Novel TREK-1 activators suppress neuronal excitability and pain behavior in rodent model.

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The TWIK-related potassium channel-1 (TREK-1) is a member of two-pore domain potassium (K2P) channel family that plays an essential part in the regulation of resting membrane potential and cellular excitability. TREK-1 is involved in many physiological processes, such as chronic pain, epilepsy and overactive bladder. TREK-1 is activated downstream of mu receptor and involved in the antinociceptive activity of morphine without its adverse side effects. We discovered novel and potent TREK-1 activators, NCC-0768 and NCC-0850, which activated human TREK-1 channel and their EC₅₀ were 1.2 μ M and 0.51 μ M, respectively. EC₅₀ of BL-1249, a well-known TREK-1 activator, was 9.1 μ M in our assay. TREK-1 is expressed in dorsal root ganglion (DRG) neurons that are associated pain perception. We investigated membrane potential changes in rat DRG neurons. NCC compounds showed hyperpolarization shift and decreased cell excitability. Oral administration of NCC-0768 and NCC-0850 dose-dependently suppressed mouse phenyl benzoquinone-induced writhing behavior. Furthermore, NCC-0768 had anti-allodynic effect in rat neuropathic pain induced by chronic constriction injury. The efficacy of NCC-0768 was equivalent to the pregabalin at 10 mg/kg. Our novel TREK-1 activator, NCC-0768, has a potent analgesic effect on neuropathic pain model, and our results suggest that TREK-1 activator may be an attractive anti-pain agent. In addition, TREK-1 activator can be expected to be applied to the other neuroexcitatory diseases.