PACAP signaling in amyotrophic lateral sclerosis: friend and foe?

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PACAP and its receptors PAC1, VPAC1 and VPAC2, are expressed in several neuronal circuits throughout the central nervous system. PACAP has putative neuroprotective and immune regulatory, mostly immunosuppressive properties as demonstrated in several models of neuro-degenerative and neuro-inflammatory diseases. Since PACAP has been found in vitro to protect somatomotor neurons against glutamate-induced excitotoxicity, a mechanism discussed to cause amyotrophic lateral sclerosis (ALS) we hypothesized a role for endogenous PACAP also in this disease.

Using in situ hybridization histochemistry we investigated the mRNA expression patterns of PACAP and its three receptors in somato- and visceromotor neurons from wildtype (WT) and SOD1-G93A transgenic (a mouse model of ALS) mice to find a possible correlate between PACAP ligand-receptor-systems and motor neuron survival. We also investigated if PACAP expression is regulated in ALS-vulnerable motor neurons during disease progression, and finally studied the outcome of a PACAP deficiency on the clinical, behavioral, and cellular levels in the SOD1-G93A ALS mouse model.

While PACAP mRNA was found absent from somatomotor neurons (e.g. spinal cord and hypoglossal nucleus) of WT mice, all pre-ganglionic sympathetic and parasympathetic (e.g. dorsal vagal nucleus) visceromotor neurons contained PACAP messages. PAC1 mRNA was present in all investigated motor neurons, VPAC2 mRNA expression restricted to somatomotor neurons, and VPAC1 mRNA undetectable in all motor neuron pools. At disease end-stage in SOD1-G93A mice only a subset of remaining vulnerable somatomotor neurons (<20% in spinal cord) had induced PACAP message, and receptor expression patterns were seemingly unaffected. Although disease-related neuropathological signs, i.e. vacuolar swellings in neurites, were prominent in all investigated somato- and visceromotor nuclei, motor neuron counts revealed that in contrast to the massive degeneration of somatomotor neurons, sympathetic visceromotor neurons survived until end-stage. A genetic depletion of PACAP in SOD1-G93A mice reduced the number of pre-ganglionic sympathetic visceromotor neurons, while leaving somatomotor neuron survival unaffected. Surprisingly, PACAP deficiency decelerated disease progression resulting in prolonged life expectancy (about 8 days). Most notably tongue motor function, but not spinal motor function was preserved in spite of PACAP deficiency. The only non-neuronal change so far seen in brain stem and spinal cord of PACAP deficient ALS mice was a switch in microglial phenotype from hypertrophic to amoeboid, while astrocyte hypertrophy and lymphocyte infiltration were unaffected indicating that endogenous PACAP, unexpectedly, furthers a hypertrophic microglial phenotype in the SOD1-G93A ALS model.

Conclusions: i) Endogenous PACAP protects pre-ganglionic visceromotor neurons that express both PACAP and PAC1 receptors possibly via a direct autocrine loop. Somatomotor neurons, although expressing PAC1 and VPAC2, are not protected by endogenous PACAP, presumably because they do not express PACAP. ii) PACAP may further disease progression in SOD1-G93A mice possibly by being permissive for the development of a presumed neuro-destructive hypertrophic microglial phenotype. iii) This suggests the dilemma that both PACAP agonists and PACAP antagonists may have both beneficial and disadvantageous effects. PACAP agonists may protect somatomotor neurons from degeneration but may also

foster neuro-destructive microglia and thus neuroinflammation. PACAP antagonists may reduce neuroinflammation but could lead to visceromotor neuron degeneration. As there is no satisfactory ALS treatment available to at least slow down this deadly disease it may be still worthwhile to test which of the two treatment regimens may have a net beneficial effect.