

VGF Involvement on Parkinson's disease

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Parkinson's disease (PD) is a neurological disorder characterized by a progressive degeneration of dopaminergic neurons of the substantia nigra, that results in dopamine depletion in the striatum with a deregulation of a number of substances/neurotransmitters. A previous study demonstrated a clear-cut decrease of certain peptides derived from the VGF gene in the parietal cortex from patients affected by PD. Hence, we used an animal model of PD, and plasma samples from PD patients and control subjects to investigate the role of VGF in PD. Rats (Sprague Dawley) were treated with injections of 6 hydroxydopamine into the medial forebrain bundle, anesthetized and perfused with 4% paraformaldehyde 3 weeks (group 1: n= 8) or 6 weeks (group 2: n=17) after injection. In addition, subcutaneous injections of L-DOPA (6mg/Kg) were carried out one week before the sacrifice in rats from group 1 and 2 (n=4 and n=6, respectively). We raised antibodies to the C-terminal end of the human VGF sequence, for immunohistochemistry (IHC) and enzyme-linked immunosorbent assay (ELISA, IC50 = 15 pmol/ml). For pilot experiments, human plasma samples were taken from subjects affected by PD (n=13, age range: 51–84 years), and from age matched controls (n=10), to be used for ELISA experiments. We analysed the substantia nigra (SN) of the PD rats using VGF-C-terminus antiserum in double staining with antibodies to glutamate decarboxylase (GAD), tyrosine hydroxylase (TH), serotonin and Substance P. In the control side, VGF-C-terminus peptides were found in neurone terminals/axons within the pars compacta (SNC) and reticulata (SNR) of the substantia nigra, co-localised with GAD and substance P (but not with serotonin or TH) and in closed connection with TH cell bodies of the SNC. In the PD side, while the GAD staining remains unaffected, VGF-C-terminus and substance P immunoreactivities disappeared (compared to the control side) in a large population of neurone terminals of both SNC and SNR, and in relation with the TH decrease. When L-DOPA was applied to the animals, VGF-C-terminus immunoreactivity on the PD side returned comparable to the control side. By ELISA, high concentrations of proVGF, in the order of 600-2000 pmol/ml were shown in the plasma from controls with a significant decrease in PD samples (p=0,0029). In conclusion, using the animal models, we showed here for the first time that VGF is involved into nigro-striatal circuits and down-regulated in PD. Besides, of a great interest, is the finding that a deregulation of VGF can occur also in humans.

Keywords

Parkinson's disease, VGF peptides, substantia nigra.