TRPV4

Transient receptor potential cation channel subfamily V member 4 is an ion channel protein that in humans is encoded by the TRPV4 gene.

The TRPV4 gene encodes TRPV4, initially named “vanilloid-receptor related osmotically activated channel” (VR-OAC) and “OSM9-like transient receptor potential channel, member 4 (OTRPC4)”, a member of the vanilloid subfamily in the transient receptor potential (TRP) superfamily of ion channels. The encoded protein is a Ca2+-permeable, nonselective cation channel that has been found involved in multiple physiologic functions, dysfunctions and also disease. It functions in the regulation of systemic osmotic pressure by the brain, in vascular function, in liver, intestinal, renal and bladder function, in skin barrier function and response of the skin to ultraviolet-B radiation, in growth and structural integrity of the skeleton, in function of joints, in airway- and lung function, in retinal and inner ear function, and in pain. The channel is activated by osmotic, mechanical and chemical cues. It also responds to thermal changes (warmth). Channel activation can be sensitized by inflammation and injury.

A range of neurological pathologies may lead to secondary hydrocephalus. Treatment has largely been limited to surgical cerebrospinal fluid diversion, as specific and efficient pharmacological options are lacking, partly due to the elusive molecular nature of the cerebrospinal fluid secretion apparatus and its regulatory properties in physiology and pathophysiology.

Cerebrospinal fluid obtained from patients with subarachnoid hemorrhage (SAH) and rats with experimentally inflicted intraventricular hemorrhage (IVH) was analyzed for lysophosphatidic acid (LPA) by alpha-LISA. Toft-Bertelsen et al. employed the in vivo rat model to determine the effect of LPA on ventricular size and brain water content, and to reveal the effect of activation and inhibition of the transient receptor potential vanilloid 4 (TRPV4) ion channel on intracranial pressure and CSF secretion rate. LPA-mediated modulation of TRPV4 was determined with electrophysiology and an ex vivo radio-isotope assay was employed to determine the effect of these modulators on choroid plexus transport.

Elevated levels of LPA were observed in CSF obtained from patients with subarachnoid hemorrhage (SAH) and from rats with experimentally-inflicted intraventricular hemorrhage (IVH). Intraventricular administration of LPA caused elevated brain water content and ventriculomegaly in experimental rats, via its action as an agonist of the choroidal transient receptor potential vanilloid 4 (TRPV4) channel. TRPV4 was revealed as a novel regulator of ICP in experimental rats via its ability to modulate the CSF secretion rate through its direct activation of the Na+/K+/2Cl- cotransporter (NKCC1) implicated in CSF secretion.

Together, these data reveal that a serum lipid present in brain pathologies with hemorrhagic events promotes CSF hypersecretion and ensuing brain water accumulation via its direct action on TRPV4 and its downstream regulation of NKCC1. TRPV4 may therefore be a promising future pharmacological target for pathologies involving brain water accumulation [1)].

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found that activation of TRPV4 resulted in a robust, multiphasic change in electrogenic ion flux and increase in conductance accompanied by substantial fluid secretion. This response appears to be

modulated by a number of different effectors, implicating phospholipase C (PLC), protein kinase C (PKC) and phosphoinositide 3-kinase (PI3K) in TRPV4-mediated ion flux. The HIBCPP cell line is a representative model of the human BCSFB, which can be utilized for studies of transporter function, intracellular signaling and regulation of CSF production [2)]

Distinct dominant mutations in the calcium-permeable ion channel TRPV4 (transient receptor potential vanilloid 4) typically cause nonoverlapping diseases of either the neuromuscular or skeletal systems. However, accumulating evidence suggests that some patients develop mixed phenotypes that include elements of both neuromuscular and skeletal disease.

A 2-year-old with a novel R616G mutation in TRPV4 with a severe neuropathy phenotype and bilateral vocal cord paralysis. Interestingly, a different substitution at the same residue, R616Q, has been reported in families with isolated skeletal dysplasia. To gain insight into clinical features and potential genetic determinants of mixed phenotypes, we perform an in-depth analysis of previously reported patients along with a functional and structural assessment of selected mutations.

They described a wide range of neuromuscular and skeletal manifestations and highlight specific mutations that are more frequently associated with overlap syndromes. We find that mutations causing severe, mixed phenotypes have an earlier age of onset and result in more marked elevations of intracellular calcium, increased cytotoxicity, and reduced sensitivity to TRPV4 antagonism. Structural analysis of the two mutations with the most dramatic gain of ion channel function suggests that these mutants likely cause constitutive channel opening through disruption of the TRPV4 S5 transmembrane domain.

These findings demonstrate that the degree of baseline calcium elevation correlates with the development of mixed phenotypes and sensitivity to pharmacologic channel inhibition, observations that will be critical for the design of future clinical trials for TRPV4 channelopathies [3)]

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