The effect of valproic acid treatment on the dopaminergic neuron survival in a 6-hydroxydopamine rat model of Parkinson's disease

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Parkinson's Disease (PD) is characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) resulting in the loss of dopaminergic innervation to the striatum. In recent years increasing number of in vitro and in vivo studies demonstrate the neuroprotective effects of valproic acid (VPA), which is a commonly used drug in the treatment of epilepsy and bipolar disorders, through many mechanisms (1). In this study, we aim to determine whether VPA protects dopaminergic neurons from 6-hydroxydopamine (6-OHDA) induced neurotoxicity.

Male Wistar albino rats (250–300 g) were assigned to 4 groups (n=4) as follows: Sham operated (S), sham operated and VPA treated (SV), 6-OHDA injected (PD) and 6-OHDA injected and VPA treated (PV). The rats were stereotaxically injected either with 6-OHDA (8μg/2μL) or saline to the SNpc. Only the rats showing rotational behaviour (≥5 contralateral turns/min) were included into the study after apomorphine (0.5 mg/kg sc) test. Two weeks following the operation, rats were intraperitoneally injected with either VPA (300 mg/kg) or saline for 10 days. Coronal sections were taken through the substantia nigra on a freezing microtome at a thickness of 16 μm. Each section was examined under Stereo Investigator version 7.5 image analysis software for tyrosine hydroxylase (TH) immunoreactive cells (2). One-way Anova followed by Tukey post-hoc test was used for statistical analysis.

The number of TH positive neurons was not different between S and SV groups. There was a pronounced loss of TH positive neurons in 6-OHDA lesioned right SNpc in PD group as compared to sham-operated groups (p<0.001). VPA treatment significantly increased the number of TH positive neurons in PV group as compared to PD group (p<0.05). However, the numbers of TH positive neurons were still significantly lower in PV group as compared to S and SV groups (p<0.01) (Figure 1 and 2).

In our study, we have demonstrated that VPA treatment may have neuroprotective effects on dopaminergic cell survival in a 6-OHDA lesioned rat model of Parkinson's Disease.

References:
2) Decressac M., Mattsson B., Björklund A., 2012 Comparison of the behavioural and histological characteristics of the 6-OHDA and α-synuclein rat models of Parkinson's disease

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Fig. 1: TH immunoreactivity was decreased in PD group and increased in PV group. Photomicrographs demonstrating sections taken from right SNpc stained with TH. Groups: A; S, B; PD, C; SV, D; PV. Dopaminergic neuron is demonstrated with arrow and mononuclear cell infiltration is star. The magnification is x10. Scale bar represents 200 μm.

Fig. 2: Graphs comparing the S, PD, SV, PV groups. Data are presented as percentage of right SNpc neurons compared to total neurons in right and left SNpc. Data are expressed as mean ± SEM (*p<0.05, **p<0.01 and ***p<0.001).