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2. **Title**

   Drug Development and Nicotinic Acetylcholine Receptors in Alzheimer's Disease Therapy

3. **Period**

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4. **Summary**

We introduced a potent T-VGCC enhancer, SAK3 and characterized its pharmacological properties in the brain. Based on whole cell patch-clamp analysis, SAK3 (0.01-10 nM) significantly enhanced Cav3.1 and Cav3.3 currents in neuro2A cells ectopically expressing Cav3.1 and Cav3.3. Notably, T-VGCCs were localized in the cholinergic nervous systems in the hippocampus and in the medial septum of mouse brain. Indeed, acute oral administration of SAK3 (0.5 mg/kg, p.o.), but not donepezil (1 mg/kg, p.o.) significantly enhanced acetylcholine (ACh) release in mouse hippocampal CA1 region. Likewise, acute SAK3 administration (0.5 mg/kg, p.o.) significantly enhanced the hippocampal Ach release in App knock-in (NL-GF) mice, thereby rescuing impaired memory-related behaviors. The SAK3-induced ACh releases were significantly blocked in the hippocampus from Cav3.1 knockout (KO) mice. We next investigated the effects of SAK3 on the proteasome activity in NL-GF mouse brain. The chronic oral administration of SAK3 (0.5 mg/kg/day) in 9 month-aged female mice recovered the reduced proteasome activity in NL-GF mice. The enhanced proteasome activities were well corelated with elevation of CaMKII activity and Rpt-6 phosphorylation of proteasome subunits. In the next. twelve-month-old female mice were orally administered a vehicle or SAK3 by acute or chronic and measured BPSD-like behaviors. The acute SAK3 administration improved BPSD, including less anxious and depressive-like behaviors, and ameliorated aggressive behaviors. As unexpected, NL-GF mouse revealed less anxious behavior. Furthermore, acute and chronic SAK3 administration improved less anxious and depressive-like behaviors. Taken together, novel Alzheimer’s disease therapeutic candidate SAK3 enhances ACh release and improves proteasome activity. These mechanisms possibly underlie the cognitive improvement and reduced amyloid beta plaques in App knock-in mice.