Discovery of Kv2.1 potassium channel selective blocker for neuroprotection

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Kv2.1 potassium channel is widely expressed in hippocampal and cortical neurons. It is the major delayed rectifier potassium channel subtype in the central nervous system. It has been known that Kv2.1 participates in regulating the neuronal excitability and is closely related to neuroprotection. Especially, excessive potassium efflux caused by Kv2.1 channel opening is one of the important mechanisms of neuronal apoptosis during ischemia and hypoxia. We designed and synthesized more than 200 small molecular compounds targeting at Kv2.1. We combined electrophysiological screening and structural modification and optimization and obtained a selective Kv2.1 potassium channel blocker Zj6901. It inhibits Kv2.1 currents with an IC_{50} of 0.33 μM. While Zj6901 inhibits other subtype ion channels such as Kv1.5, Kv3.1, TREK-1, hERG, and neuronal sodium channels and calcium channels with IC_{50} higher than 30 μM, indicating selective inhibition for Kv2.1. *In vitro* experiments showed that Kv2.1 current amplitude increased significantly after oxygen glucose deprivation (OGD) for 4 h, and Zj6901 significantly improved the cell viability of HEK293/Kv2.1 cells and cortical neurons after OGD treatment, suggesting that Zj6901 can protect against oxidative damage. *In vivo* results showed that Zj6901 1-10 mg/kg significantly prolonged the respiratory time of ICR mice after decapitation and significantly prolonged the survival time of ICR in suffocation experiment. Intravenous injection of Zj6901 significantly reduced the infarct volume of rat brain after MCAO model. Both *in vitro* and *in vivo* results indicate that Zj6901 has significant anti-ischemic and anti-hypoxic effects. Therfore, Kv2.1 is expected to become a therapeutic target for the treatment of hypoxic and ischemic brain diseases. Zj6901 might be developed as a new class of anti-cerebral ischemia drug candidate.