SGK1

Accumulating evidence indicates that phosphorylated serum- and glucocorticoid-regulated kinase 1 (SGK1) is associated with spinal nociceptive sensitization by modulating glutamatergic N-methyl-D-aspartate receptors (NMDA Receptors).

Xiao et al., determined whether spinal SGK1 signaling contributes to the development of morphine analgesic tolerance. Chronic morphine administration markedly induced phosphorylation of SGK1 in the spinal dorsal horn neurons. Intrathecal injection of SGK1 inhibitor GSK-650394 reduced the development of morphine tolerance with a significant leftward shift in morphine dose-effect curve. Furthermore, spinal inhibition of SGK1 suppressed morphine-induced phosphorylation of nuclear factor kappa B (NF-κB) p65 and upregulation of NMDAR NR1 and NR2B expression in the spinal dorsal horn. In contrast, intrathecal administration of NMDAR antagonist MK-801 had no effect on the phosphorylation of SGK1 in morphine-treated rats. In addition, morphine-induced upregulation of NR2B, but not NR1, was significantly abolished by intrathecal pretreatment with PDTC, a specific NF-κB activation inhibitor. Finally, spinal delivery of SGK1 small interfering RNA exhibited similar inhibitory effects on morphine-induced tolerance, phosphorylation of NF-κB p65, as well as upregulation of NR1 and NR2B expression. Our findings demonstrate that spinal SGK1 contributes to the development of morphine tolerance by enhancing NF-κB p65/NMDAR signaling. Interfering spinal SGK1 signaling pathway could be a potential strategy for prevention of morphine tolerance in chronic pain management [1].

The WNK1 gene encodes a cytoplasmic serine-threonine kinase expressed in the distal nephron.

The protein appears to be part of the ERK5 MAP kinase pathway upstream of MEKK2 / MEKK3 and to function as a tetramer. It selectively binds to and phosphorylates synaptotagmin 2 (SYT2) within its calcium-binding C2 domains. It activates the serum- and glucocorticoid-inducible protein kinase SGK1, leading to activation of the epithelial sodium channel. It along with WNK4 stimulates clathrin-dependent endocytosis of renal outer medullar potassium 1 (ROMK1). It (and WNK4) interactes with intersectin (ITSN1, ITSN2).

In a study, the novel regulatory role of NgR in a serine-threonine kinase WNK1 was identified. NgR's transcriptional regulation of WNK1 was identified by RT-qPCR and semiquantitative western blot after the overexpression or knockdown of NgR, and the regulation is specific to WNK1, which is not the same for its family members, WNK2, WNK3 and WNK4. Furthermore, NgR inhibition by NEP fails to affect WNK1, which indicates that WNK1 functions outside of the Nogo-A/NgR pathway. By performing a proliferation, migration and axonal extension assay, we also identified that overexpressed NgR critically regulated these processes and impairment by overexpressing NgR was rescued with coexpression of WNK1, indicating the partial role of WNK1 in NgR-mediated morphological regulation. The study identifies a separation of functions for the NgR-regulated WNK1 in mediating proliferation, migration and axonal extension in PC12 cells as well as a specific regulatory role between NgR and WNK1 that is important for recovery from central nervous system injury [2].

1)
Xiao L, Han X, Wang XE, Li Q, Shen P, Liu Z, Cui Y, Chen Y. Spinal serum- and glucocorticoid-regulated kinase 1 (SGK1) signaling contributes to morphine-induced analgesic tolerance in rats. Neuroscience. 2019 Jun 17. pii: S0306-4522(19)30413-0. doi: 10.1016/j.neuroscience.2019.06.007. [Epub ahead of print] PubMed PMID: 31220544.

2)
Yang T, Zhao K, Shu H, Chen X, Cheng J, Li S, Zhao Z, Kuang Y, Yu S. The Nogo receptor inhibits proliferation, migration and axonal extension by transcriptionally regulating WNK1 in PC12 cells. Neuroreport. 2017 May 6. doi: 10.1097/WNR.0000000000000800. [Epub ahead of print] PubMed PMID: 28489665.