

The Effectors of the Transient Receptor Vanilloid Potential Type 4 in the Choroid Plexus
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Hydrocephalus is a deadly disease that affects 1-2 births in 1000. When severe, this disease can result in irreversible brain damage. There are no drugs to treat hydrocephalus and the standard therapy is to surgically implant shunts to drain the excess cerebrospinal fluid (CSF) into other parts of the body. However this approach often results in a less than optimal outcomes. Shunt failures due to blockage, infection, and other causes are as high as 50% even in major medical centers which specialize in these procedures. Our laboratory is using a Meckel-Gruber syndrome rat model to study the development of severe hydrocephalus. Immunohistochemistry has been used to show the overexpression of Transient Receptor Vanilloid Potential Type 4, TRPV4 on the choroid plexus epithelial membrane. Because the choroid plexus is responsible for the majority of the cerebrospinal fluid that contributes to the progression of hydrocephalus, the TRPV4 calcium channel is a potential target that could contribute to the disease development. The endogenous activators of this channel in the choroid plexus are yet to be determined. Consequently, the current study is using a cultured choroid plexus cell line to identify endogenous activators of this channel. Potential activators include homovanillic acid (HVA), lysophosphatidic acid, and arachidonic acid. In addition, the introduction of novel compounds that act as sensitizers of the channel led to a set of experiments that were conducted to confirm the existence and identification of the sensitizers such as inflammatory cytokines. The effect of these compounds on the activation of the TRPV4 channel are being investigated using electrophysiological techniques in a porcine choroid plexus cell line with the characteristics of the in vivo choroid plexus. This cell line exhibits a robust increase in ion transport in response to a TRPV4 agonist. . The determination of the endogenous TRPV4 activators and sensitizers will provide important information in the development of a drug that can be used to treat hydrocephalus with minimal side effects by altering the activity of TRPV4.