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REVERSAL OF SUPERSENSITIVE STRIATAL DOPAMINE D_1 RECEPTOR SIGNALING AND EXTRACELLULAR SIGNAL-REGULATED KINASE ACTIVITY IN DOPAMINE-DEFICIENT MICE†

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Abstract—Lesions of dopaminergic nigrostriatal neurons cause supersensitivity to dopamine in the striatum. Previous work has shown that such supersensitivity, an important aspect of rodent models of Parkinson's disease, is associated with anatomically abnormal patterns in the activation of extracellular signal-regulated kinase. After lesions of dopaminergic neurons, dopamine D_1-receptor agonists activate extracellular signal-regulated kinase in the dorsal striatum, something not observed in intact animals. Here we used a more selective method of dopamine depletion. Dopamine-deficient mice, in which the tyrosine hydroxylase gene is specifically inactivated in dopaminergic neurons, were used to investigate dopamine D_1-receptor-mediated activation of extracellular signal-regulated kinase. In wild-type mice, acute treatment with a dopamine D_1-receptor agonist results in activation of extracellular signal-regulated kinase in the nucleus accumbens without activation in the dorsal striatum. In contrast, in dopamine-deficient mice, dopamine D_1-receptor-agonist treatment results in activation of extracellular signal-regulated kinase not only in the nucleus accumbens, but also throughout most of the dorsal striatum. Chronic replacement of dopamine by repeated injection of L-DOPA for 36 h reverses this supersensitive extracellular signal-regulated kinase activation. This reversal displays a dorsal to ventral progression such that, by 36 h, extracellular signal-regulated kinase activation is virtually restricted to the nucleus accumbens, as in wild-type mice. The reversal of dopamine D_1-receptor activation of extracellular signal-regulated kinase in dopamine-deficient mice following chronic L-DOPA treatment shows that the lack of dopamine, rather than absence of other factors secreted from dopaminergic neurons, is responsible for dopamine supersensitivity. © 2005 Published by Elsevier Ltd on behalf of IBRO.

Key words: dopamine receptor, L-DOPA, supersensitivity, extracellular receptor kinase, striatum, Parkinson's disease.

Rodents lacking dopaminergic input to the striatum manifest a supersensitive response to dopamine D_1-receptor (D1R) agonists, as evidenced by the induction of over 30 immediate early genes (IEGs) including *c-fos* at concentrations of agonists that have a negligible effect in control animals (Berke et al., 1998; Gerfen et al., 1995). In the normal striatum, IEGs may be induced in D1R-bearing neurons by psychostimulants such as amphetamine and cocaine (Graybiel et al., 1990) that cause large increases in extracellular dopamine, by combined treatments with agonists for both D1R and dopamine D2 receptors (D2R) (LaHoste and Marshall, 1993) and by treatment with full D1R agonists (Gerfen et al., 2002). In the normal striatum, D1R induction of IEGs is mediated by activation of the signal-transduction pathway linked to protein kinase A (Andersson et al., 2001), whereas in the striatum of rodents with dopamine neuron lesions, the D1R-mediated induction of IEGs is due to activation of extracellular signal-regulated kinase (ERK) (Gerfen et al., 2002), which modulates transcriptional states thought to underlie neuronal plasticity (Impey et al., 1999; Adams and Sweatt, 2002; Thomas and Huganir, 2004). Activation of ERK occurs in the normal striatum in response to corticostriatal stimulation (Sgambato et al., 1998) or following treatment with a D2R antagonist, which unmasks the activation of corticostriatal inputs (Gerfen et al., 2002). Also in the normal striatum, relatively high doses of the psychostimulant cocaine (30 mg/kg) activate ERK in a large proportion of nucleus accumbens cells but in only a relatively small subset of D1R-bearing neurons in the dorsal striatum (Valjent et al., 2000). However, in the dorsal striatum, D1R-agonist activation of ERK appears to be specific to the supersensitive D1R response that occurs following dopamine depletion. In accord with this idea, D1R-agonist treatments that result in robust induction of IEGs in the normal striatum do not activate ERK (Gerfen et al., 2002). Another characteristic of the D1R-supersensitive response following dopamine depletion is that it does not desensitize with repeated D1R-agonist treatments (Steiner and Gerfen, 1996). This study uses a mouse model in which dopamine production is selectively inactivated in dopaminergic neurons by specific targeting of the tyrosine hydroxylase gene (Zhou and Palmiter, 1995). These dopamine-deficient (DD) mutants display a heightened sensitivity to L-DOPA and D1R agonists in terms of locomotor behavior

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Abbreviations: Dbh, dopamine b-hydroxylase gene locus; DD, dopamine-deficient; D1R, dopamine D_1-receptor; D2R, dopamine D2 receptor; ERK, extracellular signal-regulated kinase; IEG, immediate early gene; MAPK, mitogen-activated protein kinase; PBS, phosphate-buffered saline; *Th*, tyrosine hydroxylase gene locus; TH, tyrosine hydroxylase; 6-OHDA, 6-hydroxydopamine.

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and striatal IEG induction, in the absence of changes in total dopamine receptor levels (Kim et al., 2000), although the fraction of D2R in a high-affinity state for dopamine is elevated (Seeman et al., 2005). Dopamine production can be restored in brains of mutant mice either acutely or chronically by administration of the dopamine precursor, L-DOPA. Here we report that chronic restoration of dopamine production is able to reverse the activation of ERK by D1R-agonist treatment.

EXPERIMENTAL PROCEDURES

Mice

All mice were used in accordance with guidelines for animal care and experimentation established by the National Institutes of Health and the University of Washington Animal Care Committee. In the conduct of this study, efforts were made to minimize animal suffering and to use the minimum number of animals required. The DD mice ($Th^{-/-};Dbh^{Th/+}$) mice were generated as described (Zhou and Palmiter, 1995; Zhou et al., 1995). Null alleles at the tyrosine hydroxylase (*Th*) gene locus were introduced by gene targeting. Tyrosine hydroxylase (TH) function was restored in the noradrenergic and adrenergic cells of $Th^{-/-}$ mice by targeting the *Th* coding region downstream of the transcriptional regulatory elements of the dopamine b-hydroxylase (*Dbh*) gene locus. Control and $Th^{-/-};Dbh^{Th/+}$ mice were bred by intercrossing $Th^{\pm};Dbh^{Th/+}$ mice and were on a mixed C57BL/6×129/SvEv genetic background. Control mice included animals that had at least one wild-type *Th* allele and one wild-type *Dbh* allele, because one allele is sufficient for nearly normal noradrenaline and dopamine production.

Acute D1R-agonist administration

Adult control and DD mice were injected with either 0.9% saline (10 μl/g, i.p.) or with a D1R agonist 7.5 mg/kg (±)-SKF 81297 (10 μl/g, i.p.; 0.75 mg/mL in 0.9% saline; Sigma/Research Biochemicals International, St. Louis, MO, USA). After 15 min, mice were anesthetized with CO_2 and perfused transcardially with 4 mg/mL sodium fluoride in phosphate-buffered saline (PBS) and then sodium fluoride and 4% paraformaldehyde in PBS. Brains were dissected, immersed in sodium fluoride and paraformaldehyde, and cryoprotected in 30% sucrose. DD mice fail to eat and drink enough to survive after weaning without intervention. Daily treatment of mutants starting approximately two weeks after birth with 50 mg/kg L-DOPA (33 μl/g, i.p.; 1.5 mg/mL in 0.25% ascorbic acid in PBS; Sigma) stimulates ingestive behavior comparable to that of control mice and is adequate to support survival (Szczypka et al., 1999). In the experiments described here, adult DD mice were treated at least 24 h after their last daily 50 mg/kg L-DOPA injection, a time when striatal dopamine levels are <1% of normal levels (Szczypka et al., 1999).

Chronic L-DOPA administration

DD mice were injected with 100 mg/kg L-DOPA (66 μl/g, i.p.) once every 4 h, five times a day, such that the daily L-DOPA dose was 500 mg/kg/day. Subsets of these mice were treated acutely with 7.5 mg/kg (±)-SKF 81297 at 0, 12, 24, and 36 h after the chronic L-DOPA treatment had begun. After 15 min, mice were anesthetized, perfused transcardially, and their brains were dissected and processed as described above.

Immunohistochemistry

Immunostaining using an anti-phospho-ERK1/2 antibody (Cell Signaling Technology, Beverly, MA, USA) on 30-μm, cryoprotected, coronal brain sections were performed as described (Gerfen et al., 2002). Additionally, immunolabeling for TH (mouse anti-TH, PelFreeze, Trenton, NJ, USA) to verify the genotype of the mice, and for calbindin-28kD (rabbit anti-calbindin, Sigma Chemical Co., St. Louis, MO, USA)

RESULTS

Activation of ERK by D1R-agonist stimulation in control and DD mice was determined by immunohistochemistry using antisera directed against the phosphothreonine-202 and phosphotyrosine-204 form of rat ERK p42 ERK2, which cross-reacts with mouse pERK1 and pERK2. Virtually no pERK immunoreactive neurons were observed in the dorsal striatum in either control or DD mice 15 min after saline injection, and only a few scattered cells were present in the nucleus accumbens (Fig. 1A, B). To analyze D1R activation of ERK, mice were treated with the D1R agonist, SKF 81297 (7.5 mg/kg), killed 15 min later, and their brains analyzed for pERK immunolabeling of striatal neurons. This dose of SKF 81297 was chosen because it does not have a significant effect on the locomotor activity of D1R-knockout mice (Xu et al., 1994). Control mice treated with the D1R agonist, displayed strong pERK staining in numerous neurons in the nucleus accumbens (Fig. 1C), but only a few, scattered pERK-labeled neurons in the dorsal striatum. DD mice treated with the D1R agonist exhibited greater numbers of pERK-immunoreactive neurons in both the nucleus accumbens and dorsal striatum (Fig. 1D) as compared with treated control mice. The increase in the number of labeled neurons in the dorsal striatum in the DD mice was most dramatic, as control mice display so few D1R-agonist-activated ERK neurons in the dorsal striatum. In the dorsal striatum, there was some regional and compartmental heterogeneity in the distribution of pERK immunoreactive neurons (Fig. 1D). The most dorsal and lateral regions of the striatum were labeled less, demonstrating a ventral to dorsolateral gradient in labeling intensity. Also, immunoreactive neurons displayed a heterogenous distribution pattern (Fig. 1D and 2D), suggestive of greater number of neurons labeled in the matrix compartment of the striatum. Adjacent sections labeled for calbindin-immunoreactivity to mark the striatal compartmental organization (Gerfen et al., 1985), show that in the striatal patch compartment D1R activation of pERK is not as robust as in the matrix compartment (Fig. 3).

To determine whether the D1R-mediated activation of ERK in DD mice is reversible, dopamine was restored in the brains of mutants by chronic administration of L-DOPA (100 mg/kg, every 4 h), and the acute response to D1R agonist was determined. At the initiation of L-DOPA treatment (0 h L-DOPA time point) DD mice treated for 15 min with SKF 81297 exhibited abundant pERK immunoreactivity in the nucleus accumbens and dorsal striatum (Fig. 4A), in agreement with previous results. Twelve hours after the chronic L-DOPA administration began, DD mice exhibited pERK in the nucleus accumbens comparable to the 0 h time point (Fig. 4B), but there was a marked decrease in the number of

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