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Brain-derived neurotrophic factor controls dopamine D3 receptor expression: therapeutic implications in Parkinson's disease

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Abstract

Brain-derived neurotrophic factor (BDNF) belongs to a family of proteins related to nerve growth factor, which are responsible for neuron proliferation, survival and differentiation. A more diverse role for BDNF as a neuronal extracellular transmitter has, nevertheless, been proposed. Here we show that BDNF synthesized by dopamine neurons is responsible for the appearance of the dopamine D3 receptor during development and maintains its expression in adults. Moreover, BDNF triggers behavioral sensitization to levodopa in hemiparkinsonian rats. In monkeys rendered parkinsonian with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, which develop levodopa-induced dyskinesia, we show an overexpression of this receptor. Administration of a dopamine D3 receptor-selective partial agonist strongly attenuated levodopa-induced dyskinesia, while leaving unaffected the therapeutic effect of levodopa. These results suggest that the dopamine D3 receptor participates in both dyskinesia and the therapeutic action of levodopa and that partial agonists may normalize dopamine D3 receptor function and correct side-effects of levodopa therapy in PD patients.

Keywords: Dopamine; BDNF (brain-derived neurotrophic factor); Parkinson's disease; Behavioral sensitization; Dyskinesia

1. Introduction

Brain-derived neurotrophic factor (BDNF), like other neurotrophins, was initially regarded as being responsible for neuron proliferation, differentiation and survival, after its neuronal uptake and retrograde transport to the soma (Thoenen, 1995). A more diverse role for BDNF as an extracellular transmitter has, nevertheless, been inferred from observations that it is anterogradely transported (Altar et al., 1997; von Bartheld et al., 1996), released upon neuron depolarization and triggers rapid intracellular signals (Altar and Di Stefano, 1998; Thoenen, 1995) and action potentials in central neurons (Kafitz et al., 1999), via intracellular transduction of its high-affinity membrane receptor TrkB (Blum et al., 2002). BDNF can alter fast synaptic transmission by speeding up the development of excitatory and inhibitory synapses (Vicario-Abejon et al., 1998), but also by modulating synaptic efficacy (Huang et al., 1999; Lohof et al., 1993). In particular, BDNF is necessary for the induction and maintenance of hippocampal long-term potentiation (Figurov et al., 1996; Korte et al., 1995; Kovalchuk et al., 2002; Patterson et al., 1996). Although some observations suggest a role of BDNF in nociception (Kerr et al., 1999), mechanosensation (Carroll et al., 1998) and learning (Linnarsson et al., 1997; Minichiello et al., 1999), little is known, however, about the consequences of BDNF-induced synaptic plasticity on physiological functions.

Converging evidence implicates the dopamine D3 receptor in the physiopathology and treatment of Parkinson's disease (Bordet et al., 1997). In rat brain, the dopamine D3 receptor expression density is highest in the islands of Calleja and in the shell part of the nucleus accumbens (Diaz et al., 1995; Lévesque et al., 1992), which receives its dopaminergic innervation from the ventral tegmental area and other innervations from the cerebral cortex, hippocampus and amygdala (Pennartz et al., 1994; Zahm and Brog, 1992). The shell of the nucleus accumbens projects indirectly to entorhinal and prefrontal cortices and participates

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in a neuronal circuitry subserving the control of emotion, motivation and reward (Willner, 1997). In the human brain, dopamine D3 receptor distribution is similar, yet less restricted, with a significant expression in the striatum, which controls movement, and in cortical areas processing sensorimotor information (Susuki et al., 1998). In post-mortem brain, the D3 receptor density is lowered in Parkinson's disease (Ryoo et al., 1998) and the intensity of this loss is correlated with the loss of response to dopaminergic drugs (Joyce et al., 2002).

Here, we examine the hypothesis that BDNF is a factor controlling dopamine D3 receptor expression and then controls the plasticity of dopaminergic neurons. Moreover, we show that the dopamine D3 receptor in animal models of Parkinson's disease is a target for correcting abnormal behavior seen in this model.

2. BDNF controls D_3 receptor expression during development

In adults, the expression of the dopamine D3 receptor in medium-sized neurons of the nucleus accumbens, but not in granule cells of the islands of Calleja, is highly dependent upon the dopaminergic innervation: ablation of the afferent neurons by unilateral 6-hydroxydopamine results in a dramatic decrease in dopamine D3 receptor density in the ipsilateral nucleus accumbens (Lévesque et al., 1995). This paradoxical change (the dopamine D2 receptor is up-regulated under these circumstances) was shown to depend on the lack of an anterogradely transported factor from dopaminergic neurons, distinct from dopamine itself and its known peptide co-transmitters, and which is released upon dopamine neuron activation (Lévesque et al., 1995).

Among the candidate factors for regulating dopamine D3 receptor expression, BDNF is particularly attractive, since it is expressed by dopamine neurons (Seroogy et al., 1994). BDNF immunoreactivity is prominent in the shell of the nucleus accumbens of normal rats (Conner and Lauter, 1997), and its receptor, the tropomyosin-related kinase B (TrkB), co-localizes with the dopamine D3 receptor (Guillin et al., 2001). Moreover, BDNF and dopamine D3 receptor expressions, which are both very low at birth, increase in parallel during postnatal development (Fig. 1). Local infusion of BDNF reverses the 6-hydroxydopamine-induced decrease in dopamine D3 receptor gene expression, indicating that exogenous BDNF compensates for the loss of dopamine neurons (Guillin et al., 2001).

We have examined the effect of a BDNF-null mutation on dopamine D3 receptor expression in developing mice. In wild-type $BDNF^{+/+}$ mice, dopamine D3 receptor binding and mRNA in the shell of the nucleus accumbens increase sharply from postnatal days 9–14 to 17–23, whereas in homozygous $BDNF^{-/-}$ mice, dopamine D3 receptor binding and mRNA are low at postnatal day 9–14, and do not increase at later stages (Fig. 1). Moreover, dopamine D3 receptor expression is unaffected by BDNF gene mutation in the islands of Calleja (Fig. 1), a region where TrkB is not expressed. These results show that BDNF is required for the normal development of dopamine D3 receptor expression in the shell of the nucleus accumbens.

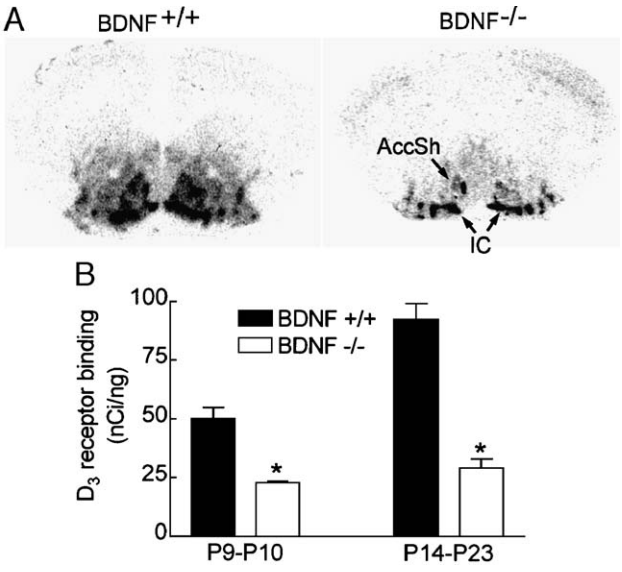

Fig. 1. Impaired dopamine D3 receptor expression in developing $BDNF^{-/-}$ mice. (A) Autoradiographic pictures of dopamine D3 receptor binding, obtained with [^{125}I]7-OH-PIPAT, in wild-type $BDNF^{+/+}$ or $BDNF^{-/-}$ mice on postnatal day 23. (B) Pictures obtained as in (A) with animals on P9-P10 or P14-P23 were analyzed. Means ± S.E.M. of values from 4–11 animals. *$P<0.01$ versus $BDNF^{+/+}$ littermates. (D_3 receptor, dopamine D3 receptor; Accsh, shell of the nucleus accumbens; IC, islands of Calleja).

The BDNF gene mutation does not impair the early development of dopamine neurons (Ernfors et al., 1994), nor their later development, since tyrosine hydroxylase, a marker of these neurons, was not significantly affected by the lack of BDNF (Guillin et al., 2001). This suggests that BDNF acts directly on dopamine D3 receptor-expressing neurons rather than indirectly via an effect on the development of dopamine neurons. Moreover, BDNF deprivation selectively reduces the expression of the dopamine D3 receptor, and not that of the homologous dopamine D1 and D2 receptors (Guillin et al., 2001), which are not, or only marginally, down-regulated by 6-hydroxydopamine lesions (Bordet et al., 1997).

3. BDNF triggers ectopic dopamine D3 receptor expression and behavioral sensitization in denervated rats

In unilaterally 6-hydroxydopamine-lesioned rats, repeated administration of levodopa, leading to extraneuronal dopamine formation, triggers dopamine D3 receptor overexpression, not only in the shell of the nucleus accumbens,

but also in the denervated striatum, a brain structure in which dopamine D3 receptor expression is hardly detectable (Bordet et al., 1997). During levodopa treatment of 6-hydroxydopamine-lesioned rats, infusion into the denervated striatum of a selective BDNF antagonist, formed by fusion between the Fc-tail of human immunoglobin G (IgG) and a part of TrkB (IgG-TrkB) (Cabelli et al., 1997), impairs induction of both dopamine D3 receptor mRNA and protein expression (Fig. 2). This indicates that BDNF is necessary for this process (Guillin et al., 2001).

This dopamine D3 receptor overexpression has been shown to be responsible for the development of behavioral sensitization to levodopa, i.e. a progressive enhancement of responsiveness, which appears as an increased number of levodopa-induced rotations: the development and extinction of behavioral sensitization parallel dopamine D3 receptor expression in the striatum during the treatment with levodopa and after its cessation (Fig. 3A). Moreover, the increase in the number of rotations is blocked by a preferential dopamine D3 receptor antagonist (Bordet et al., 1997) and induced by a selective partial dopamine D3 receptor agonist (Pilla et al., 1999). Infusion of IgG-TrkB dose-dependently inhibits behavioral sensitization (Fig. 3B), indicating that behavioral sensitization is triggered by BDNF.

Striatal BDNF in fact originates mainly from cortical neurons (Altar et al., 1997). In agreement, cortical ablation

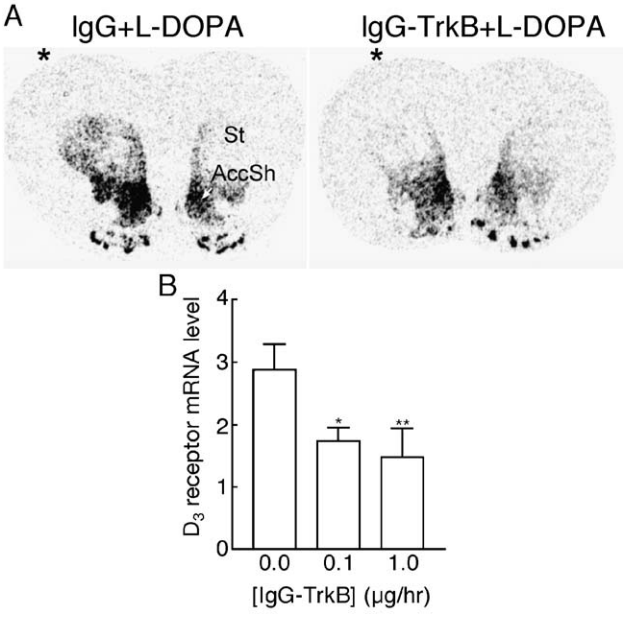

Fig. 2. Levodopa-induced dopamine D3 receptor expression in 6-hydroxydopamine-lesioned rats require BDNF. The asterisk denotes the lesioned side. (A) In situ hybridization signals of dopamine D3 receptor mRNA in animals receiving continuous infusions into the striatum of IgG (control animal, left) or IgG-TrkB, a BDNF antagonist (*right*) for 7 days and levodopa for 5 days. (B) Quantitative analysis of pictures as in (A) $*P<0.05$ and $**P<0.01$ versus IgG-treated animals. (D_3 receptor, dopamine D3 receptor; 6-hydroxydopamine, 6-OHDA).

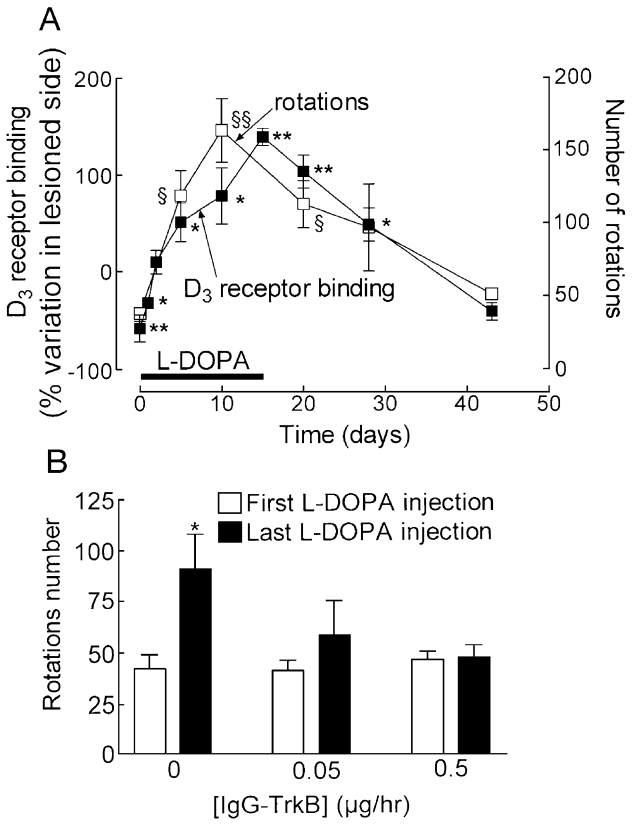

Fig. 3. (A) Parallel changes in dopamine D3 receptor binding and levodopa-induced rotations in hemiparkinsonian rats during and after repeated administration of levodopa. Rats with an unilateral 6-hydroxydopamine-induced lesion of the ascending mesencephalic dopaminergic pathways, made 3 weeks earlier, received levodopa (50 mg/kg, i.p., b.i.d.) for up to 15 days and were challenged with a single same dose of levodopa. (B) Rotations were recorded after the first and last levodopa administrations in 6-hydroxydopamine-lesioned animals receiving increasing doses of IgG-TrkB during levodopa treatment. $*P<0.05$ versus first L-dopa injection. (D_3 receptor, dopamine D3 receptor; 6-hydroxydopamine, 6-OHDA; L-dopa, levodopa).

partially impairs the induction of dopamine D3 receptor overexpression in the striatum and behavioral sensitization, indicating that both processes require the participation of corticostriatal neurons. Levodopa also induces BDNF mRNA on the frontal cortex in the 6-hydroydopamine-lesioned side, mainly in cortical layer V, containing pyramidal cell bodies, and in layer VI, which sends projections to various subcortical areas, notably striatal and accumbal areas (Berendse et al., 1992). This effect critically depends upon activation of a dopamine D1 or D5 receptor (Guillin et al., 2001) and is consistent with the presence of dopamine D1 receptors on cortical pyramidal cells (Huang et al., 1992) and with the observation that stimulation of a dopamine D1 or D5 receptor under similar circumstances phosphorylates cAMP response element-binding protein (Cole et al., 1994), a factor that activates BDNF gene transcription (Shieh et al., 1998; Tao et al., 1998). We conclude that the induction of dopamine D3 receptor expression in striatum is triggered by a dopamine D1/D5 receptor stimulation-dependent elevation

of BDNF in cortico-striatal neurons, a process that is more prononced in the 6-hydroxydopamine-lesioned side as compared to the control side, which accounts for the induction of dopamine D3 receptor expression restricted to the lesioned side. Moreover, BDNF-induced dopamine D3 receptor expression causes a more pronounced disequilibrium in responsiveness to dopamine between the two sides, which leads to enhanced rotational behavior.

4. Normalization of dopamine D3 receptor function attenuates dyskinesia induced by levodopa

Parkinson's disease associates several symptoms such as akinesia, rigidity and tremor, which result from the lack of the brain neurotransmitter dopamine (Hornykiewicz, 1963). Substitution treatment of Parkinson's disease, e.g. by levodopa, initially reduces motor symptoms, but eventually induces, in most of patients, debilitating and pharmacoresistant involuntary movements, i.e. dyskinesia, presumably resulting from an excessive response to dopamine (Bezard et al., 2001). This excessive response to dopamine results from behavioral sensitization to the drug (Bezard et al., 2001).

Enhanced responses to levodopa in 6-hydroxydopamine-lesioned rats could reflect either the progressive motor recovery occurring at treatment initiation or the development of levodopa-induced dyskinesia in long-term treated Parkinson's disease patients (Cotzias et al., 1969). This could not be assessed in Parkinson's disease-like rats, which do not develop typical levodopa-induced dyskinesia. We have presently used monkeys treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which destroys dopamine neuron terminals and cell bodies and produces a variety of Parkinson's disease-like symptoms, including akinesia and rigidity (Burns et al., 1983). Long-term treatment of these monkeys with levodopa elicits dyskinesia, the repertoire and the severity of which are not distinguishable from levodopa-induced dyskinesia occurring in Parkinson's disease patients (Bezard et al., 2001).

Dopamine D3 receptor binding has been measured in the brain basal ganglia. MPTP alone produces a severe loss of dopamine D3 receptor binding in the caudate nucleus (Bezard et al., 2003), a brain structure involved in associative locomotion, an effect which is compensated by treatment with levodopa in MPTP-intoxicated animals without levodopa-induced dyskinesia (Fig. 4). However, in MPTP-intoxicated monkeys with levodopa-induced dyskinesia, dopamine D3 receptor binding is higher than in non-dyskinetic monkeys in the putamen and internal part of the globus pallidus and even higher than in normal monkeys (Bezard et al., 2003). Moreover, dopamine D3 receptor binding levels in the putamen correlate with the occurrence and severity of levodopa-induced dyskinesia. These results show that Parkinson's disease-like symptoms and levodopa-induced dyskinesia are accompanied by

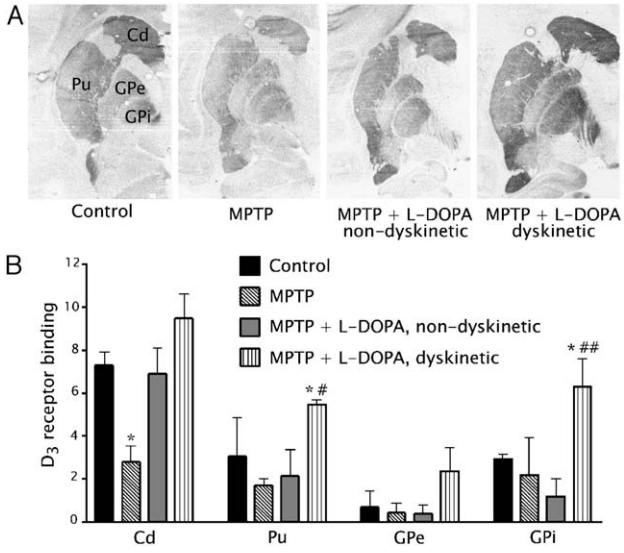

Fig. 4. Dyskinesia is accompanied by dopamine D3 receptor overexpression. (A) Typical receptor autoradiograms obtained with [^{125}I]7-OH-PIPAT, a selective dopamine D3 receptor radioligand, in the brain from a typical normal monkey, untreated MPTP-intoxicated monkeys (MPTP), and non-dyskinetic and dyskinetic MPTP-intoxicated monkeys treated with levodopa (L-dopa). Cd, caudate nucleus; GPe, external part of globus pallidus; GPi, internal part of globus pallidus; Pu, putamen. (B) Quantitative analysis of autoradiograms obtained as in (A). Results are means ± S.E.M. of values in μCi/mg. $^{*}P<0.05$ vs. control; $^{\S}P<0.05$, $^{\S\S}P<0.01$ vs. non-dyskinetic.

down- and up-regulation of dopamine D3 receptor expression, respectively, while such a correlation does not exist for either dopamine D1 or D2 receptors under comparable experimental conditions (Bezard et al., 2001, 2003). In addition, the occurrence of dyskinesia does not correlate with the severity of the lesion (Bezard et al., 2003), which indicates that the level of dopamine D3 receptor expression level is an accurate maker of dyskinesia.

The changes in dopamine D3 receptor expression are likely to reflect fluctuations in dopamine D3 receptor function, as it is the case in Parkinson's disease-like rats in which such changes are responsible for alterations of motor responses (Bordet et al., 1997; Guillin et al., 2001; Pilla et al., 1999). To test this hypothesis, we used a selective partial agonist, BP 897, as a stabilizing agent, which could limit neurotransmitter fluctuations in either direction, i.e. maintain substantial but blunt excessive receptor stimulation (Bezard et al., 2003).

BP 897 was administered to dyskinetic MPTP-intoxicated monkeys in combination with levodopa, using a randomized, crossed-over, placebo-controlled design, in which the animals were repeatedly treated (4–12 times by each treatment) and evaluated for levodopa-induced dyskinesia and Parkinson's disease-like symptoms by experimenters unaware of the treatment received (Bezard et al., 2003). BP 897 attenuated levodopa-induced dyskinesia by 66% (calculated from area under curve, see Fig. 5A), but had almost no influence on the therapeutic effect

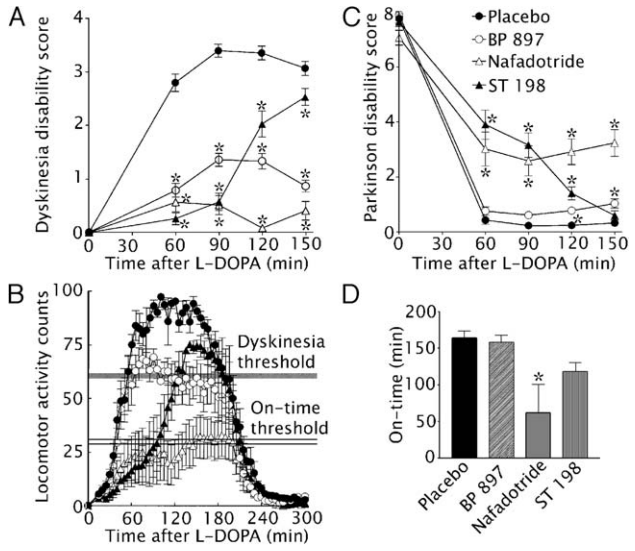

Fig. 5. A partial dopamine D3 receptor agonist, but not dopamine D3 receptor antagonists, reduced levodopa-induced dyskinesia (LID) without affecting the therapeutic effects of levodopa. (A–C) LID (A), PD-like symptoms (B), and locomotor activity (C) as a function of time in MPTP-intoxicated monkeys treated with either placebo, the dopamine D3 receptor partial agonist BP 897 administered at an optimal dosage, or the dopamine D3 receptor antagonists nafadotride or ST 198, both administered at a minimal dosage. Dopamine D3 receptor-acting agents significantly affected both the dyskinesia disability score and Parkinson disability score over the time course. *$P<0.05$ vs. placebo. (D) On-time duration measured from locomotor activity counts over a 5-h period. *$P<0.05$ vs. placebo.

of levodopa, i.e. it did not reverse the improvement of Parkinson's disease-like symptoms (Fig. 2B). Both hyperkinesia (that is not true dyskinesia and thus not rated as one) and choreic/athetoid movements were improved. The kinetics of activity counts (Fig. 5C) highlighted this characteristic pharmacological behavior by showing the ability of BP 897 to undermine the levodopa-induced activity around the dyskinesia threshold, defined from a correlation with clinically assessed levodopa-induced dyskinesia. In addition, the monkey receiving repeated administration of BP 897 (12 times) did not show any obvious signs of decline of the antidyskinetic effect with treatment, and nor did the Parkinson's disease-like symptoms reappear. Nafadotride, a dopamine D3 receptor-preferring antagonist or ST 198, a novel highly dopamine D3 receptor-selective antagonist (Bezard et al., 2003; Weber et al., 2001), elicited a reduction of levodopa-induced dyskinesia similar to that obtained with BP 897 (Fig. 5A), which was, however, accompanied by a reappearance of Parkinson's disease-like symptoms (Fig. 5B). We conclude that the worsening of Parkinson's disease-like symptoms was produced by antagonism of levodopa at the dopamine D3 receptor. Our results indicate that attenuation of levodopa-induced dyskinesia, leaving intact the therapeutic effect of levodopa, can be obtained by administration of a dopamine D3 receptor-selective partial agonist.

5. Conclusions

The regulatory mechanism controlling dopamine D3 receptor expression markedly differs from that of various neurotransmission systems, in which receptor density and sensitivity are primarily controlled by the endogenous ligand (Laufer and Changeux, 1989; Schwartz et al., 1978). These observations, together with those showing that BDNF modulates synaptic transmission, strengthen the view that BDNF elicits adaptive changes in cerebral neurotransmission, demonstrating a role of this neurotrophin in the plasticity of dopaminergic neurons.

Modulation of dopamine responsiveness by BDNF could be an important determinant in the etiopathology and/or treatment of several conditions involving dopamine. Thus, progressive treatment-dependent elevation of corticostriatal BDNF, which may occur in Parkinson's disease as it does in 6-hydroxydopamine-lesioned rats, is a previously unraveled mechanism possibly accounting for the enhanced response to levodopa, which underlies its initial beneficial effect, but leads to the abnormal movements often present in long-term treated patients.

Schizophrenia, assumed to result from a neurodevelopmental disorder, is characterized by neuroanatomical abnormalities, such as ventricle enlargement (Weinberger, 1987) possibly related to a defect in neuroepithelium proliferation. A role for the dopamine D3 receptor in this pathological process might be inferred from the selective expression of this receptor in the neuroepithelium during the prenatal period (Diaz et al., 1997) and is supported by genetic studies (Dubertret et al., 1998; Williams et al., 1998). In addition, in later stages of development and in adulthood, dopamine D3 receptor expression in neurons is positively controlled by BDNF, the level of which is elevated in the cortex of patients with schizophrenia (Takahashi et al., 2000). This may explain the overexpression of dopamine D3 receptors found in these patients (Gurevich et al., 1997).

Mesolimbic dopaminergic neurons projecting to the nucleus accumbens have been suggested to be involved in the neurobiology of depression and in the therapeutic actions of some antidepressant drugs (Willner, 1997). This hypothesis postulates that decreased dopamine activity is involved in depression, while increased dopamine function contributes to mania. The expressions of BDNF and dopamine D3 receptor genes are both lowered by stress, a major risk factor in depression, and increased by chronic antidepressant treatment (Lammers et al., 2000; Nibuya et al., 1995; Smith et al., 1995). This suggests a primary action of stress and antidepressant treatment on BDNF, causing changes in dopamine responsiveness through the dopamine D3 receptor, which may participate in the etiology and treatment of depressive symptoms, such as anhedonia.

The shell of the nucleus accumbens also receives innervations from areas highly enriched in BDNF (Conner and Lauter, 1997), such as the hippocampus, lesions of which also down-regulate dopamine D3 receptor expression

(Flores et al., 1996), presumably by a mechanism similar to that described here, and the basolateral amygdala, from which BDNF is also anterogradely transported (Conner and Lauter, 1997). These brain areas, and notably the amygdala (Whitelaw et al., 1996), process conditioned aspects of the environment, such as contextual drug taking-associated cues, the reactivity to which is controlled by the dopamine D3 receptor (Pilla et al., 1999). We suggest that, via the above pathways and mechanisms, progressive changes in BDNF expression occurring during repeated drug-taking might alter dopamine responsiveness and induce drug-conditioned responses, a key process in drug addiction (O'Brien et al., 1992). This is supported by the observations that intra-accumbal infusion of BDNF induces enhancement of behavioral sensitization to cocaine and responding to cocaine-related stimuli in rats (Horger et al., 1999), and dopamine D3 receptor expression is elevated in accumbens of cocaine addicts (Staley and Mash, 1996).

More generally, via the feedback loops through which the shell of the nucleus accumbens forms with the prefrontal cortex, BDNF could affect the control of emotions and sensorimotor gating, which is disturbed in some psychiatric disorders (Carlsson, 1988).

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