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Title: Understanding subtype-selective allosteric modulation of GABA-A receptors

GABA-A receptors are major mediators of inhibitory neurotransmission in the brain and belong to the superfamily of pentameric ligand-gated ion channels (pLGIC). They are targets of many clinically important drugs, such as benzodiazepines (Bz), barbiturates, neurosteroids, anticonvulsants and general anesthetics. The existence of many subtypes of these receptors results in a very complex pharmacology. Structural information on drug binding sites would be helpful for a better understanding of unselective binding of ligands to multiple subtypes, and to rationally design selective ligands for specific subtypes. This would lead to improved and novel therapeutic principles for many malfunctions of the central nervous system, such as insomnia, anxiety disorders, epilepsy, depression, schizophrenia and many more.

Already before a crystal structure of the GABA-A receptor was available, comparative models based on several bacterial and eukaryotic homologues allowed some structural insights (paper 1 and 2). In the course of paper 1, novel Bz-site ligands were identified in an experiment-guided virtual screening process. In paper 2, a rational design of an open channel blocker was conducted using the 5-fold symmetry of the pore. The crystal structure of the homopentameric β3 GABA-A receptor was solved by Miller and Aricescu in 2014. A systematic analysis of this structure and of different X-ray structures of homologous proteins with interesting ligands bound was performed for paper 3. For novel binding sites, which were seen in the X-ray structures, it was assessed if those binding sites could also exist in GABA-A receptors.

The aim of this study was to examine the newly generated GABA-A receptor models, which were based on several superfamily members, in the light of experimental evidence. That allowed us to derive more complete models of ligand-bound receptors. These homology models may serve as a basis for binding site confirmation, binding mode confirmation and ultimately, structure-guided drug design. Experiments can be designed on the basis of these models to test if they correctly depict GABA-A receptors.