DISCUSSION

SOME ASPECTS OF BLOCKADE OF INHIBITORY ADRENERGIC RECEPTORS OR ADRENOCEPTIVE SITES

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One factor contributing to understanding the pharmacology of peripheral effector systems has been the availability of relatively specific antagonists of the various neurohormones. Adrenergic blocking agents, like curariform drugs, represent important tools for the study of the interaction of drugs with receptor sites. The recent demonstration (6) of inhibitory adrenergic blockade with 1-(3′,4′-dichlorophenyl)-2-isopropylaminoethanol (Lilly compound 20522, DCI) may be another relevant case, for it throws additional light on the old Sympathin E and I problem. These data seem to provide verification of Ahlquist's (1) division of α- and β-adrenergic receptors. In anesthetized cats, this dichloro analogue of isoproterenol has been shown to antagonize the myometrial relaxation, hypotension and tachycardia caused by isoproterenol (6), but not the hypertension and nictitating membrane contraction following epinephrine. Of itself, the compound caused a transient fall in blood pressure and an increase in heart rate. The epinephrine- or isoproterenol-induced relaxation of pilocarpine-induced bronchospasm, in pithed dogs or in isolated guinea pig tracheal chains, was also blocked by 20522.

Thus it would appear that 20522 had little effect on α-receptors but interacted with β-receptors and, in spite of its low intrinsic activity, hindered the normal agonists from exerting their characteristic effects.

Moran and Perkins (4, 5) have used 20522 to study the nature of the adrenergic receptors in both intact dog and isolated rabbit heart. While the drug of itself had some positive inotropic and chronotropic activity, it blocked or reduced the effect of subsequent doses of epinephrine or isoproterenol. They postulated an equilibrium type of blockade but were unable to establish whether it was competitive in character. They felt that the blockade was relatively specific for adrenergic mechanisms since the actions of calcium, digoxin and theophylline were not materially altered. As further evidence for specificity Moran and Perkins showed that ephedrine, which caused comparable increases in heart rate and force, failed to antagonize the catecholamines. These workers, as well as Moore and Swan (3) and others, have shown that 20522 antagonizes epinephrine-induced arrhythmia in a variety of situations.

Dresel (2), using isolated cat papillary muscle, found that small doses of 20522 increased cardiac force and that somewhat larger doses antagonized the positive inotropic effect of epinephrine. Moran and Perkins concluded "that the adrenergic receptors of mammalian hearts are functionally homologous to the adrenergic inhibitory receptors of other tissues."

The antagonism of inhibitory effects of epinephrine and isoproterenol on intestine provides another bit of qualitative information. In several experiments, rabbit intestine, pretreated with 20522, increased in tone after epinephrine, suggesting the possibility of a dual receptor mechanism in this organ.

Our early experiments with isolated guinea pig tracheal chain indicated that the blockade is of an equilibrium type (6). After 20522, small doses of epinephrine or isoproterenol were without effect, but larger doses were still able to reduce pilocarpine-induced spasm. Attempts to establish the kinetics of this drug-receptor interaction, using intestine, uterus, aorta or tracheal chains, have not been very successful since 20522 itself may show weak β-receptor activity and even at relatively high concentrations may fail to block completely. This peculiar plateau has also been noted by Dresel (2) in cat papillary muscle.

Thus, 20522 can be considered a useful tool for the qualitative separation of α- and β-receptor sites, but for the present it must be used with caution for the quantitative aspects

are not clear. In any event, the data seem to add support for the Ahlquist concept of α- and β-adrenergic receptors and suggest that this separation provides a useful frame of reference in discussions of sympathomimetic amines.

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