

Mechanism of Clozapine's Action on Neuronal Nicotinic Receptors

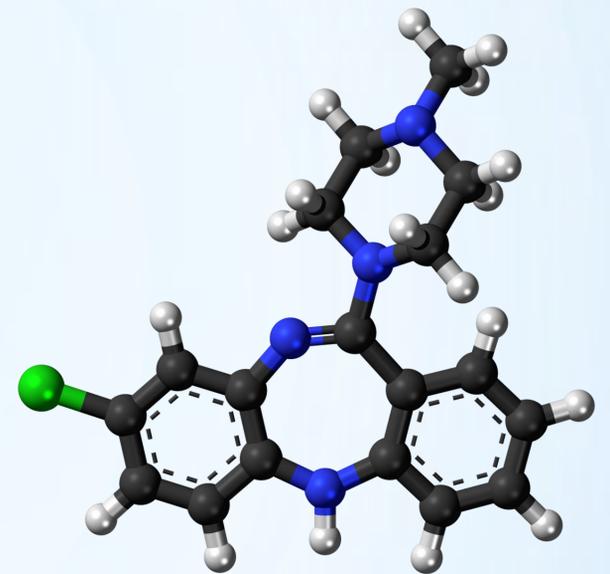
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Clozapine is the most effective therapy currently available for the treatment of schizophrenia; however, this drug is associated with a number of toxic side effects.

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 McClean Hospital recently identified a clozapine target with high homology to **nicotinic acetylcholine receptors (nAChRs)**.



Clozapine - 8-Chloro-11-(4-methylpiperazin-1-yl)-5H-dibenzo[b,e][1,4]diazepine



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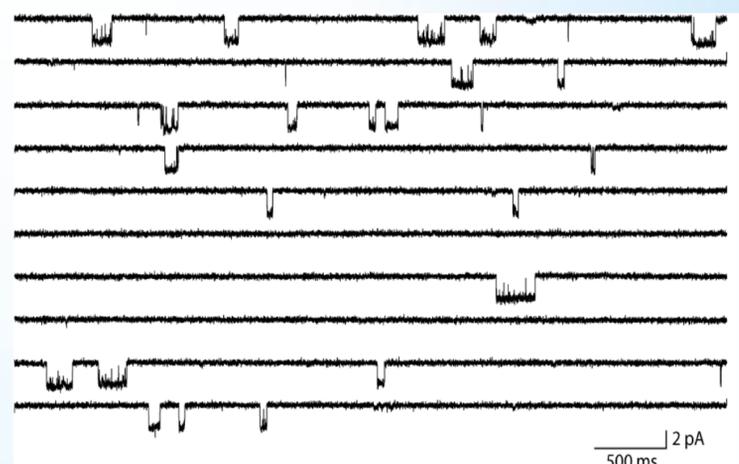
Research Goals

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.



Gating data from Demmerly, Hirt, and Hessler-Knoll