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Research Report

Preserved dichotomy but highly irregular and burst discharge in the basal ganglia in alert dystonic rats at rest

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ABSTRACT

Despite its prevalence, the underlying pathophysiology of dystonia remains poorly understood. Using our novel tri-component classification algorithm, extracellular neuronal activity in the globus pallidus (GP), STN, and the entopeduncular nucleus (EP) was characterized in 34 normal and 25 jaundiced dystonic Gunn rats with their heads restrained while at rest. In normal rats, neurons in each nucleus were similarly characterized by two physiologically distinct types: regular tonic with moderate discharge frequencies (mean rates in GP, STN and EP ranging from 35–41 spikes/s) or irregular at slower frequencies (17–20 spikes/s), with a paucity of burst activity. In dystonic rats, these nuclei were also characterized by two distinct principal neuronal patterns. However, in marked difference, in the dystonic rats, neurons were primarily slow and highly irregular (12–15 spikes/s) or burst predominant (14–17 spikes/s), with maintained modest differences between nuclei. In GP and EP, with increasing severity of dystonia, burstiness was moderately further increased, irregularity mildly further increased, and discharge rates mildly further reduced. In contrast, these features did not appreciably change in STN with worsening dystonia. Findings of a lack of bursting in GP, STN and EP in normal rats in an alert resting state and prominent bursting in dystonic Gunn rats suggest that cortical or other external drive is normally required for bursting in these nuclei and that spontaneous bursting, as seen in dystonia and Parkinson's disease, is reflective of an underlying pathophysiological state. Moreover, the extent of burstiness appears to most closely correlate with the severity of the dystonia.

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Abbreviations: BC, bimodality coefficient; BO, burst order; BP, burst percentage; BPM, bursts per minute; CS, clinical score; DA, dopamine; EP, entopeduncular nucleus; GPe, globus pallidus externa; GPi, globus pallidus internus; HDS, Hartigan's dip statistics; ISI, interspike interval; KPSS, Kwiatkowski-Phillips-Schmidt-Shin test; PCA, Principal Component Analysis; PD, Parkinson's disease; STR, striatum; STN, subthalamic nucleus.

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1. Introduction

Dystonia is a devastating condition characterized by ineffective, twisting movements, prolonged co-contractions, and contorted postures (Kernich, 2003). Despite its prevalence, the etiology for two-thirds of dystonia cases is not known and the underlying pathophysiology remains poorly understood. Although some investigators suggest a role for the cerebellum, most evidence from strokes (Münchau et al., 2000), from microelectrode recording studies in humans undergoing globus pallidus internus (GPi) ablation or deep brain stimulation (DBS) surgery (Vitek et al., 1999; Lenz et al., 1999; Zhuang et al., 2004; Starr et al., 2005), and in animal models of dystonia (Chiken et al., 2008; Nambu et al., 2011; Baron et al., 2011; Richter and Loscher, 1993; Loscher et al., 1989) suggest a principal role of the basal ganglia in most forms of dystonia. Compared to normal monkeys, neuronal discharge activity in the GP externus (GPe), subthalamic nucleus (STN) and GPi in humans with dystonia shows reduced rates and prominent discharge irregularity (Lozano et al., 1997; Zhuang et al., 2004; Vitek et al., 1999). In one study (Zhuang et al., 2004), approximately 80% of neurons in GPe and STN were found to show irregular and grouped discharge activity with intermittent pauses and low frequency burst activity. Comparable abnormal alterations have also been reported in GPi in humans with dystonia relative to the discharge characteristics in normal monkeys (Hashimoto, 2000; Lenz et al., 1999; Lozano et al., 1997; Zhuang et al., 2004). Although specific alterations in basal ganglia neuronal discharge activity are likely to account for most of the characteristic motor features of dystonia, to date, the abnormally patterned discharge activity has not yet been systematically investigated in animal models of dystonia.

The present study was designed to define and compare single cell activity in GP (rodent equivalent of GPe), STN, and the entopeduncular nucleus (EP, rodent equivalent of GPi) in alert, head restrained jaundiced dystonic Gunn rats (Chaniary et al., 2009) and healthy control rats at rest. Although normal and abnormally patterned basal ganglia discharge activity have been described previously in many rodent studies, these reports were regularly compromised by a number of technical limitations, including the frequent use of anesthesia, infrequent control for the influence of movement in alert animals, and inadequate methodology to effectively differentiate different types of neurons. We previously developed a novel multiple metric optimization neuronal classifier based on a representative large set of simulated spike trains. Subsequently, a subset of the data from the present study, along with diverse representative neuronal recordings from the cerebral cortex, hippocampus and thalamus, were used to validate the algorithm (Kumbhare and Baron, 2015). The new algorithm, in turn, was used here to classify an extensive normal and dystonic neuronal pool in GP, STN and EP as regular, irregular, or burst predominant.

While DBS surgery is highly beneficial for treating primary dystonias, the surgery is largely ineffective for most secondary forms of dystonia, including kernicterus and thus, alternative mechanistic based strategies for reversing the underlying pathophysiology are critically needed. Presently, we postulated that definable changes in neuronal rates and, in particular, in patterned discharge activity, in GP, STN and EP would correlate with the severity of dystonia. Parts of these data were published previously in the proceedings of the 10th Triennial Meeting of the International Basal Ganglia Society (Baron et al., 2011).

2. Results

2.1. Clinical characteristics of dystonic animals

Table 1 summarizes the clinical features of the animals. Of 49 dystonic animals, 7 rats were subjectively scored as slight to mildly dystonic (dyst-1) and 18 as moderate (dyst-2) and together compromised the dystonic recording cohort. The remaining 24 dystonic rats were severely affected (dyst-3) and either died or were considered too moribund to tolerate the surgery. EMG recordings from hip and stifle muscles in all rats were silent at rest and exclusively, in dystonic rats,

Table 1 – Summary of clinical characteristics and data collection.

Groupings	Dyst-0	Dyst-1	Dyst-2	Dyst-3
Number of rats	34	7	18	24
Dystonia severity	None	Slight to mild	Moderate	Severe
Gait	Normal gait	Mild gait abnormality	Prominent spread of hindlimbs	Moribund with inability to ambulate
Righting reflex	Normal	Prolonged	Impaired	Absent
Final clinical score (mean±SD (range))	0	$1.2\pm0.2^{D0***}$ (1–2)	$2.8\pm0.3^{D0 \text{ and } D1***}$ (2.5–3)	$4.0\pm0.33^{D0,D1 \text{ and } D2***}$ (3.5–5)
EMG during limb movement	No co-contractions	Occasional co-contractions in antagonistic muscle pairs	Frequent co-contractions of antagonist pairs and multi-joint	NA
Hind paw spread (mm)	35.4±3.7	$40.2\pm2.3^{D0***}$	$47.2\pm4.6^{D0 \text{ and } D1***}$	NA
Mean number of nuclei (GP, STN, EP) recorded per rat	1.6±0.3	1.9±0.2	1.3±0.2	NA
Number of analyzable neurons	344	70	184	NA

*$p<0.05$, **$p<0.01$, ***$p<0.005$, ****$p<0.001$ (for all figures and tables).$^{D0,\ D1,\ D2}$denote significant differences from dyst-0, dyst-1, and dyst-2 groups, respectively.