BIOBUSINESS BRIEFS

TARGET WATCH

K_{Na}1.1 channels as a target for treating early-onset epilepsy

Potassium channels are the largest group of ion channels, and various diseases caused by mutations in genes encoding these channels have been identified. One such sodium-activated potassium channel includes K_{Na}1.1 subunits, encoded by *KCNT1*. Gain-of-function mutations are associated with drug-resistant, early-onset epileptic encephalopathies, and so K_{Na}1.1 channels could be a promising therapeutic target.

Functions and disease associations

Sodium-activated potassium channels (K_{Na}) are opened by high concentrations of Na^+ in the cytoplasm. The resulting K^+ outflux counteracts the membrane potential change caused by the Na^+ influx and regulates neuronal firing patterns.

The pores of the K_{Na} channels are either homomers or heteromers, containing four subunits encoded by *KCNT1* or *KCNT2*. The KCNT1 and KCNT2 proteins are ~74% identical, and both proteins consist of six transmembrane domains (S1–S6) and an extended cytosolic region at the C terminus (*ISRN Neurosci.* **2013**, 354262; 2013). The C-terminal region includes two regulators of conductance of K^+ (RCK) domains, which serve as Na^+ sensors and control the opening of the K^+ channel, and a binding site for nicotinamide adenine dinucleotide (NAD^+), which modulates the sensitivity of the channel to the Na^+ concentration (FIG. 1a). The fifth and sixth transmembrane domains form the channel pore.

Genetic studies in humans revealed that mutations in the pore-forming region and the C-terminal regions of *KCNT1* often lead to increased channel activity. These gain-of-function mutations in *KCNT1* cause two types of early-onset epilepsy, with more than 100 cases reported in the literature: epilepsy of infancy with migrating focal seizures (EIMFS) and autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) (*Nat. Genet.* **44**, 1255–1259; 2012; *J. Med. Genet.* **53**, 217–225; 2016). Both conditions not only cause severe seizures but are also accompanied by long-term developmental and psychiatric complications.

To study the function of *KCNT1* and its role in disease, *Kcnt1* has been ablated both globally and selectively in sensory neurons in mice (*J. Neurosci.* **35**, 1125–1135; 2015). Both mouse models show increased sensitivity to neuropathic pain, suggesting that K_{Na}1.1 channels selectively control the sensory input in neuropathic pain states. However, the role of K_{Na}1.1 channels in the central nervous system remains unclear. Mechanistic understanding of how gain-of-function mutations in *KCNT1* cause epilepsy is also lacking.

Potential therapeutic opportunities

Treatment options for *KCNT1*-related epilepsy are extremely limited. Patients do not respond to conventional anticonvulsants, such as levetiracetam, benzodiazepines and stiripentol. As the disease-causing mutations in *KCNT1* lead to gain-of-function, inhibiting K_{Na}1.1 activity could be a therapeutic strategy. Studies have demonstrated that quinidine, a partial K_{Na}1.1 inhibitor, can alleviate epilepsy in infants (*Ann. Neurol.* **76**, 457–461; 2014). However, the use of quinidine is limited because it acts on multiple K^+ channels, including those in the heart, and so more specific inhibitors are needed.

Several small-molecule compounds that potently inhibit K_{Na}1.1 channels with limited cytotoxicity have recently been reported (FIG. 1b), which could provide starting points for the development of drugs to treat *KCNT1*-related epilepsy (*iScience* **23**, 101100; 2020). Our groups are also studying K_{Na}1.1 channels and developing peptide and nanobody-based probes that could modulate K_{Na}1.1 channel activity.

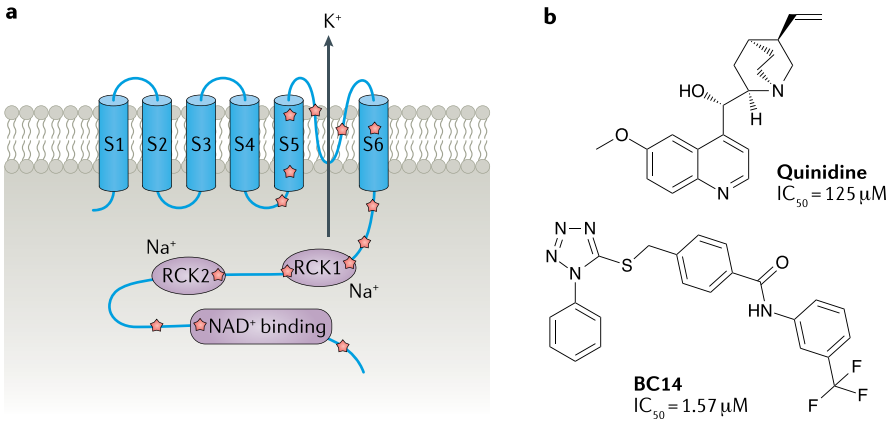

Fig. 1 | **Structure of K_{Na}1.1 and selected inhibitors. a** | *KCNT1* encodes the sodium-activated potassium channel subunit K_{Na}1.1. Channels composed of four such subunits open in response to increased intracellular Na^+ concentration. The K_{Na}1.1 subunit contains six transmembrane domains (S1–S6) and an extended cytosolic region at the C terminus, including two regulators of conductance of K^+ (RCK) domains and an NAD^+-binding site. Mutations in the S5, S6 and C-terminal regions of the protein often lead to increased channel activity. The red stars indicate the general location of the gain-of-function mutations. **b** | Structures of two existing K_{Na}1.1 inhibitors. Quinidine has been used to treat *KCNT1*-related epilepsies. BC14 is a newly developed K_{Na}1.1 inhibitor with higher potency.

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Competing interests

The authors declare no competing interests.

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