K5

Allosteric modulation of GABAB receptor

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Overstimulation of GABAB receptor system could worsen the symptoms of depression [1]. Compound that binds to GABAB receptor and reduce the overstimulation can be a therapeutic strategy of depression. The functional GABAB receptor is a dimer that consists of subunit 1a and 2b. The natural substrate GABA binds to the extracellular part of subunit 1a (orthosteric site), while known allosteric modulators bind into the transmembrane helical bundle of subunit 2b (allosteric site). Based on a homology model of 2b subunit, several potential allosteric hits are identified and will be tested on CHO-K1 cell line that stably overexpressing GABAB receptor. The effects of allosteric binding compounds can be any combination of positive, neutral or negative modulation of natural substrate GABA's affinity and efficacy. In our case, the goal of ongoing experiment is to find negative allosteric modulators as potential antidepressant drugs.

[1] Ghose S. et al. *British Journal of Pharmacology*. 162(1) (2011) 1.

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