Neurotransmitters, Drugs and Brain Function.
Edited by Roy Webster

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Section B

NEUROTRANSMITTERS AND SYNAPTIC TRANSMISSION

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5 Basic Pharmacology and Drug Effects on Neurotransmitter Function

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INTRODUCTION

Drugs have the potential to bind to neurotransmitter receptors. Indeed that is the rationale for using them. If they combine with a receptor and activate it, they are called agonists but if they merely sit there to stop the NT, or another agonist drug, from binding to the receptor and producing an effect, they are called antagonists.

To bind to, i.e. have *affinity* for, a receptor, the drug, whether it is agonist or antagonist, must have the appropriate chemical structure but only agonists have the further ability, so-called *efficacy* (or *intrinsic activity*), to activate the receptor and the cellular mechanism to which it is linked. Ideally an antagonist has high (strong) affinity but zero efficacy. It is the chemical structure which determines to which receptor a drug combines and how specific it is in its action. Ideally a drug should only bind to one receptor type 1 but in reality very few, if any, are that specific, especially at high concentrations.

DRUG–RECEPTOR INTERACTIONS

The effect of an agonist drug whether it is measured as the ability to fire a neuron, inhibit an enzyme or reduce motor function, increases with the concentration of the drug and the number of receptors it occupies. In fact the magnitude of the response, like that of a chemical reaction, is proportional to the product of the concentration of the reactants, in this case the drug and its receptors, and as such obeys the law of Mass Action. Thus the rate at which a drug [D] combines with the receptor [R] to give occupied receptors (or drug receptor complexes [DR]), can be represented by its rate constant K_1 so that

$$[\mathrm{D}] + [\mathrm{R}] = K_1[\mathrm{DR}]$$

Since the drug–receptor interaction is reversible the drug also dissociates from the receptor at a rate K_2 when

$$[\mathrm{DR}] = K_2[\mathrm{D}] + [\mathrm{R}]$$

The equilibrium constant (K_A) for the reaction is thus given by

$$K_A = \frac{K_1}{K_2} = \frac{[D][R]}{[DR]}$$

When 50% of the receptors are occupied [R] and [DR], free and occupied receptors, must be equal and cancel out so that $K_A = D$, the concentration of drug required to bind to 50% of the receptors. Thus the lower the concentration of drug required to achieve this occupancy, the greater its affinity. Unfortunately its affinity does not necessarily reflect its potency in producing an effect.

The relationship between the dose (concentration) of a drug and the response it produces provides the so-called dose (or concentration) response curve (DRC). This is hyperbolic but is transformed to a sigmoid shape, which is linear over a large dose range, when the dose is plotted on a log scale (Fig. 5.1). Comparison of the concentrations of two or more drugs required to produce the same response is a measure of their relative potency. In Fig. 5.1 the dose–response curves for drugs A and B are one log unit apart and so A is ten times more potent than B. Often the potency of a drug is defined as the dose or concentration of drug required to produce 50% of the maximal response, i.e. the ED_{50} dose (or EC_{50} concentration). Drug C in Fig. 5.1 presents a different DRC. It obviously has agonist activity but since it cannot produce a maximal response it is known as a partial agonist. While such a property may seem unwanted the drug could still produce an adequate effect and avoid the danger of that becoming too great with increasing dose.

There are some points about the dose–response curve that justify consideration.

DOSE OR CONCENTRATION?

When a drug is administered to either humans or animals we obviously know the dose but not the concentration at its site of action. In this instance the relationship between the amount of drug and its effect really is a dose–response curve.

If a drug is added to an *in vitro* system in an organ or tissue bath then, provided the volume of the bathing solution is known, the concentration of drug can be calculated. Concentration is also known if a tissue is superfused with a prepared drug solution. In these instances, the response reflects drug concentration. Even then, the actual concentration of drug at the receptor site is not really known, since there can be a steep gradient between the concentration of drug in the medium and that at the actual receptor, especially if the drug is only in contact with the tissue for a short time. A proportion of most NTs is likely to be metabolised in, or taken up by, the tissue before reaching the receptor, although this is less likely with synthetic drugs.

POTENCY, AFFINITY AND EFFICACY

When looking at Fig. 5.1 it is pertinent to ask why drug A is more active than drug B. It could be that they are achieving the same response by acting through different receptors and that those targeted by A are either more numerous or better equipped to initiate the response. If they are both acting on the same receptor then obviously A has a more appropriate chemical structure to fit that receptor than B, but whether this has conferred on it a greater ability to combine with the receptor (affinity) or to activate it (efficacy) is unclear. It certainly should not be assumed that the EC_{50} is a measure of the affinity of the drug for the receptor. All responses are the result of a series of

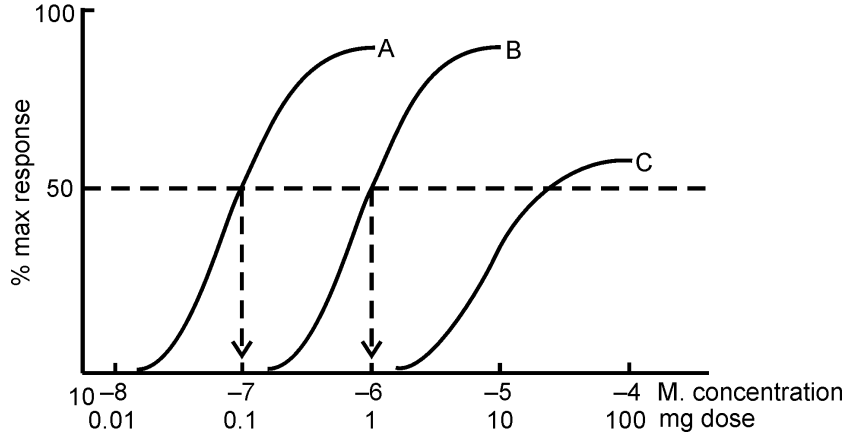


Figure 5.1 Dose (concentration) response curves for three drugs. Percentage response is plotted against log dose. The curves show that drug A achieves the same responses as drug B but at lower doses. A is in fact ten times more active than B since the same effect (e.g. 50% maximal response, ED_{50}) is obtained with 10^{-7} M (or 0.1 mg) A compared with 10^{-6} M (or 1.0 mg) B. Drugs A and B can both produce the maximal response and are full agonists. Drug C cannot produce a maximal response even at large doses and is known as a partial agonist

cellular events and, with the possible exception of studies on single-channel opening, not a direct measure of receptor occupancy. In any case, the efficacy of the drug must also be considered and since antagonists are devoid of that property their affinity and activity cannot be measured directly through a response (see below).

These problems can be overcome to some extent by using drugs labelled with a radioisotope (generally ^{3}H, ^{14}C or ^{125}I) and then directly determining the amount of label bound when the drug is incubated with samples of the appropriate tissue or, as with the nervous system, fragments of specially prepared isolated neuronal membranes that contain the receptors. Even this approach is not ideal since drugs will combine non-specifically with cellular elements other than the receptor. In practice this can be largely overcome (see Chapter 3). Experimentally, the test tissue is incubated with varying concentrations of the labelled drug (called ligand) until equilibrium is reached. The tissue is then separated from the incubation medium by filtration or centrifugation and dissolved in scintillation fluid which is measured for its radioactivity. This gives the total amount of drug bound, including specific binding to its receptors and any other non-specific tissue binding. The non-specific binding is estimated by running a parallel set of tissue samples incubated with medium containing both the labelled drug and an excess concentration of another unlabelled drug which binds to the same receptor. This should inhibit all the receptor binding of labelled drug. Any residual binding will be to non-specific sites (Fig. 5.2(a)). Subtraction of this non-specific binding from the total binding gives the specific receptor binding for the drug which is a saturable process. The relationship between the amount of ligand bound (B) and its concentration X can be represented, for a preparation where the total number of binding sites is B_{max}, as

$$B = \frac{B_{max}X}{X+K} \text{ where } K \text{ is the dissociation (affinity) constant}$$

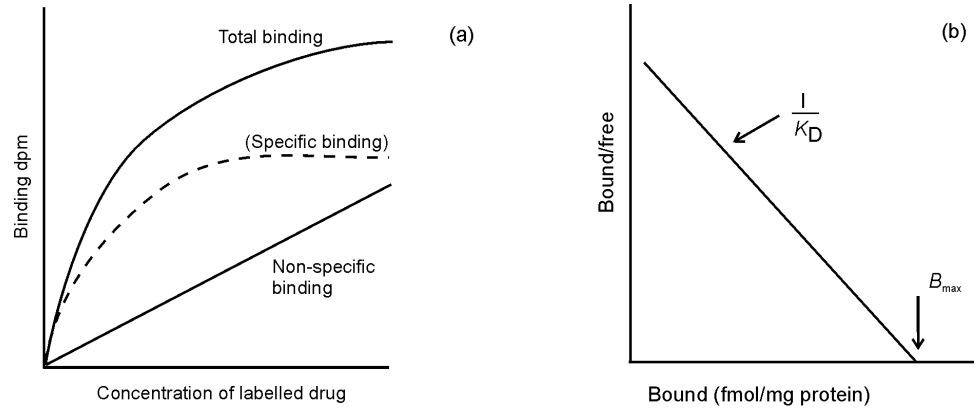


Figure 5.2 Measurement of specific saturable drug binding. (a) Plot of quantity of labelled drug bound against its increasing concentration in the bathing medium. Subtraction of non-specific from total binding gives the specific binding for the drug. (b) Scatchard plot of B/F (bound/free drug) against level of bound drug (B) gives a straight line the slope of which is $1/K_D$, while the intercept is B_{max}, the maximum number of that drug's binding sites, expressed as fmol/mg tissue protein. For experimental detail see text

Thus

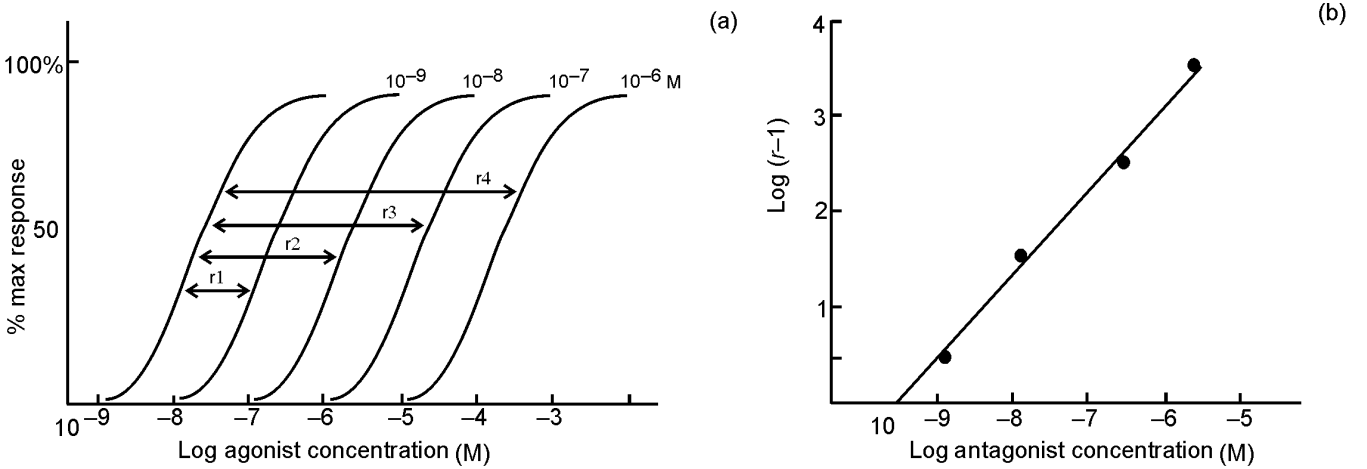
$$\frac{B}{X} = \frac{B_{max}}{K} - \frac{B}{K}$$

If B/X is plotted against B (the Scatchard plot) it should give a straight line (Fig. 5.2(b)) with the slope ($1/K_D$) giving K and the intercept on the abscissa providing the maximal binding (B_{max}), expressed as fmol per mg tissue protein. The steeper the slope, the higher the affinity.

In many binding studies the relative abilities of a series of unlabelled drugs to displace a labelled ligand from a particular receptor is taken as a guide to their affinity for that receptor. This is normally represented as K_i, the concentration of drug required to displace half of the labelled ligand. Its accuracy depends on the chosen ligand only binding to the receptor it is intended to study and no other receptor. It must be emphasised that binding studies only measure the ability of a drug to combine with a receptor, they do not indicate whether it is an agonist or antagonist. Also compared with an antagonist the binding of an agonist may be affected in an uncertain manner by the change in state caused by the activation of the receptor.

DRUG ANTAGONISM

One drug can overcome the effect of another or reduce the activity of an endogenously released and active substance such as a neurotransmitter, either by competing with that substance for its receptor site (receptor antagonism) or stimulating a different receptor to induce an opposing effect (physiological or functional antagonism). The former may be regarded as true antagonism for in the latter case both drugs are actually agonists. It is epitomised by the use in asthma of beta adrenoceptor agonists like salbutamol to dilate bronchi that have been constricted by a cocktail of local mediators such as



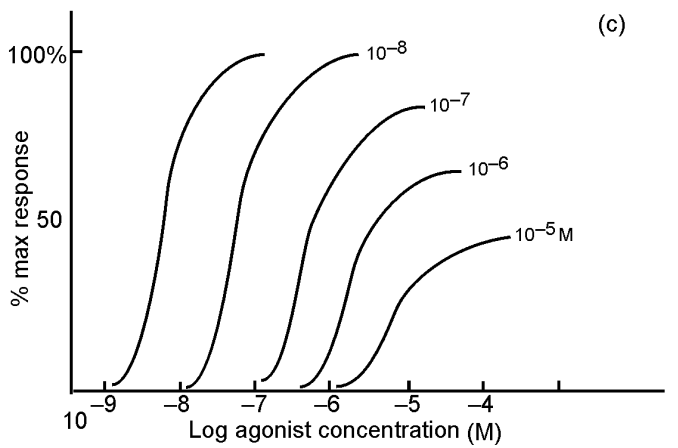


Figure 5.3 Drug antagonism. (a) Surmountable competitive antagonism. Dose–response curves are shown for an agonist alone and in the presence of increasing concentrations of the antagonist. The antagonism is surmountable because even in the presence of a large concentration of antagonist the agonist can still produce a maximal response and it is competitive because equal increments in the concentration of antagonist produces equal shifts in the DRCs. The shift is known as the dose ratio (r), and is the amount by which the dose of agonist must be increased in the presence of antagonist to produce the same response as in its absence. (b) A Schild plot. This shows dose ratio (r) measured as in (a) and plotted as $\log(r-1)$ against log concentration of antagonist. In true competitive antagonism the graph should have a slope of 1 and its intercept with the abscissa gives pK_B. The negative logarithm of this value is Schild's pA_2 measure of drug antagonism. In the example shown a K_B of 3.2×10^{-10} gives a pA_2 of 9.5. (c) Unsurmountable irreversible antagonism. In the presence of low concentrations of antagonist the agonist can still produce a maximum response because the antagonist does not occupy all the receptors and there are sufficient 'spare receptors' available for the agonist. As the concentration of antagonist is increased fewer spare receptors remain and since the antagonist does not dissociate from the receptors (as its binding is irreversible) the agonist is unable to produce a full response, i.e. the antagonism is unsurmountable

histamine, acetylcholine and kinins. In the CNS the inhibitory NT (GABA) could be regarded as the physiological antagonist of the excitatory NT (glutamate). When the agonist and antagonist compete for the same receptor the binding of the agonist and the response it produces are both reduced. Thus to obtain the same response in the presence, as in the absence of antagonist, the concentration of agonist must be increased and over a range of agonist concentrations this results in a parallel shift to the right in the position of its DRC (Fig. 5.3).

The degree of this shift, the amount by which the agonist concentration has to be increased in order to produce the same response in the presence as in the absence of the antagonist, is known as the dose ratio (r). The larger this ratio, the greater the shift in the DRC and the more potent is the antagonist. In fact if the antagonism is really competitive then the degree of shift of the DRC will be proportional to the increase in concentration of the antagonist used. From Fig. 5.3(a), it can be seen that increasing the antagonist concentration from 10^{-9} M to 10^{-8}, 10^{-7}, 10^{-6} M always produces the same tenfold increase in dose ratio (i.e. 10, 100, 1000). Also if the antagonism is competitive not only will the DRCs remain parallel but it should always be possible to restore the maximal response to the agonist by giving more of it, irrespective of the amount of antagonist present. This is known as reversible or surmountable competitive antagonism. Since both agonist and antagonist are continuously combining with and dissociating from the receptor the likelihood of either occupying it at any time will depend on their relative concentrations.

The dose ratio $r = (X_B/K_B) + 1$ where X_B is the concentration of antagonist and K_B its equilibrium constant. This can be expressed logarithmically as

$$\log(r - 1) = \log X_B - \log K_B$$

and a plot of $\log(r - 1)$ against $\log X_B$ (the Schild plot) should give a straight line with slope of 1, which intercepts the abscissa at the value $-\log K_B$ (pK_B) for the antagonist (Fig. 5.3(b)). This is frequently converted into a simple number by taking its negative logarithm, much as pH values represent hydrogen ion concentration, so that K_Bs of 10^{-7} or 3.2×10^{-7} mol/l become simply 7 or 6.5. This pA_2 value was defined by Schild as the negative logarithm of the molar concentration of antagonist required to give a dose ratio of 2. Thus the larger the pA_2 value, the smaller the concentration of antagonist needed and the greater its affinity and effectiveness. In practice full DRCs are rarely obtainable especially in studies on the CNS, or even necessary, provided that responses to two doses of agonist can be obtained at each concentration of antagonist. This will establish the position of the DRC and allow r to be calculated.

If the antagonist does not readily dissociate from the receptor, because it is bound firmly, then the agonist will not be able to displace it and restore a maximal response. At low concentrations of antagonist this may not be apparent. An agonist can often achieve a maximal response by activating only a small percentage of its receptors, so in the presence of low concentrations of a non-dissociating antagonist there may be sufficient spare receptors available for increased concentrations of the agonist still to achieve a maximal response. As the concentration of antagonist is increased, however, fewer unoccupied receptors are left and since the agonist cannot displace the antagonist a maximal response cannot be achieved (Fig. 5.3(c)). This is unsurmountable or irreversible competitive antagonism. It is still competitive because the drugs are competing for the same receptor. Sometimes an antagonist can inhibit the effect of an

agonist not by occupying the same binding site on the receptor but some adjacent site or process necessary for the agonist's effect, such as the ion channel itself. This is non-competitive antagonism which may, or may not, be reversible, depending on the action of the antagonist. There are a number of drugs with this action on the glutamate NMDA receptors (Chapter 10).

PHARMACOKINETICS

This is generally accepted as the term to describe the absorption distribution and metabolism of a drug *in vivo* and it is these factors which determine how quickly and how much of the administered drug can actually reach its site of action (in the CNS) and be maintained there for the required time (see Fig. 5.4). Experimentally drugs are

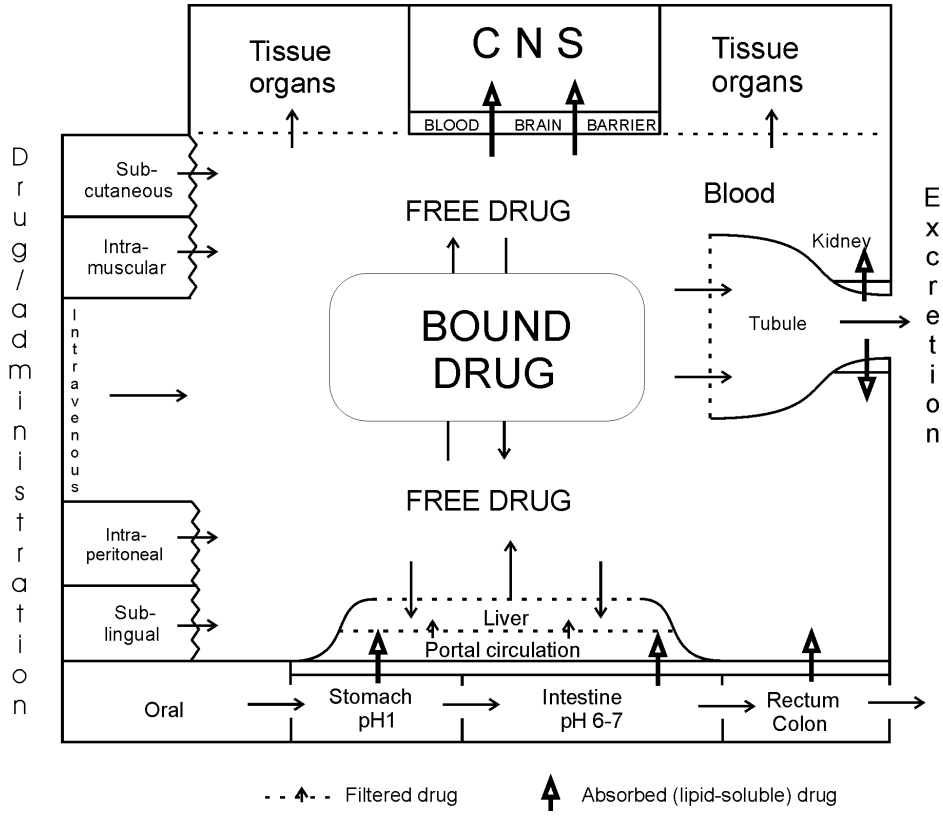


Figure 5.4 Pharmacokinetics. The absorption distribution and fate of drugs in the body. Routes of administration are shown on the left, excretion in the urine and faeces on the right. Drugs taken orally are absorbed from the stomach and intestine and must first pass through the portal circulation and liver where they may be metabolised. In the plasma much drug is bound to protein and only that which is free can pass through the capillaries and into tissue and organs. To cross the blood–brain barrier, however, drugs have to be in an unionised lipid-soluble (lipophilic) form. This is also essential for the absorption of drugs from the intestine and their reabsorption in the kidney tubule. See text for further details

usually given intravenously or intraperitonealy, but therapeutically most of them are taken orally.

The speed of onset of action of a drug depends primarily on how quickly it reaches the circulation. For this reason alone it is not surprising that intravenous administration produces the quickest response. Thereafter the rate and degree of absorption depends on the blood flow to the injected site and the surface area of vessels exposed to the drug. The response to an intramuscular injection in humans is quite rapid since our muscles are large and have a good blood supply. In laboratory animals muscle mass is small and so an intraperitoneal administration may be more effective because the drug solution can be given in relatively large volumes which disperse over a large surface area (the abdominal wall and intestinal surfaces).

Drugs taken orally are slow to act. Most are absorbed in the small intestine where the villi, which penetrate into the lumen, present a large surface area. Unfortunately in order to pass through the gut wall into the bloodstream the drug has to become dissolved in its cell's membranes and to achieve this it needs to be lipid-soluble.

Generally it is only the non-dissociated or unionised drug that is lipid-soluble and a drug's degree of ionisation depends on its dissociation constant (pK) and the pH of the environment in which it finds itself. For an acidic drug this is represented by the Henderson–Hasselbalch equation as

$$\mathrm{p}K - \mathrm{pH} = \log \frac{\text{conc-unionised drug } (Cu)}{\text{conc-ionised drug } (Ci)} \qquad (\mathrm{p}K - \mathrm{pH} = \log \frac{Ci}{Cu} \text{ for basic drug})$$

Thus an acidic drug with a relatively low pK of 3 will be largely unionised (hundredfold) in the acidic environment (pH = 1) of the stomach since

$$3 - 1 = \log 2 = 100 = \frac{Cu}{Ci}$$

but in the more basic intestine it will be ionised, i.e.

$$3 - 6 = \log 3 = \frac{1}{1000} = \frac{Cu}{Ci}$$

It will then depend for its absorption on the large surface area of the intestine.

Drugs absorbed along the length of the gut do not enter straight into the general circulation but pass initially into the portal circulation to the liver where they may be subject to metabolism. In fact a high proportion of some orally administered drugs can be lost in this way without even reaching the main bloodstream but those given sublingually (under the tongue) or by suppository into the rectum bypass the portal system. Some drugs can also stimulate the production of microsonal-metabolising enzymes (e.g. phenobarbitone) in the liver and so increase the destruction of other drugs being taken at the same time.

Once in the blood most drugs will leave the circulation by being filtered through pores in the capillaries, provided they have a molecular weight below 6000, which is almost always the case, and are not bound to plasma protein (albumin) which is too large to be filtered. Although such binding, which commonly accounts for over 90% of plasma drug, does restrict movement, it also acts as a drug store. Unfortunately one drug can displace another from such binding and so elevate its free plasma concentration and create the potential for toxicity.

There are two sites in the body where a drug is not able to pass freely into the tissue. One is the placenta and the other the brain where the blood–brain barrier (see Chapter 1) is a formidable hindrance. Without pores in the capillaries a drug can only enter the CNS (or cross the placenta) by virtue of lipid solubility, as in the gut.

Since a drug is a foreign object, the body does its best to get rid of it. As the organ of excretion, the kidney has a copious blood supply and drugs are easily filtered through the glomerular capillaries into the kidney tubule and urine unless they are very large (e.g. hormones, heparin) or bound to plasma albumin. In fact most drugs would be rapidly lost if they were not so bound or showed sufficient lipid solubility to be reabsorbed through the wall of the kidney tubule back into the bloodstream. Thus a drug which is present in the unionised lipid-soluble form is more readily absorbed from the gut, can enter the CNS and is potentially longer acting as it will avoid excretion, unless it is rapidly metabolised.

To increase the chance of removing a drug, the body converts it into a water-soluble, ionised and so excretable form. This is generally a two-stage process involving initial metabolism (e.g. oxidation, reduction or hydrolysis) and then conjugation with something like glucuronic acid. The metabolite may occasionally be as, or more, active than the parent compound but is generally less so and can sometimes even be toxic.

The rate at which a drug is metabolised is generally proportional to its concentration (so-called first-order kinetics) but if there is an excess of drug and the metabolic process becomes saturated, then metabolism proceeds at a constant rate, the maximum possible, irrespective of concentration (zero-order kinetics). With some drugs, such as alcohol, this occurs even at low concentrations. The duration of action of a drug is represented by its half-life ($\frac{1}{2}t$) which is a measure of the time taken for its plasma concentration to fall by 50%. Obviously drugs with a short half-life have to be taken more frequently. To use a drug properly it is necessary to know not only what constitutes an effective plasma concentration but also how long that is maintained following dosage. This information can be obtained from pilot studies in humans but since there is considerable variation in how an individual responds to and metabolises a drug the effect of a drug can vary considerably between subjects.

This leads to the concept of therapeutic index. The potency of a drug is almost irrelevant. It is its specificity that matters. Thus if two drugs A and B are effective at the same dose in a patient, say 1 mg, but A produces toxic effects at 10 mg which are only seen with 500 mg of B then B is clearly a much safer drug than A, in that patient. The ratio of toxic to effective dose is the therapeutic index (TI). It is often expressed as

$$\frac{\text{toxic dose in 50\% of patients}}{\text{effective dose in 50\% of patients}}$$

In practice it is obviously difficult to actually determine the toxic and effective dose in 50% of treated patients in the same population but the concept of a maximum tolerated dose compared with an effective dose is of great importance.

DRUG EFFECTS ON NEUROTRANSMITTER FUNCTION

To establish the role of a particular NT experimentally it is necessary to modify its synaptic activity. This can be done most easily with drugs.

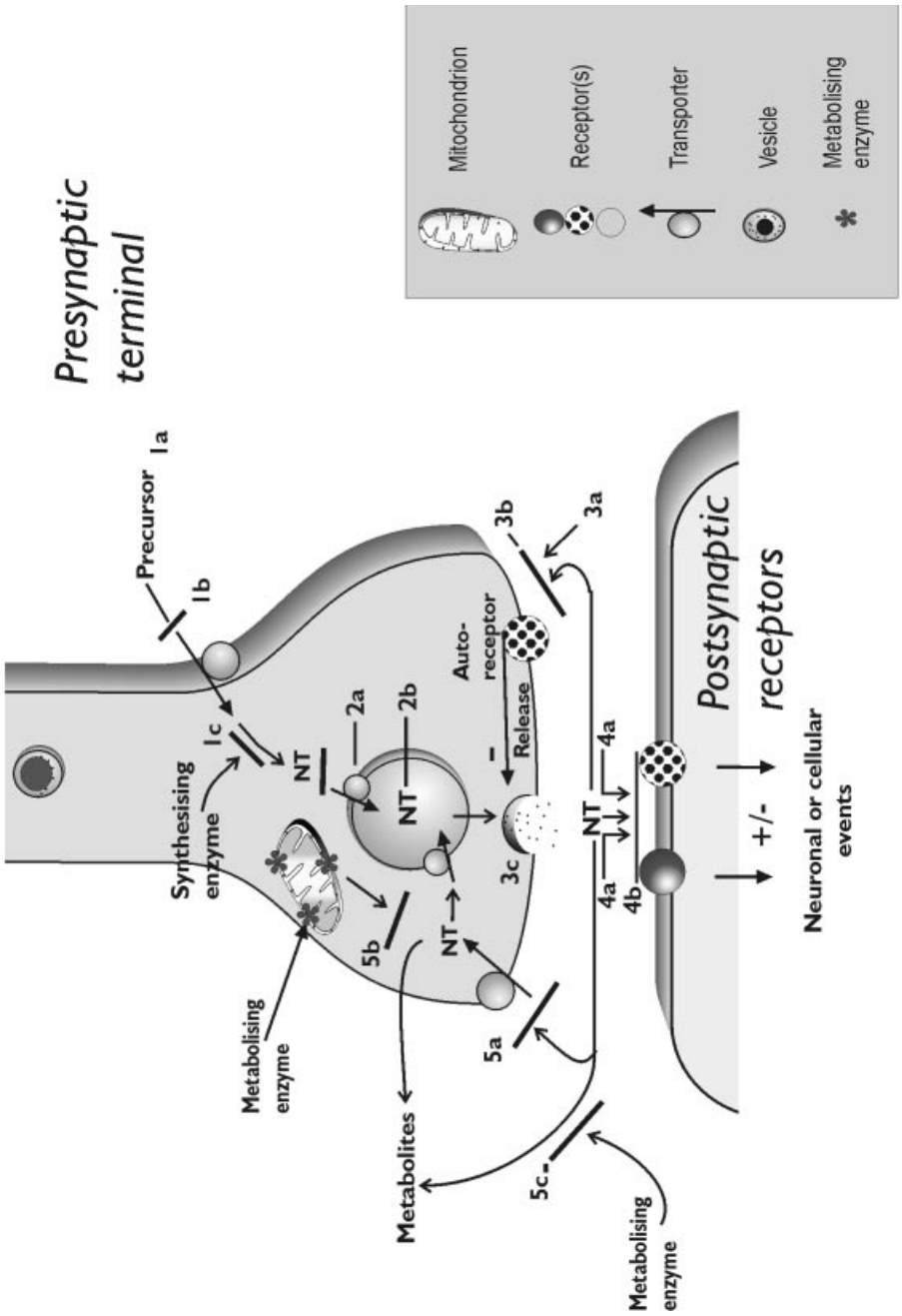


Figure 5.5 Diagrammatic representation of a synapse showing the sites at which drugs may act to increase or decrease the concentration and action of a neurotransmitter. Drugs can affect the synthesis (1), storage (2), release (3), action (4) and destruction (5) of the transmitter. The different ways in which they achieve this (a, b, c) are outlined in Table 5.1

Table 5.1 Drug modification of the different aspects of neurotransmitter function in synaptic transmission as illustrated in Fig. 5.5

	Aspect	Modification	Effect on NT function
1	Synthesis	(a) Supplement precursor	+
	(i)	(b) Block precursor uptake	−
		(c) Inhibit synthesising enzyme	−
2	Storage	(a) Inhibit NT uptake into vesicle	− (+)
	(ii)	(b) Inhibit NT binding in vesicle	− (+)
3	Release	(a) Stimulation of negative autoreceptors	−
	(exocytotic)	(b) Blockade of autoreceptors	+
	(iii)	(c) Disrupt release (exocytotic) mechanism	−
4	Action	(a) Mimic effect of NT on receptor	+
	(iv)	(b) Block postsynaptic receptor	−
5	Destruction	(a) Block uptake into neuron (and/or glia)	+
	(v)	(b) Inhibit intraneuronal metabolism	+
		(c) Inhibit extracellular metabolism	+

(+) = increased; (−) = decreased.

Notes:

(i) Synthesis may have multiple steps within the terminal process which provides more than one site for drug modification and one stage may even be within the vesicle. Providing extra synthesising enzyme is not a practical proposition but altering the availability of certain co-factors can have an influence (e.g. impaired vitamin V6 intake reduces GABA synthesis).

(ii) Drugs affecting storage (e.g. reserpine) are not likely to affect only one NT. Also although any reduction in the vesicular storage of NT will eventually lead to a reduction (−) in its normal exocytotic release by action potential, it is possible that the extra NT will build up sufficiently in the cytoplasm (if not metabolised) to diffuse out of the neuron or even induce its reverse transport out of the neuron through the membrane transporter that normally brings it in from the synapse (+).

(iii) Some terminals may also have receptors which augment release when activated by the NT as well as receptors for NTs other than that being released. Drugs that affect the actual release process, e.g. Ca^{2+} influx, are unlikely to have a specific effect on just one NT system unless concentrated in particular neurons by specific uptake.

(iv) Most NTs act on more than one postsynaptic receptor. This provides the opportunity to design drugs that will act specifically on just one of them although reproduction of the full effect of the NT may require the participation of more than one of its receptors (e.g. DA function in the basal ganglia). It should also be remembered that even if a drug is specific for just one NT receptor its effects will depend on how numerous and widely distributed that receptor is. This is particularly true of the much-used amino acids glutamate and GABA. Also many different functions could be linked to the same receptor (e.g. the numerous peripheral actions mediated by cholinergic muscarinic receptors).

(v) A NT may be taken up into glia (e.g. GABA) or even nerve terminals other than those from which it is released. As with synthesis, it is difficult to augment the action of the metabolising enzymes.

The concept that a drug is either an agonist or antagonist that acts at a receptor site is a simple one, especially if it is acting at the receptor for a NT that is linked either directly or indirectly through second messenger systems, to the control of ion channel opening and the excitability (discharge) of a neuron. The receptor or perhaps more precisely the receptive site can, however, also be part of an enzyme involved in the synthesis or metabolism of that NT, the transporter responsible for taking the NT (or its precursor) across the membrane of a storage vesicle or axon terminal or even the actual NT binding site within a vesicle. This means that a drug can modify the action of a NT and the function of the synapse where it acts in a number of ways. These will now be outlined in general and then covered in more detail for each particular NT in the following chapters (6–13).

At most synapses a conventional NT is synthesised from an appropriate precursor in the nerve terminal, stored in vesicles, released, acts on postsynaptic receptors and is

then destroyed either by extraneuronal metabolism or intraneuronal metabolism after reuptake. Its release is triggered by invading action potentials and controlled by presynaptic autoreceptors. Although some NTs, e.g. peptides, are not synthesised in the terminal and others, e.g. NO, are formed on demand, some features of the 'typical' synapse, as described above, still apply to them. The mechanisms by which drugs may modify synaptic function through their effects on the synthesis, storage, release, action and destruction of a NT are shown in Fig. 5.5 and outlined in Table 5.1. They constitute what may be regarded as a template for how a drug may affect synaptic transmission.

Manipulating the activity of a NT in these ways helps to determine its function either at a synaptic level or in more general behavioural terms. Thus the clearest way of establishing the identity of the NT at a particular synapse is to ascertain which NT receptor antagonist blocks transmission there.

OTHER MEANS OF AFFECTING NEUROTRANSMITTER FUNCTION

Apart from the use of drugs the activity of a NT can be modified using one of the following approaches:

(1) Surgical or electrolytic lesions of a particular pathway or nucleus. Even with precise location and subsequent histological verification this approach rarely ablates all the axons (or neurons) in a pathway using the NT under study and can also affect other axons (or neurons).
(2) Toxins that gain access to a neuron through its uptake process and then destroy it in some way. This approach has been used mainly to destroy monoamine neurons with 5,6 or 5,7-dihydroxytryptamine targeting 5-HT neurons, 6-hydroxydopamine for dopamine (and to a lesser extent noradrenergic) neurons and MPTP for dopamine neurons (see Chapter 7). Only the latter is fully specific and effective systemically. The others need to be administered directly into the appropriate brain areas and while they may only affect the intended NT neurons, the injection may not affect all of them.
(3) Genetically bred animals in which the gene encoding a particular NT receptor, receptor subclass or synthesising enzyme has been knocked out. This approach becomes more realistic as we learn more of the subunit and amino-acid structure of receptors. While the effects will be more widespread than lesions it could have some advantage over drugs. It is difficult to design chemicals that are totally, or even adequately, specific as either agonists or antagonists for a particular subclass of receptor but if we know their structure then it should be possible to knock out a specified receptor subgroup.