DOI 10.18699/BGRSSB-2018-184

Exploring neuroprotective potential of astrocytes

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Key words: oxidative stress, astrocytes, neuroprotective pathways, ligand-receptor interaction

Our laboratories are interested in signaling systems and novel receptors expressed by astrocytes which could be used as potential novel drug targets. Discovery of neuroprotective pathways is one of the major priorities for neuroscience. Astrocytes are the natural neuroprotectors and it is likely that brain resilience can be enhanced by mobilizing their protective potential. Among G-protein coupled receptors expressed by astrocytes, two highly related receptors, GPR37L1 and GPR37, are of particular interest. Previous studies suggested that these receptors are activated by a peptide Saposin C and its neuroactive fragments (such as prosaptide TX14), which were demonstrated to be neuroprotective in various animal models by several groups. However, pairing of Saposin C or prosaptides with GPR37L1/GPR37 has been challenged and presently GPR37L1/GPR37 have regained their orphan status. Here we demonstrate that in their natural habitat, astrocytes, these receptors mediate a range of effects of TX14, including protection from oxidative stress. The Saposin C/GPR37L1/GPR37 pathway is also involved in the neuroprotective effect of astrocytes on neurons subjected to oxidative stress. The action of TX14 is at least partially mediated by Gi-proteins and the cAMP-PKA axis. On the other hand, when recombinant GPR37L1 or GPR37 are expressed in HEK293 cells, they are not functional and do not respond to TX14, which explains unsuccessful attempts to confirm the ligand-receptor pairing. Therefore this study identifies GPR37L1/GPR37 as the receptors for TX14, and, by extension of Saposin C, and paves the way for the development of neuroprotective therapeutics acting via these receptors.