Mechanism of Clozapine’s Action on Neuronal Nicotinic Receptors

Dr. Brian Edmonds, Jonathon McMahon, Alfred Wright

Clozapine is the most effective therapy currently available for the treatment of schizophrenia; however, this drug is associated with a number of toxic side effects. Development of improved compounds has been limited because clozapine’s target and mechanism of action are unknown.

As part of a collaborative effort with the Buttner group, we aim to confirm that the nAChR is the clozapine target, and investigate clozapine’s mechanism.

Using the nematode Caenorhabditis elegans, Buttner and coworkers of McLean Hospital recently identified a clozapine target with high homology to nicotinic acetylcholine receptors (nAChRs).

Research Goals

1. Use the patch-clamp method to confirm the presence of (ACR-7) nAChRs in the anterior bulb of the pharynx.

2. Confirm that these channels are not present in the ACR-7 knockout strain EAB 200.

3. Test the hypothesis that clozapine activates ACR-7 receptors in C. e. pharynx without desensitizing them.

4. Determine if these mechanisms are also utilized by other antipsychotic drugs.

In C. e., clozapine causes larval arrest via inhibition of pharyngeal pumping. Clozapine’s effects on both arrest and pumping are dependent on expression of ACR-7, a protein orthologous to human nAChRs.

Using the protocol of Avery et al., we plan to test two hypotheses for the action of clozapine:

1) Clozapine binds to nAChRs at the agonist binding site to yield prolonged activation of the receptors.

2) Clozapine binds to an allosteric site and potentiates the action of agonist.

References:


Gating data from Demmerly, Hirt, and Hessler-Knoll