Key concepts in psychopharmacology

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Abstract

Drugs are one of the key treatment modalities in psychiatry, so an understanding of their pharmacology is critical for all people involved in the treatment of psychiatric disorders. This contribution covers the key elements of drug pharmacology. It explains their target proteins, either receptors or enzymes, and how drugs' specificity can vary. In addition, key aspects of agonist efficacy and dose–effect responses, partial agonists and the meaning and effects of antagonists and inverse agonists are described. Key examples relevant to psychiatry are used.

Keywords agonist; antagonist; dose–response curve; partial agonist; receptors

Pharmacology is the study of how drugs interact with biological processes; psychopharmacology is the study of the effects of drugs on brain processes such as cognition, mood and other psychological phenomena. Much psychiatric practice revolves around the appropriate use of drugs' or medications, and understanding the key elements of psychopharmacology can therefore help optimize treatment.

In psychiatry, drugs are generally small synthetic molecules. These act in a number of different ways (see Table 1 for details and examples).

Agonists act to mimic the action of an endogenous neurotransmitter, though their net action is not necessarily to promote synaptic transmission because of the effect that presynaptic autoreceptors may have.

Antagonists block the effects of endogenous neurotransmitters and oppose normal synaptic transmission, although in some cases if they act predominantly on presynaptic receptors they may increase neuronal firing and so increase neurotransmitter release (see below).

Partial agonists act somewhat like agonists in that they directly act on receptors, but if used in the presence of an agonist they compete for the receptor and so can have partial blocking properties; hence they are sometimes called agonist–antagonists. For example, Figure 1 shows that the maximal effect of the partial agonist aripirazole is between that of the full agonist dopamine and and antagonist (e.g. haloperidol on dopamine D_2 receptors). Once aripirazole has been taken it will occupy brain receptors, and in brain regions where dopamine is high it will partially block the effects of dopamine, so leading to an antipsychotic effect. However, in brain regions where dopamine levels are lower, then aripirazole will act as an agonist to increase dopamine transmission in these regions. These dual effects of partial agonists means that they are sometimes called agonist–antagonists. The weak agonist activity of aripirazole means that it never blocks dopamine function as much as an antagonist, which explains why it produces fewer extrapyramidal side effects (EPS). It is thought

Agonists, antagonists and partial agonists and antagonists at dopamine D_2 receptors

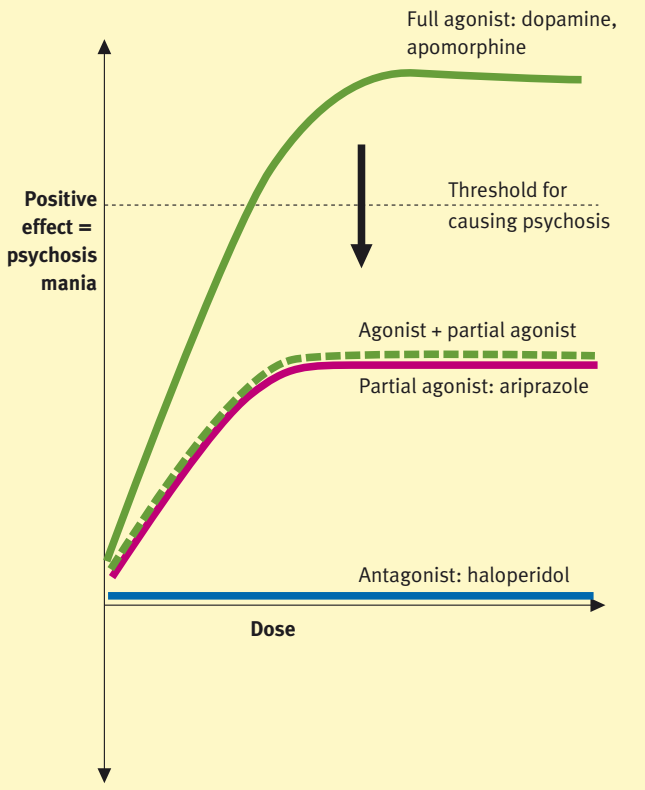

Figure 1

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Properties of drugs used in psychiatry

Site	Agonist	Antagonist	Partial agonist
Receptors	Noradrenaline – clonidine Opiate – morphine	Dopamine D_2– neuroleptics Benzodiazepine – flumazenil Opiate – naltrexone	Dopamine – aripiprazole 5-HT_{1A} – buspirone
	$GABA_A$ – benzodiazepines	5-HT_2 – clozapine	Opiate – buprenorphine
Enzyme	n/a	Noradrenaline – MAOIs Acetylcholinesterase – donepezil GABA transaminase – vigabatrin	n/a
Uptake sites	n/a	SSRIs – paroxetine TCAs – imipramine NARIs – reboxetine GABA – tiagabine	n/a
Ion channels	n/a	Most anticonvulsants	n/a

$GABA_A$, γ-aminobutyric acid A; MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; NARI, noradrenaline reuptake inhibitor.

Table 1

that there is always enough dopamine function from the aripiprazole to allow normal basal ganglia function.

Receptors

Receptors are proteins expressed on the surface of neurons (and other brain cells) that have specialized peptide conformations which allow the binding of neurotransmitters or hormones. These specialized binding pockets are called the pharmacophore and they convey the exquisite selectivity of receptors for substances such as neurotransmitters and drugs. The avidity (or stickiness) with which a neurotransmitter or drug binds to a receptor is called its affinity. This is usually measured in nanomolar concentrations (nM), as for example the Ki (inhibitory constant), which gives an indication of the concentration of neurotransmitter or drug needed to displace half of the binding of a tracer from a receptor in binding studies.

Receptors can be classified in a number of different ways, such as their site of localization and the way in which they transmit information across the cell membrane (Figure 2 and Table 2).

Postsynaptic receptors are the typical receptors that mediate the actions of the released neurotransmitter. These receptors can have one of two actions: some are excitatory, which means they produce depolarization of the target postsynaptic neuron, which can lead to the generation of an action potential that allows the nerve signal to be transmitted; or they can be inhibitory, switching off the target neuron. It is important to realize that it is the receptor, not the neurotransmitter, which determines whether excitation or inhibition occurs. Thus a single neurotransmitter can be both

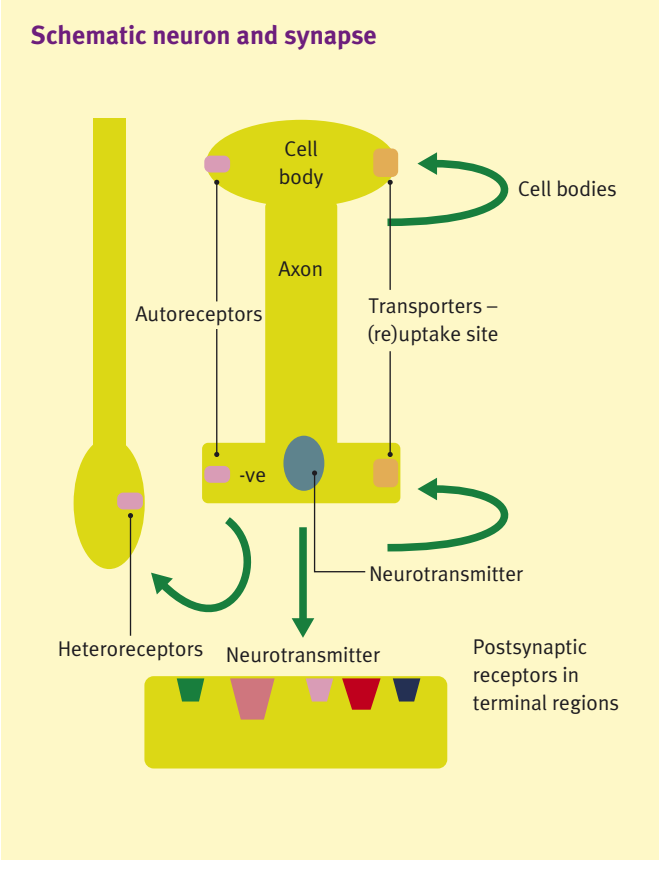

Figure 2

Receptors classified according to location

Location	Action	Examples in psychiatry	Implications
Postsynaptic	Stimulatory or inhibitory	Ropinirole – D_2 dopamine Benzodiazepines – GABA-A	Parkinson's Anxiety, insomnia
Presynaptic autoreceptor	Usually inhibitory	Clonidine/lofexidine – α_2 adrenoceptor Low dose amisulpride – dopamine $D_{2/3}$	Opiate withdrawal Improve cognition?
Presynaptic heteroreceptors	Usually inhibitory	Clonidine – 5HT neurons	May lead to depression

Table 2

excitatory and inhibitory, depending on the receptor subtype it acts on (see Table 3).

Presynaptic autoreceptors are located both on the cell bodies/dendrites of neurons and on the terminal axonal processes. They detect neurotransmitter released from the parent neuron (hence the term 'auto') and, because in general they are inhibitory, they act as a 'brake' on further release of the neurotransmitter. They represent important regulating mechanisms to limit excessive release of neurotransmitter into the synapse and have critical roles in the action of many psychotropic drugs such as the antidepressants and antipsychotics.

Presynaptic heteroreceptors (sometimes called heteroceptors) are located on neurons that release different neurotransmitters from those that act on the receptor, hence the term 'hetero'. Again, they are generally inhibitory in nature and, although they are not as well studied as the autoreceptors, there is growing evidence for their importance as potential new targets for drug treatment. For example, noradrenaline acting on heteroreceptors of the α_2-adrenoceptor type found on 5-HT (serotonin) neuronal terminals inhibits 5-HT release; blockade of these with antagonists such as mirtazapine therefore indirectly increases 5-HT release.

Receptor subtypes

Receptors are grouped into families based on several different features, most usually the neurotransmitter that binds to them and the way in which they pass information into the target cell – the second-messenger system they are coupled to. Molecular genetic studies have shown that there are at least 15 different genes that can produce proteins that look like (i.e. have significant amino-acid homology with) known 5-HT receptor proteins, and these are now considered the class of 5-HT receptor subtypes. As they all bind 5-HT (though with quite different affinities) it is assumed that 5-HT is the endogenous neurotransmitter for them all. They are classified into families based on their linkage to second-messenger systems (see Table 3).

Different receptor families act through different second messenger systems because the proteins that make up the binding site or receptor also act to transmit a signal into the cell after the transmitter binds to the receptor. This transmission of signal can be in the form of a change in second messengers, such as cAMP or phospholipids catalysed by enzymes that the receptor protein activates: these are metabotropic receptors. Alternatively, receptor activation by a ligand can result in a change in the conductance of an ion channel that alters ion flux across the cell membrane; these are ionotropic receptors. Each of these processes can either stimulate or inhibit the target cell, depending on whether the metabotropic or ionotropic processes that are initiated are excitatory or inhibitory. Some examples that are important in psychiatry are given in Table 4. In some cases, such as the benzodiazepines, the drug ligand does not directly alter a second messenger process but potentiates the effects of the endogenous transmitter (in this case, γ-aminobutyric acid, or GABA); these are allosteric mechanisms.

The major families of 5-HT receptors

Family	Subtypes	Second messengers	Effect	Agonists (other than 5-HT)	Antagonists
5-HT_1	5-HT_{1A} 5-HT_{1B} 5-HT_{1C} 5-HT_{1D}	G-proteins	Inhibition	Buspirone The sartan class of anti-migraine drugs	Pindolol, WAY100635
5-HT_2	5-HT_{2A} 5-HT_{2C}	Phospho-inositol (PI)	Excitation	mCPP	Mirtazapine Many atypical antipsychotics
5-HT_3	None	Sodium ions	Excitation	None	Ondansetron etc.

(Plus 5-HT_{4567} subtypes, which at present are little understood in terms of psychiatric disorders and treatments.)

Table 3

Receptor activation

Receptor	Effect	Receptor type	Signal process	Antagonists in clinical use
Dopamine $D_{1,5}$	Excitation	Metabotropic	Inc. cAMP	None
Dopamine $D_{2,3,4}$	Inhibition	Metabotropic	Dec. cAMP	Haloperidol
$GABA_A$	Inhibition	Ionotropic	Chloride ions	None
Benzodiazepine	Inhibition	Allosteric		Flumazenil
Noradrenaline α_1	Excitation	Metabotropic	Inc. cAMP	Prazosin
Noradrenaline α_2	Inhibition	Metabotropic	Dec. cAMP	Mirtazapine
Noradrenaline $\beta_{1\text{-}3}$	Inhibition	Metabotropic	Dec. cAMP	Propranolol
Glutamate	NMDA	Ionotropic	Calcium ions	Mg^{++} ions
Glutamate	Autoreceptor	Metabotropic	Dec. cAMP	None
Glutamate	AMPA	Ionotropic	Sodium ions	None

Inc., increases; Dec., decreases; NMDA, *N*-methyl-D-aspartate; AMPA, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid.

Table 4

Effects of chronic drug administration

It is rare in medicine for drugs to be given once only so the changes that may be seen on repeated drug administration are of importance. These come in two classes, tolerance and sensitization.

Tolerance is a state of reduced drug action following repeated use. It is generally found with agonist drugs only and reflects homeostatic compensatory mechanisms that can occur in the target neuron or can be due to adaptive changes in neural circuitry. Tolerance is often associated with a reduction in the number or density of the target receptors (down-regulation). Tolerance results in the loss of action of an agonist and is revealed by the need for higher doses to produce the same effect. There are few clear examples of therapeutic tolerance in psychiatric treatment, but the loss of side effects seen on repeated use of many drugs is a form of tolerance (e.g. nausea with the SSRIs, sedation with antihistamines). In neurology, a good example of drug tolerance is the need for larger doses of anticonvulsant benzodiazepines such as clonazepam on chronic use in epilepsy.

Sensitization describes the increase in function of a drug when it is used repeatedly. This is rarely seen in psychiatry but has been put forward as an explanation of why repeated stimulant use (e.g. cocaine) may lead to psychotic phenomena. Following chronic use of antagonists, a form of supersensitivity to agonist drugs may be seen when they are stopped. This is thought to be due to an increase in receptor density (up-regulation) and may explain some of the phenomena seen in drug withdrawal.

Withdrawal

When drug treatment is stopped the person may experience a variety of different phenomena which come under the general term of withdrawal (Figure 3). Withdrawal can be divided into two distinct components, rebound and discontinuation symptoms (see Table 5).

Rebound is the worsening of the original condition for which the drug was used, manifested by an increase in symptoms that were originally a reason for the prescription of the drug. It can be considered as the reappearance of the underlying disorder and, if severe enough, may equate to a relapse. A good example of rebound is seen in epilepsy treatment: suddenly stopping benzodiazepines such as clonazepam can lead to severe worsening of the seizure disorder. In some cases, rebound can result in worse symptoms than those at the outset of drug therapy; this

Phases of withdrawal, with a few possible profiles of symptomatic change

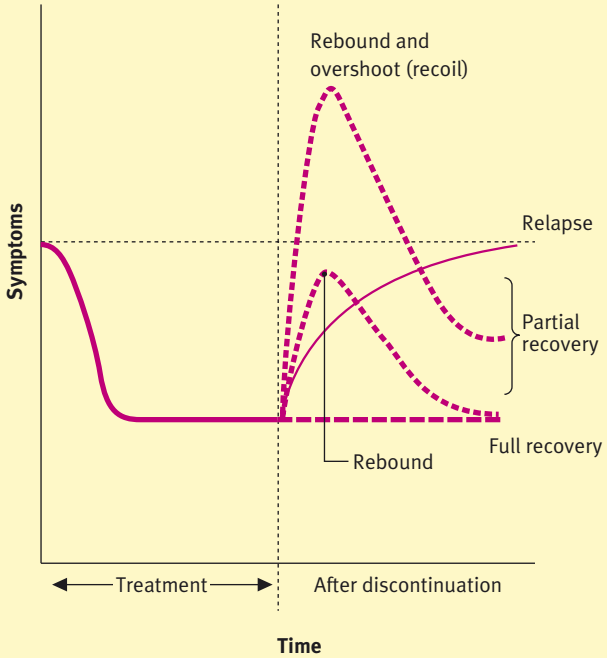

Figure 3

Withdrawal phenomena

	Rebound	Discontinuation
Original illness symptoms	Yes	No
Novel symptoms	No	Yes
Symptoms of original drug	No	Yes
Overshoot?	Possible	n/a
Can occur in absence of tolerance	Yes	Yes

Table 5

is considered as rebound with overshoot (or recoil). This can be both extremely distressing and even, as in the case of rebound seizures, potentially lethal. It is likely that the increased risk of mania on stopping lithium and the severe psychotic reactions to sudden clozapine withdrawal are other examples of rebound plus overshoot in psychiatric practice.

Rebound can happen without discontinuation phenomena (e.g. in the case of lithium). Rebound can continue even when blood levels of the drug are undetectable, so presumably it indicates adaptive changes in brain function that are a consequence of drug use directly, or the physiological changes produced by the drug, rather than being simply the removal of the drug from its binding site.

Discontinuation syndrome is a term that has been used in recent years in an attempt to clarify the phenomenon of selective serotonin reuptake inhibitors (SSRI) withdrawal symptoms. The key feature of a discontinuation syndrome is that it is a reaction occurring during drug withdrawal (i.e. as plasma/brain levels of the drug are falling) whose symptoms are not features of the underlying disorder. Thus discontinuation syndromes can be distinguished from rebound, and frequently (but not exclusively) the symptoms do not bear any relation to the known pharmacology of the drug. They can be seen in people who have not had a therapeutic response to the drug, and have been seen in volunteers. Some discontinuation symptoms are quite bizarre, such as electric-shock-like feelings, whereas others are like the original side effects of the drugs (e.g. nausea with the SSRIs).

Discontinuation reactions have been reported for a variety of psychotropic agents, including the neuroleptics, monoamine oxidase inhibitors and tricyclic antidepressants. Discontinuation phenomena are found with many different classes of drugs, including opiates, caffeine and nicotine. Withdrawal from each is associated with symptoms that were not originally reasons for taking the drug, as in the following examples:

- opiates: nausea/diarrhoea, bone pains, shivering
- caffeine: headache
- nicotine: irritability, loss of concentration, low mood.

Discontinuation phenomena are little studied and poorly understood, despite their long history and clinical relevance, but presumably reflect adaptive changes in brain receptor or neurotransmitter function as a consequence of chronic drug action. ◆

FURTHER READING

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