New targets for fast onset antidepressants

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Major depressive disorder (MDD) is a common neuropsychiatric disorder characterized by diverse symptoms. There are big limitations of clinic medicine which highlighted an urgent and clear need for more efficacious and faster-acting therapeutic agents to treat patients with MDD, especially those who are refractory to the traditional antidepressants. In the present study, we assessed a novel compound, YY-21, from timosaponin B-III derived from sarsasapogenin of Anemarrhenae Rhizoma. We found that YY-21 obviously increased presynaptic glutamate release and enhanced long-term synaptic activity within 10 minutes as determined by excitatory postsynaptic current (EPSC) and field excitatory postsynaptic potential (fEPSP) in medial prefrontal cortex (mPFC) slices. YY-21 demonstrated anxiolytic-like effects following acute administration in animals and reversed the depressive-like and anxiety phenotypes induced by chronic unpredictable mild stress (CMS) with a relatively fast therapeutic onset. Our mechanism research reveals that NMDA receptors and K2P(TREK1) channels emerged as new drug targets for faster acting antidepressants. Two-pore domain potassium (K2P) channels generate leak currents that are responsible the maintenance of resting membrane potential. They are potential targets for the treatment of multiple diseases. Here we identify TKDC, an inhibitor of the TREK subfamily, including TREK-1, TREK-2 and TRAAK channels. Using TKDC as a chemical probe, a combined study of computations, mutagenesis, and electrophysiology reveal an allosteric ligand-binding site in the extracellular cap of the channels. The molecular dynamics simulations suggest that ligand-induced allosteric conformational transitions cause a blockage of the ion conductive pathway. The identification of the extracellular ligand-binding site is confirmed by the discovery of new inhibitors targeting this site using virtual screening. These results suggest that the extracellular cap of a K2P channel can act as a new allosteric site and may serve as a direct drug target.