Abstract citation ID: bvac150.1518

Steroid Hormones and Receptors

RF15 | PMON305

Membrane Progesterone Receptor α (mPRα/PAQR7) Promotes Survival and Axonal Sprouting in Human Neuronal Cells Lines Through Direct and Human Schwann-Cell Like Differentiated Adipose Stem Cells-Mediated Mechanisms

Luca F. Castelnovo, PhD and Peter Thomas, PhD

Injuries to peripheral nerves affect millions of people worldwide. These injuries can be significantly detrimental to the patients' quality of life. While central nervous system neurons have extremely limited regenerative potential, peripheral nerves are able to regenerate after injury. However, this regeneration process often leads to unsatisfactory regenerative outcomes. Improving peripheral nerve regeneration is therefore a strong medical need. Schwann cells, the glial myelinating cells of the peripheral nervous system, are known to play an important role in promoting peripheral nerve regeneration. However, their limited in vitro expansion capability and limited availability has led several research groups to investigate the possibility of using differentiated stem cells as a potential tool to promote nerve regeneration, in association with other tools such biomaterial tubes. The activation of membrane progesterone receptor α (mPRα, PAQR7) with the selective agonist 19-ethenylprogesterone (02-0) was recently shown to elicit potentially pro-regenerative effects in a model of human Schwann cell-like (SCL) differentiated adipose stem cells (ASC). Indeed, mPRα activation led to increased SCL-ASC migration, proliferation and neurotrophin (specifically BDNF) release. All these outcomes are expected to be beneficial for nerve regeneration. In this project, we investigated the effect of mPRα activation in SCL-ASC on neuronal cell lines to demonstrate that the positive effects previously observed in SCL-ASC have a beneficial effect in neuronal cells. We first investigated how the conditioned medium of untreated SCL-ASC (CM-) and SCL-ASC treated with the selective mPR agonist 02-0 (CM+) affected cell survival and neuronal sprouting in two different neuronal cell lines, IMR-32 and SH-SY-5Y. In both cases, CM- had a beneficial effect, reducing cell death, as assessed in starvation experiments, and promoting axonal sprouting, with the presence of longer cell

processes in the two cell models compared to control. In both cases, CM+ had an even stronger effect than CM-, suggesting that mPRα activation may lead to the release of specific molecules that promote nerve regeneration. Moreover, CM- and CM+ treatments were effective in increasing the gene expression of selected peripheral regeneration markers (CREB3, ATF3 and GAP46) in SH-SY-5Y cells. Since mPR receptors are present in neuronal cells, we performed another series of cell death and axonal sprouting experiments in SH-SY-5Y6 cells, comparing CM- and CM+ effects to an experimental group in which 02-0 was added to CM- after incubation with SCL-ASC. These experiments showed that the effect on cell death was mostly due to direct activation of mPR receptors in neuronal cells. On the other hand, the effect on axonal sprouting depended on mPRα activation in SCL-ASC and subsequent release of active molecules in the medium. Our results support the hypothesis that mPRα activation in SCL-ASC may represent a promising pharmacological target to promote peripheral nerve regeneration.

Presentation: Sunday, June 12, 2022 12:42 p.m. - 12:47 p.m., Monday, June 13, 2022 12:30 p.m. - 2:30 p.m.