European Neuropsychopharmacology (2017) **27**, 87–90

www.elsevier.com/locate/euroneuro

SHORT COMMUNICATION

Inverse agonists – What do they mean for psychiatry?

David Nutt[a,*], Stephen Stahl[b], Pierre Blier[c], Filippo Drago[d], Joseph Zohar[e], Sue Wilson[a]

[a]*Centre for Psychiatry, Imperial College London, UK*
[b]*Department of Psychiatry, University of California San Diego, San Diego, CA, USA*
[c]*Institute of Mental Health Research, The Royal Mental Health Care Centre, Ottawa, Canada*
[d]*Biometec, University of Catania School of Medicine, Catania, Italy*
[e]*Department of Psychiatry, Sheba Medical Center & Sackler School of Medicine, Tel Aviv University, TelHashomer, Israel*

Received 26 October 2016; accepted 21 November 2016

KEYWORDS
Inverse agonist;
Antagonist;
Serotonin;
5-HT2A

Abstract
The nomenclature of drugs is a critical aspect of science, since it can direct research and optimize treatment choices. Traditionally drugs acting on CNS receptors have been classified as either agonists or antagonists. Recently a new class of ligand, the inverse agonist, has been identified in some receptor systems. Inverse agonists have opposite actions to those of agonists but the effects of both of these can be blocked by antagonists. Pimavanserin is a new 5-HT2A receptor acting drug that has been given market authorization for psychosis in Parkinson's disease. The FDA have termed it an inverse agonist, but this conclusion is based on in-vitro data. In this paper we discuss the evidence for such a claim being made for pimavanserin in the human brain and conclude that this is not currently sufficient. It is therefore premature to conclude that the actions of pimavanserin in humans are due to inverse agonism, and we are of the opinion that it should be called a 5-HT2A antagonist until better evidence emerges.

Most psychiatrists who prescribe drugs are familiar with the basic concepts of receptor agonism and antagonism. The vast majority of drugs we use in our profession are antagonists i.e. they block something. Usually they block the effects of an endogenous neurotransmitter such dopamine in the treatment of schizophrenia or the serotonin transporter in the case of serotonin reuptake inhibitors for depression. Direct agonist drugs are less common because they are harder to use on account of tolerance development but include opioids for pain

*Corresponding author.
E-mail address: d.nutt@imperial.ac.uk (D. Nutt).

http://dx.doi.org/10.1016/j.euroneuro.2016.11.013
0924-977X/

(mostly mu-opioid receptor agonists) and benzodiazepines for insomnia (that act as agonists or partial allosteric modulators at the benzodiazepine receptor).

About 30 years researchers working in the benzodiazepine receptor field discovered drugs that had opposite actions to benzodiazepine agonists i.e. they **caused** rather than reduced anxiety and seizures in rodents (Nutt et al., 1982; File et al., 1982). These were originally called contragonists but later the term inverse agonist gained acceptance (Nutt and Linnoila, 1988).

The proof that the opposite actions of agonist and inverse agonist drugs were produced via the same receptor came with the discovery of flumazenil, a drug that blocked both sets of actions, and so was an antagonist at the benzodiazepine receptor (Nutt et al., 1982). Inverse agonism at the benzodiazepine receptor has since been demonstrated to reverse deficits in a human model of memory impairment (Nutt et al., 2007), leading to one inverse agonist (basmisanil) being taken into clinical trials for cognitive impairments in Down's syndrome.

A prerequisite for a drug to be considered as an inverse agonist is that its receptor must have ongoing intrinsic level of activity in the absence of any ligand. For the benzodiazepine receptor, this is provided by the activity of the neurotransmitter GABA acting at the GABA-A receptor that is part of the larger macromolecular complex that also includes the benzodiazepine binding site. In the case of G-protein coupled receptors, this can be provided by constitutive activity of the receptor, i.e. activity in the absence of the transmitter ligand; an agonist then will increase activity of the receptor above its basal level, whereas an inverse agonist will decrease activity below its basal level (Kenakin, 2004).

More recently inverse agonism has been reported in other biological systems, including calcium channels and G-protein linked receptors. One of the more interesting aspects of G-protein research has emerged with drugs acting on the serotonin (5-HT)2A receptor. Many drugs currently in use in psychiatry act as antagonists at the 5-HT_{2A} receptor. The best example is risperidone that has ten-fold greater affinity at this receptor than at the dopamine D2 receptor (Table 1), so that in clinical practice all 5-HT_{2A} receptors are blocked by doses of 6mg per day or above (Nyberg et al., 1999). Other drugs used in psychiatry with significant 5-HT_{2A}

Table 1 Comparative affinity for 5-HT2A and dopamine D2 receptors for a range of drugs for psychosis and some selected drugs for depression with high 5-HT2A affinity. All numbers nMolar. Drugs other than pimavanserin are ranked in order of 5-HT2A receptor affinity with those with highest at top.

DrugShaded=inverse agonist in vitro	5-HT2A receptor affinity nM	5-HT2AInverse agonismstatus *in-vitro*	DopamineD2 receptor affinity	Relative affinity ratio 5-HT2A/D2	EffectsonSWSin humans(lessgood data in brackets)
Pimavanserin	<1nM	++++	>1000 nM	>1000	Increase
Drugs for psychosis					
Asenapine	<1	NA	1.3	1.3	NA
Risperidone	<1	++++	3	3	No change
Ziprasidone	<1	NA	5	5	Increase
Lurasidone	2	NA	2	1	(No change)
Olanzapine	2	+++	25	1/13	Increase
Zotepine	3	NA	8	1/2	NA
Thioridazine	6	+	8	1	(Increase)
Clozapine	10	++	200	1/20	No change
Aripiprazole	10	NA	1	1/10	NA
Chlorpromazine	12	++	7	1.5	NA
Pimozide	14	NA	29	2	NA
Haloperidol	100	+	2	1/50	No change
Quetiapine	120	+	600	1/5	No change
Sulpiride	1000	0	10	1/100	NA
Amisulpride	2000	0	1	1/1500	NA
Drugs for depression					
Mirtazapine	2	0	>1000	>500	No increase
Amitriptyline	18	0	>1000	>55	No increase
Trazodone	25	0	>1000	>40	Increase
Other drugs					
Eplivanserin	<1	+++			Increase
Volinanserin(MDL100907	<1	++++			NA
Nelotanserin	<1	++			Increase
Ritanserin	5	++++			Increase
Ketanserin	8	NA			Increase

Inverse agonist status ++++ IC50<1nM +++ IC50 1-10nM ++ IC50 10-100nM + IC50 >100 nM NA=not available. From (Weiner et al., 2001; Vanover et al., 2006; Al-Shamma et al., 2010).