Prosaposin exerts neuroprotective effects through the receptors GPR37L1 and GPR37

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Video Abstract

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Abstract

For nearly 25 years, scientists have known of the neuroprotective properties associated with the protein called prosaposin. But exactly how prosaposin exerts these effects has been a matter of debate. Initial research using a neuroactive fragment of the protein, called TX14(A), identified two closely related receptors thought to mediate the actions of prosaposin. But this work was later challenged. Now, an international team of scientists has reported strong evidence that prosaposin does activate these receptors, which may help pave the way for a new class of neuroprotective drugs. Uncertainty over the status of prosaposin as an endogenous ligand for GPR37L1 and GPR37 has stemmed from the use of widely varying experimental conditions. The main inconsistency with past work was the use of cell lines derived from ovary, kidney or yeast to study the receptors. But this creates a physiological mismatch, as the receptors are almost exclusively expressed in the brain. Because of this disparity, prior studies have generated conflicting results. To gain clarity on the matter, the researchers looked at the receptors in their native environment: astrocytes, the star-shaped cells that keep the nervous system in good working order. The team prepared primary cultures of astrocytes from rats. After confirming that the receptors were expressed in the cells, the team set out to determine whether they are indeed activated by TX14(A). The researchers applied the peptide to the cells and found that it decreased levels of cAMP, a downstream signaling molecule. Knocking down receptor expression obliterated this effect. The researchers next looked at how the receptors function in astrocytes and found that they play a critical role in astrocyte motility. Using wound-healing assays, the team showed that the presence of prosaposin and TX14(A) mobilized astrocytes to facilitate wound closure. TX14(A) was also highly effective in protecting astrocytes from oxidative stress, and prosaposin-exposed astrocytes even protected neighboring neurons from oxidative stress. These results are consistent with the idea that prosaposin engages astrocytic signaling to generate neuroprotection. These effects disappeared when receptor expression was eliminated in astrocytes. Overall, these findings demonstrate that prosaposin is the natural ligand for GPR37L1 and GPR37. With this discovery, it's expected that small molecules based on the structure of TX14(A) would be astro- and neuroprotective, providing new possibilities for the treatment of neurologic injury and disease.