TAK-071, a novel M_1 positive allosteric modulator with low cooperativity, improves cognitive function in rodents with few cholinergic side effects

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The muscarinic M_1 receptor (M_1R) is a promising target for treating cognitive impairment associated with cholinergic deficits. We found that cooperativity (α-value) was key to lowering the risk of diarrhea by M_1R positive allosteric modulators (M_1 PAMs), and discovered a low α-value M_1 PAM, TAK-071 with α-value of 199 and inflection point (IP) of 2.7 nM. T-662, a reference M_1 PAM with high α-value of 1786 and IP of 0.62 nM, but not TAK-071, augmented isolated ileum motility. TAK-071 and T-662 improved scopolamine-induced cognitive deficits in rats at 0.3 and 0.1 mg/kg, respectively, and induced diarrhea at 10 mg/kg and 0.1 mg/kg, respectively, in rats. TAK-071 might have a wider margin between cognitive improvement and diarrhea induction than T-662. M_1R activation increases neural excitability via membrane depolarization, reduced afterhyperpolarization, and generation of afterdepolarization in prefrontal cortical pyramidal neurons. T-662 induced all three processes, whereas TAK-071 selectively induced afterdepolarization. Combining sub-effective doses of TAK-071, but not T-662, with an acetylcholinesterase inhibitor, significantly ameliorated scopolamine-induced cognitive deficits in rats. TAK-071 may therefore provide new therapeutic opportunities for cognitive dysfunction with minimum cholinergic side effects.