Available online at www.sciencedirect.com
SCIENCE DIRECT
Brain Research 1035 (2005) 41–50
BRAIN RESEARCH
www.elsevier.com/locate/brainres

Research report

Dopamine manipulation alters immediate-early gene response of striatal parvalbumin interneurons to cortical stimulation

Jennifer T. Trevitt[a], Joseph Morrow[a], John F. Marshall[b,*]

[a]Psychology Department, California State University, Fullerton, 92631, USA
[b]Department of Neurobiology and Behavior, University of California, 2205 McGaugh Hall, Irvine, CA 92627-4550, USA

Accepted 19 November 2004
Available online 22 January 2005

Abstract

Cortical projections provide the major excitatory inputs to the striatum. In addition to innervating medium spiny cells, these axons contact striatal interneurons that are parvalbumin-immunoreactive (PV-ir). PV-ir interneurons make synaptic connections with many medium spiny cells, and thus can modulate striatal output. The striatum also receives dopaminergic projections from the substantia nigra, but it has been challenging to study the impact of dopamine (DA) cell injury on corticostriatal activity in vivo due to limitations in the methods used to induce cortical activity. Using epidural application of the $GABA_A$ antagonist picrotoxin, which produces a topographically restricted region of striatal immediate-early gene expression, we have investigated the effect of DA cell injury or DA receptor antagonism on immediate-early gene (IEG) expression in striatal medium spiny cells and PV-ir interneurons. Epidural application of picrotoxin to the rat's M1 motor cortex induced Fos in ipsilateral dorsolateral striatum. Animals previously given 6-hydroxydopamine (6-OHDA) injections into the ascending DA pathways had greater total numbers of cortical stimulation-induced striatal Fos-ir cells but *fewer* Fos-ir/PV-ir cells, compared to sham-operates. In a separate experiment, rats given cortical stimulation and treated with the DA D_2-class antagonist eticlopride (0.10 mg/kg) exhibited fewer Fos-ir/PV-ir cells than did vehicle-treated rats. Taken together, these results indicate that DA may importantly control striatal output via influences on PV-ir interneurons. Possible mechanisms for these influences are discussed.

Theme: Motor systems and sensorimotor integration
Topic: Basal ganglia

Keywords: Striatum; Immediate-early gene; Parvalbumin; Interneuron; Dopamine; GABA

1. Introduction

The basal ganglia are a set of subcortical structures prominently involved in the regulation of movement. All areas of the neocortex project to the striatum, and evidence indicates that corticostriatal neurons synapse with equal frequency on striatopallidal and striatonigral neurons [18]. However, studies have indicated that cortical stimulation preferentially induces immediate-early gene (IEG) response in striatopallidal neurons and parvalbumin-containing (PV-ir) interneurons [3,4,31]. PV-ir interneurons receive direct contacts from cortical neurons, may receive convergent projections from several cortical neurons, and make synaptic connections to multiple medium spiny cells [2,16]. PV-ir interneurons appear to communicate through gap junctions, a mechanism that would allow for the coordinated inhibition of thousands of projection neurons, and recent data indicate they may exert a powerful inhibitory effect on striatal output [20,22,29]. Although PV-ir interneurons account for only 3–5% of the total number of striatal cells, it has been proposed that they represent the main inhibitory control of projection neurons [17].

In addition to glutamatergic cortical projections, the striatal neurons also receive dopaminergic projections from

* Corresponding author. Fax: +1 949 824 2447.
E-mail address: jfmarsha@uci.edu (J.F. Marshall).

0006-8993/$ - see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainres.2004.11.039

the substantia nigra (SNc), and the latter are thought to modulate the striatal response to cortical inputs [12,30]. While dopaminergic control of the striatofugal pathways has been extensively characterized [13,32], it remains unclear how dopamine (DA) modulates the response of striatal projection neurons to cortical inputs. Electrophysiological studies have indicated that DA depletion increases the striatal neuron response to cortical stimulation [7], but other investigations suggest greater complexity, with DA potentiating NMDA receptor responses but attenuating non-NMDA receptor-mediated effects [25]. Physiological and anatomical evidences indicate that PV-ir interneurons may also be modulated by DA: PV-ir interneurons receive DAergic projections and show decreased GAD_{67} expression following DA denervation [20,23,35], and at least some of these cells contain mRNA for the DA D_2 receptor [24].

Few studies have attempted to characterize the effect of striatal DA depletion on IEG expression in response to cortical stimulation [11,27] and none has attempted to characterize the IEG response of the striatal parvalbumin interneurons under conditions of altered dopaminergic transmission. Electrical stimulation of cerebral cortex in rats typically produces widespread IEG induction through the cortex and striatum, effects that may mask the influences of DA depletion. The epidural application of pharmacological agents via a cranial well [3] appears better suited to address the issue of the effect of DA depletion on striatal response to cortical input. The cranial well technique is relatively non-invasive, avoiding mechanical damage to cortical neurons of interest, resulting in a more spatially restricted induction of immediate-early genes in cortex and striatum. Using this technique, we conducted two studies to examine the effects of 6-hydroxydopamine-induced nigrostriatal injury as well as selective DA D_2-class antagonist administration on cortically activated IEG activity in PV-ir interneurons and striatal projection neurons. We found that animals with DA depletions had greater cortical activation of Fos in striatal cells but *fewer* striatal Fos-ir/PV-ir cells as compared to control animals.

2. Materials and methods

2.1. Experimental design

Two studies were conducted. The first study, which examined the effect of dopamine depletion and cortical stimulation on striatal IEG response, was comprised of three groups of animals: one group (n = 7) received unilateral 6-hydroxydopamine (6-OHDA) lesions and epidural application of 75 μM picrotoxin, the second group (n = 6) received unilateral 6-OHDA lesions and epidural application of saline, and the third group (n = 4) received unilateral sham lesions and epidural application of 75 μM picrotoxin. Prior to data analysis, the lesions of all animals that received 6-OHDA were verified using TH immunocytochemistry. The second study, examining the effect of a selective DA D_2-class antagonist and cortical stimulation on striatal IEG response, used four groups of animals: one group (n = 5) received epidural application of 50 μM picrotoxin and intraperitoneal (i.p.) administration of 0.10 mg/kg eticlopride, the second group (n = 3) received epidural application of 50 μM picrotoxin and i.p. saline vehicle, a third group (n = 10) received epidural application of saline and i.p. 0.10 mg/kg eticlopride, and the fourth group (n = 8) received epidural application of saline and i.p. saline vehicle. All experiments were carried out in accordance with the *National Institute of Health Guide for the Care and Use of Laboratory Animals*, and every effort was made to minimize any pain or discomfort the animals may have experienced.

2.2. Surgical procedures

In the first study, adult male Sprague–Dawley rats (Charles River, Cambridge, MA) weighing 185–215 g received unilateral 6-OHDA infusions along the medial forebrain bundle. Thirty minutes prior to surgery, animals were pretreated with desipramine HCl (3 mg/ml i.p., 5 mg/kg; Sigma, St. Louis, MO), to limit uptake of 6-OHDA into noradrenergic terminals. Under Ketamine/Xylazine anesthesia (25.0 mg + 5.0 mg/ml; 2.0 ml/kg, i.p.) animals underwent stereotaxic surgery. A 26-gauge cannula attached to a 10-μl syringe via PE tubing was used to inject 8 μg 6-OHDA (as free base) in 4 μl 0.1% ascorbic acid solution (rate = 1.0 μl/min) at the following coordinates: AP +2.6 mm anterior to the interaural plane, LM −1.0 mm to midline, and DV −7.8 mm ventral to dura. Animals in the lesion-control condition received injections of the same volume of 0.1% ascorbic acid solution at a locus 2.0 mm dorsal to the site of 6-OHDA injection. The burr hole was sealed with bone wax and the skull wound was sutured. The effectiveness of the lesion procedure was evaluated by testing the animals for their orientation to tactile stimuli applied to each body surface 5 days following the 6-OHDA (or vehicle) injections and on the day before implantation of the cranial well (day 20). Animals were systematically touched along each body surface with a von Frey hair (4 g force) under red light illumination, and the data from the ipsilateral and contralateral sides analyzed. 6-OHDA-lesioned animals in which contralateral orientation scores were 30% or greater of ipsilateral scores were not tested further [1].

Twenty-one days later, the animals underwent a second surgery. Under Ketamine/Xylazine anesthesia, a 2.0-mm-diameter circle of skull was excised above the M1 area of motor cortex (AP +0.5, LM −1.7, from bregma) on the side ipsilateral to the previous 6-OHDA (or vehicle) injection. A cranial well, fashioned from a 300-μl polypropylene microcentrifuge tube (Fisher, Pittsburgh, PA), was affixed to the surface of the skull, centered above the hole, using dental acrylic and skull screws. When the dental acrylic had cured, the well was filled with sterile 0.9% saline and the cap snapped into place. The animal was then returned to its home cage to recover.