New Perspectives in GABAergic Drug Design – Null Allosteric Ligands

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The γ-aminobutyric acid type-A receptor ($GABA_AR$) is the main inhibitory neurotransmitter receptor in the central nervous system. $GABA_AR$ controls the synaptic and extrasynaptic GABA-mediated inhibitory signals in the brain, and is the target of general anesthetics, sedatives, anxiolytics and anticonvulsants.[1] In the past, using photabeling techniques and diazirine-modified general anesthetics, we have determined binding sites of most transmembrane domain (TMD) binding drugs.[2] Our new focus is to develop Null Allosteric Ligands (NALs) for $GABA_AR$ as reversal agents to general anesthesia. The rapid recovery from general anesthesia is associated with fewer postoperative anesthesia-related complications. Flumazenil is the only known NAL that binds to the receptor's extracellular domain (ECD), displacing benzodiazepines and reducing the weaning time form the benzodiazepine action.[3] There are no known NALs that antagonize general anesthetics that bind to TMD sites. The lecture will present our newly published results where we discovered the conformationally constrained analogs of mephobarbital and phenytoin counteract the action of known general anesthetics such as propofol, barbiturates, etomidate and neurosteroids. The analogs bind to a hitherto unknown binding site in ECD of $GABA_AR$. The occupancy of this site controls the TMD anesthetics site. Our discovery lays the groundwork for design and development of antidotes for sedatives and anesthetics that target $GABA_AR$.

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