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Intrastriatal Dopamine D1 Antagonism Dampens Neural Plasticity in Response to Motor Cortex Lesion

E. J.H. Davis^{a,b,*}, C. Coyne^b, and T. H. McNeill^{a,b}

a Neuroscience Graduate Program, University of Southern California, Los Angeles, CA 90089, USA

b Department of Cell and Neurobiology, University of Southern California, Keck School of Medicine, Los Angeles, CA 90033, USA

Abstract

Motor cortex lesions in rats partially denervate the striatum, producing behavioral deficits and inducing reactive neuroplasticity. Plastic responses include changes in growth-associated protein marker expression and anatomical restructuring. Corticostriatal plasticity is dependent on dopamine at the striatal target, where D1 receptor signaling reinforces behaviorally relevant neural activity. To determine whether striatal dopamine D1 receptor signaling is important for the growth-associated protein responses and behavioral recovery that follow unilateral motor cortex aspiration, the dopamine D1 receptor antagonist SCH23390 was intrastriatally infused in cortically lesioned animals. After a cortical aspiration lesion in Long Evans rats, the growth-associated proteins SCG10 and GAP-43 were upregulated in the cortex contralateral to the lesion at 30 days post-lesion. However, continuous unilateral intrastriatal infusion of SCH23390 prevented this aspiration-induced upregulation. Furthermore, lesioned rats demonstrated spontaneous sensorimotor improvement, in terms of limb-use symmetry, about one month post-lesion. This improvement was prevented with chronic intrastriatal SCH23390 infusion. The D1 receptor influence may be important to normalize corticostriatal activity (and observable behavior), either in a long-term manner or temporarily until other more permanent means of synaptic regulation, such as sprouting or synaptogenesis, may be implemented.

Keywords

cortical ablation; striatum; SCH23390

The ability to reorganize neural connections according to changing environmental cues is essential to the formation of the wide network of limbic, striatal, and cortical circuits that regulate the complex array of human behaviors. Generally referred to as neural plasticity, these adaptive processes are most obvious in the developing brain, but are also utilized throughout adulthood as new skills and memories are acquired. Likewise, when the brain is damaged by trauma or disease, adaptive mechanisms of plasticity are brought into play and are critical for determining the limits of functional recovery (Ivanco and Greenough, 2000, Johansson, 2000, Nudo et al., 2001, Gonzalez and Kolb, 2003). These adaptive processes are governed by local extra- and intracellular signals and can be manipulated by various experimental interventions including: exercise (Cotman and Berchtold, 2002, Gomez-Pinilla et al., 2002),

*Corresponding author: University of Southern California, Department of Cell and Neurobiology, BMT 403, 1333 San Pablo St., Los Angeles, CA 90033, USA. Tel: 323- 442-2126; Fax: 323- 442-2127. E-mail address: elizabjd@usc.edu

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complex environments (van Praag et al., 2000), motor skills training (Plautz et al., 2000, Bury and Jones, 2002), and pharmacological treatment with monoamine affecting drugs (Feeney, 1997, Stroemer et al., 1998, Goldstein, 2003, Ivy et al., 2003). Understanding the cellular mechanisms and local factors that modulate neuroplasticity is the first step in developing novel treatment strategies that can facilitate the recovery of function after brain damage.

Evidence suggests that endogenous factors that regulate synaptic strength are likely to play key roles in the formation and maintenance of reactive innervation following injury (reviewed in Keyvani and Schallert, 2002, Butefisch, 2006). With strong influences on corticostriatal synaptic efficacy and striatal function, dopamine is one such putative factor. Nigrostriatal dopaminergic fibers densely innervate the striatum (Bjorklund and Hokfelt, 1984), and both dopaminergic and corticostriatal glutamatergic afferent axons synapse onto target medium spiny neurons (Bouyer et al., 1984, Groves et al., 1994, Smith et al., 1994, Centonze et al., 2003b). Within the striatum, dopamine is instrumental in determining the efficacy of glutamatergic signaling at corticostriatal synapses (Centonze et al., 1999, Centonze et al., 2001, Cepeda et al., 2001, West et al., 2003), and striatal dopamine-glutamate interactions may play a role in the re-formation of behaviorally relevant functional connections after cortical injury. Indeed, as shown in previous studies from our laboratory, nigrostriatal denervation in combination with unilateral cortical lesion results in an aberrant nervous system response to the cortical lesion, evident in an elevated degree of reactive morphological change, altered growth-associated protein profile, and dampened behavioral improvement (Meshul et al., 2000, Hughes-Davis et al., 2005).

The effects of dopamine within the striatum are mediated by D1 and D2-type receptors located postsynaptically on striatal target neurons, as well as presynaptically by D2-type receptors. Although balance between D1 and D2 receptor signaling is vital for appropriate motor system function, the localization and normal role of D1 receptors support their differential involvement in reparative processes. In support of influential D1 receptor involvement, it has been observed that neighboring and contralateral cortical neurons that are recruited to participate in adaptive structural and functional plasticity after focal cortical injury include a corticostriatal population that preferentially contacts D1-expressing striatal neurons (Hersch et al., 1995, Lei et al., 2004). In addition, D1 receptor signaling is linked with several identified mechanisms of glutamate receptor regulation, as well as corticostriatal long-term potentiation (Dunah and Standaert, 2001, Flores-Hernandez et al., 2002, Centonze et al., 2003a, West et al., 2003, Pei et al., 2004, Cepeda and Levine, 2006, Hallett et al., 2006). Downstream consequences of striatal D1 receptor signaling include an influence on basal ganglia output, which ultimately feeds forward to the cortex (Steiner and Kitai, 2000, Blandini et al., 2002, Blandini et al., 2003). Regulation of synaptic or motor loop activity by D1 receptors may act to sustain a degree of function within this system after lesioning, reflected in preserved or recovered motor abilities. Indeed, animals that have behaviorally recovered from unilateral frontal cortex aspiration rely on D1 receptor signaling to maintain this behavior (Vargo et al., 1995). Given the evidence supporting dopaminergic involvement in maintaining corticostriatal and basal ganglia activity, and the role of D1 receptors in regulating these effects, we wanted to determine the importance of this activity in supporting recovery following denervation.

To test the hypothesis that striatal D1 receptor signaling regulates behavioral recovery and lesion-induced expression of genes thought to underlie neurite outgrowth and remodeling, we carried out a series of analyses on rats that underwent motor cortex lesioning in combination with intrastriatal infusion of the selective D1-type receptor antagonist SCH23390. Western blot analysis was used to examine changes in expression of two growth-associated protein genes previously linked with reactive structural adaptations in the deafferented striatum: SCG10 and GAP-43. Protein levels were assessed at three post-lesion timepoints. In addition, the timecourse of growth-associated protein changes was determined in parallel with the

progression of sensorimotor recovery in an evaluation of spontaneous forelimb use for postural support.

Experimental Procedures

Animals

Young adult male Long Evans rats (Harlan Sprague-Dawley, Indianapolis, IN) were housed in pairs in a standard care facility with a 12 hour light/dark cycle. Animals were fed standard rat chow *ad libitum* and weighed between 340 and 460 g at the time of surgery. Experimental groups consisted of rats that received unilateral intrastratial infusions of either the D1 antagonist SCH23390 or saline, in combination with unilateral aspiration lesion of the forelimb representation area of motor cortex or no lesion. Subsets of each group were killed at 4, 10, and 30 days post-lesion (N = 4–6 rats per group per timepoint). Animal care followed the guidelines set forth by the NIH Guide for the Care and Use of Laboratory Animals, and the Institutional Animal Care and Use Committee at the University of Southern California approved all experimental protocols. All efforts were made to minimize animal suffering and the number of animals used.

Surgery

At 12 weeks of age, animals (N = 63) received ketamine/xylazine anesthesia (100 mg/kg ketamine and 20 mg/kg xylazine, i.p.) and underwent one of two surgical procedures: a cortical aspiration lesion in combination with intrastratial cannula implantation and subcutaneous osmotic minipump insertion, or the cannulation procedure alone. For the cortical lesion, a craniotomy was performed to remove a rectangle of skull from 2 mm anterior to 1 mm posterior to bregma, spanning from 1 to 4 mm lateral to the midline on the right side. After cutting and gently removing the dura, a fine-tipped glass pipette connected to a vacuum pump was used to aspirate the forelimb representation area of the motor cortex from the exposed region. All cortical layers were removed, with care taken not to penetrate the underlying corpus callosum (Fig. 1). A small piece of gelfoam (Pharmacia, Kalamazoo, MI) was gently placed into the lesion cavity, which was then covered with a small piece of adhesive foil. For the infusion cannulation, an osmotic minipump (Alzet Model 2004, Durect, Cupertino, CA) containing the D1 receptor antagonist SCH23390 (Sigma-Aldrich, St. Louis, MO) dissolved in sterile 0.9% saline, or only vehicle was implanted in a subcutaneous pocket in the scapular region. SCH23390 is selective for the D1-like receptor family, but it also has affinity for serotonin receptors, and can inhibit some potassium channels (Millan et al., 2001, Kuzhikandathil and Oxford, 2002). The pump was connected via a catheter to a 5.0 mm long infusion cannula (Durect), which was stereotactically implanted at 1.5 mm anterior and 4.0 mm lateral to bregma on the right side (ipsilateral to the lesion). These coordinates were chosen to allow for diffusion of SCH23390 into the dorsolateral striatum, a region receiving both ipsilateral and relatively dense crossed corticostriatal projections, without imparting local damage due to the cannula track (McGeorge and Faull, 1989, Ebrahimi et al., 1992). Minipumps infused SCH23390 into the striatum at a rate of 0.25 μ l/hr at a concentration (0.67 mg/ml) amounting to 4 μ g/day delivered throughout the postoperative survival time (Caine et al., 1995, Steiner and Kitai, 2000, Baldo et al., 2002). The infusion assembly was cemented in place and anchored to a stainless steel surgical screw fastened to the skull. Following these procedures, the scalp was closed over the wound. If an animal underwent both the lesion and cannula implantation procedures, they occurred during the same surgical session. Animals recovered in their home cages without complications.

Forelimb-use Asymmetry

Sensorimotor ability was monitored with the Schallert cylinder test (Schallert et al., 2000). Asymmetry in forelimb postural support was assessed once before surgery and at 4, 10, 20,

and 30 days post-surgery. All animals participated in the cylinder test pre-surgery and at indicated timepoints up to the point at which they were killed. On each test day, rats were placed on the floor of a 30 cm tall clear acrylic cylinder (20 cm diameter) for a 2 minute session. The cylinder was positioned over a mirror so that the rats' activity could be observed from all angles and captured with a digital video recorder (JVC GRD270US, Cypress, CA) for later analysis. The number of times each animal used its forepaws for support against the wall of the cylinder while in an upright position was tallied to produce an asymmetry score using the formula: $\% \text{ (number of ipsilateral supports} + \frac{1}{2} \text{ number of bilateral supports)} / \text{(number of ipsilateral supports} + \text{number of contralateral supports} + \text{number of bilateral supports)}$, where "ipsilateral supports" represents the number of support movements made by the forelimb ipsilateral to the lesion, and "bilateral supports" represents the number of supports made using both limbs at the same time (Adkins et al., 2004). To account for the ipsilateral component of bilateral movements, one-half the total number of bilateral supports was added to the ipsilateral-only tally. By including ipsilateral limb usage in the numerator, the formula arbitrarily assigns performance with an ipsilateral bias values over 50%, and limb use with a contralateral bias values below 50%. Scores were compared using a two-way ANOVA at each timepoint with infusion solution and lesion status as the factors (SigmaStat, Chicago, IL).

Protein Expression

At 4, 10, and 30 days post-lesion, subsets of each experimental group were killed and their brains removed for western blot analysis. The brains were quickly dissected over ice to isolate the cortex contralateral to the lesion and striatum ipsilateral to the lesion, and visually inspected to verify corpus callosum penetration and dorsolateral intrastriatal cannula placement. Cortex and striatum were frozen on dry ice. Tissue samples were sonicated in lysis buffer containing a protease inhibitor cocktail, centrifuged, and the supernatant extracted for gel electrophoresis. NuPAGE 10% bis-tris gels (Invitrogen, Carlsbad, CA) were used to separate the proteins, which were then transferred to nitrocellulose membranes. After blocking with 5% dry milk in tris-buffered saline, blots were immunoblotted with antibodies to SCG10 (1:1000; Abcam, Cambridge, MA), or GAP-43 (1:4000; Sigma, St. Louis, MO), and GAPDH (1:1000; Abcam) as a loading control, followed by appropriate secondary antibody incubation and signal detection using ECL (Amersham Biosciences, GE Healthcare, Piscataway, NJ). Exposed films were scanned and band densitometry conducted (Scion Image, Frederick, MD). Brains from a group of rats that did not receive any surgical treatment were also processed (N = 5), and experimental band densities from each blot were normalized against values obtained from bands representing these intact animals. Normalized band densities were compared using a two-way ANOVA at each timepoint with infusion solution and lesion status as the factors (SigmaStat).

Results

Forelimb-Use Asymmetry

Asymmetry scores derived from cylinder test performance describe the degree of preference for using one forelimb over the other for support against the cylinder wall while rearing, and reflect bias in sensorimotor capacity. Equal use of the forelimbs for upright support produces a score of 50%, which is normal for unlesioned Long Evans rats (Gonzalez and Kolb, 2003; Adkins et al., 2004). All groups actively explored the cylinder and used their forepaws for support when rearing against the wall. Animals with unilateral vehicle or SCH23390 infusions but no cortical lesion did not display significant asymmetrical use of the forelimbs at any tested timepoint (Fig. 2). In comparison, unilateral cortical lesion, which affects motor function on the side of the body contralateral to the lesion more strongly, produced an initial bias toward use of the ipsilateral limb. When aspiration was accompanied by vehicle infusion, this bias diminished with time. In contrast, unilateral intrastriatal SCH23390 sustained the

lesion-induced asymmetry. At 4 and 10 days post-surgery, lesioned animals that received vehicle or SCH23390 displayed the same degree of asymmetrical preference for the limb ipsilateral to the lesion, but by 20 days the performance of these groups diverged. At this timepoint, lesioned animals receiving vehicle returned to baseline, displaying balanced use of the forelimbs for support, while animals that received SCH23390 maintained a high level of asymmetry. This difference persisted through the final tested timepoint, 30 days post-lesion.

Protein Expression

Cortex contralateral to the lesion, the origin of corticostriatal afferents which make up a population of reactive fibers in this model (Napieralski et al., 1996, Cheng et al., 1998, McNeill et al., 1999), and denervated ipsilateral striatum, a region of synaptic remodeling, were examined with regard to growth-associated protein expression. GAP-43 and SCG10 in these regions were not influenced by unilateral pump implantation with vehicle or SCH23390 infusion alone, but lesioning and SCH23390 infusion did alter growth-associated protein expression (Fig. 3). Long Evans rats with a cortical lesion and vehicle infusion upregulated both SCG10 and GAP-43 in the cortex contralateral to the lesion at 30 days post-lesion. However, intrastriatal SCH23390 infusion prevented this upregulation, resulting in sustained baseline protein expression at all timepoints (Fig. 3a and 3b). Cortical GAP-43 expression corresponded with increased striatal expression at the same timepoints, but no change in striatal SCG10 was detected (Fig. 3c and 3d).

Discussion

Chronic intrastriatal SCH23390 infusion, begun immediately after cortical aspiration injury, prevents behavioral improvement and dampens the growth-associated protein response that normally follows this denervation. These data support the idea that compensatory neural reactions in the motor cortex lesion model can be mediated, in part, through striatal dopamine signaling pathways.

SCG10 and GAP-43 proteins are typically associated with sprouting responses to neural injury. SCG10 is a member of the stathmin gene family and is proposed to play a key role in linking growth cues to the regulation of microtubule dynamics during neurite extension (Marklund et al., 1996, Riederer et al., 1997). It is highly concentrated in the growth cones of developing neurites (Stein et al., 1988a, Di Paolo et al., 1997), and its mRNA and protein increase in contralateral cortical neurons following a unilateral aspiration lesion of the cortex (McNeill et al., 1999). GAP-43 is also induced during axonal growth in both early development and regeneration, and has been proposed to play a role in mediating pathfinding signals from the growing neurite (Skene and Virag, 1989, Strittmatter et al., 1995). GAP-43 is often used as a marker for sprouting responses to injury (Stroemer et al., 1993, Li et al., 1998, King et al., 2001). Both are functionally implicated in axon terminal remodeling within the striatum, but these proteins are synthesized within cortical somata of corticostriatal neurons. Consistent with our findings, both proteins accrue within the somata of corticostriatal neurons, as well as along fibers and in growth cones (Goslin et al., 1990, Gavet et al., 1998). GAP-43 protein and mRNA appear to be axonally transported, suggesting that somatic induction may be followed by distal distribution. This protein may also be synthesized within the growth cone, perhaps explaining the enhanced striatal GAP-43 protein levels detected here (Meiri et al., 1991, Perrone-Bizzozero and Bolognani, 2002, Smith et al., 2004). Although most striatal GAP-43 originates extrinsically, intrinsic sources of GAP-43 may also contribute to this change (DiFiglia et al., 1990, Iwata et al., 1999).

The reported maintenance of growth-associated protein levels with SCH23390 infusion, rather than induction as typically follows cortical lesion, suggests that corticostriatal lesion-induced plasticity requires dopaminergic support in this model. Striatal dopaminergic activity regulates

function of the basal ganglia-thalamo-cortical circuit, and temporary dopamine-mediated adjustments in synaptic strength following motor cortex lesion may feed forward via this motor loop, leading to gene induction and activation of mechanisms for long-term signaling maintenance (Steiner and Kitai, 2000, Blandini et al., 2002, Blandini et al., 2003). In support of this idea, it has been shown that striatal dopamine depletion attenuates cortical gene expression (Steiner and Kitai, 2001). More specifically, unilateral intra-striatal dopamine D1 antagonism prevents apomorphine-induced immediate early gene expression in the cortex (Steiner and Kitai, 2000), whereas striatal D1 receptor agonism enhances it (Blandini et al., 2002, Blandini et al., 2003). These findings support a D1 receptor-mediated striatal influence on cortical activity. Similarly, the D1 receptor antagonist-induced lack of SCG10 and GAP-43 upregulation reported here may reflect attenuated systemic activation (Stein et al., 1988b, Sheng and Greenberg, 1990, Chou et al., 2000).

Unilateral D1 receptor antagonism did not significantly affect baseline cylinder performance at the dose tested, suggesting that its role in this study was not strictly in the prevention of movement, but rather as an impediment to compensation/recovery mechanisms in response to the lesion. Normal dopaminergic function primes striatal neurons for cortical input, and provides a mechanism for adjusting corticostriatal strength (Reynolds et al., 2001, West et al., 2003). In addition, dorsal striatal D1 receptors are implicated in the rewarding aspects of motor function associated with learning (Beninger and Miller, 1998, Reynolds et al., 2001, Breitenstein et al., 2006a), and feedback via D1 receptor signaling may reinforce successful behavioral strategies, strengthening those remodeled synapses that prove their utility. Indeed, dopamine-mediated activation of latent alternative routes may be sufficient to stimulate motoneurons and generate appropriate behaviors (Vargo et al., 1995).

GAP-43 and SCG10 upregulation are associated with neuronal remodeling, and such structural adjustments may form the foundation for long term functional maintenance. Prevention of motor-system growth-associated protein induction by D1 antagonist and subsequent deficits in neuronal remodeling may underlie enduring functional impairment. Acutely, however, neural remodeling need not be a prerequisite to behavioral improvement. The late upregulation of GAP-43 and SCG10 proteins in Long Evans rats suggests that D1 signaling after lesioning may act first to stabilize or refine activity at existing basal ganglia synapses, supporting both neural circuit and observable behavioral function. Synaptic adaptation is sufficient to support functional improvement, as shown by the observation that changes in performance do not require new physical connections, but may come about by altering the strength of existing synapses (Jacobs and Donoghue, 1991, Kleim et al., 2004, Butefisch, 2006). Striatal D1 signaling may thus directly support motor system activity and behavioral function, followed indirectly by growth-associated protein mediated remodeling.

The evidence presented here supports the idea that, under certain circumstances, dopamine D1 signaling is involved in spontaneous recovery from cortical injury. However, mechanistic questions remain and the step to beneficial dopamine therapy to improve functional recovery is not clear-cut. Overall, the literature suggest that blocking dopamine may be detrimental to recovery, but augmenting it does not necessarily show benefit (Boyeson and Feeney, 1990). L-DOPA therapy has shown some positive effects on motor function for stroke patients (Scheidtmann et al., 2001), but amphetamine trials have been somewhat inconsistent (Crisostomo et al., 1988, Walker-Batson et al., 1995, Sonde et al., 2001, Goldstein, 2003, Treig et al., 2003, Platz et al., 2005, Gladstone et al., 2006). Variable modes of dopaminergic action may account for these discrepancies: enhanced phasic dopamine release facilitates learning, but tonic dopamine release inhibits it (Breitenstein et al., 2006a, Breitenstein et al., 2006b). Similarly, neurochemical reinforcement with self-administered dopamine agonists and amphetamine-mediated promotion of motor recovery are noted primarily at mid-range doses (Goldstein, 1990, Self and Stein, 1992, Beninger and Rolfe, 1995, Ranaldi et al., 1995).

Together, these findings suggest that direct acting or high doses of dopamine agonists may mask critical temporal associations between dopamine release and external or internal cues, causing a net antagonistic effect (Beninger and Miller, 1998). If the reinforcing effect of context specific dopamine release and D1 signaling is important to adaptive remodeling, maintaining the temporal associations between these events may be critical. Thorough consideration of agonist dose and mechanism of action is essential to assess the benefit of dopaminergic intervention.

In summary, our data show that recovery from significant initial post-lesion impairment of contralateral forelimb sensorimotor function is modulated by a D1 receptor-dependent mechanism. D1 receptor signaling may be important to normalize corticostriatal activity (and observable behavior), either in a long-term manner or temporarily until other more permanent means of synaptic regulation, such as sprouting or synaptogenesis, may be implemented.

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Fig 1. Diagram depicting the cortical area targeted by aspiration (shading) and infusion cannula placement. Antero-postero levels relative to bregma. Coronal sections adapted from Swanson (1998). cc = corpus callosum, cx = cortex, st = striatum.

Fig 2.

Effect of SCH23390 infusion on cylinder test asymmetry scores. Limb-use asymmetry was scored prior to surgery and at 4, 10, 20, and 30 days post-surgery. Symmetrical forelimb usage is indicated by the dashed line at 50%. Closed markers represent SCH23390 infused groups, and triangles represent lesioned groups. The symbol (#) indicates between-group differences determined by two-way ANOVA at each timepoint, # $p < 0.05$. One-way repeated measures ANOVA was used to determine within-group differences over time, * $p < 0.005$ SCH/ASP compared with pre-surgery, † $p < 0.005$ VEH/ASP compared with pre-surgery. All post hoc pairwise comparisons were conducted using the Holm-Sidak method. VEH = vehicle infusion, SCH = SCH23390 infusion, ASP = aspiration lesion.

Fig 3.

Effect of intrastratial SCH23390 infusion on SCG10 and GAP-43 protein expression in cortex contralateral to and striatum ipsilateral to the lesion. Western blot film densitometry was used to measure protein expression at 4, 10, and 30 days post-surgery. Results are expressed as a percentage of densities determined for intact animals $\pm$ SEM. Solid bars represent SCH23390 infused groups, and black color represents lesioned groups. (a) Contralateral cortex SCG10, (b) contralateral cortex GAP-43, (c) ipsilateral striatum SCG10, (d) ipsilateral striatum GAP-43. Two-way ANOVA at each timepoint, * $p < 0.05$ compared with VEH and SCH/ASP. VEH = vehicle infusion, SCH = SCH23390 infusion, ASP = aspiration lesion.