NON-TRANSCRIPTIONAL REGULATION OF ALPHA-SYNUCLEIN BY VALPROIC ACID IN RAT PRIMARY ASTROCYTES

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Background and aims: Although the role of alpha-synuclein aggregation on Parkinsonism is relatively well known, the physiological role and the regulatory mechanism governing the expression of alpha-synuclein is not clear yet. In this study, we tried to elucidate the effect of valproic acid (VPA), which had been suggested to provide neuroprotection by increasing alpha-synuclein in neuron, on alpha-synuclein expression in rat primary astrocytes.

Methods: We assessed the regulatory effect of alpha-synuclein by valproic acid on protein and mRNA expression using Western blotting and RT-PCR in rat primary astrocytes. Furthermore, we tested if VPA increase the stability of alpha-synuclein via the inhibition of proteasome pathway.

Results: VPA concentration-dependently increased the protein expression level of alpha-synuclein in cultured rat primary astrocytes without affecting mRNA expression level. Likewise, the level of secreted alpha-synuclein was also increased by VPA. Interestingly, a proteasomal inhibitor MG132 increased alpha-synuclein and the level of exogenously over-expressed alpha-synuclein using adenoviral expression system was also increased by VPA, which suggests that VPA increased alpha-synuclein by nontranscriptional stabilization of the protein. VPA increased the phosphorylation of Erk1/2 and JNK, and pretreatment of SP600125 prevented the VPA-induced increase in alpha-synuclein.

Conclusions: VPA induced alpha-synuclein expression by non-transcriptional control mechanism, possibly via the regulation of protein stability in rat primary astrocytes. The search for physiological and pathological significance of the findings may provide insights into the understanding of the exact role of alpha-synuclein in brain as well as the identification of new targets for the regulation of alpha-synuclein level in Parkinson disease.