THE CATECHOL AMINES AND THEIR RECEPTORS

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In 1905, Dale showed in a series of classical experiments that pretreatment with ergot not only abolished the pressor action of adrenaline but also reversed it, producing a depressor effect.[1,2] Thus he was the first to show that the catechol amines (adrenaline and noradrenaline) act on at least 2 types of receptors. The findings that adrenaline and noradrenaline, though chemically very similar, produce qualitatively different effects on some tissues can only be interpreted in this way as well.[3,4] The receptors on which adrenergic drugs act, were named the alpha and beta receptors by Ahlquist in 1948.[3] Recent research has provided drugs which will selectively prevent the action of the catechol amines on either the alpha or the beta receptors.[4]

In this article the effect of adrenergic drugs on the cardiovascular system and the modifying effect of blocking agents will be discussed, while mention will be made of receptors present in other body tissues. Finally, recent research into the basic mechanism of action of adrenergic drugs will be referred to.

THE EFFECT OF CATECHOL AMINES ON THE CARDIOVASCULAR SYSTEM

A. In the Normal Animal

Noradrenaline is a net vasoconstrictor; consequently, the total peripheral resistance (TPR) is increased. Noradrenaline also increases the contractile force of the heart. The systolic blood pressure is raised owing to the increase in TPR and in cardiac contractility. The rise in diastolic pressure results from the increased TPR. In the intact animal, the raised mean blood pressure causes a reflexly induced increase in vagal tone with resultant bradycardia.[4-7]

Adrenaline produces vasodilatation in skeletal muscle blood-vessels and thus the TPR falls. The cardiac output and pulse rate increase. The rise in systolic pressure produced results from the increase in cardiac output. Because of the reduced TPR, there is a slight fall in the diastolic blood pressure.[4-7]

Blood-vessels have 2 receptors for adrenergic drugs.[3,7,29] Firstly these are the alpha constrictor receptors which respond to noradrenaline. Secondly there are beta dilator receptors which respond to isoprenaline. Adrenaline stimulates both strongly. Alpha constrictor receptors are widely distributed, but are lacking in the cardiac and cerebral vascular beds.[29] Beta receptors are most active in skeletal muscle blood-vessels.[29]

When adrenergic drugs act on the heart directly, they are acting on the beta receptors only.[4,5]

The observed effects of adrenaline and noradrenaline on the cardiovascular system (see above) can be explained by assuming that adrenaline acts on both alpha and beta receptors,[3,5] whereas noradrenaline acts primarily on alpha receptors,[3,5] but has, in addition, potent beta actions on the heart.[5] Thus adrenaline produces vasodilatation in skeletal muscle, while elsewhere in the body, with the exception of the coronary vessels, both adrenaline and noradrenaline produce vasoconstriction.[29] The actions of adrenaline and noradrenaline on the isolated heart are qualitatively and quantitatively similar.[5]

B. After the Administration of Adrenergic Blocking Agents

The adrenergic blocking agents may be divided into 2 groups, viz.:

1. *Those that block the alpha receptors.* Examples of such drugs are the ergot alkaloids, phenoxybenzamine, phentolamine, dibenamine and chlorpromazine.[3,4,5,7,8] Pretreatment with these drugs produces progressive blockade of the vasoconstrictor actions of adrenaline and noradrenaline. This leads to a reversal of the pressor action of adrenaline (as a result of its unopposed action on the beta receptors) and abolition of that of noradrenaline.[5,9] There is no antagonism of the direct effects of either adrenaline or noradrenaline on the heart.[5,9]

2. *Those that block the beta receptors.* Examples of such drugs are pronethanol,[10] Inderal[11] and dichloroisoprenaline.[12] These drugs do not block the vasopressor effect of either adrenaline or noradrenaline but antagonize the cardiac actions of both amines and the vasodilatation of adrenaline.[5] Thus the administration of adrenaline now produces a rise in both systolic and diastolic blood pressure with bradycardia.[13]

It should be noted that many of these blocking agents have important actions of their own in addition to blockade of responses to adrenaline and noradrenaline.[9]

THE CLASSIFICATION OF ADRENERGIC RECEPTORS IN OTHER TISSUES

The general effects of adrenaline and noradrenaline have been well reviewed elsewhere.[4,6,7,9] The receptors for the various organs, etc., have been classified by several authors.[3,4,7-9,14-16,29] The following classification is based on the above references, namely,

(a) *Alpha receptors.* Vascular smooth muscle, pilomotor muscle, the radial fibres of the iris;
(b) *Beta receptors.* Vascular smooth muscle (in skeletal muscle), myometrial muscle, cardiac muscle, bronchial muscle; and
(c) *Both alpha and beta receptors.* Intestinal smooth muscle.

There has not been universal agreement on the classification of certain effects of the catechol amines, particularly their metabolic effects.[34] A recent article by Volle reviews research which does not easily accord with traditional classifications.[35]

THE PHYSIOLOGICAL BASIS FOR THE EFFECTS OF THE CATECHOL AMINES

Adrenaline promotes the formation of a cyclic nucleotide, adenosine-3,5-phosphate. The cyclic nucleotide formed stimulates the formation of active phosphorylase which

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then in turn stimulates glycogenlysis. Thus, when activated in liver, an end-product is glucose, while lactate is formed by skeletal muscle. There is some correlation between the phosphorylase concentration in the heart and the effects of the catechol amines on cardiac contractility. This would suggest that the beta receptors for cardiac contractility are very similar to, or identical with, those for the formation of the cyclic nucleotide.[18] A 'cyclase system' may be the actual beta receptor, involving cyclase, magnesium ions and ATP.[19] There is no evidence that the vascular alpha receptors have anything to do with the formation of the cyclic nucleotide.[18] It has also been claimed that the inhibition of plain muscle is due to the accumulation of lactic acid,[20] but not all authors agree with this theory.[21]

Recent advances in the methods used for measuring the electrophysical changes of muscle have also provided more evidence about the action of the catechol amines. Studies have suggested that adrenaline causes relaxation, secondary to metabolic changes. Relaxation may be due to an increase in the amount of energy available for the sodium pump. Adrenaline has also a direct effect causing depolarization and thus contraction. The action in any situation is thus the net result of these two actions. When the transmembrane potential is high, the direct depolarizing action will predominate causing contraction. When the transmembrane potential is low, adrenaline will cause a rise in potential and thus relaxation.[4,22-24] However, the above explanation has been contested.[25]

There has also been much research performed on the biochemical, structural and functional relationships between catechol amines, blocking agents and adrenergic receptors.[26-28]

SUMMARY

The effects of adrenaline and noradrenaline on tissues and their possible relationship to receptors, are discussed. The modifying effect of adrenergic blocking agents are outlined. Theories concerning the basic action of the catechol amines are presented.

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