

INVERSE AGONISTS

by Norm Keltner

In my last entry into this forum I suggested that I might briefly discuss inverse antagonism for this effort. I got the idea from an article I had just read in *Current Psychiatry* (September, 2016) concerning the new drug being offered to treat Parkinson's Disease caused psychosis (i.e. pimavanserin).

In order to understand the effect of an inverse agonist, it seems to me that one must realize that neurons affected by these actors must have a basal level of functioning that is enhanced by agonists but not altered by antagonists. Said a different way, an antagonist does not "shut down" a neuron but it does prevent an agonist from enhancing the neuron's functioning. On the other hand, an inverse agonist actually causes the neuron to be underactive and does prevent an agonist from activating the cell. Its effect is opposite that of an agonist.

Inverse agonism is the mechanism of a number of drugs we all know. For example, clozapine and haloperidol are inverse agonists at dopamine receptors. Though touted as D2 antagonists, they actually go beyond the effects of a dopamine antagonist and reduce dopamine below the above mentioned basal level. Chlorpromazine and risperidone are inverse agonists at the 5HT_{2A} receptor thus enlarging our understanding of the role this receptor plays in schizophrenia. For most of my career I was blissfully ignorant of this concept but once introduced to it, I felt in broadened my understanding of psychopharmacology.