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0. INTRODUCTORY REMARKS

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The catecholamines influence metabolic processes and physiological functions in most tissues and organs of the body. It may be asked whether this multiplicity of effects has its counterpart in an equal number of points of attack in biochemical and biophysical reactions. This appears *a priori* rather improbable. Stimulation of *one* cellular process may result in secondary reactions on *several* physiological functions. An important question is therefore how many primary biochemical or biophysical points of attack the catecholamines have and how these are linked to the physiologic and pharmacologic actions of the amines.

Ahlquist's (1) classification of the adrenotropic receptors in α- and β-types and the demonstration of drugs with selective α- (119) and β-receptor (17, 39, 116, 121, 123) blocking effects may indicate that the primary actions of catecholamines can be reduced. There are however certain adrenergic receptors, *e.g.*, those in the liver that mediate the glycogenolytic-hyperglycemic effects of the catecholamines, which are somewhat different from α- and β-receptors—α_2-receptors according to Kennedy and Ellis (67). This may mean that yet another receptor mechanism for the mediation of certain metabolic effects should be considered.

The investigations of Sutherland and co-workers (118, 124, 125, 137–139), have established that the phosphorylase-activating effect of the catecholamines in the liver and skeletal muscles is mediated *via* cyclic 3′,5′-AMP. This nucleotide is formed by the stimulation of an enzyme or enzyme system—adenyl cyclase—which is found in the cell membrane (36). According to Krebs *et al.* (68) and Posner *et al.* (122) cyclic 3′,5′-AMP activates phosphorylase *b* kinase, the enzyme which produces phosphorylase *a* from *b*. How the catecholamines stimulate the cyclase activity is unknown. Belleau (11) has speculated on this subject. Cyclic 3′,5′-AMP influences the activity of other enzymes besides phosphorylase, among others phosphofructokinase (98) and the catecholamine-sensitive triglyceride lipase (127). Its production is also stimulated by other hormones. These subjects have recently been reviewed by Haugaard and Hess (52) who also have discussed the relationship between metabolic and functional effects of the catecholamines in the heart. Some of the metabolic effects of the catecholamines can therefore be traced back to an increased production of cyclic 3′,5′-AMP.

There are observations, however, which more indirectly indicate that the stimulation of cyclic 3′,5′-AMP production may be of importance for mediation of other adrenergic effects, such as calorigenic, vasodilating, smooth muscle relaxing, and cardiac stimulating effects. Adrenergic β-receptor blocking drugs inhibit the increased production of cyclic 3′,5′-AMP (118), the phosphorylase

activation (3, 61, 99, 111), and the calorigenic (89, 136, 143) and β-receptor effects (17, 116, 123) provoked by catecholamines. Methylxanthines inhibit the enzymatic inactivation of cyclic 3′,5′-AMP (29), and they have a positive chronotropic and inotropic effect on the heart (30). They relax smooth muscle, stimulate the central nervous system, have a calorigenic effect (100), and stimulate phosphorylase activity (29, 55, 56). The methylxanthines also potentiate and protract the cardiac stimulating (126), lipase activating (127), and smooth muscle relaxing (86) effects of the catecholamines. Although the methylxanthines may act in other ways too, this relationship is suggestive. Some objections may, however, be raised against the hypothesis of a more general causative connection between stimulation of adrenergic receptors and production of cyclic 3′,5′-AMP.

It seems hardly probable that any pharmacologic action of the catecholamines can be ascribed to one metabolic effect alone. It is more likely—as discussed in more detail below—that several metabolic effects contribute, varying in importance according to the animal species, tissue, and catecholamine derivative. The role of cyclic 3′,5′-AMP in the mediation of these metabolic effects has not been generally demonstrated.

The evaluation of the role of cyclic 3′,5′-AMP as an intermediary in the cardiac stimulating and smooth muscle relaxing effects of the catecholamines is also rendered difficult by the incompleteness of our knowledge on the mechanisms that regulate muscle contraction. The demonstration of a parallel between the effect of the catecholamines on the production of cyclic 3′,5′-AMP and some of their muscular actions is no proof of a relationship between these factors as long as the mechanism underlying the influence of cyclic 3′,5′-AMP on the function in question remains unknown. Cyclic 3′,5′-AMP can influence a number of different enzymatic reactions in the body. Several metabolic reactions (indicator reactions) which vary parallel with the content of cyclic 3′,5′-AMP in the tissues can probably be demonstrated. These reactions need not necessarily be those which provoke the pharmacological effects of the catecholamines, but only parallel phenomena. Some caution should probably be observed when interpreting the connection between concurrently varying effects induced by catecholamines.

In the following, the metabolic processes which have been shown to provoke or occur simultaneously with some of the pharmacodynamic effects of the catecholamines will be discussed in more detail, and also the possible extent to which these processes may be induced by stimulation of the production of cyclic 3′,5′-AMP.

CALORIGENIC EFFECTS

The calorigenic effects of the catecholamines have been reviewed previously by Lundholm (73), Griffith (50), Ellis (40) and Lundholm and Mohme-Lundholm (79).

The catecholamines have been shown under different conditions to stimulate oxygen consumption in the liver (10, 131, 133), skeletal muscle (42, 90), cardiac muscle (49, 134), smooth muscle (25), adipose tissue (96), and anterior pituitary

(128). The mechanism responsible for the calorigenic effect is probably not the same in all these tissues. There is reason to believe that in the liver and adipose tissue it is induced by the stimulation of carbohydrate and lipid metabolism by the catecholamines, *i.e.*, that it is traceable to activation of phosphorylase and lipase. The calorigenic effect of the catecholamines is inhibited by β-blocking agents (19, 89, 136, 143). Methylxanthines also have a calorigenic effect (100). There is therefore both direct and indirect reason for believing that stimulation of the production of cyclic 3′,5′-AMP can mediate at least some of the calorigenic effects of the catecholamines.

In the following, the calorigenic effects of epinephrine (E) and norepinephrine (NE) will be discussed separately, since the mechanisms for their actions are probably not identical. The different ways in which the catecholamines may produce a calorigenic affect is schematically shown in figure 1.

Epinephrine. In the rabbit under normal conditions an increase in lactic acid production and its metabolism appears to be of importance for the calorigenic effects of E (73). A quantitative and temporal correlation was shown between the lactic acid content of the blood and this effect. Infusion of *l*(+) lactate in such a quantity that the concentration of lactic acid in the blood was raised to the same level as after E, provoked the same stimulation of oxygen consumption as did E. Under conditions in which lactic acid oxidation was inhibited, no calorigenic effect was seen. Ergotamine (73), yohimbine (102), chloroisoprenaline (88), and pronethalol (143) inhibited the lactic acid production and calorigenic effect of E to the same extent. In fed animals the calorigenic and lactic acid-producing effects of E were greater than in fasted animals (93). The relative potencies of the calorigenic and lactic acid-producing effects of *l*-isoproterenol, *l*-E and *l*-NE in rabbits were 1:9:120 (89). According to Svedmyr (140), thyroxine treatment in the rabbit potentiated the calorigenic and lactate-elevating effects of E, but not its effects of increasing the concentration of blood sugar or free fatty acid (FFA) in plasma. In thyroxine-treated rabbits the rate of lactate

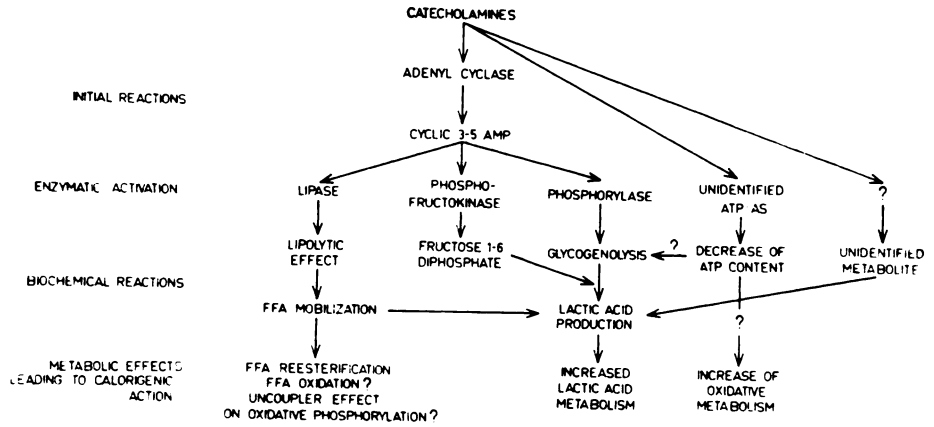

FIG. 1. Different mechanisms which may be of importance for the calorigenic action of the catecholamines. For further information see the text.

oxidation was increased (141). The calorigenic effect of NE was not potentiated by thyroxine (140), but thyroidectomy (140) diminished the effects of E on lactic acid production and oxygen consumption. The elevating effect of E on plasma FFA in the rabbit was weak and transient, and was not correlated to the calorigenic effect (143). Nicotinic acid, in a dose which selectively blocked the lipolytic effect of E without influencing its effect on lactic acid production, had no influence on the calorigenic effect either (94).

In the dog, according to Havel (53), the calorigenic effect of E was accompanied by stimulation of the carbohydrate metabolism but inhibition of fatty acid oxidation.

In man, infusion of *l*(+) lactate, in such a dose that the same blood level was reached as after E, provoked a calorigenic effect about one half of that caused by E (144). Triiodothyronine potentiated the calorigenic and lactate-elevating effects of E but not the hyperglycemic effect, or the effect on the plasma FFA (142). E doubled the oxygen consumption and blood flow of the liver and at the same time increased the lactic acid extraction from the blood (10). E-infusion also stimulated the oxygen consumption in forearm muscles by about 40% (90). This effect was already maximal after 3 min infusion and was not correlated to changes of the lactic acid or FFA content in the blood.

Norepinephrine. The calorigenic effect of NE in normal adult animals and man is weaker than that of E (10, 74). NE has only a slight lactate-elevating effect (32, 74, 92), but its influence of FFA content in plasma is more pronounced than that of E when they are given by continuous intravenous infusion (53).

In man, Steinberg *et al.* (135, 136), and in the dog, Havel (53), showed that the calorigenic effect of NE was accompanied by a marked increase of the turnover rate of FFA and the oxidation of infused palmitic acid-1-C^{14}. The calorigenic effect of NE was considered to arise partly as a result of increased oxidation of FFA, since their plasma concentration rose, and partly as a result of reesterification of the mobilized FFA. Carlsson and co-workers (30, 31, 45) found that nicotinic acid selectively blocked the lipolytic effect of catecholamines. Nicotinic acid reduced but did not abolish the calorigenic effect of NE in man (54) and rabbit (94).

Hsieh and Carlsson (62) showed that in cold-adapted rats the calorigenic effect of NE was potentiated and exceeded that of E. The sympathetic nervous system also mediated a calorigenic effect or "non-shivering thermogenesis" in these animals (63). These effects have been verified both in rats (37, 51) and in man (35, 65). The calorigenic effect of NE in the rat has been localized to the skeletal muscles (37, 51), liver and other viscera (51), and brown adipose tissue (19, 132). Since the lipolytic effect of NE was increased in cold-adapted rats and its calorigenic effect was accompanied by a decrease of respiratory quotient (51), it has been considered that the calorigenic effect of NE in cold-adapted rats depends on an increased oxidation of lipids (51).

The calorigenic effect of NE is also increased in newborn animals (19, 115) and babies (66). The effect disappears with age. It seems probable that this response to NE is a manifestation of non-shivering thermogenesis (19), and it has been assumed to be associated with the lipolytic effect of NE (115).

The importance of the lipolytic action of NE for its calorigenic effect, however, is not quite clear. The rate of oxidation of FFA of isolated tissues was shown to be proportional to its concentration in the medium, but the total oxygen consumption did not increase; instead, the oxidation of other substrates decreased so that the total oxygen consumption was unchanged (135). If the oxygen consumption is stimulated by NE *via* some other mechanism than its lipolytic action, it is clear that the oxidation of different substrates and also of FFA must increase. A stimulation of FFA-mobilization may perhaps be necessary to furnish substrate if there is a large increase in oxygen consumption. An increase in the oxidation of FFA can certainly take place as *a result* of an increased oxygen consumption but it is uncertain whether an increase in plasma FFA *causes* increased oxygen consumption. It is debatable whether the lipolytic effect of NE can provoke an increase of oxygen consumption as much as double the basal value which has been observed in cold-adapted rats. Beyer (16) has pointed out that a simple plethora of lipids or carbohydrates scarcely stimulates the oxygen consumption. The calorigenic effect must be accompanied either with an increased rate of ATP-hydrolysis or ATP-utilization or with some mechanism which uncouples or by-passes the relation of oxidation to phosphorylation. Havel (53) has pointed out that esterification of FFA is an ATP-utilizing reaction and that the augmented esterification of FFA resulting from their increased mobilization probably accounts for part of the calorigenic effect of NE.

It is probable that NE and to a certain extent also E can stimulate oxygen consumption by some other mechanisms than their glycogenolytic and lipolytic effects. It is of interest in this connection that E reduced the content of high-energy phosphate compounds in isolated rat diaphragm simultaneously with stimulation of the carbohydrate metabolism (112). Methylxanthines also stimulate metabolism in skeletal muscle and increase the hydrolysis of ATP (100). The significance of an ATPase activation for the calorigenic effect of the catecholamines should be studied more closely.

THE EFFECT OF E ON CARBOHYDRATE METABOLISM IN STRIATED MUSCLE

The phosphorylase-activating effect of the catecholamines has been assumed to explain its glycogenolytic action and stimulation of lactic acid production. Lyon and Porter (97), however, found a mouse strain that lacked phosphorylase *a* and phosphorylase *b* kinase. In spite of this deficiency, E stimulated the glycogenolysis to the same extent as in normal mice. Morgan and Parmeggiani (117) have found that ATP is a strong inhibitor of the activating effect of AMP on phosphorylase *b*. E can reduce the ATP concentration in isolated rat diaphragm and also in smooth muscle (110, 112). It is therefore possible that E, *via* changes in the ATP concentration, could influence the phosphorylase *b* activity and thereby provoke a glycogenolytic effect.

The way in which the catecholamines stimulate cyclase activity and thereby increase the production of cyclic 3′,5′-AMP is not understood. Tinder *et al.* (146) found that the phosphorylase-activating effect of glucagon in the liver was preceded by an increased elimination of K^+. These observations may indicate

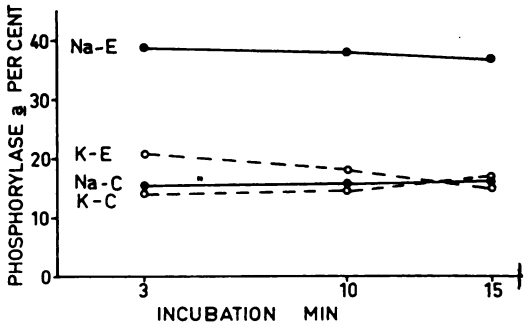

FIG. 2. Influence of E (1×10^{-6}M) on the phosphorylase *a* activity in percent of total phosphorylase activity in isolated rat diaphragm. Na-E and Na-C: tests with and without E in normal, glucose-free Krebs-Henseleits bicarbonate buffer media aerated with 95% O_2 + 5% CO_2 at 37°C. K-E and K-C: tests with and without E in Krebs-Henseleits buffer media where the Na^+ has been replaced by K^+. Each point is the mean of 5 tests. The effect of E on phosphorylase *a* activity although still significant in K^+-Krebs-Henseleits buffer media was reduced and its duration shortened in comparison with the effect in normal buffer solution.

that an increase in permeability to K^+ is included among the reactions leading to the phosphorylase-activating effect of the catecholamines. Lundholm *et al.* (87) found that, if the Na^+ in the suspension solution was replaced by K^+, the phosphorylase-activating effect of E was reduced and its duration shortened (fig. 2). These findings suggest a relation of the activation of an enzymatic process to permeability changes and ionic movements through the cell membrane.

VASODILATING EFFECT

The vasodilating effect of the catecholamines, like the calorigenic effects, can be provoked by means of different mechanisms. Traditionally the dilating effect is ascribed to stimulation of β-receptors in the vascular smooth muscle. This mechanism is probably mainly of importance, however, for part of the dilating effect of isoproterenol and "adrenaline-reversal" after adrenergic α-blocking drugs; in these cases it can be shown that isolated vessels (having no contact with surrounding tissue) are relaxed by E (15, 46, 85). But E neither relaxes skeletal muscle vessels when they are isolated nor dilates them on local application to the vessel wall (20, 48, 75), although the same vessels relax on intravenous injection of E. The only isolated vessels which are relaxed by E without previous administration of adrenergic α-blocking drugs are coronary vessels from certain animals, but since these are not constricted by the catecholamines even in high concentrations, they probably lack α-receptors which mediate constriction (81). In other isolated vessels the contracting effect of E and NE probably predominates over the relaxing tendency so that relaxation is not apparent until the α-receptors have been blocked.

The stimulation of metabolic processes in the tissues supplied by particular vessels is often of greater importance for the vasodilating effect of the catecholamines than a direct action on β-receptors in the smooth muscle of these

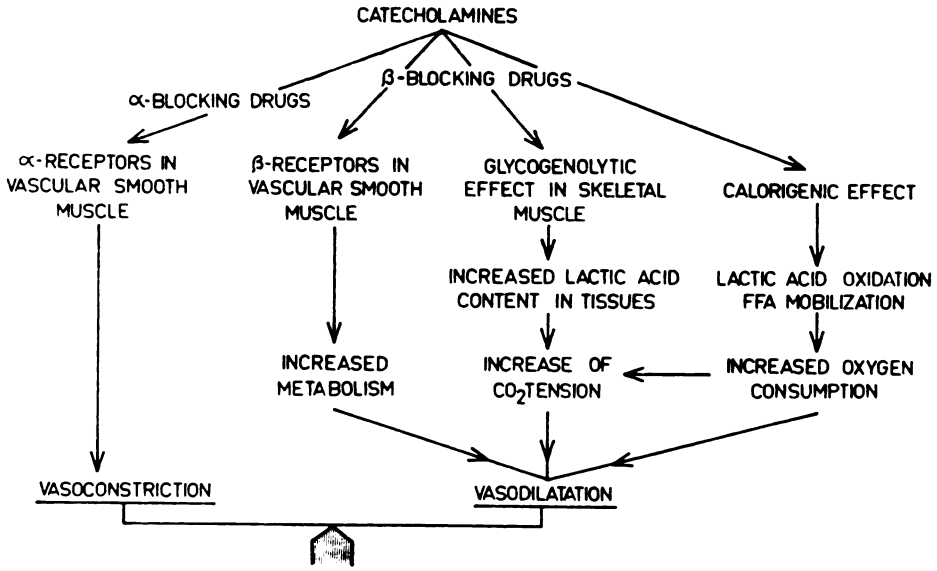

FIG. 3. Different mechanisms by which the catecholamines may induce vasodilatation. The vasodilating effect is antagonized by the vasoconstrictive action and there is a balance between these two effects of the catecholamines. For further information see the text.

vessels. It is probable that the calorigenic effects of the catecholamines are associated with an increase in the nutritive blood flow. The rise of lactic acid concentration in the tissues which is induced by the glycogenolytic action is also probably of importance for the vasodilating effect, *via* an increase in pCO_2 in the tissues (75). In the following, the vasodilating effects of E, NE, and isoproterenol are discussed separately. In figure 3 the different mechanisms discussed in the following are schematically presented. There often exists a balance between the vasodilating and vasoconstricting effects of the catecholamines, as indicated in this figure.

Epinephrine. Lundholm (75) found in the cat that the dilating effect of E in skeletal muscle was accompanied by an increase in lactic acid production, while the oxygen consumption in the muscle did not increase. On intraarterial administration of the same quantity of lactic acid as was formed on E infusion, a vasodilatation was provoked, the duration and magnitude of which were similar to those noted after E. Inhibition of the lactic acid-producing effect of E by Cu^+ or NaF changed its dilating effect to a constricting action. The vasodilating effect was better correlated to the increase in CO_2 production than to the increase in lactic acid formation. It was considered that the direct cause of the dilating effect of E was increased pCO_2 in the tissues resulting from the fact that CO_2 was liberated from the tissue bicarbonate by lactic acid. This hypothesis was supported by experiments of Gosselin (47), who found that an increase in pCO_2 had a vasodilating effect in the skeletal muscle of the cat. An increase of the lactic acid concentration had no such effect.

In further experiments in the cat Lundholm (83) found a marked parallel between the depressor effect of E and its stimulation of lactic acid production. E given in doses which had a vasoconstrictive-hypertensive effect, however, also stimulated lactic acid production. If the α-effect was blocked with dihydroergotamine, the stimulation of lactic acid production remained almost unchanged and an adrenaline-reversal occurred. When subsequently the lactic acid production was blocked with Cu^+ or NaF, the vasodilating effect also disappeared.

In experiments in man Barcroft and Cobbold (9) found a parallel between the dilating effect of E in the forearm, and the lactic acid concentration in the blood. De La Lande *et al.* (33), Allwood and Cobbold (4), and Baltzan *et al.* (8) showed that E increased lactic acid elimination from the forearm. This effect was not influenced by dibenzyline, but instead the vasodilating effect of E was augmented (4). De La Lande and Whelan (34), however, observed no dilating effect on infusion of sodium lactate or lactic acid solution with a pH of 3.3 (=0.0003 N). Lundholm and Svedmyr (90) found that the vasodilating effect of E in the forearm was accompanied by stimulation of both the lactic acid production and the oxygen consumption of the muscle. The latter increased by about 40%. To be able to reproduce the lactic acid-producing effect of E in the forearm by intra-arterial infusion of lactic acid into the brachial artery, it was calculated that approximately 1.2 ml of 0.1 N lactic acid had to be infused per minute. The quantities of lactic acid used by De La Lande and Whelan (34) were therefore probably too small. Lundholm and Svedmyr (90) found also an increase in CO_2 production in the forearm during infusion of E. The pCO_2 increased in both the arterial and venous blood, and this effect was considered to be, at least in part, the immediate cause of the vasodilating effect of E. All these metabolic effects and the vasodilating effect of E were blocked by pronethalol (95).

Bearn *et al.* (10) found in man that the blood flow, oxygen consumption, and lactic acid extraction of the liver increased on infusion of E. In experiments on rabbits (77), infusion of sodium lactate induced the same percent increase of the cardiac output and oxygen consumption without change of blood pressure. Infusion of lactic acid, however, induced an increase of the cardiac output (with no change in mean blood pressure) which was greater than the increase in oxygen consumption, and this dilatating action was ascribed to an increase of the pCO_2 in the tissues.

Norepinephrine. The glycogenolytic and calorigenic effects of NE are in general considerably weaker than those of E. This can probably explain the usual weaker vasodilating effect of NE (77). In those cases where NE has a pronounced metabolic effect, it also has a vasodilating action. Evonuck and Hannon (44) found that in normal rats NE increased the average peripheral resistance and very slightly affected oxygen consumption. In experiments on rats adapted to cold, in which NE considerably increased oxygen consumption, the peripheral resistance was reduced. NE stimulates the oxygen consumption of adipose tissue, especially the brown adipose tissue, and induces vasodilatation there (76, 120).

Isoproterenol. The glycogenolytic and calorigenic effects of isoproterenol are

considerably stronger than those of E. Isoproterenol can also relax isolated vessels, probably by means of selective stimulation of β-receptors in the vascular smooth muscles (46, 85). Only in very high concentrations does isoproterenol have a vasoconstrictive action. These circumstances can probably explain the stronger vasodilating effect of this drug in relation to that of E. The relative significance of this contributory factor in the individual case is not yet clear. In the rabbit a parallel was found between the vasodilating effect of isoproterenol in skeletal muscle, and its stimulation of lactic acid production (89). In man isoproterenol had a pronounced vasodilating effect in the forearm in doses which only slightly stimulated the lactic acid production but which had a definite calorigenic effect (95).

SMOOTH MUSCLE

Traditionally, the contractile action of catecholamines in smooth muscle has been regarded as an α-receptor effect, and the relaxant action a β-receptor effect (1). It is probable, however, that as a rule both α- and β-receptors are stimulated in smooth muscle that is contracted by catecholamines, although the relaxant effect of the β-receptors does not become apparent until the α-receptors have been blocked (83, 108). In intestinal smooth muscle the α-receptors can also mediate a relaxant effect (1, 2, 21, 72). Smooth muscles from different organs and species exhibit considerable physiological differences. Hence the relationships between the metabolic and functional effects of the catecholamines in smooth muscle are complicated. Since our knowledge of the reactions which provoke contraction or relaxation in smooth muscle is incomplete, the relationship between metabolic reactions and these effects is difficult to interpret. A marked parallel between the metabolic and relaxing effects of the catecholamines in smooth muscle has been demonstrated, however (6, 7, 22, 26, 101, 103, 105, 106). Methylxanthines relax smooth muscle and stimulate its carbohydrate metabolism (86, 105). Also in certain cases they potentiate the relaxant effect of the catecholamines (86), and this may indicate that cyclic 3′,5′-AMP plays a role in this connection. In the following, the metabolic processes associated with the contractile and relaxing effects of the catecholamines will be discussed. The suggested mechanisms are schematically presented in figure 4.

Contractile effect. The contractile effect of E on isolated vascular smooth muscle was accompanied, under anaerobic and aerobic conditions, by stimulation of lactic acid production (104). The stimulation of metabolism was considerably greater on isometric than on isotonic contraction (105). If the contraction was inhibited by dihydroergotamine or by suspending the muscle in ion-free (6 % dextran) solution (93) or Ca^{++}-free solution (85), lactic acid production was stimulated to approximately the same extent as during isotonic contraction. E contracted K^+-depolarized vascular muscle and stimulated its lactic acid production (85). Isoproterenol stimulated the lactic acid production without contracting the muscle, but a muscle that was contracted with K^+ relaxed. The stimulation of carbohydrate metabolism by isoproterenol was inhibited by pronethalol (85). Catecholamines thus stimulate the carbohydrate metabolism in vascular muscles

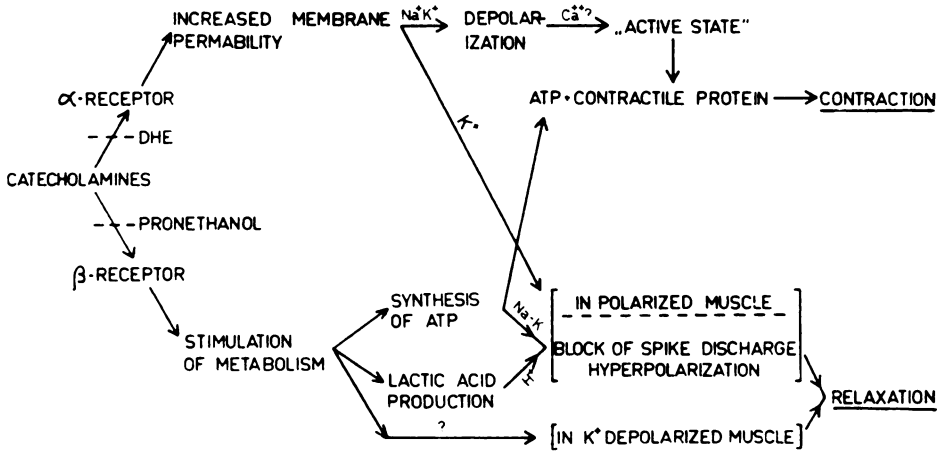

FIG. 4. Schematic presentation of the metabolic effects of the catecholamines in smooth muscle. Stimulation of the α-receptors may lead to a more generalized increase of the permeability to ions and depolarization of the membrane. In the presence of Ca^{++} the muscle contracts. If the permeability increases selectively to K^+, as in intestinal smooth muscle, the membrane may be hyperpolarized and the muscle relax. Selective stimulation of β-receptors may increase the metabolism and in different ways lead to a relaxing effect. If the α- and β-receptors are simultaneously stimulated the action of the former dominate, but the stimulation of the metabolism through β-receptors delivers ATP to the contractile effect. For further information see the text.

partly *via* the contraction process, an effect most pronounced on isometric contraction, and partly *via* a more direct mechanism.

The effect of catecholamines on lactic acid production in vascular smooth muscle was not accompanied by increased glycogenolysis (84), although in the presence of glucose glycogen synthesis was stimulated, and phosphorylase activity was not increased (107). In vascular smooth muscle, however, about 4 millimoles of lactate per g muscle were formed from other sources than glycogen (80). Even in the absence of glucose, E increased the concentration of hexose phosphates in the vessel musculature and probably stimulated the phosphofructokinase reaction (14). These effects on carbohydrate metabolism were noted even when the contractile effect of E had been blocked by dihydroergotamine and E had a relaxing effect on the muscle (15).

The contractile effect of E on the vascular smooth muscle was combined with a decrease of the content of energy-rich phosphate compounds (adenosine triphosphate and creatine phosphate) (13). This decrease was of the order of magnitude which from thermoelectric measurements could be estimated to occur on contraction of smooth or striated muscle (18, 57, 58). When the contraction process was blocked by dihydroergotamine, E *increased* the concentrations of ATP and creatine phosphate in the vessel musculature, which then relaxed (15).

It is probable that catecholamines stimulate the carbohydrate metabolism in vascular smooth muscle partly by means of the contraction process (α-receptor

stimulation) and partly *via* a separate mechanism, possibly associated with β-receptor stimulation. Stimulation of the carbohydrate metabolism is not accompanied by increased glycogenolysis or phosphorylase activation, but despite this there is an increase of the concentration of hexose phosphates in the muscle.

Relaxing effect. The relaxing effect of the catecholamines on smooth muscle was shown by Mohme-Lundholm (101, 103, 105) to be accompanied by stimulation of the carbohydrate metabolism. The relaxing effects of the catecholamines and their stimulation of lactic acid production ran parallel in isolated rabbit intestine, guinea pig uterus, and tracheal muscle. Glycolysis-inhibiting substances and adrenergic blocking agents inhibited both the metabolic and the relaxing effects of E. Lactic acid, in the same concentration as was formed by E, relaxed the muscle when added to the suspension solution. Like E, H^+ in a low concentration inhibited the action potentials in taenia coli and relaxed the muscle (110). Higher concentrations of H^+ also hyperpolarized the membrane. The lactate ion, on the other hand, had a depolarizing and contractile effect. In K^+-depolarized taenia coli the E effect was almost completely blocked, and H^+ had a contractile action (114).

Axelsson *et al.* (7) found that removing and readmitting glucose had a striking similarity to the action of E on the electrical and mechanical activity of taenia coli from guinea pig.

The question of whether the stimulation of lactic acid production by E was associated with a glycogenolytic effect has also been studied (78). In smooth muscle relaxed by E, a glycogenolytic effect has been shown (41, 70, 78, 145), but the lactic acid production, in the absence of glucose, was greater and occurred more rapidly than the glycogen breakdown (78). As in vascular smooth muscle, considerable quantities of lactic acid were formed from other sources than glycogen (80), and these pathways were probably stimulated by E. Only in case of extreme substrate deficiency were the magnitudes of glycogenolysis and lactic acid production on an equal level (106). The glycogenolytic action of E in smooth muscle suggested that it could have a phosphorylase-activating effect in this tissue. Several investigators have demonstrated such an effect (5, 6, 38, 70, 71, 107). Axelsson *et al.* (6) found a very close relationship among the phosphorylase-activating, relaxing, and hyperpolarizing effects of E in taenia coli from the guinea pig. Bueding *et al.* (24) later found, however, that the relaxing and phosphorylase-activating effects of E could be dissociated in this muscle. E in low concentrations relaxed the muscle without activating phosphorylase. Chloroisoprenaline also showed a selective blocking action on the phosphorylase-activating effect.

Mohme-Lundholm (109) studied phosphorylase in smooth muscle (tracheal muscle from the cow) and the factors which influenced its activity. Phosphorylase *a* and *b* were demonstrated, and also inactive and active phosphorylase-*b*-kinase. Inactive phosphorylase-*b*-kinase was activated, as in skeletal muscle (68), by cyclic 3′,5′-AMP, Ca^{++}, and an increase in pH. Bueding *et al.* (22) have shown that E increased the concentration of cyclic 3′,5′-AMP in taenia coli. It is there-

fore probable that E increases the phosphorylase activity in smooth muscle *via* cyclic 3′,5′-AMP.

As a result of stimulation of metabolism, catecholamines can increase the concentration of ATP in smooth muscle. This effect was first demonstrated by Lange (69) in rabbit gastric muscle, and later also, under certain conditions, in mesenteric arteries (79, 82). E can also increase the ATP content in taenia coli from guinea pigs, as was first shown by Bueding *et al.* (22, 23). The magnitude of this effect was dependent upon the length of the muscle. The ATP-increasing action of E in taenia coli from the guinea pig was noted as an initial effect (within 30 sec) during the summer months (July–August). During the winter (November–December), on the other hand, the initial effect on the ATP concentration was a reduction, and this was not superseded by an increase until after incubation for 10 min. In human taenia coli, E provoked an initial ATP increase during the winter months also (January–February). Even when E reduced the ATP content, the muscle relaxed (110). In taenia coli therefore, as in mesenteric arteries, E has both an elevating and a reducing effect on the content of energy-rich phosphate compounds. Seasonal changes in the carbohydrate metabolism of vascular smooth muscle have been observed (80). There was a maximum in lactic acid production during the winter and a minimum during the summer months. It may be possible that these changes in the metabolism of smooth muscles are acclimatization phenomena and a part of "nonshivering thermogenesis."

Burnstock (27), Bueding and Bülbring (22), and Bülbring (26) considered that the increase of the ATP content in the muscle stimulates the Na-K pump in the cell membrane and thereby hyperpolarizes the membrane so that the action potentials are inhibited and the muscle is relaxed. This effect has also been considered of importance for the fixation of Ca^{++} to the membrane. Digitalis glycosides, which inhibit the Na-K pump, did not, however, inhibit the relaxing effect of E, and such an effect appeared even when the ATP concentration decreased (110). The hyperpolarizing effect of the catecholamines on the taenia coli has also been explained by another mechanism. Burnstock *et al.* (12, 28) found that on stimulation of inhibitory nerves to the taenia coli, the membrane was hyperpolarized and the muscle relaxed. The magnitude of the hyperpolarization varied with the external K^+ concentration. They believed that this effect was due to a selective increase in permeability of the membrane of K^+. Jenkinson and Morton (64) showed that NE increased the efflux of radioactive K^+ from taenia coli but did not affect the uptake of Na^+. The effect of NE was blocked by phentolamine but not by pronethalol. Isoproterenol had a more pronounced relaxing effect on K^+-depolarized taenia coli than NE, but no effect on the K^+ efflux. Its effect was inhibited by pronethalol. These authors suggested that NE could induce a relaxing effect by stimulation of α-receptors leading to a selective increase in permeability to K^+, while the relaxing effect of the isoproterenol could be ascribed to β-receptor stimulation and a metabolic effect. These observations are of great interest, but it should be pointed out that even the effect of the catecholamines on the K^+-permeability may be associated with an action on the carbohydrate metabolism (see above).

Schild and co-workers (43, 129, 130) have shown that catecholamines can relax K^+-depolarized smooth muscles. None of the hypotheses hitherto discussed (fig. 4) regarding the actions of the catecholamines—which may be of importance in the polarized muscle—are able to explain the relaxing effect in depolarized muscle. E antagonized the contracting effect of Ca^{++} on depolarized taenia coli (130). In high concentrations Ca^{++} also blocked the relaxing and metabolic effects of E in polarized muscle (104). Schild (130) suggested that catecholamines produce contraction or relaxation of smooth muscle according to whether they raise or lower the intracellular free calcium level. Uchida and Mommaerts (147) found that cyclic 3′,5′-AMP in low concentrations inhibited the contracting effect of ATP, Mg^{++}, and low Ca^{++} on actomyosin; this inhibition was overcome by Ca^{++} in higher concentrations. Honig and Van Nierop (59) reported that cyclic 3′,5′-AMP and a protein functioned as a cardiac relaxing system. These effects of cyclic 3′,5′-AMP were, however, later found not to be reproducible (60, 114).

In summary it may be said that many factors favor the view of a close relationship between the relaxing and metabolic effects of the catecholamines in smooth muscle. It is not clear, however, how this relationship functions and among the unsolved problems is that how the relaxing effect of the catecholamines is induced in K^+-depolarized muscle.

CONCLUDING REMARKS

Catecholamines induce metabolic effects in different organs. The nature and strength of these effects is dependent upon the catecholamine derivative, animal species, and organ system. Considerable variations in metabolic activity may occur even in the same individual, under different conditions. There is no general indicator of the metabolic activity of the catecholamines; this has to be determined in each individual case.

A number of facts indicate that a causative relationship exists between the phosphorylase-activating effects of the catecholamines and its calorigenic, vasodilating, and respiration-stimulating actions. The lipolytic effect is also probably of importance for these actions. It is highly probable that the phosphorylase-activating effect of the catecholamines can be traced back to an increase in the production of cyclic 3′,5′-AMP, and there is some probability that the same holds for the lipase-activating effect. The biochemical background of certain of the pharmacological effects of the catecholamines can therefore be localized. In both smooth and striated muscle, however, the catecholamines induce metabolic effects, the dependence of which on an increased production of cyclic 3′,5′-AMP has not yet been investigated. The pharmacologic effects of the methylxanthines, which inhibit the enzymatic destruction of cyclic 3′,5′-AMP, and likewise their ability to potentiate the action of the catecholamines in certain cases, may suggest a relationship between stimulation by the catecholamines of cyclic 3′,5′-AMP production, their metabolic effects, and their stimulation of β-receptors, *i.e.*, their relaxing effect in smooth muscle and stimulating effect on cardiac muscle. The blockade by the adrenergic β-blocking agents of these effects of the

catecholamines also points to such a relationship. Owing to the incompleteness of our knowledge on the reactions which regulate muscle contraction and relaxation, however, it cannot be stated at present whether there is a causative relationship between these effects or whether they are parallel phenomena.

The phosphorylase-activating effect of the catecholamines in the liver is accompanied and possibly preceded by an efflux of K^+. Since the phosphorylase-activating effect of E is reduced in isotonic K^+ solution it is possible that permeability changes and ionic movements through the cell membrane may be of importance for the phosphorylase-activating effect of the catecholamines. This may indicate a relationship between the action of the catecholamines on membranes and their enzyme-activating effects.

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