

# Structural Basis for the Allosteric Modulation of GABAA Receptors by Diazepam

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GABAA receptor (GABAAR), a pentameric ligand-gated ion channel, is activated by GABA, a major inhibitory neurotransmitter in the human brain. GABAAR dysfunction is implicated in several CNS disorders, including anxiety, depression, and epilepsy. Drugs such as benzodiazepines, which allosterically modulate GABAAR, have been used extensively to treat the diseases despite many side effects, including tolerance and potential for abuse. Recently, two neurosteroids (allopregnanolone and ganaxolone) have been approved by the US FDA to treat epilepsy and depression, and these drugs show higher efficacy and fewer side effects. Recent advances in structural biology resulted in multiple cryo-EM structures of GABAAR bound to various allosteric modulators providing valuable insight. However, the mechanistic details of how these allosteric modulators affect GABAAR (in open, closed, and desensitized functional states) remain poorly understood. In this study, I used long-timescale classical molecular dynamics simulations to investigate the mechanism of diazepam and compared it with that of ganaxolone. Specifically, the effects of the ligands on the stability and binding interactions of GABA at the orthosteric sites, global conformational changes, and changes in the pore characteristics were investigated. The obtained results indicate that diazepam and ganaxolone have distinct allosteric mechanisms. Specifically, ganaxolone facilitates recovery of the receptor from its desensitized state by promoting GABA dissociation, whereas diazepam only had a moderate effect on the desensitized state. These results provide valuable insights into the fundamental mechanisms of these widely used drugs and will facilitate the design of new drugs with higher efficacy and better safety profiles.