richter and Löscher, 1998): stage 1, flat body posture; stage 2, facial contortions, rearing with forelimbs crossing, disturbed gait with hyperextended forepaws; stage 3, hyperextended hindlimbs so that the animals appear to walk on tiptoes; stage 4, twisting movements and loss of balance; stage 5, hindlimbs hyperextended caudally; stage 6, immobilisation in a twisted, hunched posture with hind- and forelimbs tonically extended forward. After reaching the individual maximum stage the hamsters recover within 2–5 h. The individual maximum stage of dystonia is usually reached within 3 h after the hamsters were placed in the new cage. Therefore, the animals have to be observed for 3 h after the induction of dystonic attacks to determine the individual maximum stage reached after administration of drugs or of vehicle (for pre- and post-drug control recordings).

In the present study, all animals were examined for the presence of dystonia after weaning at the age of 21 days by the triple stimulation procedure, including injections of saline. All hamsters used for investigations were repeatedly tested by triple stimulations (injections of saline) every 2 to 3 days after weaning until the severity of dystonia and latencies to the different stages were reproducible.

2.3. Autoradiographic analyses

Quantitative autoradiographic analysis of dopamine D3 receptors was carried out groups of 7 mutant hamsters and 8 age- and gender-matched non-dystonic control hamsters. The hamsters were killed by decapitation at an age of 35 days and the brains were rapidly removed, frozen on dry ice, and then stored at −80 °C until cryostat sectioning. Coronal cryostat sections (20 µm) from frozen brains were cut at −20 °C (Leica Microsystems, Wetzlar, Germany), thaw-mounted onto Superfrost slides (Fisher Scientific, Ottawa, ON, Canada) and then stored at −80 °C until binding assays were performed. As recently described (Harrison and Nobrega, 2009), for D3 receptor autoradiography, slides were pre-incubated for 30 min at 30 °C in 50 mM TRIS buffer (pH 7.4), containing 100 mM NaCl, and 50 mM guanylyl-imido-diphosphate. For total binding, slides were incubated for 90 min at room temperature in a 50-mM TRIS buffer (pH 7.0) containing 40 mM NaCl, 50 mM guanylyl-imido-diphosphate (Sigma-Aldrich, Canada), 5 mM 1,3-di(2-tolyl)guanidine (Sigma-Aldrich), 1 mM ethylenediaminetetraacetic acid (EDTA; Sigma-Aldrich), and 0.2 nM [^{125}I]7-OH-PIPAT (PerkinElmer Life Sciences, Boston, MA, USA). For nonspecific binding, representative slides were incubated with 10 mM unlabeled 7-OH-DPAT HBr (Tocris Bioscience, Ellisville, MO, USA) added to the radioligand solution. Slides were washed three times in 50 mM TRIS buffer (pH 7.4) at 4 °C for 30 min each then dipped in ice-cold distilled water for 10 s and dried under a steady stream of cool air. Dried slides along with calibrated standards were exposed on Kodak Biomax MR-1 film for 3 days and then developed. Densitometric analysis was performed using the MCID software program (Imaging Research, St. Catherine's, ON, Canada). A standard curve was generated that relates optical density to known quantities of [^{125}I] (in microcurie per gram of tissue). For any subject, the final binding value for any given brain region represented an average of multiple readings on 3–6 brain sections. Brain regions were defined according to Stereotaxic Atlas of Hamster Brain (Morin and Wood, 2001). Binding values were averaged for each region and each subject, and group means were compared independently for each of the regions sampled. Data were analysed by ANOVA using Systat 5.0 Software (Systat, Evanston, IL), followed by independent t Test comparisons for brain regions where significant F values (p at least <0.05) were obtained.

2.4. Pharmacological studies

The preferential dopamine D3 versus D2 receptor antagonist 2,3-dihydro-5,6-dimethoxy-*N*,*N*-dipropyl-1*H*-inden-2-amine-maleate (U-99194) (Tocris Cookson, Avonmouth, UK) was freshly dissolved in saline prior to the experiments. The effects of 10, 20 and 40 mg/kg i.p. were examined in groups of 7–10 dt^{sz} hamsters at an age between 30 and 45 days, when the animals are highly sensitive to stressful stimuli and develop high severity scores. The doses were chosen on the basis of several previously described experiments in rats and mice (Gyertyán and Sághy, 2004; Jones et al., 2007).

Dystonic attacks were induced by the procedure of triple stimulation, as described above, but instead of saline the active compound was injected (injection volume: 5 ml/kg i.p.). Pre- and post-drug control trials with the vehicle (injection volume: 5 ml/kg isotonic saline i.p.) were undertaken 2–3 days before and 2–3 days after drug testing in the same animals. Since the individual maximum stage of dystonia is usually reached within 3 h, the hamsters were observed for 3 h after triple stimulation. During this period, the severity of dystonia, the latencies to the different stages and the side effects were noted. The side effects were not quantified, but locomotor activity was determined according to a score system, as previously described (Richter and Löscher, 1995).

The significance of differences in severity of dystonia and in latency to the onset of dystonia (latency to occurrence of unequivocal dystonic symptoms, stage 2) between control trials (pre- and post-drug) and drug trial in the same group of animals was calculated by the Friedman test. If there was a significant difference (at least $p<0.05$), the Wilcoxon signed rank test for paired replicates was used post hoc to determine which pairs differed. Significant differences in the locomotor activity scores between different doses were determined by the Mann–Whitney Rank Sum Test.

3. Results

The distribution of dopamine D3 receptors in hamster brains (Fig. 1) was comparable to the previously reported [^{125}I]-7-OH-PIPAT

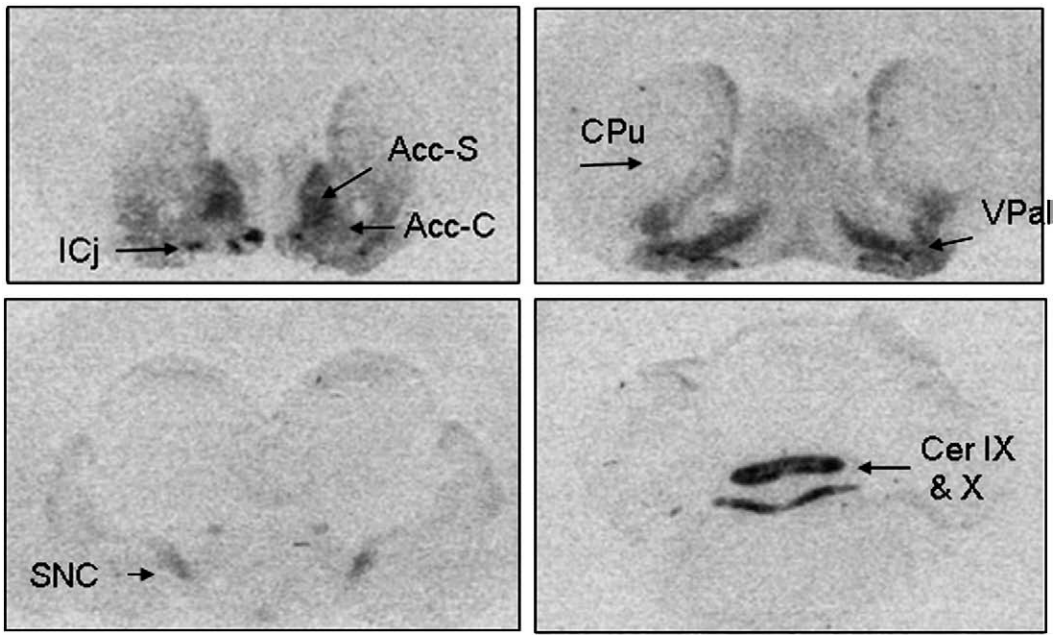

Fig. 1. Illustration of [^{125}I]7-OH-PIPAT binding in normal hamster brain. The overall binding distribution was very similar to that previously described for rats and mice, with high levels in the n. accumbens (Acc), islands of Callejas (ICj), ventral pallidum (VPal) and lobules IX and X of the cerebellum. No differences were found between dystonic and control hamsters in any brain area.

binding in rat and mouse brains (Harrison and Nobrega, 2009; Stanwood et al., 2000). The [^{125}I]-7-OH-PIPAT binding data in hamster brains are summarized in Table 1. Binding was determined in different subregions of the caudate-putamen, in which previous studies have shown several neurochemical changes in mutant hamsters, and in regions of the highest levels (nucleus accumbens, ventral pallidum and lobules 9 and 10 of the cerebellum). In these regions, no significant differences in [^{125}I]-7-OH-PIPAT binding were detected between mutant hamsters and control hamsters.

As shown in Fig. 2, the dopamine D3 receptor antagonist U-99194 failed to exert any significant effects on the severity of dystonia at doses of 10 to 40 mg/kg i.p. Furthermore, the latencies to different stages were not significantly influenced (not illustrated). After application of 10 mg/kg, 9 of 10 hamsters developed a slight hyperlocomotion (median score 1, minimum score 0, maximum score 1). 20 mg U-99194 provoked a slight hyperlocomotion in 6 of 7 seven animals, one animal showed a more marked increase of the locomotor activity (median score 1, minimum score 1, and maximum score 2). In contrast to the lower doses, the injection of 40 mg/kg did not induce hyperlocomotion in the 7 tested hamsters (median score 0, minimum score 0, and maximum score 0). The median locomotor activity score was significantly lower in these animals in comparison to those receiving doses of 10 mg/kg ($p = 0{,}002$) or 20 mg/kg ($p < 0{,}001$). After treatment with the highest dose, the hamsters exhibited an abnormal gait with sudden interruptions in forward moving during the first hour.

Table 1
[^{125}I]7-OH-PIPAT binding to dopamine D3 receptors in hamster brains.

Region	Control	Dystonic	*p* Value
	Hamsters	Hamsters	
Accumbens n., core	516.5 ± 97.7	548.9 ± 42.4	0.741
Accumbens n., shell	489.8 ± 83.6	422.1 ± 67.8	0.063
Caudate-putamen			
Dorsomedial	170.2 ± 12.4	154.4 ± 11.4	0.545
Dorsolateral	132.1 ± 10.6	120.0 ± 9.2	0.279
Ventromedial	147.8 ± 9.6	134.0 ± 12.0	0.823
Ventrolateral	123.0 ± 8.8	111.6 ± 11.7	0.377
Cerebellum, lobe 9–10	722.0 ± 83.4	625.6 ± 40.9	0.712
Ventral pallidum	529.6 ± 63.2	483.0 ± 40.9	0.840

Values are means ± SEM in nCi per gram of tissue. No significant differences in dopamine D3 receptor binding were observed between dystonic and control animals in any region sampled ($p > 0.05$, *t* tests).

4. Discussion

The present [^{125}I]-7-OH-PIPAT autoradiography did not reveal any changes in dopamine D3 receptor density in mutant hamsters. In contrast, previous autoradiographic analyses of dopamine D1 receptor density, using the ligand [3H]SCH 23390, have shown significant decreases of D1 binding in several parts of the striatum and the binding of the D2 ligand [3H]YM-09151-2 was lower in the dorsomedial striatum of dystonic hamsters (Nobrega et al., 1996). These changes could be related to a receptor down-regulation provoked by enhanced dopamine release because extracellular dopamine levels were found to be increased in the striatum during the expression of dystonia (Hamann and Richter, 2004) and intrastriatal injections of D1 and D2 receptor antagonists exerted strong antidystonic effects in mutant hamsters (Rehders et al., 2000). In line with this interpretation, in the *hph-1* mice, which have defective tetrahydrobiopterin biosynthesis and share many neurochemical similarities with levodopa-responsive dystonia in humans, low brain levels of dopamine are associated with increased D2 receptor ([3H]spiperone) binding (Zeng et al., 2004). As observed in the present study in the *dt^{sz}* mutant, the D3 receptor binding densities were found to be unaltered in *hph-1* mice (Zeng et al., 2004). Thus, changes in dopamine levels do not necessarily lead to altered D3 receptor binding. On the other hand, the unaltered [^{125}I]-7-OH-PIPAT binding in dystonic brain suggest that phasic increases of striatal dopamine levels found in mutant hamsters during dystonic episodes (Hamann and Richter, 2004) are not related to changes in D3 receptor-mediated regulation of the dopamine release. This is in line with the hypothesis that intermittent dopaminergic overactivity during stress-induced dystonic attacks is probably secondary to the significant deficit of striatal GABAergic interneurons in the *dt^{sz}* mutant hamster (Richter, 2005).

Since functional changes cannot be detected by autoradiographic studies, additional pharmacological examinations were done in the

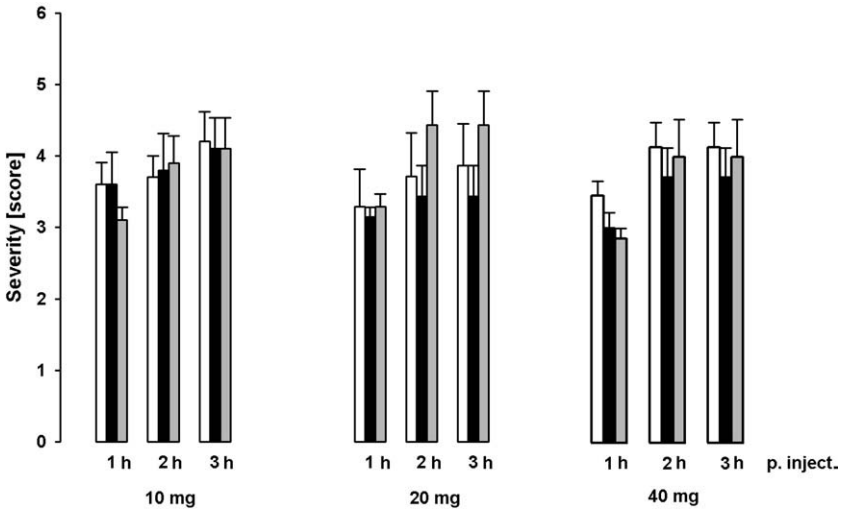

Fig. 2. Effect of U-99194 (10, 20 and 40 mg/kg i.p.) on severity of dystonia in dt^{sz} mutant hamsters. The white and grey bars in each set of three bars indicate the control values obtained 2 days before (pre drug control) drug administration (white bar) and 2 days after (post-drug control) drug administration (grey bar). The black bar refers to the day of the drug administration in the same animal groups. The individual maximum severity of dystonia is usually reached within 3 h after the induction of dystonia by triple stimulation including the injection of drugs or vehicle. The figure shows the average of the maximum individual severity scores of dystonia reached within the 1st, 2nd and 3rd h post injection (p. inj.) of vehicle or U-99194, reflecting the progression of dystonia in dt^{sz} hamsters during control recordings and after treatment with the active compound. Data are shown as means + S.E.M. of 10 (10 mg/kg) or 7 (20 and 40 mg/kg) animals.

present study. It should be noted that the functional role of the dopamine D3 receptor is difficult to study because of the lack of selective agonists and antagonists (Boeckler and Gmeiner, 2006). The preferential dopamine D3 versus D2 receptor antagonist U-99194 did not significantly influence the severity of dystonia or the progression of dystonic symptoms during a dystonic episode at doses which enhanced the locomotor activity in mutant hamsters. Putative D3 receptor antagonists increase locomotor activity in rodents (Gyertyán and Sághy, 2004) and mutant mice lacking functional D3 receptors exhibit hyperlocomotion (Accili et al., 1996; Xu et al., 1997). Therefore, the more marked hyperlocomotion induced by 10 and 20 mg/kg of U-99194 in comparison to 40 mg/kg might be related to higher D3 than D2 receptor inhibition, suggesting that the chosen doses were appropriate. U-99194 significantly increases locomotor activity in rats at doses that do not increase dopamine release in the striatum or in the nucleus accumbens (Boeckler and Gmeiner, 2006). Therefore, the lack of prodystonic effects of U-99194 in mutant hamsters does not argue against the hypothesis that intermittent increases of dopamine play a crucial role in the manifestation of dystonia (Hamann and Richter, 2004). Inhibition of postsynaptic D3 receptors by U-99194 can enhance locomotor activity (Boeckler and Gmeiner, 2006). Since U-99194 did not show significant effects on dystonia at doses which induced hyperlocomotion, neither presynaptic nor postsynaptic D3 receptor function seems to be altered in dt^{sz} hamsters.

In contrast to the absence of significant effects of U-99194 on dystonia, the dopamine D2/D3 receptor agonist quinpirole was previously found to worsen dystonia after systemic and after intrastriatal injections in dystonic hamsters (Rehders et al., 2000). The aggravation was thought to be related to the activation of dopamine D2 receptors, although quinpirole shows a higher affinity for dopamine D3 than for D2 receptors (Boeckler and Gmeiner, 2006). Indeed, the prodystonic effects of quinpirole occurred at doses that provoked hyperlocomotion, which is probably based on activation of D2 rather than D3 receptors (see above). Furthermore, the combined injections of D1 and D2 receptor antagonists into the striatum or systemic co-administrations exerted a striking improvement of dystonia. Likewise neuroleptics reduced the severity of dystonia in the hamster model (Rehders et al., 2000; Richter and Löscher, 1993). Although single administration of D1 blockers or of D2 receptor antagonists were less effective, these pharmacological observations together with receptor autoradiographic analyses suggest that changes in D1 and particularly in D2 receptor function are more important than D3 receptors abnormalities. However, at least the higher doses of U-99194 were expected to exert D2 receptor-mediated antidystonic effects in the present study. It remains an open question whether this was counteracted by the D3 receptor blockade. Further studies on the interaction between dopamine receptor subtypes appear to be interesting, because there is evidence that D1 and D3 receptors may affect neurons in either synergy or opposition according to the cell or signal generated. For example, in the rat model of levodopa-induced dyskinesia, repeated levodopa administrations induce the appearance of D3 receptors on striatonigral neurons of the dorsal striatum, which is thought to be secondary to D1 receptor stimulation in neurons of the denervated side, and fully accounts for the occurrence of dystonia-associated dyskinesias (Schwartz et al., 1998).

In summary, the present data did not reveal changes in dopamine D3 receptor binding or function. Therefore, it is unlikely that previously detected intermittent increases of striatal dopamine levels during stress-inducible dystonic attacks are related to dysfunctions of the dopamine D3 receptors.

Acknowledgement

This study was supported by DFG (RI845/1-3). We thank A. Russ for his helpful assistance.

References

Accili D, Fishburn CS, Drago J, Steiner H, Lachowicz JE, Park BH, et al. A targeted mutation of the D3 dopamine receptor gene is associated with hyperactivity in mice. Proc Natl Acad Sci USA 1996;93:1945–9.

Audinot V, Newman-Tancredi A, Gobert A, Rivet JM, Brocco M, Lejeune F, et al. A comparative in vitro and in vivo pharmacological characterization of the novel dopamine D3 receptor antagonists (+)−S 14297, nafadotride, GR 103, 691 and U 99194. J Pharmacol Exp Ther 1998;287:187–97.

Boeckler F, Gmeiner P. The structural evolution of dopamine D3 receptor ligands: structure-activity relationships and selected neuropharmacological aspects. Pharmacol Ther 2006;112:281–333.

Breakefield XO, Blood AJ, Li Y, Hallett M, Hanson PI, Standaert DG. The pathophysiological basis of dystonias. Nat Rev Neurosci 2008;9:222–34.

Fahn S, Bressman SB, Marsden CD. Classification of dystonia. Adv Neurol 1998;78:1-10.

Gyertyán I, Sághy K. Effects of dopamine D3 receptor antagonists on spontaneous and agonist-reduced motor activity in NMRI mice and Wistar rats: comparative study with nafadotride, U 99194A and SB 277011. Behav Pharmacol 2004;15:253–62.

Hackling AE, Stark H. Dopamine D3 receptor ligands with antagonist properties. Chembiochem 2002;3:946–61.
Hamann M, Richter A. Striatal increase of extracellular dopamine levels during dystonic episodes in a genetic model of paroxysmal dyskinesia. Neurobiol Dis 2004;16:78–84.
Harrison SJ, Nobrega JN. Differential susceptibility to ethanol and amphetamine sensitization in dopamine D3 receptor-deficient mice. Psychopharmacology 2009;204:49–59.
Jones CD, Bartee JA, Leite-Browning ML, Blackshear MA. Methamphetamine-induced locomotor activity and behavioral sensitization: are dopamine D3 receptors involved? Cell Mol Biol (Noisy-le-grand) 2007;53:15–22.
Joseph JD, Wang YM, Miles PR, Budygin EA, Picetti R, Gainetdinov RR, et al. Dopamine autoreceptor regulation of release and uptake in mouse brain slices in the absence of D(3) receptors. Neuroscience 2002;112:39–49.
Joyce JN. Dopamine D3 receptor as a therapeutic target for antipsychotic and antiparkinsonian drugs. Pharmacol Ther 2001;90:231–59.
Meador-Woodruff JH, Damask SP, Wang J, Haroutunian V, Davis KL, Watson SJ. Dopamine receptor mRNA expression in human striatum and neocortex. Neuropsychopharmacology 1996;15:17–29.
Morin LP, Wood RI. A stereotaxic Atlas of The Golden Hamster Brain. San Diego: Academic Press; 2001.
Nobrega JN, Richter A, Tozman N, Jiwa D, Löscher W. Quantitative autoradiography reveals regionally selective changes in dopamine D1 and D2 receptor binding in the genetically dystonic hamster. Neuroscience 1996;71:927–36.
Rehders JH, Löscher W, Richter A. Evidence for striatal dopaminergic overactivity in paroxysmal dystonia indicated by microinjections in a genetic rodent model. Neuroscience 2000;97:267–77.
Richter A. The genetically dystonic hamster: an animal model of paroxysmal dystonia. In: LeDoux M, editor. Animal Models of Movement Disorders. San Diego: Elsevier Academic Press; 2005. p. 459–66.
Richter A, Löscher W. The atypical neuroleptic, clozapine, exerts antidystonic activity in a mutant hamster model. Comparison with haloperidol. Eur J Pharmacol 1993;242: 309–12.
Richter A, Löscher W. Alterations in dystonia in response to pharmacological manipulation of serotonin receptors in the genetically dystonic hamster. Pharmacol Biochem Behav 1995;52:655–65.
Richter A, Löscher W. Pathophysiology of idiopathic dystonia: findings from genetic animal models. Prog Neurobiol 1998;54:633–77.
Schwartz JC, Levesque D, Martres MP, Sokoloff P. Dopamine D3 receptor: basic and clinical aspects. Clin Neuropharmacol 1993;16:295–314.
Schwartz JC, Diaz J, Bordet R, Griffon N, Perachon S, Pilon C, et al. Functional implications of multiple dopamine receptor subtypes: the D1/D3 receptor coexistence. Brain Res Brain Res Rev 1998;26:236–42.
Schwartz JC, Diaz J, Pilon C, Sokoloff P. Possible implications of the dopamine D(3) receptor in schizophrenia and in antipsychotic drug actions. Brain Res Brain Res Rev 2000;31:277–87.
Sokoloff P, Diaz J, Le Foll B, Guillin O, Leriche L, Bezard E, et al. The dopamine D3 receptor: a therapeutic target for the treatment of neuropsychiatric disorders. CNS Neurol Disord Drug Targets 2006;5:25–43.
Stanwood GD, Artymyshyn RP, Kung MP, Kung HF, Lucki I, McGonigle P. Quantitative autoradiographic mapping of rat brain dopamine D3 binding with [(125)I]7-OH-PIPAT: evidence for the presence of D3 receptors on dopaminergic and nondopaminergic cell bodies and terminals. J Pharmacol Exp Ther 2000;295: 1223–31.
Wichmann T. Commentary: dopaminergic dysfunction in DYT1 dystonia. Exp Neurol 2008;212:242–6.
Xu M, Koeltzow TE, Santiago GT, Moratalla R, Cooper DC, Hu XT, et al. Dopamine D3 receptor mutant mice exhibit increased behavioral sensitivity to concurrent stimulation of D1 and D2 receptors. Neuron 1997;19:837–48.
Zeng BY, Heales SJ, Canevari L, Rose S, Jenner P. Alterations in expression of dopamine receptors and neuropeptides in the striatum of GTP cyclohydrolase-deficient mice. Exp Neurol 2004;190:515–24.