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VGF peptides: differential expression in motor neurons, and possible changes in Amyotrophic Lateral Sclerosis (ALS)

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The *vgf* gene shows delayed-early induction by neuronal Growth Factors. It encodes the VGF protein precursor (615/617 aa, in man/rat), which yields an incompletely characterized neuropeptides, some of which are involved in synaptic strengthening, anti-depressant and anti-apoptotic actions. Proteomic studies revealed clear-cut reduction of a 4.8kD VGF fragment in human CS fluid from ALS patients. In primary cultures of spinal motoneurons from SOD1-G93A mice (as a model of ALS), exogenous adenoviral expression of VGF attenuated excitotoxic injury. In the same animals, a decrease of VGF was seen in CSF and serum, in parallel to progression of muscle weakness. Hence, we aimed at delineating VGF multi-peptide profiles in (normal) rat motoneurons, as well as possible changes of such peptides in plasma from human ALS patients vs controls. Specific antisera were raised against short sequences at the C- and N-termini ("C-t", and "N-t") of the VGF precursor, and of known / predicted cleaved VGF peptides, and were used in immunohistochemistry and ELISA. Spinal cord, frontal cortex and brainstem samples were taken for immunohistochemistry from rats (N=9) perfused with 4% paraformaldehyde. Plasma was obtained from ALS and control subjects (N=26/14 respectively, age range: 50-60yrs). Immunohistochemistry showed selective localization of VGF peptides in motoneurons in all regions tested. In the frontal cortex, VGF C-t peptides were widely distributed in perikarya of internal layers (III-VI), and in axons in superficial layers (I-II). Axons and terminal were brightly stained in the ventral horn of the spinal cord, and in a number of brainstem motor nuclei (trigeminal, facial, hypoglossal and ambigus N.). Conversely, VGF N-t antibodies labelled mostly perikarya in all areas tested, while NERP-1 and –2, and PGH ($VGF_{422-430}$) peptides were restricted to occasional cell bodies in frontal cortex. In a few sections, PGH and TLQP-21($VGF_{556-576}$) labelling was seen in ventral horn perikarya. As to human plasma, NERP-1 and –2 as well as PGH peptides showed a significant reduction in ALS patients, versus controls (peptide concentration measured: 37%, 43% and 29% of controls, respectively, $p<0.025$), while C-t peptides were unchanged. In conclusion, at least in rat several specific VGF peptides are selectively distributed in areas critical to ALS, while certain VGF peptides appear to decrease in plasma in advanced cases of ALS. A possible role for specific VGF peptides in such disease is suggested.

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