Experimental Neurology 265 (2015) 122–128

Contents lists available at ScienceDirect

Experimental Neurology

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

Regular Article

Corticostriatal interactions in the generation of tic-like behaviors after local striatal disinhibition

Vladimir Pogorelov [a,1], Meiyu Xu [a], Haleigh R. Smith [b], Gordon F. Buchanan [b,2], Christopher Pittenger [a,c,d,e,*]

[a] Department of Psychiatry, Yale University School of Medicine, USA
[b] Department of Neurology, Yale University School of Medicine, USA
[c] Department of Psychology, Yale University School of Medicine, USA
[d] Department of Child Study Center, Yale University School of Medicine, USA
[e] Interdepartmental Neuroscience Program, Yale University School of Medicine, USA

ARTICLE INFO

Article history:
Received 7 July 2014
Revised 11 December 2014
Accepted 5 January 2015
Available online 15 January 2015

Keywords:
Tourette syndrome
Tic
Movement disorders
Basal ganglia
Animal model

ABSTRACT

The pathophysiology of the tics that define Gilles de la Tourette syndrome (TS) is not well understood. Local disinhibition within the striatum has been hypothesized to play a pathogenic role. In support of this, experimental disinhibition by local antagonism of GABA-A receptors within the striatum produces tic-like phenomenology in monkey and rat. We replicated this effect in mice via local picrotoxin infusion into the dorsal striatum. Infusion of picrotoxin into sensorimotor cortex produced similar movements, accompanied by signs of behavioral activation; higher-dose picrotoxin in the cortex produced seizures. Striatal inhibition with local muscimol completely abolished tic-like movements after either striatal or cortical picrotoxin, confirming their dependence on the striatal circuitry; in contrast, cortical muscimol attenuated but did not abolish movements produced by striatal picrotoxin. Striatal glutamate blockade eliminated tic-like movements after striatal picrotoxin, indicating that glutamatergic afferents are critical for their generation. These studies replicate and extend previous work in monkey and rat, providing additional validation for the local disinhibition model of tic generation. Our results reveal a key role for corticostriatal glutamatergic afferents in the generation of tic-like movements in this model.

Introduction

Tics are involuntary stereotyped motor and vocal behaviors often associated with subjective premonitory urges; they are a defining symptom of Gilles de la Tourette syndrome (TS) and are frequently seen in other neuropsychiatric conditions. TS has childhood onset, with a prevalence among school aged children of 0.3–0.8%, and is diagnosed worldwide (Knight et al., 2012; Robertson and Stern, 1997; Scharf et al., 2012). Tics are often chronic, disruptive, and stigmatizing, producing substantial morbidity (Leckman, 2002). The pathophysiology of tic disorders is not well understood, and causative genes have proven elusive (State, 2011; Williams et al., 2013). The most effective pharmacological management of tics consists of antagonists of the dopamine (DA) D2 receptor, such as haloperidol. However, the substantial side effects of these agents limit their use, especially in children, and treatment drop-outs are common (Bloch, 2008).

Dysfunction of the cortico-basal ganglia circuitry is thought to be central to the pathophysiology of tic disorders (Leckman et al., 2010; Williams et al., 2013). Structural imaging has revealed a reduction in the size of caudate and putamen (Peterson et al., 2003) that correlates with disease persistence (Bloch et al., 2005). Functional imaging studies have similarly implicated this circuitry (Rickards, 2009). The sensorimotor cortex is thinned in children with TS, with cortical thickness negatively correlated with the severity of tic symptoms (Sowell et al., 2008). In contrast, regional volumes of dorsal prefrontal and parietal cortex are significantly increased in children with TS (Peterson et al., 2001); this may relate to compensatory responses or volitional tic suppression (Peterson et al., 1998). Structural abnormalities have also been described in the thalamus (Miller et al., 2010), cerebellum (Tobe et al., 2010), and elsewhere in the brain. Recently, post-mortem investigations have shown alterations in striatal microcircuitry in severe, refractory TS, with a reduction in the density of several populations of striatal interneuron (Kalanithi et al., 2005; Kataoka et al., 2010; Lennington et al., 2014).

It has been proposed that tics arise from foci of pathological disinhibition within the striatum (caudate–putamen) (Mink, 2001, 2003). In support of such a model, small, discrete strokes of the caudate and putamen have been observed to produce both motor and phonic tics (Kwak

* Corresponding author at: 34 Park Street, W315, New Haven, CT 06519, USA.
E-mail address: Christopher.pittenger@yale.edu (C. Pittenger).
[1] Current address: Duke University, Durham, NC, USA.
[2] Current address: Department of Neurology, University of Iowa, IA, USA.

http://dx.doi.org/10.1016/j.expneurol.2015.01.001
0014-4886/

and Jankovic, 2002). Direct injections of GABA-A receptor antagonists into the monkey or rat striatum produce contralateral tic-like movements of the limbs and face (Bronfeld et al., 2011, 2013; Marsden et al., 1975; McCairn et al., 2009, 2013; Tarsy et al., 1978; Worbe et al., 2013), providing experimental support for this concept as well as an animal model in which the consequences of local striatal inhibition can be examined (Pittenger, 2014).

Non-human primates, in which most work on local striatal disinhibition has been performed, are well suited for electrophysiological studies, but less so for pharmacological or genetic investigations. Here we replicate the local striatal disinhibition model in mice using local striatal infusion of picrotoxin, producing phenomenology similar to that reported in non-human primates and in rats (Bronfeld et al., 2011, 2013; McCairn et al., 2009, 2013; Tarsy et al., 1978; Worbe et al., 2013). This permits pharmacological investigations of the model. Specifically, we investigated the ability of local modulation of glutamate and GABA within the corticostriatal circuitry to modulate tics produced by local striatal inhibition, to increase construct validity of the model and to probe the underlying neuronal mechanisms. Past studies of local disinhibition in non-human primates and rats have used the GABA-A antagonist bicuculline (Bronfeld et al., 2011, 2013; McCairn et al., 2009, 2013; Worbe et al., 2013). We used a more specific GABA-A receptor antagonist, picrotoxin, because bicuculline has been reported to also block calcium-activated potassium SK channels and produce epileptiform oscillations in the thalamic network (Kleiman-Weiner et al., 2009).

Materials and methods

Subjects

Adult male C57Bl/6 mice, aged 2.5–5 months, were purchased from Jackson Laboratories (www.jax.org) and used in all experiments. Mice were housed under a 12/12 h light/dark cycle under controlled temperature and humidity conditions. All procedures were performed in accordance with the NIH Guide for the Use of Experimental Animals and were approved and overseen by Yale University's IACUC.

Drugs

Picrotoxin (PTX), muscimol (Musc), and (RS)-4-(phosphonomethyl)-piperazine-2-carboxylic acid (PMPA), were all purchased from Sigma, St. Louis, MO. They were dissolved in sterile saline for intracranial or intraperitoneal administration.

Procedures

Stainless steel single- or double-injection guide cannulae (Plastics One, Roanoke, VA) were unilaterally implanted 1 week before experiments, using standard stereotaxic methods under ketamine/xylazine anesthesia. Initial mapping experiments (Fig. 1A) used a range of targeting coordinates; subsequent experiments focused on three regions: AP + 0.5, L −2.2, V −3.2 for dorsolateral striatum (DLS);

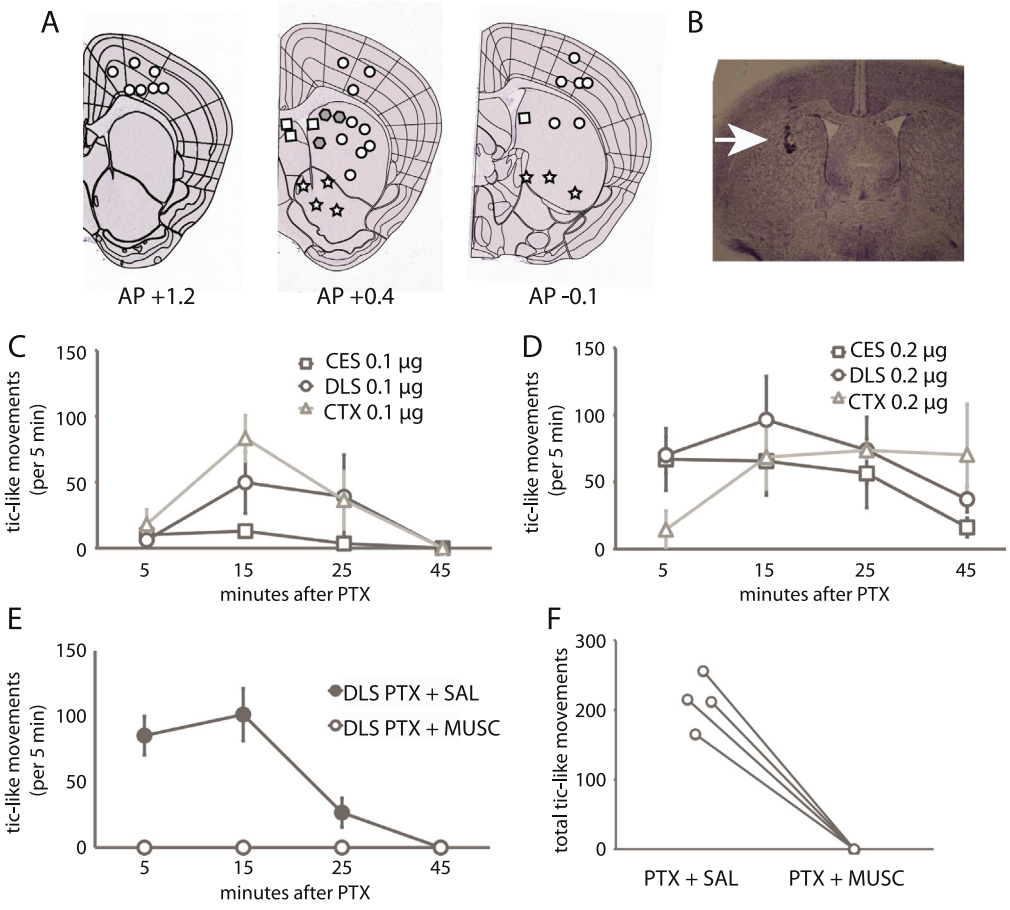

Fig. 1. A. Diagram of frontal sections (from www.brain-map.org) showing sites of injections and evoked effects in exploratory pilot experiments: ○ tic-like movements; ⬡ no apparent behavioral effect; ⋆ locomotor activation, sniffing, hindpaw licking; ◻behavioral depression. B. Cresyl violet staining of a typical injection site in striatum after infusion of 0.3 µL toluidine blue 20 min before euthanasia. C. Time course of tics, quantified in 5 minute bins starting 5, 15, 25, and 45 min after 0.1 µg of PTX injected into CES, DLS, and Cx. D. Same for 0.2 µg of PTX. E. Pharmacological blockade of PTX-induced tic-like movements by muscimol (MUSC). Saline (SAL) or Musc 0.2 µg was injected 10 min before PTX using the same cannula, targeting the DLS (n = 4; all animals received both treatments, several days apart). F. All tic-like movements were eliminated by muscimol pretreatment.