NKCC1

- Growth Factors and the Choroid Plexus: Their Role in Posthemorrhagic Hydrocephalus
- Development of a BRET based chloride biosensor for high throughput screening of KCC2 modulators
- Prenatal modulation of NADPH-oxidase reverses the deranged GABA switch and rescues behavioral deficits in valproate ASD rat model
- Mechanism of Ammonia-Induced Brain Damage in Chinese Striped-Necked Turtle (Mauremys sinensis)
- An Evaluation of Cation-Chloride Cotransporters NKCC1 and KCC2 in Carbamazepine-Resistant Rats
- Intergenerational postoperative neurocognitive disorder in a rat model: Initiating mechanisms and pharmacological prevention
- Furosemide sodium enhanced AQP3 expression by inhibiting NKCC1 leading to improved vitrification freezing rates of mouse and bovine blastocysts
- nNOS/NO in nucleus accumbens medicates NKCC1 in neonatal repetitive pain

The Na-K-Cl cotransporter (NKCC) is a protein that aids in the secondary active transport of sodium, potassium, and chloride into cells. In humans there are two isoforms of this membrane transport protein, NKCC1 and NKCC2, encoded by two different genes (SLC12A2 and SLC12A1 respectively). Two isoforms of the NKCC1/Slc12a2 gene result from keeping (isoform 1) or skipping (isoform 2) exon 21 in the final gene product.

In some cases of epilepsy, it has been observed that the expression or function of the NKCC1 cotransporter in astrocytes and neurons may be altered. The NKCC1 cotransporter is responsible for importing chloride ions into cells, and increased activity of NKCC1 can result in elevated intracellular chloride levels. This, in turn, can lead to a shift in the GABAergic response from inhibitory to excitatory, a phenomenon known as “GABAergic depolarization.”

GABAergic depolarization can contribute to hyperexcitability in the brain, potentially facilitating the generation and propagation of epileptic seizures. Astrocytes may modulate the expression and function of NKCC1, influencing chloride homeostasis and, consequently, the balance between excitatory and inhibitory neurotransmission [1)]

With-no-lysine kinase (WNK) and Na+-K+-2Cl- cotransporter 1 (NKCC1) are involved in the pathogenesis of hypertension. In this study, we investigated the WNK-NKCC1 signaling pathway in spontaneously hypertensive rats (SHR) and their associated susceptibility to stroke injury. Basal NKCC1 protein levels were higher in SHR than in normotensive Wistar Kyoto (WKY) rat brains. After inducing ischemic stroke, adult male WKY and SHR received either saline or NKCC1 inhibitor bumetanide (10 mg/kg/day, i.p.) starting at 3-h post-reperfusion. NKCC1 inhibition blunted the extent of ischemic infarction in SHR and improved their neurobehavioral functions. Interestingly, ischemia led to increased NKCC1 phosphorylation in SHR but not in WKY rats. Pronounced elevation of WNK1, WNK2 and WNK4 protein and downregulation of WNK3 were detected in ischemic SHR, but not in ischemic WKY rats. Upregulation of WNK-NKCC1 complex in ischemic SHR brain was associated with increased Ca2+-binding protein 39 (Cab39), without increases in Ste20-related proline alanine-rich kinase or oxidative stress-responsive kinase-1. Moreover, subacute middle cerebral artery stroke

human brain autopsy exhibited increased expression of NKCC1 protein. We conclude that augmented WNK-Cab39-NKCC1 signaling in SHR is associated with an increased susceptibility to ischemic brain damage and may serve as a novel target for anti-hypertensive and anti-ischemic stroke therapy.

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 [2].

[1]
Untiet V, Nedergaard M, Verkhratsky A. Astrocyte chloride, excitatory-inhibitory balance and epilepsy. Neural Regen Res. 2024 Sep 1;19(9):1887. doi: 10.4103/1673-5374.390981. Epub 2023 Dec 15. PMID: 38227511.
[2]
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.