Central nervous actions of \(\beta\)-adrenoreceptor antagonists

**J. CONWAY, D. T. GREENWOOD AND D. N. MIDDLEMISS**

Departments of Biology and Biochemistry, Imperial Chemical Industries, Pharmaceuticals Division, Macclesfield, Cheshire, U.K.

Since the introduction of the \(\beta\)-adrenoreceptor antagonists to clinical practice in the late 1960s, their use has become established in a variety of cardiovascular diseases in which their mode of action depends upon the attenuation of effects of sympathetic stimulation. In hypertension, however, the mode of action is uncertain and a centrally mediated action has been proposed. Furthermore a beneficial effect in disorders of the central nervous system has been suggested but not proven.

In the last 2 years, the presence of \(\beta\)-adrenoreceptors in the central nervous system has been convincingly demonstrated and this has provided an approach to the rational use of these drugs in central nervous system dysfunction. We intend briefly to present the evidence that there are \(\beta\)-adrenoreceptors in the central nervous system, that the \(\beta\)-adrenoreceptor antagonists have central effects in animals and man and that these may be responsible for some of their therapeutic effects. Caution must, however, be exercised in making this interpretation from the available evidence since we also draw attention to the hitherto unexpected finding that many \(\beta\)-adrenoreceptor antagonists also affect responses to 5-hydroxytryptamine and bind specifically to its receptor in central nervous system tissues.

**Evidence for \(\beta\)-adrenoreceptors in the central nervous system**

The first biochemical demonstration of \(\beta\)-adrenoreceptors in the central nervous system was by Kakiuchi & Rall (1968). They showed that an adenylate cyclase from rabbit cerebellum, when stimulated by isoprenaline, produced an increase in cyclic AMP, which was blocked by dichloro-

isoprenaline. Later reports (Chasin, Rivkin, Mam- rak, Samaniego & Hess, 1971) indicated that \(\alpha\)-adrenoreceptors in the central nervous system also respond to stimulation by an increase in cyclic AMP, although these receptors are not blocked by \(\beta\)-adrenoreceptor antagonists. Further work on the \(\beta\)-adrenoreceptor in the central nervous system was hampered by the technical difficulties of preparing catecholamine-responsive adenylate cyclases, particularly in homogenates. These problems have recently been overcome by the introduction of high-affinity radiolabelled ligands which can be used directly to quantify \(\beta\)-adrenoreceptors.

The radioligands used have been \([\text{H}]\)-propranolol (Nahorski, 1976); dihydro[\text{H}]-alprenolol (Alexander, Davis & Lefkowitz, 1975; Bylund & Snyder, 1976) and \([\text{I}]\)iodohydroxybenzylpindolol (Sporn & Molinoff, 1976). The binding of these ligands to central nervous system homogenates was rapid, reversible, stereospecific and of high affinity. When dihydroalprenolol was used as the radiolabelled ligand, the order of potency of the catecholamine agonists was isoprenaline > adrenaline ~ noradrenaline (Bylund & Snyder, 1976). The order of potency of the catecholamine agonists in displacing these ligands from their binding sites satisfied the criteria for \(\beta\)-adrenoreceptors.

On the basis of electrophysiological experiments at the Purkinje cell layer in the cerebellum, Hoffer, Siggins & Bloom (1971) postulated a role for the \(\beta\)-adrenergic system in synaptic transmission. The synaptic location of the dihydroalprenolol-binding sites in rat brain homogenates is in accord with these findings (Bylund & Snyder, 1976; Davis & Lefkowitz, 1976). Further convincing evidence for the presence of \(\beta\)-adrenoreceptors in the Purkinje cell layer has been provided by the use of a fluorescent analogue of propranolol, 9-amino-acridinopropranolol, which has been shown to selectively label, *in vivo*, this area of the cerebellum (Melamed, Lahav & Atlas, 1976).
There is considerable variation in the density of dihydroalprenolol-binding sites in brain areas of both the rat and the monkey (Alexander et al., 1975; Bylund & Snyder, 1976). β-Adrenoceptors have been identified in the limbic forebrain, the extrapyramidal areas, the hypothalamus, the medulla, the cerebellum and the pineal gland. In the pineal it has been shown that the number of β-adrenoreceptors varies during the diurnal light–dark cycle (Kebabian, Zatz, Romero & Axelrod, 1975). These changes, which have been suggested to contribute to the phenomena of super- and subsensitivity during treatment of both animals and man with β-adrenoreceptor antagonists.

**Neuropharmacological and behavioural properties of β-adrenoreceptor-blocking drugs**

Few drugs are entirely specific in their actions and β-adrenoreceptor antagonists are no exception. It is also important in any consideration of the central actions of these agents to appreciate their pharmacological heterogeneity with respect to such factors as penetration of the blood–brain barrier, intrinsic sympathomimetic activity and membrane stabilization. Difficulties in interpretation arising because of actions on peripheral β-adrenoreceptors may be largely eliminated, in animal studies, by direct application of agonist and/or antagonist drugs into the cerebroventricular system, specific brain structures or on to individual neurons. Thus micro-iontophoretic application of sympathetic agonists and antagonists has convincingly demonstrated the presence of inhibitory β-adrenoreceptors in cerebral cortical neurons (Straughan, Roberts & Sobiezek, 1968; Bevan, Bradshaw & Szabadi, 1977) and in cerebellar Purkinje cells (Hoffer et al., 1971). Similarly, micro-injection and superfusion techniques have implicated the existence of β-adrenoreceptor systems in hypothalamic regions, which may be involved in the normal control of feeding behaviour (Leibowitz, 1970) and blood pressure (Philippu & Kittel, 1977).

The majority of available information on the central actions of β-adrenoreceptor-blocking drugs has, however, been derived by use of more conventional routes of administration and controversy therefore still surrounds not only the relative importance of central as opposed to peripheral receptor antagonism, but also the possible contribution of actions other than those on β-adrenoreceptors. In the case of propranolol the latter may include alterations in the activity of tyrosine hydroxylase (Peters & Mazurkiewicz-Kwilecki, 1975; Raine & Chubb, 1977) or dopamine β-hydroxylase (Raine & Chubb, 1977) or of monoamine oxidase (Milmore & Taylor, 1976). Conflicting reports on the effect of acute and chronic administration of β-adrenoreceptor antagonists on brain biogenic amine concentrations have been published (Laverty & Taylor, 1968; Herman, Kmiecik-Kolada, Drybanski, Sokola, Trzeciak & Chrusciel, 1971; Mahon, O'Donnell & Leonard, 1977; Milmore & Taylor, 1976). The origins of the discrepancies in these reports are not clear. Studies on amine turnover in rats after acute administration of propranolol are claimed to show a selective enhancement of dopamine turnover in the limbic regions of the brain (Fuxe, Bolme, Agnati & Everitt, 1976a), whereas L- and D-propranolol cause reduced and increased turnover of noradrenaline respectively in the cortex cerebri (Fuxe, Bolme, Agnati & Everitt, 1976b).

Evidence is also accumulating which indicates that propranolol and other β-adrenoreceptor antagonists, including oxprenolol and pindolol, may not possess the specificity of action formerly attributed to them. They share an ability to antagonize certain peripheral actions and specific forms of behaviour in which 5-hydroxytryptamine is involved (Weinstock & Schechter, 1975; Green & Grahame-Smith, 1976; Weinstock, Weiss & Gitter, 1977). Furthermore, the recent demonstration of a stereospecific interaction of propranolol and other β-adrenoreceptor antagonists with rat brain synaptosomal membranes has provided more direct evidence for the involvement of 5-hydroxytryptamine in the central action of these drugs (Middlemiss, Blakeborough & Leather, 1977).

Notwithstanding difficulties of interpretation, information derived from animal experiments demonstrates that β-adrenoreceptor-blocking drugs exert profound effects on the mammalian central nervous system. This may be relevant to an understanding of the clinical findings discussed below. Most investigations have centred upon propranolol, but other β-adrenoreceptor antagonists including oxprenolol and sotalol share many of the described effects. A variety of neuropharmacological and behavioural actions have been described, including inhibition of locomotor activity (Murmamn, Almirante & Saccani-Gueffi, 1966), muscle relaxation and inhibition of centrally evoked tremor (Agarwal & Bose, 1967; Sharma, Singh &
Central actions of β-adrenoreceptor antagonists

Dhawan, 1971; Leslie, Hayman, Ireson & Smith, 1972), elevation of seizure thresholds (Leszkovszky & Tardos, 1965), behavioural disinhibition (Sepinwall, Grodsky, Sullivan & Cook, 1973; Noble & Delini-Stula, 1976) and attenuation of various states of hyperarousal whether these be evoked by brain lesions (Bainbridge & Greenwood, 1971), isolation (Weinstock & Speiser, 1973) or by the administration of stimulant drugs (Weinstock & Speiser, 1974; Delini-Stula & Meier, 1975). Although the majority of these effects indicate a depressant action on the central nervous system, propranolol and sotalol also antagonize alcohol-induced narcosis (Smith, Hayashida & Kim, 1970; Hayashida & Smith, 1971) and nifenalol (INPEA) possesses overt central nervous stimulant properties.

In contrast to the reported findings in animals, there is a paucity of unequivocal evidence indicative of direct effects of β-adrenoreceptor antagonists on the human central nervous system. Although observations in psychotic patients have suggested that doses of propranolol which effectively block peripheral β-adrenoreceptors also produce electroencephalographic (EEG) changes and in visually evoked potentials (Orzack, Brancouner & Gardos, 1973), such findings are generally unsupported by EEG studies which have been conducted in volunteers. Thus propranolol has no significant effects on either normal or amphetamine-influenced sleep patterns (Dunleavy, Maclean & Oswald, 1971), on auditory-evoked potentials (Lader & Tyrer, 1972) or on the EEG response known as the contingent negative variation (Ashton, Millman, Telford & Thompson, 1976). Impaired performance in several psychomotor function tests, e.g. pursuit rotor and reaction time, have been demonstrated after administration of single doses of oxprenolol or propranolol (Glaister, Harrison & Allnutt, 1973; Bryan, Efiong, Stewart-Jones & Turner, 1974) but other, similar, studies have yielded conflicting results (Tyrer & Lader, 1974a, b; Ogle, Turner & Markomihelakis, 1976). It is noteworthy that performance of those tests dependent primarily on cerebral function, e.g. serial subtraction and critical flicker frequency, invariably remains unimpaired by β-adrenoreceptor-blocking drugs. Thus the decrement in performance noted by some authors may be a reflection of an action on skeletal muscle rather than a depressant effect on the central nervous system.

Reference has already been made to the apparent involvement of β-adrenoreceptors in the control of certain hypothalamic functions. Thus the observation that propranolol modifies human growth hormone secretion (Imura, Kato & Ikeda, 1968; Massara & Camanni, 1972) and the sensitivity of the baroreceptor reflex (Eckberg, Abboud & Mark, 1976), and possibly that of the medullary chemoreceptors to carbon dioxide (Mustchin, Gribbin, Tattersfield & George, 1976), suggests a possible role for β-adrenoreceptors in midbrain function.

β-Adrenoreceptor antagonists in the treatment of disorders of the central nervous system

Whatever the significance of the various biochemical, neuropharmacological and behavioural properties of β-adrenoreceptor antagonists, there is increasing interest in the use of these drugs in the treatment of several psychiatric and neurological conditions in which a direct action on the central nervous system may be at least partly implicated.

The use of β-adrenoreceptor antagonists in the control of anxiety stems from the studies of Granville-Grossman & Turner (1966), who showed propranolol to be more effective than placebo in relieving the autonomically mediated symptoms of pathological anxiety. Numerous subsequent clinical trials have confirmed the value of β-adrenoreceptor antagonists in alleviating the ‘somatic’ manifestations of anxiety. These symptoms, e.g. tachycardia, palpitations, sweating and gastrointestinal disturbances, arise as a consequence of excessive stimulation of peripheral β-adrenoreceptors and they commonly occur during states of acute emotional arousal.

Although the ‘psychic’ elements of anxiety also respond to β-adrenoreceptor antagonists, the balance of opinion favours a predominantly peripheral site of action. Of particular relevance in this context are the clinical observations that the D-propranolol, which is virtually devoid of β-adrenoreceptor antagonistic activity, is ineffective in treating anxiety (Bonn & Turner, 1971).

Excessive stimulation of the sympathetic nervous system is also a common finding in alcoholism and drug dependence, particularly during withdrawal, and this would suggest a logical place for β-adrenoreceptor antagonists in the management of such conditions. Conflicting reports have appeared in recent years concerning the effects of propranolol in the treatment of alcoholics (Carlsson & Johansson, 1971; Noble, Parker, Alkana, Cohen & Birch, 1973), opiate addicts (Grosz, 1972; Lowen-
stein, 1973) and in alleviating LSD psychoses (Linken, 1971). The behavioural interactions between β-adrenoreceptor antagonists on the one hand and alcohol and certain stimulant drugs on the other, might indicate that central actions are involved in addition to those of peripheral β-adrenoreceptors.

Of increasing interest and theoretical importance are the claims for beneficial effects of high doses of propranolol in various psychotic states. Interest was initially aroused after the observation of an improved mental state during treatment of acute porphyria with propranolol (Atsmon & Blum, 1970). Dramatic improvements in florid symptomatology have subsequently been reported in both acute and chronic schizophrenics and manic patients (Atsmon, Blum, Steiner, Latz & Wijsenbeek, 1972; Atsmon, 1973; Yorkston, Zaki, Malik, Morrison & Havard, 1974; Von Zerssen, 1976; Yorkston, Gruzelier, Zak, Hollander, Pitcher & Sergeant, 1977). Where beneficial effects have been observed doses have been high in relation to those normally required to effect peripheral β-adrenoreceptor blockade, suggesting that other actions of the drug or a metabolite might be involved. Patients who improved appear to be those who exhibit a high urinary excretion of catecholamines and 3-methoxy-4-hydroxyphenylglycol (MHPG) while taking the drug. In contrast, other investigators (Orzak et al., 1973; Gardos, Cole, Volicer, Orzack & Oliff, 1973) have observed little if any benefit and the outcome must await further controlled studies. If β-adrenoreceptor antagonists prove to be useful in certain forms of psychosis important theoretical issues will be raised since these drugs are clearly devoid of the classical antipsychotic (neuroleptic) activity possessed by the phenothiazine and butyrophenone drugs.

Hypotensive action of β-adrenoreceptor agonists

A central action may account for the antihypertensive effect of β-adrenoreceptor-blocking agents since the administration of many of these substances into the lateral cerebral ventricle leads to a fall in blood pressure in conscious animals (Day & Roach, 1973; Reid, Lewis, Myers & Dollery, 1974). For propranolol, the effect is specific for the L-isomer and it has been shown that the fall in blood pressure is accompanied by a reduction in the rate of splanchnic nerve discharge (Lewis & Haeusler, 1975). This is a preganglionic nerve and the inference is that propranolol induces a reduction in sympathetic nervous activity. In support of this suggestion is the finding in rabbits of a gradual decline in tyrosine hydroxylase and dopamine β-hydroxylase activities in the superior cervical ganglion after the administration of propranolol for 6 days (Raine & Chubb, 1977). This effect, which is attributed to a decrease in sympathetic nervous activity, was also observed with other β-adrenoreceptor-blocking agents, but not with D-propranolol. It has also been shown that propranolol affects the sensitivity of the baroreceptor reflex in man particularly after the assumption of the upright position (Eckberg et al., 1976).

These findings indicate that β-adrenoreceptor-blocking agents possess a central action affecting the control of blood pressure. It remains, however, to be shown whether this is responsible for their antihypertensive action in man.

Conclusion

Biochemical and neuropharmacological studies in animals have provided convincing evidence for the existence of central β-adrenoreceptors and that several β-adrenoreceptor antagonists possess marked central effects in animals is clearly established. There is also little doubt that these drugs exert central effects in man, since reported side effects include vivid dreams, insomnia, visual and tactile hallucinations (Stephen, 1966; Prichard & Gillam, 1964; Hinshelwood, 1969; Tyrer & Lader, 1973). However, in none of the clinical states is it possible to distinguish, with certainty, between the undoubted peripheral actions of β-adrenoreceptor antagonists and possible effects at central sites. It is difficult, however, to believe that the effect in psychoses and in the production of hallucinations is not attributable to actions on the central nervous system.

Key words: β-adrenoreceptors, central nervous system.

References


