Is the Habenula the key nucleus linking emotional and motor impairments in Parkinson's disease?

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Introduction and Hypothesis:

A large percentage of Parkinson's disease (PD) patients exhibit emotional and psychiatric deficits in addition to motor impairments [1]. These emotional disorders are thought to be related to limbic areas and alteration in serotonin levels but the ways in which the basal ganglia (BG) is functionally connected to the limbic system and how this connectivity is affected during PD is unknown. Since converging evidence points to the involvement of the habenular complex (Hab) in emotional, psychiatric and reward systems[2], and anatomical studies have revealed the presence of a BG-Hab connection, we investigated whether the Hab serves as a relay nucleus linking the BG and the limbic systems. Manganese chloride ($MnCl_2$) was directly injected to the output nuclei of the BG – the entopeduncular nucleus (EP) and the substantia nigra (SN) - and to the Hab, in the unilateral 6-hydroxydopamine (6-OHDA) rat model for PD and in control rats. Manganese neuronal transport was followed using Manganese-Enhanced Magnetic Resonance Imaging (MEMRI)[3]. The results indicate enhanced bilateral projections from the EP and SN to the Hab, as well as enhanced projections from the Hab to the raphe and the interpeduncular (IP) nuclei during the Parkinsonian state, thus suggesting that the Hab plays a fundamental role in PD.

Methods:

Direct $MnCl_2$ injections to the EP, SN and Hab were performed on adult SD rats (n=6, 5 and 7, respectively) two weeks after the 6-OHDA was injected directly to the substantia nigra pars compacta (SNc) (to the same hemisphere) and to the EP, SN and Hab in sham-operated rats (n=6, 5 and 5, respectively). Accuracy of SNc destruction was verified by tyrosine hydroxylas immunofloroscent staining and by the rate of circling after apomorphine injections. High spatial resolution T1 weighted images for the MEMRI (TR=156ms, TE=6.7ms, 30 averages, 1 mm slice thickness, FOV=3cm, 256X256 resolution) were acquired before, 3, 24 and 48 hours after $MnCl_2$ injection, using a 4.7 T Bruker Biospec System.

Results and Discussion:

Significant ipsilateral and contralateral signal increase in the Hab compared to baseline was observed at 24h and 48h post EP-injection, in both 6-OHDA and sham-operated groups. However the signal increase in the 6-OHDA group was significantly ($p<0.05$) higher than in the sham-operated group in both ipsilateral and contralateral Hab, indicating enhanced EP-Hab connectivity in the Parkinsonian state. Furthermore, significant signal enhancement in the Hab ($p<0.005$), ipsilateral and contralateral to the injection site, was observed 24h post SN-injection with no corresponding signal change in the sham-operated rat group. These SN-Hab changes indicate fundamental alternations in SN-Hab connectivity taking place in the Parkinsonian.

Twenty-four hours after $MnCl_2$ injection to the Hab the signal intensity in the IP (fig 1 a), was higher in the 6-OHDA rats as compared to baseline ($p<0.05$) and as compared to the signal increase in the sham-operated group ($p<0.05$), demonstrating the strong efficient connections between the Hab and the IP in the Parkinsonian state. Significant signal increase in the raphe nucleus (fig 1 b), the main brain region for serotonin synthesis, was only observed at 24h post injection in the 6-OHDA group ($p<0.005$), indicating efficient connectivity from the Hab to the raphe nucleus in the Parkinsonian state with no signal change in the control group. Our results thus suggest that the habenular complex plays a much more significant role in the Parkinsonian state than was thought. The enhanced connectivity between the Hab and the serotonin system further suggest that the habnular nucleus is involved in the pathogenesis of the emotional (limbic) symptoms of PD.

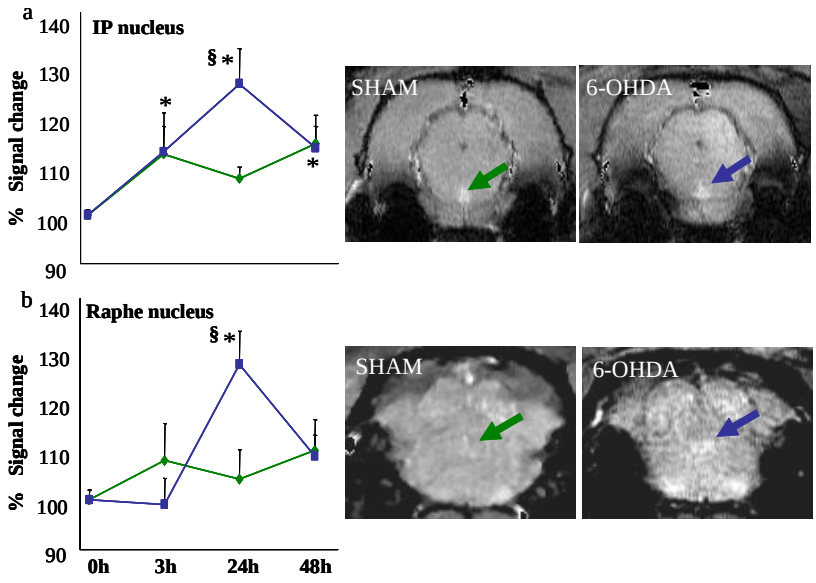

Figure 1. Percentage signal intensity changes (with +1 mean standard error) in the IP (a) and the raphe nucleus (b) after $MnCl_2$ injection to the Hab area in the sham-operated and 6-OHDA model rats, before and 3, 24 and 48 hours post injection (blue lines, 6-OHDA rats; green lines, sham-operated rats; *, $p<0.05$ signal change compared to baseline; §, $p<0.05$ difference between sham-operated and 6-OHDA rats). Right panel: MRI images of sham-operated (SHAM) and 6-OHDA (6-OHDA) rats taken 24 hours after $MnCl_2$ injection. Significantly, enhanced Mn^{2+} accumulation was found in the IP and the raphe nuclei 24h post-injection in the 6-OHDA compared to sham-operated rats.

References:

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