Sodium leak channel, non-selective

Overview: The sodium leak channel, non-selective (NC-IUPHAR tentatively recommends the nomenclature $Na_{Vi}2.1$, W.A. Catterall, personal communication) is structurally a member of the family of voltage-gated sodium channel family ($Na_v1.1$–$Na_v1.9$) (Lee *et al.*, 1999; Yu and Catterall, 2004). In contrast to the latter, $Na_{Vi}2.1$, is voltage-insensitive (denoted in the subscript 'vi' in the tentative nomenclature) and possesses distinctive ion selectivity and pharmacological properties. $Na_{Vi}2.1$, which is insensitive to TTX (10 μM), has been proposed to mediate the TTX-resistant and voltage-insensitive Na^+ leak current (I_L-Na) observed in many types of neurone (Lu *et al.*, 2007). However, whether $Na_{Vi}2.1$ is constitutively active has been challenged (Swayne *et al.*, 2009). $Na_{Vi}2.1$ is widely distributed within the central nervous system and is also expressed in the heart and pancreas (Lee *et al.*, 1999; Lu *et al.*, 2007).

Nomenclature	$Na_{vi}2.1$
Other names	NALCN, Nav2.1, Na_x, voltage-gated channel like 1
Ensembl ID	ENSG00000102452
Activators	Constitutively active (Lu *et al.*, 2007), or activated downstream of Src family tyrosine kinases (SFKs) (Lu *et al.*, 2009; Swayne *et al.*, 2009)
Blockers (IC_{50})	Gd^{3+} (1.4 μM), Cd^{2+} (0.15 mM), Co^{2+} (0.26 mM), verapamil (0.38 mM)
Functional characteristics	γ = 27 pS (by fluctuation analysis), P_{Na}/P_{Cs} = 1.3, P_K/P_{Cs} = 1.2, P_{Ca}/P_{Cs} = 0.5, linear current voltage-relationship, voltage-independent and non-inactivating

In native and recombinant expression systems $Na_{Vi}2.1$ can be activated by stimulation of NK_1 (in hippocampal neurones), neurotensin (in ventral tegmental area neurones) and M3 muscarinic acetylcholine receptors (in MIN6 pancreatic β-cells) in a manner that is independent of signalling through G proteins (Lu *et al.*, 2009; Swayne *et al.*, 2009). Pharmacological and molecular biological evidence indicates such modulation to occur though a pathway that involves the activation of Src family tyrosine kinases. It is suggested that $Na_{Vi}2.1$ exists as a macromolecular complex with M3 receptors (Swayne *et al.*, 2009) and peptide receptors (Lu *et al.*, 2009), in the latter instance in association with the protein UNC-80, which recruits Src to the channel complex (Lu *et al.*, 2009; Wang and Ren, 2009). $Na_{Vi}2.1$ null mutant mice have severe disturbances in respiratory rhythm and die within 24 h of birth (Lu *et al.*, 2007).

Further Reading

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