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ENHANCED VISUAL RESPONSES IN THE SUPERIOR COLLICULUS AND SUBTHALAMIC NUCLEUS IN AN ANIMAL MODEL OF PARKINSON'S DISEASE

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Abstract—Striatal dopaminergic denervation leads to a change in afferent activity within the basal ganglia. Coupled with the effect of local dopaminergic denervation in the subthalamic nucleus, this is likely to affect the responsiveness of subthalamic neurons to their hyperdirect inputs in Parkinson's disease. Therefore, in this report, we investigated subthalamic nucleus responses to visual stimuli relayed by one such input – the superior colliculus – in 6-hydroxydopamine (6-OHDA)-lesioned rats. We used a protocol where the superior colliculus was selectively unlocked from the inhibitory effect of anesthesia with an injection of bicuculline, attenuating GABAergic inhibition in the colliculus, which arises predominantly from the substantia nigra pars reticulata. We found that visual responses in the superior colliculus were facilitated by partial or total lesions of dopaminergic neurons in the substantia nigra pars compacta, once the colliculus was disinhibited by bicuculline. Responses were faster, larger in amplitude and lasted longer compared to those in control rats. In the subthalamic nucleus, visual responses were also increased in amplitude and magnitude in partial or total lesioned groups. A classic hypothesis in Parkinson's disease suggests that following dopaminergic denervation, the discharge of cells in the substantia nigra pars reticulata increases, thereby intensifying the inhibitory influence that this structure exerts on its targets in the thalamus and brainstem. Our results suggest that neuroadaptations may have taken place within the superior colliculus in order to maintain normal function in the face of increased inhibitory tone coming from the substantia nigra pars reticulata, which once reduced, gave rise to facilitated responding. This facilitated responding in the superior colliculus then appears to lead to facilitated responding in the subthalamic nucleus. **© 2013 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: superior colliculus, subthalamic nucleus, substantia nigra pars compacta, 6-OHDA lesion, Parkinson's disease.

INTRODUCTION

The subthalamic nucleus (STN) occupies a central position in the functional architecture of the basal ganglia (BG) (Parent and Hazrati, 1995; Joel and Weiner, 1997), an interconnected group of subcortical nuclei that represent one of the brain's fundamental processing units (Gerfen and Wilson, 1996). The STN has been classically described as a relay in the indirect pathway between the input and the output structures of the BG (Albin et al., 1989). In recent years however, evidence has accumulated that it should also be considered as another crucial entry point to this system (Nambu et al., 2002). The STN receives wide-spread connections from many brain regions via cortical motor areas (Mink, 1996; Nambu et al., 1996,2000,2002; Takada et al., 2001), but also from subcortical structures such as the thalamus (Sugimoto and Hatfori, 1983; Lanciego et al., 2004; Castle et al., 2005), the pedunculopontine nucleus (Scarnati et al., 1987) and the superior colliculus (SC) (Tokuno et al., 1994; Coizet et al., 2009). It is now widely appreciated that these so called hyperdirect connections constitute an important parallel component to the general looped architecture which has been incorporated into contemporary models of the BG (Parent and Hazrati, 1995).

Although the anatomical connectivity of the STN is now comparatively well understood, the function of the STN is still a matter of some debate. Early electrophysiological studies revealed that the STN contains neurons whose activity is related to movement (DeLong et al., 1985), leading to the classical proposal of a motor role for this structure. However, this view has

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Abbreviations: ANOVA, analysis of variance; AP, antero-posteriority; BG, basal ganglia; BSA, bovine serum albumin; CONT, control; DA, dopamine; DAB, diaminobenzidine; DV, dorso-ventral; FLI, fos-like inmmunoreactivity; LED, light-emitting diode; ML, medio-laterality; MPTP, 1 - méthyle 4 - phényl 1,2,3,6-tétrahydro pyridine; NGS, normal goat serum; NHS, normal horse serum; NMDA, acide N-méthyl-D-aspartique; PART, partial; PB, phosphate buffer; PD, Parkinson's disease; PSTHs, peristimulus time interval histograms; SC, superior colliculus; SEM, standard error of the mean; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; TH, thyrosine hydroxylase; TOT, total; TX, triton X-100; 6-OHDA, 6-hydroxydopamine.

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been extended by the discovery that the STN is strongly implicated in motivated behavior (Baunez and Robbins, 1997; Baunez et al., 2002; Uslaner and Robinson, 2006), reward processing (Darbaky et al., 2005; Lardeux et al., 2009) and in action selection (Redgrave et al., 1999; Monchi et al., 2006; Isoda and Hikosaka, 2008). Perhaps not surprisingly given the widespread functional role of the STN, a malfunctioning of this structure is thought to underlie the symptoms described in Parkinson's disease (PD). Indeed, according to the classic pathophysiological model of this disease (Albin et al., 1989; DeLong, 1990), glutamatergic neurons of the STN, which innervate the BG output nuclei, become hyperactive and their firing pattern alters following the degeneration of striatally projecting dopaminergic (DA) neurons from the substantia nigra pars compacta (SNc; Bergman et al., 1994; Hassani et al., 1996). As a consequence, the discharge of cells in the BG output nuclei increases (Burbaud et al., 1995), thereby intensifying the inhibitory influence that these GABAergic structures exert on their target nuclei in thalamus and brainstem, thus inhibiting behavioral output (Chevalier and Deniau, 1990).

However, in addition to these changes in STN function which result from striatal denervation, the consequences of a more proximal loss of dopamine must be considered. In a wide range of species, the STN itself receives a DA input (rat: Hassani et al., 1997; guinea pig: Overton et al., 1995; cat: Meibach and Katzman, 1979; monkey: François et al., 2000; and human: Hedreen, 1999), which arises in part from the SNc (Meibach and Katzman, 1979; Hassani et al., 1997; François et al., 2000). Dopamine is released in the STN at levels which are sufficient to activate post-synaptic receptors (Cragg et al., 2004), leading to an excitation of STN neurons (Overton et al., 1995; Ni et al., 2001; Cragg et al., 2004). Given that dopaminergic innervation of the STN is substantially reduced in PD (François et al., 2000) and that local dopamine denervation of the STN has motor consequences in the rat (Flores et al., 1993), it is possible that changes in dopamine-mediated transmission in PD at the level of the STN contribute to the functional loss in the disease. One likely outcome of local dopamine denervation is that the STN now responds differently to its hyperdirect inputs. This effect of local dopamine denervation is likely to be compounded by the change in BG afferent activity at the level of the STN which follows striatal dopamine denervation.

Neurons in the STN exhibit short-latency phasic increases in activity in response to the onset of visual stimuli in rats and monkeys (Matsumara et al., 1992; Coizet et al., 2009). In our previous work in the anesthetized rat, using a natural light flash stimulus during the simultaneous recording of activity in the SC and the STN, we identified the SC as the main, if not the exclusive relay of short-latency phasic visual inputs to the STN (Coizet et al., 2009). To examine the possibility that dopamine denervation may change the responsiveness of the STN to its hyperdirect inputs, we used the same protocol as before, but this time examining the effects of visual stimuli on STN responses following 6-OHDA lesions of the SNc.

EXPERIMENTAL PROCEDURES

In accordance with the policy of Lyon1 University, the Institut des Neurosciences of Grenoble (GIN) and the French legislation, experiments were done in compliance with the European Community Council Directive of November 24, 1986 (86/609/EEC). The research was authorized by the Direction Départementale des Services Vétérinaires de l'Isère – Ministère de l'Agriculture et de la Pêche, France (Coizet Véronique, PhD, permit number 381003). Every effort was made to minimize the number of animals used and their suffering during the experimental procedure. All procedures were reviewed and validated by the ''Comité éthique du GIN n°004'' agreed by research ministry.

6-OHDA injections

Long Evans rats (n = 35; male; 243–406 g) were anesthetized with an i.p. of a mixture of ketamine–xylazine (0.765/1.1 ml, 1 ml/kg, ip) and placed in a stereotaxic frame with the skull level, in the plane employed by the stereotaxic atlas of Paxinos and Watson (1998). Throughout the surgery the temperature of the rats was maintained at 37 °C by a thermostatically controlled heating blanket. All the injections of 6-OHDA Hydrobromide (Sigma–Aldrich, 3 mg/ml in sterile 0.9% NaCl and 0.1% ascorbic acid) were made via a sharpened 30 gauge injection cannula connected with polyethylene tubing to a 10-µl Hamilton syringe driven by a Harvard infusion pump (0.5 µl/min). The cannula was left in place for a further 5 min to allow diffusion. Animals were divided into three groups: (i) A group with a partial dopaminergic lesion (PART, n = 11), in which 1 µl of the neurotoxin 6-OHDA was injected into the left SNc using the following stereotaxic coordinates: Antero-posteriority (AP): +3.0 mm; Medio-laterality (ML): +2.4 mm and Dorso-ventral (DV): +2.4 mm from interaural zero; (ii) A group with a total dopaminergic lesion (TOT, n = 10), in which 3 µl of 6-OHDA was injected into the left SNc using the following stereotaxic coordinates: AP: +3.0 mm; ML: +2.1 mm and DV: +2.4 mm from interaural zero mm; (iii) A control group with no injection of the toxin (CONT, n = 14).

Electrophysiology

After a minimum of 3 weeks following the lesion, rats were anesthetized with urethane (ethyl-carbamate, 1.25 g/kg, Sigma–Aldrich). A parylene-C-insulated tungsten microelectrode (1–2 M, A-M Systems) was introduced vertically into the STN (AP: 3.6–4.1 mm, ML: 2.0–3.0 i.p., DV: 7.0–8.0 mm) and a second tungsten electrode coupled to a 30-gauge metal injector needle filled with the $GABA_A$ receptor antagonist bicuculline methiodide (40 ng per 400 nl of saline, Sigma–Aldrich) was introduced into the SC (AP: 5.8–6.3 mm, bregma; ML: 1.5–2.5 mm, bregma; DV: 3.5–5.0 mm, dura) at an

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