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Short communication

Lateralized response of oxytocinase activity in the medial prefrontal cortex of a unilateral rat model of Parkinson's disease

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ABSTRACT

Individuals in the early stage of Parkinson's disease exhibit cognitive impairments as a result of hemisphere damage. The mesocortical dopamine system, particularly the medial prefrontal cortex (mPFC), is implicated in cognitive functions and is characterized by an asymmetric organization. Oxytocinase activity (OX) is also asymmetrically distributed in the mPFC of normal rats and is involved in cognitive functions. OX was measured in the left and right mPFC of rats with left or right hemi-parkinsonism, induced by intrastriatal injections of 6-hydroxydopamine, and compared with sham controls. These results demonstrated that the striking basal left predominance of OX observed in both the left and the right sham controls was radically disrupted in lesioned animals. The bilateral distribution in lesioned animals was altered differently depending on the injured hemisphere. These results may reflect changes in the enzyme substrates and consequently in the functions in which they are involved. These results may account, in part, for the cognitive abnormalities observed in hemi-parkinsonism.
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Although symmetric in the later stages, the damage observed in Parkinson's disease (PD) begins asymmetrically [9]. In the early stages, PD patients exhibit cognitive and behavioral impairments that are unrelated to the motor symptoms that involve frontal lobe dysfunction [6,10,26] and are the result of damage to a specific hemisphere [8]. Studies in animals with hemi-parkinsonism induced by unilateral nigrostratal lesions using 6-hydroxydopamine (6-OHDA) have described several behavioral abnormalities [14]. However, no comparisons between left- and right-lesioned animals were performed. It has been proposed that the systems other than the dopaminergic pathway may also be involved in the behavioral abnormalities observed in PD [16].

The medial prefrontal cortex (mPFC), a part of the mesocorticolimbic system, is involved in cognitive functions and reward-related mechanisms in the rat brain [23]. The mesocortical dopamine system, particularly the mPFC, is characterized by an asymmetric organization [20]. Changes in this pattern may suggest, or possibly lead to, disorders in brain function [18].

Oxytocinase activity (OX) enhances learning and memory, has anticonvulsant and anti-epileptogenic properties, protects against cerebral ischemia and is involved in atherogenesis. All these properties have conducted to the idea that this enzyme might become an important target for drug development against different pathologies such as Alzheimer's disease, epilepsy or ischemia [19]. The asymmetrical distribution of this enzyme in the brain was previously reported in naïve rats [2]. In order to analyze its bilateral behavior in experimental hemi-parkinsonism, OX was measured, using L-Cys-β-naphthylamide as the substrate, in the left and right mPFC of rats with left or right hemi-parkinsonism. The animals were lesioned with left or right intrastriatal injections of 6-OHDA and compared with control animals that received left or right intrastriatal injections of saline.

Three-month-old male Wistar rats weighing 250 g at the beginning of the study were used for both sham and lesioned groups. During the experimental period, food and water were available *ad libitum*. The animals were housed under standard conditions of light (12 h of light from 7.00 h to 19.00 h and 12 h of dark from 19.00 h to 7.00 h) and temperature (22 °C).

Degeneration of the left or right nigrostriatal dopaminergic pathway was accomplished via neurochemical lesions induced with the catecholaminergic toxin 6-OHDA [15]. All animals were anesthetized with 2 mL/kg body weight equithensin (42.5 g/L chloralhydrate dissolved in 19.76 mL ethanol, 9.72 g/L Nembutal®,

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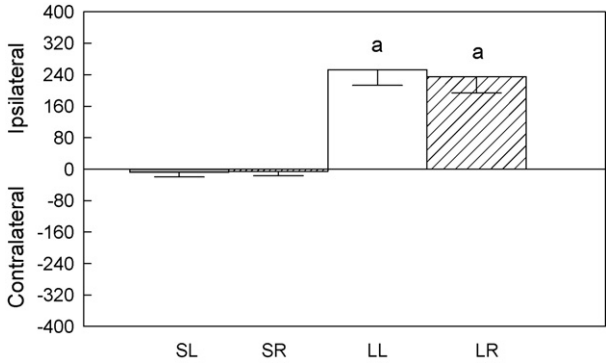

Fig. 1. Turning behaviour in lesioned left (LL) or lesioned right (LR) and sham left (SL) or sham right (SR) rats. A number of turns were determined individually in 6 periods of 10 min during 1 h. Values represent mean ± SEM ($n = 10$) of the cumulative turns recorded in 6 periods (from Banegas et al. [4] with permission). (a) Differences between the same side of lesioned vs. sham animals; $p < 0.001$.

0.396 L/L propylenglycol and 21.3 g/L magnesium sulfate in distilled water) and placed in a stereotaxic instrument (David Kopf Instruments, Palo Alto, CA, USA). Infusion of 4 μL of 6-OHDA (8 mg dissolved in 1 mL of cold saline with 0.02% ascorbic acid to inhibit oxidation) was administered into the left or right striatum [15]. A 2 mm burr hole was drilled through the skull at horizontal coordinates approximating the position of the striatum (AP 0 mm, L or R 3 mm and H −5 mm) according to the atlas by Paxinos and Watson [17]. The control rats were operated on in the same manner, but they received 4 μL of saline with 0.02% ascorbic acid. Assessment of the ipsilateral rotational behavior allowed us to verify the efficacy of the 6-OHDA-induced lesions. Turning behaviour was assessed four weeks after the administration of 6-OHDA or saline, the day before the animals were sacrificed. Compared with sham controls, a marked ipsilateral rotational behavior was observed in left- and right-lesioned animals [4] (Fig. 1). All experimental procedures involving animals, including their use and care, were in accordance with the European Communities Council Directive 86/609/EEC.

Four weeks after receiving the injections, the animals were sacrificed and the left and right mPFC samples were dissected according to the stereotaxic atlas of Paxinos and Watson [17]. The selected area of mPFC was between 13.20 mm and 11.52 mm anterior to the interaural line (Fig. 2). The samples were collected on the same day and frozen for assays. The surgical procedure, sacrifice and sample collection were performed under anesthesia between 9.00 h and 11.00 h. Left or right 6-OHDA-lesioned animals were compared with their corresponding left or right sham-operated animals in which the DA pathways were intact. Because bilateral injuries usually lead to the death of rats due to the occurrence of marked aphagia and adipsia [24], such control animals were not available.

Oxytocinase activity levels were measured in the following groups (for all groups, $n = 10$):

(a) Simulated lesion of the left hemisphere with saline (sham left, SL).
(b) Simulated lesion of the right hemisphere with saline (sham right, SR).
(c) Lesion of left hemisphere with 6-OHDA (lesion left, LL).
(d) Lesion of right hemisphere with 6-OHDA (lesion right, LR).

Membrane-bound oxytocinase activity was measured fluorometrically using L-Cys-β-naphthylamide as previously described [2]. Proteins were quantified in triplicate by the method of Bradford [5] using BSA as a standard. Specific OX was expressed as nanomoles of L-Cys-β-naphthylamide hydrolyzed per minute per milligram of

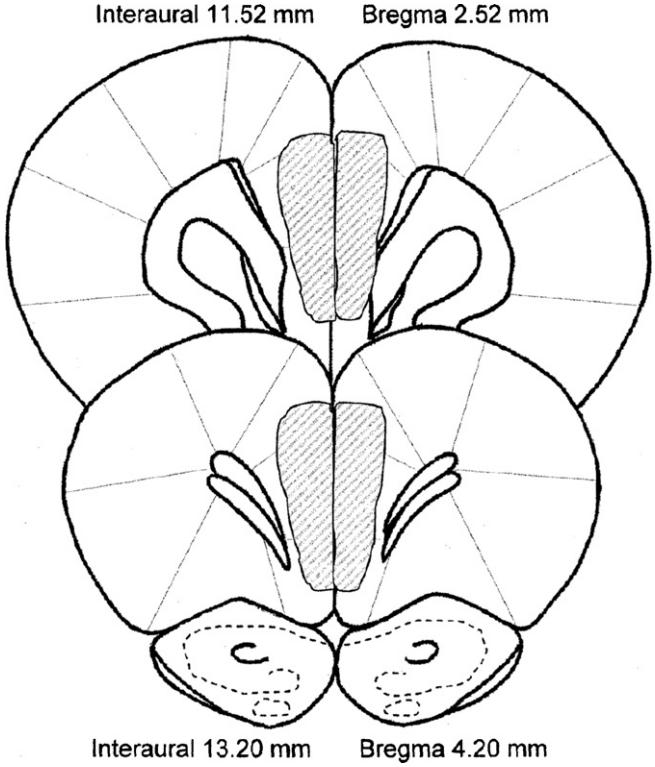

Fig. 2. Schematic diagram representing the anterior and posterior stereotaxic planes between which the mPFC (striped area) was dissected [17].

protein. Fluorogenic assays were linear with respect to the time of hydrolysis and protein content. For the statistical analysis, a two-way ANOVA was used, with lesion group (sham/6-OHDA) as the between-subject factor and hemisphere (left/right) as the within-subject factor. Post hoc comparisons were made using the paired Student's *t*-test; *p*-values below 0.05 were considered significant.

Our results are represented in Fig. 3. ANOVA test demonstrated that there were significant differences depending on the lesion group (sham vs. 6-OHDA) ($p = 0.008$), depending on the side of saline or 6-OHDA injection ($p = 0.002$) and depending on the considered hemisphere (left vs. right) ($p = 0.0000$). There was a marked asymmetry of OX in the mPFC of left and right sham-operated control animals showing left predominance in both SL (168% higher;

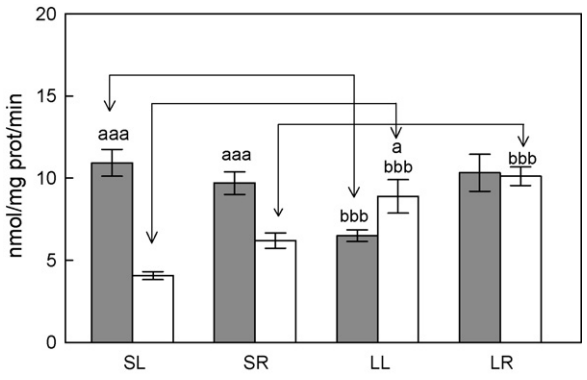

Fig. 3. Oxytocinase activity in the left (gray bars) and right (open bars) medial prefrontal cortex of left (SL) or right (SR) sham-operated and left (LL) or right (LR) 6-OHDA-lesioned rats. For each group, $n = 10$. Values represent mean ± SEM of specific oxytocinase activity expressed as nanomoles of L-Cys-β-naphthylamide hydrolyzed per minute per milligram of protein. (a) Differences between left and right sides. (b) Differences in the same side between sham and lesioned animals. Single letter: $p < 0.05$; triple letter: $p < 0.001$.

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