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Molecular mechanism of PACAP-induced EGFR transactivation in an in vitro model of ALS

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Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease affecting both upper and lower motor neurons. By analyzing the transcriptional profile of motor cortex samples from sporadic ALS (SALS) patients, we have previously selected two patient subgroups, known as SALS1 and SALS2. Since Cu/Zn-superoxide dismutase-1 (SOD1) mutation is involved some cases of familial ALS, we have also compared the gene expression profile of motor cortex from SALS patients and SOD1 G93A mice through a meta-analysis study [1]. From this analysis, 19 statistically significant genes emerged as deregulated both in mice and SALS patients, comprising: pituitary adenylate cyclase-activating polypeptide (PACAP), epidermal growth factor receptor (EGFR) and matrix metallopeptidase 2 (MMP-2) [2]. Considering the functional link between PACAP and EGFR, already described both in neurons and in cancer cells, here we have investigated the involvement of PACAP, EGFR and MMP-2 genes in this neurodegenerative disease.

The study has been performed in NSC34 motor neuronal cell lines expressing G93A SOD1.

Our data have showed that PACAP is able to rescue cells degeneration following growth factors deprivation. Its effect is induced through EGFR transactivation mediated by protein kinase A stimulation. Moreover, EGFR phosphorylation triggers the activation of MEK/ERK1/2 survival signaling pathway and increased MMP-2 expression, drastically reduced by serum starvation.

In conclusion, our findings suggest that a deeply characterization of the mechanism linking PACAP/EGFR/MMP-2 axis to SOD1 mutation may open a new perspective for ALS therapy.

References

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Key words

ALS, PACAP, EGFR, MMP-2.