Downregulation of astrocytic connexin43 leads to enhancement of neurotrophic factor production in cortical astrocytes

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background:

Connexin43 (Cx43), involved in intercellular signaling, is expressed in astrocytes. Some studies show that downregulation of Cx43 induces depressive-like behaviors in rats. Brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) produced from cortical astrocytes could be crucial players in pathology of depression. In this study, we investigated whether astrocytic Cx43 might be involved in regulation of neurotrophic factors expression.

methods:

Primary cultured astrocytes were prepared from the cortex of neonatal Wistar rats. Cx43 knockdown in cultured astrocytes was performed using RNA interference.

results:

We first examined the effect of Cx43 knockdown on noradrenaline (NA)-induced BDNF mRNA and GDNF mRNA expression. As a result, significant enhancement of NA-induced BDNF and GDNF mRNA expression was observed in astrocytes transfected with Cx43 siRNA compared to those with non-targeting siRNA. These responses were inhibited by treatment with U0126, which is an inhibitor of extracellular signal-regulated kinase (ERK). Furthermore, NA-induced ERK phosphorylation was potentiated in Cx43 siRNA-transfected astrocytes. In addition, NA-induced phosphorylation of cAMP response element binding protein (CREB), which is a transcriptional regulatory factor mediating expression of both BDNF and GDNF, was also enhanced in Cx43 siRNA-transfected astrocytes.

conclusions:

In the current study, downregulation of Cx43 could potentiate NA-induced BDNF mRNA and GDNF mRNA expression. Enhancement of ERK-CREB activity is involved in Cx43 knockdown-induced neurotrophic factor expression. These results suggest that astrocytic Cx43, which is downregulated in depression, is involved in regulation of neurotrophic factors expression, and downregulation of astrocytic Cx43 might affect functioning and reactivity of astrocytes in depression.