THE ANXIOLYTIC EFFECTS OF β-ADRENOCEPTOR BLOCKERS

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SYNOPSIS

This paper draws attention to the potential role of the β -adrenoceptor blockers in the treatment of anxiety associated with sympathetic overactivity. It reviews briefly the current controversy regarding the question of a central or peripheral mechanism of the anxiolytic action of these blockers. Focus is brought upon new information from recent investigations which, on balance, favours a peripheral site of anxiolytic action rather than one due to central depression. Reference is made to evidence suggesting the existence of β-adrenoceptors in the brain; although these are not concerned with central depression they may or may not contribute to anxiolysis when blocked.

The symptoms of anxiety are usually manifested by unreasonable feelings of fear, associated with panic, tension, insomnia and inability to concentrate, and often are accompanied by signs of overactivity of the autonomic nervous system. Overactivity of the sympathetic component, with increased adrenal catecholamine output, is the predominant feature.

Anxiolytic drugs like the barbiturates and the benzodiazepines, mainly having a central action, with little or no effect on peripheral structures, have traditionally been used with success in most cases of anxiety. In recent years, investigations have indicated that blockade of the somatic manifestations, by antagonism of the peripheral effects of sympathetic overactivity, can also be effective in the treatment of anxiety. Propranolol and other β-adrenoceptor blockers have been shown to be of value as anxiolytics and to be able to inhibit the physiological response to emotional arousal (Granville-Grossman and Turner, 1966; Bonn, Turner and Hicks, 1972; Taggart, Carruthers and Somerville, 1973; Tyrer and Lader, 1973, 1974a, b, c). Propranolol has also been used with success in relieving many of the manifestations of hyperthyroidism without affecting thyroid function (Turner, Granville-Grossman and Smart, 1965; Shanks, Hadden, Lowe, McDevitt and Montgomery, 1969; Turner, 1974). The β-adrenoceptor blockers, in fact, already have an established role in the treatment of hyperthyroidism (Turner, 1974). Evidence that β-adrenoceptor blockers relieve those manifestations of anxiety which are mainly due to stimulation of peripheral β-adrenoceptors is now unequivocal, and these drugs have been used successfully in anxiety where the somatic symptoms have been prominent (Granville-Grossman and Turner, 1966; Imhof and Brunner, 1970; Marsden, 1971; Kellner, Collins, Shulman and Pathak, 1974; Tyrer and Lader, 1974a, c). A recent report from Belfast on the anxiolytic effect of oxprenolol in somatic anxiety originating from environmental stress due to civil unrest in that city confirms this (McMillin, 1975). Anxiety not associated with complaints attributable to sympathetic activity (psychic anxiety) is, as expected, relieved only by drugs like diazepam and not by propranolol (Tyrer and Lader, 1974a). Thus, it appears that the β-adrenoceptor blockers have a useful role to play in the treatment of anxiety where somatic manifestations, due to sympathetic over-activity, trouble the patient (somatic anxiety). The main advantage of these blockers over the traditional anxiolytics is that they are quite free from sedative effects. The role of the β-adrenoceptor blockers in the treatment of somatic anxiety is, however, not yet as well established as their use in the therapy of hyperthyroidism.

There is still some controversy over the mechanism of action which is responsible for the anxiolytic effects of the β-adrenoceptor blockers. The question of a direct central depressant action or a peripheral cardiovascular effect remains to be answered conclusively. Support for a direct action on the CNS has been based mainly on findings from animal experiments, and the fact that propranolol readily penetrates the blood-brain barrier. Although propranolol has been shown to produce sedation in animals (Leskovszky and Tardos, 1965; Bainbridge and Greenwood, 1971), these effects have been obtained with extremely high doses, far in excess of the anxiolytic doses used in man. Leskovszky and Tardos (1965) attributed the sedative effects observed in their experimental animals to the local anaesthetic action of propranolol. Evidence for a peripheral mechanism due to β-adrenoceptor blockade in the cardiovascular system comes from observations in man. It has been shown by Bonn and Turner (1971) that the (d—) isomer of propranolol, which has approximately 1/60th the β-adrenoceptor blocking activity of the dl-form, does not relieve anxiety even when given in doses higher than that of the racemic

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form. Both preparations, however, have the same degree of brain penetrability. Practolol, on the other hand, has been shown to be an effective anxiolytic agent although it has difficulty in penetrating the blood-brain barrier (Bonn *et al*, 1972). The anxiolytic effects of small doses of propranolol in hyperthyroidism (Turner *et al*, 1965) also appears to be related to the degree of amelioration of symptoms attributable to cardiovascular overactivity. Propranolol has not been shown to have sedative effects even in acute oral doses of 120 mg (Dunleavy, Maclean and Oswald, 1971). No effects were shown on sleep, monitored by continuous EEG recordings. Further intensive studies by Lader and Tyrer (1972) have confirmed the findings of Dunleavy *et al* (1971). They found no evidence of CNS depression in tests on psychomotor function, in the EEG responses, and in ratings of mood and subjective symptoms, with propranolol or sotalol. Similar conclusions regarding the absence of central effects were arrived at by other workers (Stone, Gleser and Gottschalk, 1973; Gottschalk, Stone and Gleser, 1974) who examined the effects of propranolol on anxiety-evoked responses. The absence of central depressive effects has also been reported by Turner and Hedges (1973), and by Ogle and Turner (1974) who tested the effects of 160 mg oral doses of propranolol or oxprenolol on healthy volunteers. More recent work by Ogle, Turner and Markomihilakis (to be published) has shown that even extremely high oral doses of 320 mg propranolol or oxprenolol, greatly exceeding the anxiolytic dose range, do not have any central effects in healthy subjects. Thus, there is strong evidence to indicate that the anxiolytic action of β-adrenoceptor blockers is not exerted through central depression.

Only two reports have suggested the β-adrenoceptor blockers may have a central effect in man (Glaister, Harrison and Allnutt, 1973; Bryan, Efiong, Stewart-Jones and Turner, 1974). Impairment of pursuit rotor performance (Glaister *et al*, 1973) and reaction time and hand-eye co-ordination tests (Bryan *et al*, 1974) led these workers to conclude that central depression had occurred. The findings of Ogle *et al* (to be published) suggest that impairment of some psychomotor tests, as those used by Glaister *et al* (1973) and Bryan *et al* (1974), do not necessarily reflect central depression, and that the present practice of regarding impairment of CNS function tests as an indication of depression only of central origin needs to be examined further. These workers point out that the evaluation of results of CNS function tests should take into consideration the degree of muscle co-ordination that is involved in these tests when drugs which may directly affect skeletal muscle activity are investigated. As β-adrenoceptor stimulation increases the rate of relaxation of slow skeletal muscle (Bowman and Zaimis, 1958; Zaimis, 1973), which is blocked by propranolol (Marsden, Foley, Owen and McAllister, 1967), it is possible that β-adrenoceptor blockade could affect skeletal muscle co-ordination. Ogle *et al* found that those CNS function tests relying solely on central activity (critical flicker frequency and serial subtraction tests) were unimpaired by the high doses of propranolol or oxprenolol used. However, those tests relying substantially on skeletal muscle co-ordination (pursuit rotor, reaction time and disc dotting tests) were sometimes impaired. Although the theory of Ogle *et al* requires to be substantiated by further investigations, it does account for the apparently conflicting results that have been obtained with some of the currently used CNS function tests in work carried out with β-adrenoceptor blockers in relation to CNS function.

From the findings that have so far been made in this field, it can be concluded that the sedative effects of high doses of propranolol that have been demonstrated in animal experiments are quite irrelevant to the anxiolytic actions of small doses of β-adrenoceptor blockers. The CNS function tests that have been used in man, which rely solely on central activity, are extremely sensitive and will detect depression due to sedation (Hedges, Hills, Maclay, Newman-Taylor and Turner, 1971; Hedges, Turner and Harry, 1971); these tests have consistently been unaffected even by excessively high doses of propranolol or oxprenolol. The theory of a peripheral site of action, by β-adrenoceptor blockade, appears to be the probable mechanism whereby anxiolysis is effected.

The possibility of propranolol also having a central action, other than that of sedation, which may or may not contribute to its anxiolytic effects cannot yet be totally excluded. Estler and Ammon (1967, 1971) have shown that methamphetamine-induced motor activity and cerebral carbohydrate metabolism in mice can be antagonised by propranolol. However, the findings of Dunleavy *et al* (1971) are at variance as dexamphetamine-induced sleep disturbances in humans are not antagonised by propranolol. The existence of central β-adrenoceptors is suggested by the work of Connor, Rossi and Baker (1967) and Srivastava, Kulshrestha, Singh and Bhargava (1973) who found that direct introduction of propranolol into the brain of animals inhibits the central effects of catecholamines. The finding that hypothalamic β-adrenoceptors appear to be involved in human growth hormone secretion (Massara and Camanni, 1972) suggests the presence of these receptors in the human brain. As patients taking propranolol sometimes develop hallucinations (Zacharias, 1971), this could indicate that the β-adrenoceptor blocker also has a direct effect on the human brain. Much more research is required to establish the existence and function of β-adrenoceptors in the brain and, indeed, whether these receptors are also involved in the anxiolytic action of the β-adrenoceptor blockers.

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