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COMMENTARY

ANTIDEPRESSANT DRUGS AND DOWN-REGULATION OF PRESYNAPTIC RECEPTORS

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Since the observation of a reduction in the number of CNS β-adrenoceptors following chronic treatment with various antidepressant drugs, much speculation has ensued on the importance of receptor down-regulation, in general, for antidepressant effect. The significance of the reduction in β-adrenoceptor number is that most clinically effective antidepressants, and electroconvulsive shock, produce this effect in normal rats over a time course similar to that required for antidepressant action to develop in humans. But is it likely, or essential, to find a biological effect common to all antidepressant drugs? As has been pointed out in a previous commentary [1], antidepressant drugs may well exert their action by different basic mechanisms, by analogy with antihypertensive agents, and clinical depression presents in several different forms. Indeed, a false impression of change in receptor number may result from the common practice of increasing doses in animal experiments until an effect is seen. Thus, many works in this field use dose regimens for a variety of drugs of 10 mg/kg daily for 2–3 weeks even though the human antidepressant dose is far less (e.g. 150 mg daily for imipramine), and the major biological effect of the drug is also exerted at a fraction of this dose. A dose of 0.3 mg/kg desmethylimipramine in the rat produces more than 50% inhibition of amine uptake *in vivo* [2], although the drug is given at 10 or 20 mg/kg daily in chronic treatment.

While down-regulation of β-adrenoceptors is a consistent observation with antidepressant drug treatment, not all of these drugs have been shown to increase synaptic noradrenaline levels. Thus, down-regulation may result from initially increased neurotransmitter (agonist) level leading to desensitisation (reversible) in which agonist becomes complexed with receptors, followed by a second, irreversible, stage in which receptors become internalised. Down-regulation is seen here as a compensatory reaction to increased agonist levels. Alternatively, down-regulation may take place by a process not related to increased agonist levels. Acceptance of the latter possibility implies that the action of antidepressant drugs is to reduce the activity of β-adrenoceptor-mediated neuronal pathways in contrast to the well-known potentiation of catecholamine post-synaptic effects produced by drugs such as desipramine. The pros and cons of these theories have been debated elsewhere [1, 3–6].

The present article will concentrate on an analysis of adrenoceptor down-regulation by drugs with known effects on adrenergic neurons, i.e. monoamine oxidase (MAO) inhibitors and neuronal amine uptake inhibitors. Whereas other drugs, such as those acting on serotonergic neurons, may affect noradrenergic function indirectly, the intention here is to consider how adrenoceptors may adapt to the alteration in synaptic noradrenaline levels produced by those antidepressant drugs which are known to affect noradrenaline handling by the neuron. In particular, I shall concentrate on the α_2-adrenoceptor presynaptic inhibitory mechanism, which has excited much controversy.

The α_2-presynaptic adrenoceptor down-regulation theory in antidepressant action

In 1978, two groups of workers described experiments purporting to demonstrate desensitisation of α_2-presynaptic receptors following chronic treatment of rats with imipramine or desipramine. Svensson and Usdin [7] showed that the inhibitory effect of clonidine on the rate of spontaneous depolarisation of locus coeruleus (L.C.) neurons was reduced by chronic imipramine treatment, and Crews and Smith [8] showed that noradrenaline release from rat atria was enhanced by chronic desipramine treatment, with a reduction in the efficacy of phenoxybenzamine to cause a further enhancement of release. Reduction in α_2-presynaptic receptor sensitivity was invoked as an explanation for the enhanced release by chronic desipramine. Subsequently, reports of reduced binding of α_2-adrenoceptor ligands to cerebral cortical membranes from rats treated chronically with tricyclic and MAO inhibitor antidepressants appeared [9, 10]. Langer [11] suggested that α_2-presynaptic receptors down-regulate on continued exposure to agonist, and Cohen *et al.* [12] formulated an hypothesis whereby MAO inhibitor treatment leads to an increased noradrenaline level at the presynaptic receptors, leading to their down-regulation and hence enhanced neuronal release of noradrenaline. Antidepressant effect was related to correction of a pre-existing defect whereby α_2-presynaptic receptor number is enhanced in depression.

This hypothesis has provided a useful starting point in the study of neuronal regulation of noradrenaline release in the presence of antidepressant drugs, but it implies certain preconditions which must be proved to appertain. These can be stated as follows:

(a) Presynaptic α_2-receptors play a physiological

role in the limitation of neuronal noradrenaline release,

(b) Antidepressant drugs increase noradrenaline levels at the region of the α_2-presynaptic receptors, and

(c) Increased noradrenaline concentration at the level of the α_2-presynaptic receptor leads to its down-regulation.

As stressed by Cohen *et al.* [12], the initial increase in noradrenaline concentration at the presynaptic receptors may result from a constant slow leak from the neurone, as distinct from the enhanced exocytotic release which is anticipated to follow presynaptic receptor down-regulation, and which was suggested to lead subsequently to down-regulation of postsynaptic (α_1 and β) receptors [13]. The down-regulation of presynaptic (inhibitory) α_2-receptors was seen as a resetting of the braking mechanism which was necessary in order to allow the effect of the antidepressant drugs to increase noradrenergic drive along neuronal pathways critical for positive drive, motivation and cognition [13]. Down-regulation of postsynaptic receptors would play a compensatory role to the increased noradrenaline release.

Inhibitory α_2-adrenoceptors—presynaptic and postsynaptic—in the CNS

The first condition (a) above is a question that has been debated extensively, including articles in this journal [14, 15]. In spite of some negative reports, most physiological systems examined respond to α_2-adrenoceptor agonists with a decrease in noradrenaline release, and increased release is seen following α_2-adrenoceptor antagonists, when release is induced by depolarising stimuli. An objection to the situation of α_2-adrenoceptors on terminals of noradrenergic nerves (i.e. autoreceptors) was that α_2-adrenoceptors could not be detected proximal to a lesion in peripheral sympathetic nerve axons [16]; however, lack of success in detecting such binding sites could stem from choice of inappropriate methodology. Recent data using electrophysiological techniques have also raised doubts as to the existence of inhibitory α_2-presynaptic autoreceptors [17]. At present, however, the fact that α_2-adrenoceptor agonists, including noradrenaline, can limit noradrenaline release is well established [18, 19].

In the central nervous system, much misunderstanding has arisen over the use of the term "presynaptic", in describing the action of α_2-adrenoceptor agonists. To clarify how α_2-adrenoceptors can modify release of noradrenaline in the CNS, the following description of putative α-adrenoceptor sites, based on schemes proposed by others (e.g. Ref. 20), is presented (Fig. 1).

(1) An inhibitory postsynaptic receptor situated on the cell body or dendrons of a noradrenergic neuron, such as an L. C. cell. Evidence exists for catecholaminergic (adrenergic) neurons exerting an inhibitory input at L.C. neurons [21, 22], and α_2-adrenoceptor agonists (e.g. clonidine) produce inhibition. Activation at site 1 would reduce the firing rate of the L.C. cell, thus reducing release of noradrenaline from axonal terminals.

(2) Hypothetical inhibitory extrasynaptic receptor situated on the cell body or dendrons. The existence of 2 is inferred by analogy with the proposed extrasynaptic situation of α_2-adrenoceptors in the vascular system [23]. Positive identification of such extrasynaptic sites is not feasible with the techniques presently available.

(3) Presynaptic, inhibitory α_2-adrenoceptor situated on the axon terminal (autoreceptor). Activation of this receptor is suggested to cause local inhibition of release at the terminal varicosity on which it is situated, *without affecting release from other axonal branches of the neuron.* This action represents the true local negative feedback mechanism as proposed originally for peripheral sympathetic nerves [18, 20].

(4) Presynaptic α_2-adrenoceptor (heteroreceptor) located on terminal varicosity of a non-adrenergic neuron (e.g. serotonergic neuron).

In practical terms, it is extremely difficult to distinguish between agonist effects at these various sites. For example, injection of clonidine to the whole animal would activate all of the above α_2-adrenoceptor sites, and thus reduce noradrenaline release (and turnover) by an action at postsynaptic or extrasynaptic somato-dendritic sites (1 and 2), as well as presynaptic sites (3). In addition, it is important to emphasize that the consequences of receptor activation are markedly different, since agonist effects at somato-dendritic sites may alter membrane polarisation (as in L.C.), whereas agonist effects at presynaptic sites on terminal varicosities may alter neurotransmitter release by a process linked to local mobilisation of calcium ions and modulation of the exocytotic mechanism as well as causing membrane

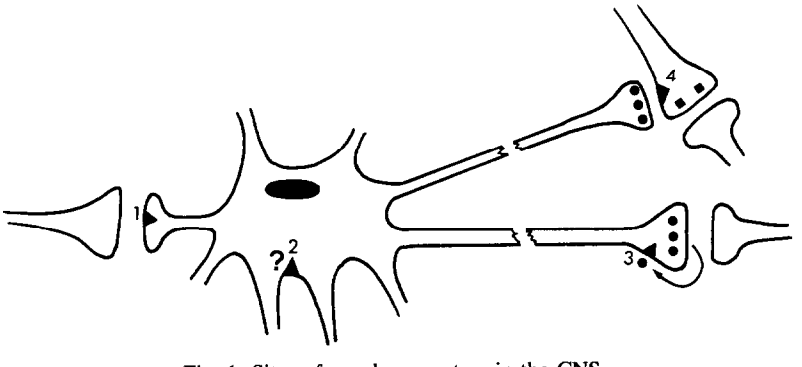

Fig. 1. Sites of α_2-adrenoceptors in the CNS.

hyperpolarisation [24]. In this context, it is of interest that subtypes of α_2-adrenoceptors have been proposed recently in peripheral tissues and in brain [25, 26].

Action of antidepressant drugs on catecholamine release

According to the α_2-presynaptic receptor down-regulation concept, initial administration of antidepressant drugs must elevate synaptic catecholamine levels although, assuming that receptor down-regulation is a process dependent on time and concentration of agonist at the receptors, the kinetics of agonist concentration will be critical. Thus, conceivably, down-regulation could result from a steady exposure to a relatively low level of agonist, in comparison to the high, episodic concentrations reached as a result of normal nerve activity.

In the case of neuronal amine uptake inhibitors, an increased synaptic amine level results as a consequence of reduced clearance of amine from the synaptic cleft. In some peripheral tissues, e.g. vas deferens, the administration of desipramine leads to a reduction in postsynaptic response, because of enhanced presynaptic receptor activation [27]. In vascular tissue, postsynaptic response and, presumably, synaptic amine levels are increased by desipramine treatment. Amine overflow, and postsynaptic response to nerve stimulation, are both enhanced markedly during administration of desipramine when an α_2-presynaptic antagonist is added [28, 29]. The difference between tissues in response to an amine-uptake inhibitor may be due to differences in synaptic cleft width and receptor topography [30]. Most synapses in the CNS are probably of the narrow cleft type, as in the vas deferens, whereas in blood vessels synapses are much wider.

In the case of MAO inhibitors, the initial effect of the drug is an increase in intracellular, rather than synaptic, amine concentration, because MAO is an intracellular enzyme [31]. Certain MAO inhibitors, e.g. tranylcypromine, may possess additional effects on amine uptake, but this should be seen as an intrinsic property of the molecule rather than the necessary consequence of MAO inhibition, and near complete MAO inhibition alone does not affect uptake of noradrenaline [32]. Neuronal uptake may be reduced considerably, however, if a reserpinised preparation is used, or if intracellular free amine concentration is increased in isolated organ preparations by addition of exogenous noradrenaline [33, 34]. Although MAO inhibition may increase cytoplasmic amine concentration, active efflux of noradrenaline may be small due to the low internal sodium concentration leading to low availability of carrier sites on the internal side of the cell membrane [35]. The initial effect of MAO inhibition, therefore, would not produce much change in synaptic noradrenaline levels, and acute MAO inhibition (by low doses of selective inhibitors) has little or no effect on neuronal events, in periphery or in CNS. As an example, in comparison with the profound effect of desipramine on L.C. firing rate, a very large dose of 10 mg/kg clorgyline had to be administered to rats in order to produce a reduction in L.C. firing [36], whereas 1 mg/kg produces substantial MAO type A inhibition. High local concentration of clorgyline may possess α-adrenoceptor antagonism, at both α_1 and α_2 sites [37, 38].

The effects of chronic treatment with tricyclic antidepressants and MAO inhibitors on noradrenaline release and turnover have been reviewed elsewhere [3, 6], but no unifying picture of changes in release can be presented. This is, to some extent, due to the difficulty in interpretation of the data from conventional techniques relying on measurement of metabolite levels as an index of turnover, when the drugs under study themselves have primary effects on amine metabolism. In the CNS, an additional problem lies in the common practice of measuring whole brain tissue levels instead of discrete areas. Thus, if a drug increased catecholamine turnover in the brain stem, inhibitory input to L.C. neurons would be enhanced, leading to reduced catecholamine turnover at terminal areas of L.C. neurons, in hippocampus or cortex. Measurement of whole brain levels of a metabolite such as 3-methoxy-4-hydroxyphenylglycol sulfate (MOPEG-SO_4) would yield the resultant of reduced cortical levels and increased brain stem levels. Much evidence points to a reduction in catecholamine turnover in the CNS following chronic treatment with both tricyclic drugs and MAO inhibitors, as shown by a reduced rate of L.C. spontaneous activity [39], reduced levels of normetanephrine [40], and reduced CSF levels of dopamine beta hydroxylase [41]. Other workers have reported increased noradrenaline turnover, and increased brain levels of MOPEG-SO_4, following chronic desipramine [42, 43]. These observations make it difficult to accept a single hypothesis of β-adrenoceptor down-regulation as being a postsynaptic response to elevated noradrenaline levels, and they point to an indirect role of serotonergic neurons or other biochemical actions of the drugs on membrane composition or fluidity [44]. On the other hand, the effect of the tricyclic drugs in producing enhanced α_2-presynaptic receptor activation, while neuronal total output of noradrenaline and metabolites is not increased, points to the possibility that these drugs may increase levels of noradrenaline at presynaptic receptors irrespective of total catecholamine turnover. Inhibition of MAO leads to a greater proportion of free noradrenaline in the perfusate of isolated tissues [45], which may also indicate a greater availability of the free amine at pre- and postsynaptic receptors. In the brain, enhanced catecholamine levels at neuronal receptor sites could result from inhibition of glial cell active amine uptake [46] or MAO activity, irrespective of neuronal release.

Recently, we observed that, following chronic but not acute MAO inhibition with clorgyline, plasma noradrenaline (and adrenaline) levels were enhanced following sympathetic stimulation in the pithed rat [47]. This and other observations point to a time-dependent process resulting from chronic MAO inhibition whereby neuronal noradrenaline release by depolarising stimuli is enhanced, probably as a result of alteration in internal compartmentalisation of the neurotransmitter. Such an event could lead, for example to a primary effect of enhanced release at

neurons presynaptic to the L.C., leading to inhibition of release from L.C. axonal terminals in other parts of the brain.

Chronic antidepressant treatment could affect adrenoceptor number by a mechanism independent of catecholamine levels. In isolated cell systems devoid of endogenous catecholamine production, exposure to desipramime (2–5 μM for 12 days) reduced B_{max} for a β-adrenoceptor ligand [48], and neuropeptide Y has been reported to increase α_2-adrenoceptor number [49]. However, it would be surprising if drugs with such divergent structures, such as MAO inhibitors and tricyclics, and with such marked effects on catecholamine metabolism, produced adrenoceptor down-regulation by an action independent of catecholamines.

Evidence for down-regulation of α_2-adrenoceptors by chronic antidepressants

Biochemical and physiological studies. A variety of behavioural and biochemical responses to the relatively α_2-selective agonist, clonidine, are reduced following chronic antidepressant treatment. These include clonidine-induced hypothermia, sedation, depression of acoustic startle, hypotension, suppression of hypothalmic self-stimulation and reduction in whole brain MOPEG-SO_4 levels (see Refs. 1, 3 and 6). While these effects may be classed as mediated by α_2-adrenoceptors, none of them can be conclusively related to an action at presynaptic receptors (type 3) in the CNS. Thus, reduction in MOPEG-SO_4 would result from an action at somatodendritic receptors situated on L.C. cells, which may also be the site of action of clonidine in suppression of L.C. firing rate. Similarly, clonidine-induced hypotension is considered to be an action at postsynaptic receptors in the CNS [50].

A further problem in the study of α_2-adrenoceptor events elicited by clonidine is that clonidine is a partial agonist, which implies that its effects may be altered markedly by the presence of high endogenous levels of agonist [51]. In this case, reduced response to clonidine would be accompanied by enhanced response to an α_2-adrenoceptor antagonist. Unfortunately, antagonist effects have been investigated in very few studies. In the work of Crews and Smith [8], a reduced response to phenoxybenzamine was seen in isolated atria of rats treated chronically with desipramine, but physiological responsiveness of the preparation may have been maximal following desipramine treatment, allowing for no further increase by the antagonist. Inhibition of the rate of depolarisation of L.C. cells by α_2-adrenoceptor agonists was reduced by chronic treatment with tricyclic drugs, but α_2-adrenoceptor antagonists still produced a large increase in firing rate [7, 43]. We have studied the effect of chronic antidepressant treatment on rat vas deferens and reported that the inhibitory action of clonidine on contractions elicited by electrical field stimulation was reduced [38]. This action of clonidine is presynaptic, but again increased endogenous noradrenaline levels could have resulted in the reduced clonidine response without a reduction in presynaptic receptor number. Recently, we observe an enhanced response of the tissue to yohimbine following chronic treatment with both MAO inhibitors and desipramine, indicating that presynaptic receptors may be occupied by endogenous agonist [52]. In pithed rats treated chronically with clorgyline, while noradrenaline release was enhanced, there was no reduction in the ability of yohimbine to further increase noradrenaline release [47].

In the CNS, inhibition of release of noradrenaline by α_2-adrenoceptor agonists from slices or synaptosomes prepared from cerebral cortex may be considered an effect at inhibitory presynaptic receptors, since the cortex contains only axonal terminals of the noradrenergic neurons. It is interesting that no desensitisation to α_2-adrenoceptor agonists was detected in such preparations following chronic treatment with both clorgyline and desipramine [53, 54] although basal efflux of labelled noradrenaline was enhanced.

Ligand binding studies. Results of receptor binding studies with α_2-adrenoceptor ligands have shown both increases [55], decreases [9] and no change [56, 57] in receptor number in rat brain following chronic antidepressant treatment. This variability may be due to the use of agonist and antagonist ligands, although Cohen, Campbell and co-workers consistently find a reduction in binding of [^{3}H]clonidine and [^{3}H]yohimbine to cortical membranes following chronic clorgyline treatment [10, 13]. Ligand-binding studies in rat brain can give no indication as to presynaptic or postsynaptic location of the receptors. Ligand binding to α_2-adrenoceptors has also been shown to be dependent on local noradrenaline concentrations, and increased antagonist ligand binding could be produced by addition of sodium ions and GTP (which displace bound agonist) when noradrenaline concentrations in the preparation were high [58]. Studies on the effects of sodium ions and GTP on α_2-adrenoceptor ligand binding in brains of rats treated chronically with antidepressants are lacking, so that some observations of reduced agonist ligand binding could be explained by retained endogenous agonist rather than a true reduction in receptor number.

α-Presynaptic receptors—up-regulation or down-regulation?

If α_2-adrenoceptors exert different functions according to their location on the neuron, it is quite conceivable that their regulation, in terms of increases or decreases in total number (B_{max}), will differ at these various locations. In the case of a postsynaptic α_2-inhibitory receptor, excess release of endogenous agonist would be expected to lead to compensatory down-regulation, as demonstrated for β-adrenoceptors, since the cell would be expected to attempt to escape from the excessive inhibitory input. In the case of a presynaptic inhibitory α_2-adrenoceptor, however, the response to excessive agonist levels should be *up-regulation*, since this is the response necessary in order to oppose the effect of enhanced neuronal release, which is the assumed function of the negative feedback system. A down-regulation of inhibitory presynaptic α_2-adrenoceptors, leading to a further increase of neurotransmitter (as postulated for the antidepressants), would be contrary to the putative function of the

receptor. Naturally, one realises that the straightforward teleological approach is not always tenable in biological systems, but it is a useful point of reference as a starting hypothesis, and one must understand the functioning of the system before the teleological approach can be ruled out. The possibility of presynaptic α_2-receptor up-regulation has been suggested by some workers in relation to antidepressant action [55, 59]. Asakura *et al.* [55] observed increased binding of α_2-adrenoceptor ligand following chronic desipramine treatment, and they suggested that this was a compensatory response to increased synaptic noradrenaline levels. The concept of up-regulation of receptor sites by prolonged increase in local agonist concentration is not new. In the field of endocrinology, prolactin, growth hormone and oestradiol have been reported to up-regulate their own receptor sites following administration of exogenous hormone for several days [60, 61]. This receptor up-regulation may represent a physiological amplification system, as in the enhanced secretion of fetal pulmonary surfactant by increased endogenous prolactin [62].

In the periphery, decreased responsiveness to clonidine occurred in vas deferens following deafferentation by surgical or pharmacological means, indicative of a reduced α_2-presynaptic effect when synaptic noradrenaline level was low [63, 64]. On the other hand, reserpinisation produced increased α_2-adrenoceptor ligand binding in the vas deferens [65].

If presynaptic up-regulation occurs, then sustained infusion of an α_2-adrenoceptor agonist should produce a more responsive presynaptic inhibitory system, although further increase in presynaptic receptor number over that existing at a normal level of neurotransmission may not occur. Interruption of prolonged clonidine treatment results in sympathetic overactivity in animals and humans [66, 67] which is probably mediated by a central increase in sympathetic outflow. Again, this effect may be the result of reduced number of α_2-postsynaptic receptors in brain stem areas, which would be expected to cause increased sympathetic efferent activity. Presynaptic α_2-adrenoceptor responsiveness has been reported to be reduced following chronic clonidine administration [68], but imidazoline derivatives may act as a site different from the phenylethylamines [69] so that chronic clonidine treatment may not be the best model in which to study regulation of the α_2-adrenoceptor.

Some stress situations, including animal handling and morphine abstinence [70, 71], have been shown recently to be accompanied by increased binding of α_2-adrenoceptor ligands in the CNS. Noradrenaline release and turnover should be enhanced in these situations, but α_2-adrenoceptor number is known to be enhanced by secondary factors, such as steroids, neuropeptide Y and purines [49, 72, 73]. This illustrates the difficulty of demonstrating receptor modulation by a single external challenge. Indeed, chronic antidepressant treatment presents a stress to the animals, being frequently accompanied by reduced food and water intake and some degree of weight loss, as well as increased daytime activity. Thus, alteration in hormonal balance could produce secondary changes in receptor number.

While the modulation of α_2-adrenoceptors by antidepressants is still not clear, a number of reports demonstrate rapid down-regulation of cortical β-adrenoceptors when antidepressants are combined with α_2-adrenoceptor antagonists [74]. One possible interpretation of these findings is that α_2-inhibitory receptor activation (pre- or postsynaptic) restrains the underlying effect of the antidepressants to enhance catecholamine release, and that desensitisation of these receptors is required in order to permit down-regulation of the postsynaptic β-adrenoceptor. Alternatively, presynaptic α_2-inhibitory stimulation could be maintained by retained agonist, so that addition of exogenous agonist will present an apparent down-regulation, as would be seen also in ligand binding studies. In the case of the β-adrenoceptor, the agonist–receptor complex has been shown to tighten with increased time of exposure [75]. Retained agonist may be bound to receptor sites which are partially internalised within the cell membrane, as a first stage of receptor internalisation. In this form, the agonist–receptor complex may maintain its inhibitory activity, and the agonist may be displaceable by antagonists which are relatively lipophilic. In any case, further investigations of the biological and clinical effects of combined antidepressant/α_2-adrenoceptor antagonist treatment will be of interest.

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