Lysophosphatidic acid

Autotaxin (ATX) is the ectoenzyme producing the bulk of lysophosphatidic acid (LPA) in circulation

---

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)].

1)
Toft-Bertelsen TL, Barbuskaite D, Heerfordt EK, Lolansen SD, Andreassen SN, Rostgaard N, Olsen MH, Norager NH, Capion T, Rath MF, Juhler M, MacAulay N. Lysophosphatidic acid as a CSF lipid in posthemorrhagic hydrocephalus that drives CSF accumulation via TRPV4-induced hyperactivation of NKCC1. Fluids Barriers CNS. 2022 Sep 6;19(1):69. doi: 10.1186/s12987-022-00361-9. PMID: 36068581.