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Sodium leak channel, non-selective (NALCN) in GtoPdb v.2025.3

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Abstract

The sodium leak channel, non selective (NALCN) is a member of the family of four-domain voltage-gated cation channels that include voltage-gated sodium (Na_V) and calcium (Ca_V) channels [13, 23]. It possesses distinctive ion selectivity and pharmacological properties compared to these latter ion channels [6, 21]. NALCN, which is insensitive to tetrodotoxin (10 µM), has been proposed to mediate the tetrodotoxin-resistant and voltage-insensitive Na^+ leak current (I_L-Na) observed in many types of neurone [14]. However, whether NALCN is constitutively active has been challenged [20, 2, 7]. NALCN is widely distributed within the central nervous system and is also expressed in the heart and pancreas specifically, in rodents, within the islets of Langerhans [13, 14]. There is now strong functional and structural evidence indicating that NALCN forms a channelosome with obligatory auxiliary subunits UNC79, UNC80 and FAM155A (also known as NALF1) [6, 3, 12, 24, 10]. NALCN is the pore-forming α subunit, UNC79 and UNC80 are massive HEAT-repeat proteins that form an intertwined anti-parallel superhelical assembly that docks intracellularly onto NALCN. FAM155A forms an extracellular dome that shields extracellular access pathways to the selective filter of NALCN. There is also increasing evidence suggesting that the NALCN-UNC79-UNC80-FAM155A channelosome is modulated by additional auxiliary subunits including G proteins [18] and neuronal SNARE complex proteins [21]. However, there remain many areas of uncertainty surrounding NALCN function.
It is worth noting that there is currently no NALCN-specific pharmacology. Inhibitors include multivalent cations ($Gd3^+$, Ca^{2+}, Mg^{2+}, Ba^{2+}, Zn^{2+}) and small molecules (verapamil, 2-APB, DPBA, fluvastatin, L-703,606) [6, 11, 8, 19].

Contents

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Channels and Subunits
NALCN

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