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SYMPATHETIC REGULATION OF METABOLISM[1]

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I. INTRODUCTION

In this review an attempt has been made to give an overall picture of the metabolic regulatory function of the sympathetic nervous system. A consideration of the metabolic effects of exogenous adrenaline or noradrenaline[3] is followed by discussions of the metabolic effects of sympathetic nerve stimulation and of the normal metabolic activity of the sympathetic nervous system. Where possible, I have tried to find explanations for contradictory results or conclusions. Since it is impossible to quote the several thousand references to work on this subject reported during the last decade, the reader will be referred to reviews when possible and emphasis will be placed on aspects not covered by previous reviewers (212, 214, 300, 308, 764), on more recent studies, and on changes in the overall picture necessitated by the recent expansion in knowledge of metabolic processes.

A major difficulty in any attempt to review the metabolic actions of adrenaline and noradrenaline is the large number of apparently contradictory results of many of the reported studies. Fortunately, on close scrutiny of the reports themselves one can often find an explanation, particularly if it is borne in mind that different effects may be produced by large and by small doses of adrenaline, the same dose given by different routes, or the same dose in animals of different species, different ages, or different environmental experience. Indeed, a complete study of the time-course of the response to a wide range of doses is usually necessary before valid comparison can be made of the effects of adrenaline or noradrenaline under different conditions or in different species.

The principal sites of production and storage of these compounds are sympathetic nervous tissue and the adrenal medulla. The latter organ is usually considered as a part of the sympathetic nervous system, but physiologically

[3] The hormones of the sympathetic nervous system are known by several different names. Thus adrenaline, epinephrine, adrenalin, and adrenine have been used as trivial names for N-methyl-3,4-dihydroxyphenylethanolamine; noradrenaline, norepinephrine, and *dl*-arterenol are trivial names for 3,4-dihydroxyphenylethanolamine. The term adrenalin (with no terminal e), avoided for many years because it was used as a trademark, is now listed in Webster's International Dictionary as the secretion of the adrenal medulla. In general, the use of one or other of these names is decided by the preference of the writer or by the editorial policies of different journals or publishers, which are usually quite arbitrary and inconsistent. When these hormones are used as therapeutic agents it is desirable, as in the case of all drugs, to use the pharmacopoeial nomenclature. The term Adrenaline in the International and British Pharmacopoeias is the equivalent of Epinephrine in the U.S. Pharmacopoeia. Likewise Levarterenol is the U.S. Pharmacopoeia term for noradrenaline; the term norepinephrine has no official standing as a drug. The terms adrenaline and noradrenaline will be used throughout this review since they are in more or less universal use and since we are considering these compounds as hormones and not as drugs. In addition, the term isopropylnoradrenaline will be used to designate the N-isopropyl derivative of noradrenaline (also known as isoproterenol, isopropylarterenol, and isoprenaline).

adrenal medulla cells differ from sympathetic neurones. Firstly, they secrete a mixture of adrenaline and noradrenaline, whereas sympathetic neurones secrete only the latter, and secondly, they secrete both these hormones from the cell body into the circulating blood to produce their physiological action at distant sites, whereas sympathetic neurones secrete noradrenaline from the terminals of their axons in intimate association with the tissue to be influenced. The relationship between adrenal medulla and other sympathetic nervous tissue has been reviewed in some detail (136, 308, 309, 508, 510). Another difficulty in considering the metabolic effects of stimulation of the sympathetic nervous system is that the metabolic effects observed when adrenaline or more particularly noradrenaline is injected or added to isolated tissues are not necessarily the same as those observed when the sympathetic nerves are stimulated. Moreover, agents that block the actions of injected noradrenaline may not always block the actions of noradrenaline liberated from nerve endings.

II. METABOLIC EFFECTS OF ADRENALINE AND NORADRENALINE

A. Lipid metabolism

1. IN VITRO. Adrenaline added *in vitro* stimulates the hydrolysis of triglycerides present in adipose tissue (see 101, 659, 698, 702), skeletal muscle (271, 590), and heart (138, 140, 436, 781), and there is also indirect evidence for a similar hydrolysis in liver (45, 234, 785). Although little is known about how adrenaline exerts this effect in muscle, heart and liver, much is known about the mechanism of breakdown of endogenous triglycerides in adipose tissue, thanks to methods of measuring the accumulation of the products, glycerol and free fatty acids (FFA), in the incubation medium and in the tissue itself. The effect of adrenaline or noradrenaline on lipolysis can be assessed by the extent to which they modify the accumulation of these products. The production of glycerol is the more reliable index of the rate of lipolysis in adipose tissue since under some conditions the FFA released can be re-esterified whereas the glycerol cannot be reutilized to any appreciable extent. In heart, on the other hand, neither the rate of glycerol production nor the rate of FFA production appears to be a good index of the rate of lipolysis (782) because heart can apparently use glycerol (323, 435) as well as FFA (139, 436).

Most studies of the action of adrenaline and noradrenaline on adipose tissue *in vitro* have been restricted to the epididymal adipose tissue of the white rat, which, although in many ways an ideal tissue for such studies, may not be representative of adipose tissue in general. Since the different adipose tissues of a single species or the same adipose tissue of different species may vary considerably in their response to adrenaline added *in vitro* (11, 314, 401, 539, 659, 775), one cannot assume that results of studies with one type of adipose tissue apply to another. Unfortunately, it is not easy to assess the effects of adrenaline or of noradrenaline on lipolysis even in rat epididymal adipose tissue because, as will be shown in the following discussion, the factors limiting the magnitude of the response may vary under different experimental conditions. Although,

because of its very large surface area per unit weight, the epididymal adipose tissue of the rat has been considered to be well suited for incubation studies without having to be sliced, it is possible that despite its thinness many of the cells of the fat pad are not readily accessible to the incubation medium. This is indicated by the observation that adrenaline can induce a much greater release of FFA and glycerol from perfused epididymal adipose tissue (370) or from incubated cells isolated from epididymal adipose tissue (606, 607) than from incubated intact epididymal adipose tissue. Moreover, in the incubated intact epididymal fat pad there are differences in metabolism between the thicker proximal portion of the pad and the thinner distal portion due to the presence in the former of internal tissue which does not readily metabolize compounds in the incubation medium (740).

The accessibility of the appropriate cellular sites to adrenaline does not seem to be the only factor determining the size of the response. The ease of removal of some of the products of lipolysis is also important, particularly because one of the products, FFA, can actually inhibit lipolysis (606) and another product, hydrogen ion, can reduce the response to adrenaline (531, 731, 773). The concentration of albumin (functioning as an FFA-acceptor) in the medium (606), the concentration of FFA already bound to the albumin (594) and the gradient of FFA concentration from the tissue cells to the medium (531) can all influence the rate of triglyceride breakdown. The marked pH-dependence of the lipolytic action of adrenaline over the physiological pH range [ranging from no response at pH 6 to maximum response at about pH 8 (531, 731, 773)] indicates that minor differences in the pH of the medium (or of the intracellular fluid) such as those brought about by the production of hydrogen ions during rapid lipolysis (621) could have a considerable effect. Since the proportion of metabolically active cytoplasm differs in adipose tissue from different sites, from the same site in fed and fasting animals, and from the same site in animals of different ages (4, 36) because of the different amounts of the weighty triglyceride, stored but not undergoing metabolism, difficulties arise in the interpretation of the results obtained.

As an example of the different conclusion that may be reached according to the method of expression of lipolytic response, one may cite the reports that the effect of adrenaline to increase the release of FFA decreases with age (4, 36, 401). This is true only when the FFA release is expressed in terms of the wet weight of the tissue; if, instead, the nitrogen content is used as a reference point, the effect of adrenaline may even appear greater in the older rats (4, 36) or similar when groups of rats of all ages are compared (401). Whether the rate of lipolysis and hence the effect of adrenaline is ever limited by the concentration of triglyceride in the cell is unknown, but changes in substrate concentration could conceivably also influence the rate of lipolysis; it is usually assumed that the lipase is working at saturating substrate concentrations and that changes in rate are due solely to changes in enzyme activity.

When the effect of different concentrations of adrenaline or noradrenaline on the release of FFA or glycerol by adipose tissue is measured, a bell-shaped

dose-response curve is obtained. This apparent autoinhibition by high concentrations of noradrenaline has been observed for the release of FFA by intact tissue (772) and for the release of FFA and glycerol by isolated fat cells (766). The concentration of noradrenaline causing a maximal response is different in these two systems (2×10^{-5} M for intact tissue, 2×10^{-6} M for isolated cells), but in both, a 10- to 20-fold increase in noradrenaline concentration over that having a maximal effect reduces the release by about half (766, 772). This does not appear necessarily to be secondary to high rates of lipolysis since considerably higher rates can be produced by other means (766); no explanation for it can be given at present. This "autoinhibition" is not observed when the response measured is, instead of the release of FFA, the accumulation of FFA within the tissue incubated without albumin in the medium (619, 620). This suggests that the factors limiting the lipolytic response differ with the preparation studied.

The importance of the incubation conditions is illustrated by some studies on the influence of adrenaline and noradrenaline on lipolysis in rabbit adipose tissue. Reports that adrenaline caused little or no stimulation of FFA release from incubated rabbit adipose tissue (618) under conditions in which stimulation has been observed with rat adipose tissue have been included in arguments supporting a hypothesis concerning the evolutionary development of alternative pituitary or sympathetic control of lipid mobilization (617, 619). Unfortunately, however, under appropriate conditions adrenaline increases the release of FFA from incubated rabbit adipose tissue (741) and also the release of FFA and glycerol by perfused rabbit epididymal adipose tissue (367). A further indication of the ability of rabbit adipose tissue to respond to noradrenaline with an increase in lipolysis is the observation that stimulation of the nerves to incubated rabbit epididymal adipose tissue increases the release of FFA (157); since it is known that rabbit adipose tissue contains noradrenaline (708), presumably in nerve endings, the assumption that the effect of nerve stimulation is mediated by noradrenaline released at nerve endings seems reasonable. It is probably justifiable to conclude, therefore, that the breakdown of lipid in rabbit adipose tissue is accelerated by adrenaline and noradrenaline but that this is not readily demonstrable *in vitro* under conditions that are suitable for studying this phenomenon in rat epididymal adipose tissue.

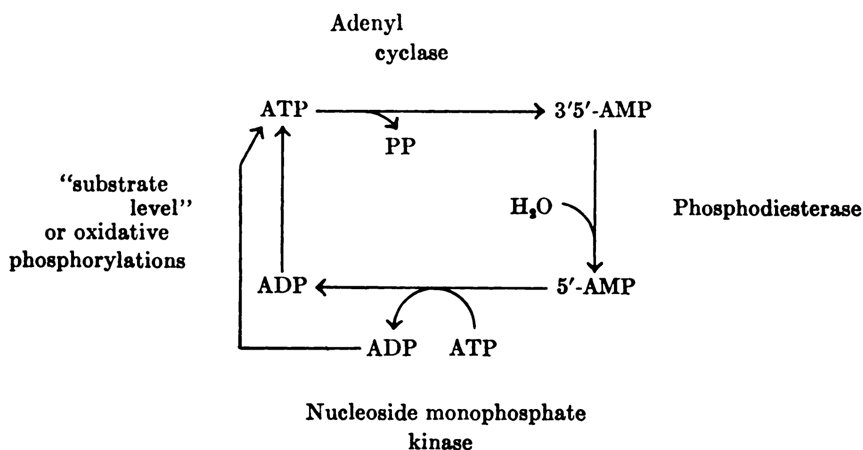
The only nonmammalian species in which the effects of adrenaline or noradrenaline on FFA release have been studied are the chicken and the pigeon. Although chicken adipose tissue appears to be unresponsive to noradrenaline or to adrenaline *in vitro* (125, 348) except at very high concentrations (278), adrenaline does increase lipolysis in incubated adipose tissue from the pigeon (290). It cannot yet be concluded that the action of adrenaline on lipid metabolism is different in birds and mammals.

The action of adrenaline or noradrenaline to increase the breakdown of triglycerides in adipose tissue is accompanied by an increase in the activity of one of the lipases present in adipose tissue (59, 294, 599, 698, 713, 741, 743). Although these lipases have not been well characterized, they apparently include a specific

monoglyceride lipase, a diglyceride lipase, a lipoprotein lipase, a triglyceride lipase, and possibly also a triglyceride-monoglyceride fatty acyl transferase (see 304, 373, 601, 602, 637, 698, 713, 741, 743). Adrenaline and noradrenaline increase the activity of the enzyme catalyzing the first step in triglyceride breakdown, which is normally the rate-limiting one (294, 713). This enzyme apparently exists in two forms (744) and since protein synthesis is not required for the activation of the lipase (236, 431) it would seem that activation of the inactive form is brought about by adrenaline.

The action of adrenaline or noradrenaline to activate adipose tissue lipase is mediated by the cyclic nucleotide 3′5′-AMP. The evidence for this may be summarized as follows: 1. Adenyl cyclase is present in adipose tissue and its activity is increased by adrenaline (427). 2. Adrenaline rapidly increases the 3′5′-AMP content of perfused or incubated adipose tissue (102, 103, 104, 718). Compounds that inhibit the hydrolysis of 3′5′-AMP, such as theophylline, potentiate this action of adrenaline (102, 103). 3. 3′5′-AMP added to intact adipose tissue cells or to homogenates exerts effects similar to those of adrenaline. These include activation of the lipase (600, 601, 718) and accelerated breakdown of triglycerides (102, 718, 766). Theophylline potentiates both these effects of 3′5′-AMP (237, 600, 742, 766). 4. Increasing the 3′5′-AMP content of adipose tissue cells by other means, *e.g.*, by inhibiting its hydrolysis with theophylline, also accelerates lipolysis (391). 5. The pH optimum for the lipolytic action of adrenaline is the same as the pH optimum of adenyl cyclase (720, 731).

Since inhibition of the hydrolysis of 3′5′-AMP leads to an increase in the concentration of this compound in the cells (391, 766) it is clear that this nucleotide is being continuously synthesized and metabolized. The action of adrenaline is to accelerate one side of this adenine nucleotide cycle and hence to cause the accumulation of one of the intermediates. It is of interest that another hormone, insulin, which inhibits adrenaline-induced lipolysis in adipose tissue



"Adenine nucleotide cycle"

(18, 238, 265, 411, 412, 425, 497, 572), may also exert its effect *via* a step in this adenine nucleotide cycle. The evidence for this suggestion is the finding that insulin antagonizes the effect of adrenaline to increase the 3′5′-AMP content of incubated adipose tissue (104), possibly by inhibiting adenyl cyclase (410). Although the 3′5′-AMP content of adipose tissue is not always directly related to the rate of triglyceride breakdown (104), under a single set of conditions (for example, in the presence of various concentrations of theophylline) there may be a direct correlation between the 3′5′-AMP content and the rate of lipolysis (391). This suggests that more than one metabolic pool of 3′5′-AMP may exist within the cell, only one of which may be in direct contact with the lipase (104).

2. IN VIVO. The concentrations of both FFA and glycerol in the blood are increased after the injection of adrenaline or noradrenaline in all species studied so far except the chicken (22 rat; 338, 517 dog; 536, 580 man; 228 cat; 173, 307, 722 rabbit; 172, 738 sheep; 535 guinea pig; 166, 359 pig; 440 cow; 286 monkey; 125, 348 chicken), and this is known to be due to increased rates of entry of FFA (207, 338) and of glycerol (338) into the blood of the intact animal, indicating accelerated lipolysis. This increase is usually attributed to a direct action of these catecholamines on adipose tissue (see 119, 337), but an alternative explanation is the reduction by adrenaline and noradrenaline of the secretion of insulin. This occurs in all species so far studied (110, 432 dog; 476, 580, 581 man; 359 pig; 437 monkey) and appears to be due to a direct action on the pancreatic islets (153, 502). Any restriction in the availability of insulin would be expected to reduce the restraint normally imposed by insulin upon lipolysis and hence to increase the rate of triglyceride breakdown in adipose tissue. However, studies in which these two effects (increase in plasma FFA concentration and inhibition of insulin secretion) have been dissociated by the use of blocking agents (579; see section III D 1) indicate that inhibition of insulin secretion is not the major factor.

Although the actions of adrenaline and noradrenaline on adipose tissue are grossly similar, there are differences between the effects on the blood FFA concentration in the intact animal. The intravenous infusion of adrenaline in dogs produces a transient rise in the concentration of FFA in blood, but the concentration returns to normal quite rapidly even during the infusion (242, 341). On the intravenous infusion of noradrenaline, on the other hand, the concentrations of FFA and glycerol rise and may remain high for as long as the infusion is continued (40, 124, 126, 242, 338, 341, 506). This difference is probably attributable to the more marked effect of adrenaline on blood glucose concentration; this hyperglycemia reduces the entry of FFA into the blood, presumably because the re-esterification of the fatty acids in the adipose tissue is enhanced by the elevated glucose concentration despite the relative lack of insulin, and leaves little FFA available for release into the blood. In keeping with this suggestion is the prolonged increase in blood glycerol concentration during continuous infusion of adrenaline, despite the maintained hyperglycemia and the early decrease of plasma FFA concentration (580).

Most of our present knowledge of adipose tissue metabolism comes from studies with rat adipose tissue *in vitro*, and relatively little is known about the behaviour of human or dog adipose tissue *in vitro*. Unfortunately, most studies of the effect of adrenaline or noradrenaline on the concentration of FFA or glycerol in blood have been carried out with man or dog as the experimental animal rather than the rat, because of the difficulty of estimating and isolating FFA or glycerol from the small blood samples available from the rat. Moreover, some characteristics of the effect of adrenaline on lipolysis in the rat are not apparent in larger mammals. For example, the effect of adrenaline to increase plasma FFA concentration in rats is age-dependent, young rats (<200 g) being more sensitive to this effect of adrenaline than older rats (335 g) and very old rats giving no response at all (401). The effect of noradrenaline on the other hand does not appear to be age-dependent to the same extent (402). In contrast, the effects of adrenaline and noradrenaline to increase plasma FFA concentration in man are not greatly influenced by age (209, 419).

Increases in the concentration of plasma lipids other than FFA (triglyceride, phospholipid, cholesterol) also occur after the administration of adrenaline or noradrenaline. The occurrence of such an increase, the nature of the lipids contributing to the increase, and the nature of the lipoprotein involved all appear to depend on the animal species, the dose of amine, the duration and route of administration and the time of sampling. An increase in plasma triglyceride concentration occurs 24 hours after the infusion of noradrenaline in dogs (120, 126) and in rats (260); the increase in the dog is due to changes in the VLDLP (very low-density lipoprotein) fraction (120, 126). Single injections of adrenaline or noradrenaline have variable effects on the plasma triglyceride concentration 24 hours later in rats (23, 260, 658) and in dogs (268, 413, 656, 657) but consistently increase plasma triglyceride concentration in rabbits (108, 202, 203); in rabbits the increase is due to changes in the VLDLP and, to a lesser extent, in the LDLP (low-density lipoprotein) (108, 202, 203). No change in triglyceride concentration occurs during the first few hours after an injection of adrenaline (223, 657 dog; 298 man) or during the first few hours of an infusion of noradrenaline (120, 126 dog), although increases in phospholipid and cholesterol concentrations may occur at this time (120, 126 dog; 298 man). A detailed study of the time-course of the changes in the lipid components of plasma during and after a prolonged infusion of noradrenaline (120, 126 dog), together with other observations on lipid metabolism in liver has provided the basis for the following interpretation of the mechanism by which noradrenaline alters the plasma lipid concentration. Infused noradrenaline activates adipose tissue lipase; this accelerates lipolysis in adipose tissue and leads to an outpouring of FFA and glycerol into the blood; the concentration of FFA and of glycerol in the blood rises and remains elevated throughout the infusion. Since the uptake of FFA by the liver is proportional to the concentration of FFA in the blood (246, 489, 690, 692), the liver takes up more FFA and incorporates them into triglyceride and, to a much lesser extent, phospholipid (547, 611, 689, 697). These simply accumulate in the liver during the infusion of noradrenaline, presumably because nora-

drenaline in some way prevents the secretion of VLDLP by the liver. Although this inhibition has been observed in isolated perfused liver (351 rat), there is no evidence for its occurrence in the intact dog, and it is not known whether it is due to a direct effect or secondary to another action of noradrenaline. After the infusion of noradrenaline is ended within about 8 hours the concentration of triglyceride in the blood slowly rises while the concentration of triglyceride in the liver falls, an observation consistent with the cessation of the inhibition of hepatic lipoprotein secretion and of the accelerated delivery of FFA to the liver. If the infusion of noradrenaline is continued for a longer time (24 hours) the plasma triglyceride concentration starts to increase during the later hours of the infusion while the concentration of triglyceride in the liver continues to rise; it is as though the rising concentration in the liver partially overcomes the inhibition of lipoprotein secretion. An observation which does not at first sight appear to be consistent with this interpretation is the failure of intraportal infusion of noradrenaline to increase liver lipid levels (242). However, the known ability of very small concentrations of noradrenaline and adrenaline to cause vasoconstriction in the liver when infused intraportally (351, 642) and the fact that many dogs receiving the intraportal infusion die (242) suggests that restricted liver blood flow causes liver damage and limits FFA uptake and lipoprotein synthesis.

To what extent the above interpretation of the effect on lipid metabolism of prolonged infusion of noradrenaline is applicable to species other than the dog or to different modes of administration is uncertain. The effect of adrenaline would be expected to differ because of the transient nature of the increase in plasma FFA concentration it produces; adrenaline causes a smaller increase than noradrenaline in the concentration of lipid in the heart in dogs (503) but the relative effects of the two hormones on liver lipid have not been reported. The apparent variability of the effect of single injections of adrenaline or noradrenaline is most probably attributable to differences in time-course of the response and to the rather small changes in total lipid concentration that result from transient changes in the turnover rates of FFA and VLDLP, although these changes in turnover rates may themselves be quite considerable; only when the altered turnover rates can be maintained for several hours are there appreciable changes in lipid content of liver and plasma.

Prolonged infusion of noradrenaline into dogs results in an accumulation of triglycerides not only in the liver but also in skeletal muscle and heart (120, 126, 506). This accumulation is apparently due to the accelerated uptake and esterification of FFA consequent upon the elevated concentration of FFA in the blood (66, 206, 281, 649, 688, 698). No direct effect of adrenaline on the esterification of FFA by muscle can be demonstrated *in vitro* (206). Curiously, both adrenaline and noradrenaline appear to exert a direct effect on the heart in the dog to reduce the proportion of delivered FFA taken up (592, 593, 649); this effect is overshadowed by the accelerated delivery of FFA to the heart during peripheral intravenous administration of noradrenaline so that the overall effect is a net increase in uptake (281, 649), but a reduction is readily demonstrable when adrenaline or noradrenaline is infused into a coronary artery (592, 593). Man

appears to differ from the dog in that intravenous administration of noradrenaline results in an increase in the proportion of FFA delivered taken up by the heart (597). It is not clear whether this is a true species difference or whether it is due to differences in experimental procedure, for example, differences in the concentration of noradrenaline reaching the heart. The effect of intracoronary infusion of noradrenaline on FFA uptake by human heart does not appear to have been studied. The measurement of the uptake of FFA by the heart is complicated by the action of adrenaline to increase the breakdown of triglycerides in the heart. This difficulty is illustrated very well by studies of the effect of adrenaline on FFA uptake by perfused rat heart (436): the uptake of FFA, as estimated from the change in concentration of titratable FFA in the perfusate, is reduced by adrenaline whereas the uptake of FFA as measured from the disappearance of palmitate-C^{14} from the perfusate is not altered by adrenaline. The most probable explanation of this discrepancy is that the release of FFA is increased by adrenaline while the uptake is not altered (436). Clearly the measurement of A-V differences in titratable FFA concentration across the heart, from which the FFA uptake was calculated in all the studies quoted above (281, 592, 593, 597, 649), is not necessarily a direct measure of uptake but may represent the balance between uptake and release.

The synthesis of triglycerides in adipose tissue is also secondarily increased by adrenaline and noradrenaline. In contrast to the increases in triglyceride synthesis in liver, heart, and skeletal muscle, which are demonstrable only in the intact animal since they are dependent upon the increased supply of FFA, the increased triglyceride synthesis in adipose tissue can be observed *in vitro* too, provided that glucose is available to the tissue either as a constituent of the incubation medium or as glycogen in the tissue. The most reliable procedure for measuring the rate of esterification of FFA in adipose tissue is to estimate the balance between the total FFA release and total glycerol release (see 702 for a discussion of the assumptions involved in this technique). Since the ratio of FFA release to glycerol release in the presence of adrenaline or noradrenaline is generally less than 3, the rate of re-esterification of FFA must be increased (293, 742); it is in fact possible to completely suppress the adrenaline-induced increase in FFA release by the provision of a sufficiently high concentration of glucose in the incubation medium (93, 293) without altering the adrenaline-induced glycerol release (293). Further evidence that adrenaline stimulates esterification in adipose tissue is provided by the increased incorporation of glucose-C^{14} into the glycerol portion of the triglycerides (107, 483, 605). Measurements of the incorportion of added radioactive fatty acids into triglycerides do not provide a reliable measure of the rate of esterification because of uncertainties about the size and changing specific activity of the precursor pool (see 702 and 745). Almost all available information about the effects of adrenaline and noradrenaline on rates of esterification has been derived from studies of rat adipose tissue and these processes in adipose tissue of other species await investigation. Indeed, in pigeon adipose tissue the esterification of FFA is not increased by adrenaline or noradrenaline (290) despite a large increase in FFA production.

Adrenaline and noradrenaline can increase fatty acid oxidation simply by increasing the proportion of total substrate available to tissues which is contributed by fatty acids. This is brought about both by the increased concentration of FFA in the blood, a consequence of the action of the catecholamine on adipose tissue, and by the increased production of FFA within tissues such as heart, muscle and liver. The oxidation of FFA by skeletal muscle (66, 206, 261, 698), by liver (547, 611, 697), heart (281), and adipose tissue (20) is proportional to the FFA concentration in these tissues. It may, therefore, be assumed that the main reason for the increase in fatty acid oxidation in these tissues after the administration of adrenaline or noradrenaline to the intact animal is the plentiful supply of FFA, this increase being accompanied by a compensatory decrease in the oxidation of other substrates such as glucose (436, 550) in the absence of any increase in energy demand. In addition the calorigenic action of adrenaline and noradrenaline (see section II D) must also be associated with an increased oxidation of available substrate, which may also be fatty acid. Indeed in man both total oxygen uptake and fatty acid oxidation are increased by noradrenaline (700). Whether adrenaline has another more direct effect on fatty acid oxidation is not clear. The interpretation of those studies in which intact tissues have been used is complicated by the dilution of the radioactive fatty acid substrate by endogenous fatty acids liberated under the influence of adrenaline. The conflict between reports of an increase (295, 597), no change (281, 436) or a decrease (436, 592) in fatty acid oxidation by the heart during contact with adrenaline is probably due to technical problems of this kind. Reports of an effect of adrenaline to increase fatty acid oxidation by liver homogenates or isolated mitochondria (319, 320, 321) need to be confirmed and extended.

As a consequence of the increased fatty acid oxidation, the production of ketone bodies is increased by adrenaline or noradrenaline. The increase has been demonstrated in perfused liver (250) and has also been produced by 3′5′-AMP in liver slices (42); it is presumably the cause of the rise in the concentration of ketone bodies in the blood after the administration of adrenaline or noradrenaline (60, 212, 419, 530, 698, 700).

The synthesis of fatty acids by adipose tissue is not usually altered by adrenaline (107) although it may be increased when for other reasons the rate of fatty acid synthesis is very high, as in the presence of insulin and sufficient glucose (252, 253). Under these conditions the rate-limiting process in lipogenesis from glucose appears to be the reoxidation of the reduced coenzymes produced in glycolysis, which in turn limits the production of acetyl CoA from glucose; adrenaline appears to stimulate the reoxidation of these reduced coenzymes (see section II D) and hence permits more rapid formation of acetyl coenzyme A (252, 253).

In summary, adrenaline or noradrenaline can cause a sequence of changes in lipid metabolism in the intact animal, which include, at various times, increased triglyceride breakdown, increased concentrations of FFA, glycerol, and ketone bodies in the blood, increased esterification of FFA, accumulation of lipid in the liver, decreased secretion of plasma lipoproteins, increased secretion of plasma

lipoproteins, and increased oxidation of fatty acids. These changes appear to be principally, if not entirely, due to the direct action of these hormones to activate adenyl cyclase; this accelerates the formation of 3'5'-AMP and, consequently, the activation of tissue lipase. Adipose tissue appears to be the main target organ for this action of adrenaline and noradrenaline, and it is the change in adipose tissue metabolism which has the most far-reaching consequences on the whole body, but other tissues (muscle, heart, perhaps liver) are also directly affected. Most other changes appear to be secondary to the increased supply of FFA, perhaps all with the exception of the decreased secretion of plasma lipoproteins by the liver of which the immediate cause is unknown. Catecholamines, therefore, modify the "physiologic fatty acid transport cycle" (698) in such a way that oxidizable substrates (FFA, glycerol, ketone bodies) are made available to other tissues; a recovery phase follows the initial net transfer of lipid from adipose tissue to other tissues.

B. Carbohydrate metabolism

It is now established that adrenaline or noradrenaline can modify the carbohydrate metabolism of tissues in at least two ways. The primary direct action of adrenaline or noradrenaline appears to be to accelerate the rate of the reaction catalyzed by adenyl cyclase to produce a temporary increase in the concentration of the product, 3'5'-AMP, which in turn alters the activities of at least two (glycogen phosphorylase and glycogen synthetase) and possibly more of the enzymes involved in carbohydrate metabolism. The consequences of this action vary according to the tissue, from increased glucose output by liver cells to increased esterification of fatty acids by adipose tissue cells. The catecholamines also alter the composition of the environment of all cells by virtue of their actions to modify the release of substrates or hormones by tissues. For example, the increased supply of FFA to cells, which is a consequence of catecholamine action in the intact animal, markedly alters carbohydrate metabolism in those cells; the relative lack of insulin in combination with a high glucose concentration produces a different pattern of glucose metabolism from that seen when glucose concentration is increased by other means. For these reasons alone, the observed actions of catecholamines on carbohydrate metabolism of tissue *in vitro* cannot be assumed to occur *in vivo* but must be shown to do so. The following discussion is divided into two parts: (1) the effect of adrenaline on carbohydrate metabolism of individual tissues; (2) the effect of adrenaline on carbohydrate metabolism of intact animals. The effect of noradrenaline is also considered where appropriate.

1. ISOLATED TISSUES. Direct actions of adrenaline or noradrenaline, or both, that result in alterations in carbohydrate metabolism have been demonstrated *in vitro* in striated muscle, heart, smooth muscle, liver and adipose tissue. Contact with adrenaline increases the concentration of 3'5'-AMP in liver slices (see 718, 721), skeletal muscle (see 721), smooth muscle (95), heart (144, 313, 603, 784, 786; see 721) and adipose tissue (101–104, 718); the 3'5'-AMP appears to be the connecting link or the "second messenger" (721) between an initial

action of the adrenaline and the final changes in activity of certain enzymes. This chain of reactions has been likened to a cascade in which the initial small change in adenyl cyclase activity is amplified (76). Current knowledge of the adenyl cyclase system in these tissues comes mainly from the work of Sutherland and his associates and has been reviewed recently by them (343, 565, 717–719, 721). It will therefore not be reviewed in detail here.

a. Skeletal muscle. In skeletal muscle the activities of two enzymes of glycogen metabolism, glycogen phosphorylase and glycogen synthetase, are altered by the increased concentration of 3′5′-AMP, the former being increased and the latter decreased. Our knowledge of the phosphorylase enzyme system of muscle has been reviewed recently (328); the reader is referred to reviews or papers by Krebs and co-workers (433, 434, 583) and by Danforth, Helmreich and Cori (170, 352–354) for detailed descriptions of the properties and kinetics of the phosphorylase enzyme system. In brief, muscle phosphorylase exists in two enzymically interconvertible forms, *a* and *b*, the latter being the predominant form in resting muscle. Phosphorylase *b* is activated by 5′-AMP, and the activation is antagonized by ATP or glucose-6-phosphate; this form of the enzyme is completely inactive in the absence of 5′-AMP. Phosphorylase *a* is also activated by 5′-AMP provided that it is not saturated by its substrate, and this activation is not antagonized by either ATP or glucose-6-phosphate; phosphorylase *a* is, however, active in the absence of 5′-AMP. Phosphorylase *b* is converted to phosphorylase *a* by an enzyme that also exists in two interconvertible forms, dephosphophosphorylase kinase. The conversion of this enzyme to the more active form can be accelerated by either 3′5′-AMP or calcium. Phosphorylase *a* is converted back to the *b* form by a phosphatase. The total phosphorylase activity in a cell depends, therefore, upon (a) the relative proportions in the two forms, which in turn depend on the concentrations of 3′5′-AMP and calcium, and (b) the concentrations of ATP, glucose-6-phosphate, and 5′-AMP, the influence of which depends on the relative proportions in the two forms of phosphorylase and on the substrate concentration. Increased activity of total phosphorylase and, therefore, increased glycogenolysis, can occur without any changes in the relative proportions of phosphorylase *a* and *b* (484, 528, 529) but an increase in the proportion of phosphorylase *a* usually accelerates glycogenolysis. Clearly the effect of adrenaline, mediated by an increase in 3′5′-AMP concentration, is superimposed on an already closely regulated system.

Current knowledge of the chemistry of the glycogen synthetase system of muscle comes principally from the work of Larner and his associates (9, 163, 259, 369, 381, 613, 614, 750). The glycogen synthetase of muscle also exists in two interconvertible forms, I and D. The D form is inactive save in the presence of glucose-6-phosphate, and the activation is antagonized by phosphate. The I form is also activated by glucose-6-phosphate but only when it is not saturated with substrate; this form is also active in the absence of glucose-6-phosphate. Glycogen synthetase I is converted to the D form by a kinase and glycogen synthetase D is converted to the I form by a phosphatase. 3′5′-AMP accelerates the kinase-catalyzed conversion of I to D. The proportion of glycogen synthetase

in the two forms also appears to be regulated by the concentration of glycogen in the cell (168), possibly by a direct inhibition of the phosphatase by glycogen (751); thus the less glycogen present, the more enzyme will be in the more active I form. The total glycogen synthetase activity, therefore, depends upon (a) the relative proportions in the I and D forms, which in turn depend on the concentrations of 3′5′-AMP and glycogen, and (b) the concentrations of glucose-6-phosphate and phosphate, the influence of which depends on the relative proportions in the two forms and on the substrate concentration. Again, the effect of adrenaline, mediated by an increase in 3′5′-AMP concentration, is superimposed on an already well-regulated system of enzymes.

An injection of adrenaline can increase the proportion of glycogen phosphorylase in the *a* form in rat skeletal muscle within 1 minute (582, 583); there are simultaneous increases in the concentration of 3′5′-AMP and in the proportion of dephosphophosphorylase kinase in the more active form (582, 583). Small increases in the proportions of glycogen phosphorylase *a* and of the more active dephosphophosphorylase kinase can also be seen during electrical stimulation of rat muscle but consistent results have not always been obtained (583). A detailed study of the time-course of phosphorylase activation in isolated frog sartorius muscle under anaerobic conditions has shown that the effect of adrenaline is fairly slow, reaching a maximum only after 30 minutes, whereas electrical stimulation can bring about a very rapid increase to maximum activity within 2 seconds (170). Similar results are obtained when adrenaline is injected into frogs, the effect of adrenaline being slower and smaller than the effect of electrical stimulation of the muscle (583). Frog and rat muscle differ, therefore, in the relative effectiveness of adrenaline and electrical stimulation to bring about an increase in phosphorylase activity; it is not clear whether this is a consistent difference between amphibia and mammals or whether it is simply a species difference. Like the activation of adipose tissue lipase, the activation of muscle phosphorylase by adrenaline *in vitro* is pH-dependent, being greatest at higher than physiological pH (596); it seems likely that this reflects the pH optimum of the adenyl cyclase of muscle.

Adrenaline, administered to the intact animal or added to muscle *in vitro*, decreases the proportion of glycogen synthetase in the I form (163, 168, 780) and inhibits the effect of insulin to increase the proportion in the I form (163). High concentrations of adrenaline may also decrease total glycogen synthetase activity by some unknown mechanism (35, 163). *In vitro*, 3′5′-AMP has the same effect on this enzyme as adrenaline (35, 382, 614). When muscle glycogen is considerably decreased by adrenaline and after the effect of the injected adrenaline has abated, there is an increase in the proportion of the glycogen synthetase in the I form (168, 169); this probably represents a change from regulation principally by adrenaline to regulation by the concentration of glycogen (168, 751).

The effect of adrenaline on the glycogen content of muscle is to decrease it when the initial concentration is high and to reduce the increase which otherwise occurs when the initial glycogen content is low both *in vivo* (65, 73, 374, 393, 484, 683) and *in vitro* (72, 73, 217, 392). In the former circumstances the principal

effect of adrenaline is probably activation of phosphorylase whereas in the latter circumstances the effect may be due principally to the superimposition of the regulatory effect of adrenaline on the control of glycogen synthetase activity by low glycogen concentration. The effect of adrenaline on the uptake of glucose by muscle incubated *in vitro* also depends on the glycogen content of the tissue. If the glycogen content is low and if glycogen synthesis is proceeding rapidly with a high glucose uptake, adrenaline reduces glycogen synthesis and reduces glucose uptake to the same extent as it reduces glycogen synthesis (72, 73). If, on the other hand, the glycogen content of the muscle is high and little glycogen deposition occurring, then the effect of adrenaline to diminish glucose uptake is correspondingly less (73). Inhibition of glucose uptake by adrenaline occurs in tissues incubated in a phosphate-buffered medium (73, 355, 757, 758) but is not always seen in tissues incubated in the more physiological bicarbonate-buffered medium (301, 355, 733a); phosphate prevents this inhibitory action of adrenaline on tissues in a bicarbonate medium (733a). There does not appear to be a simple explanation for these differences. Adrenaline inhibits glycogen deposition (355) and stimulates glycogenolysis (723) equally well in phosphate or bicarbonate buffered media. The action of adrenaline to inhibit the removal of hexose phosphates (*via* glycogenesis) and to increase the formation of hexose phosphates (*via* glycogenolysis) would be expected to lead to accumulation of hexose phosphates, as does indeed occur (see 213, 548), and to an inhibition of the utilization of glucose *via* the hexokinase reaction by the hexose phosphates (see 164, 213, 426), but the relative accumulation of hexose phosphates in muscles incubated with adrenaline in either phosphate or bicarbonate medium is unknown. Hexose phosphates do indeed accumulate in diaphragm incubated with adrenaline in a bicarbonate buffered medium (548) and there is no direct evidence for the suggestion (355) that the accumulation of hexose phosphates is less in the bicarbanate medium because the partial block of the phosphofructokinase reaction seen in the phosphate medium (661, 662) does not occur. In any case, an increase in the availability of hexose phosphates should not increase the rate of glycolysis unless the restriction of phosphofructokinase activity, which normally regulates glycolysis, were removed (see 509, 786). This is certainly true for frog muscle under anaerobic conditions, in which adrenaline does not alter lactate production unless the muscle is stimulated (417, 566). Moreover, adrenaline does not alter the concentration of fructose diphosphate in diaphragm, despite the increased concentration of hexose phosphate (548); this suggests that control at this point is not altered in the presence of adrenaline. The finding that adrenaline increases lactate production by incubated diaphragm (213, 759) is, therefore, surprising in view of the unchanged regulation of glycolysis. This finding is in fact usually interpreted as an indication of an increased rate of glycolysis (see 213, 480, 759). An alternative interpretation can now be offered: since adrenaline increases the FFA concentration in incubated diaphragm (271) and since elevated FFA concentration inhibits pyruvate metabolism and diverts pyruvate to lactate (270), the effect of adrenaline to increase lactate production may be mediated by FFA. To what extent the effect of FFA to inhibit glucose uptake and decrease the

rate of glycolysis (549, 591) also contributes in the overall effect of adrenaline is not known; FFA do not directly influence glycogen metabolism (591) and clearly do not contribute to the effect of adrenaline at that level.

b. Heart. The initial metabolic change on addition of adrenaline to a perfused heart is a rapid increase in the concentration of 3′5′-AMP (144, 197, 603, 784), which may precede (197) or accompany (144, 784) the inotropic response. Immediately after the increase of 3′5′-AMP concentration there follows an increase in phosphorylase *b* kinase activity (196, 197), which may also precede the inotropic response. An increase in phosphorylase *a* activity follows the inotropic response (see 563, 784, 786). The action of adrenaline on the glycogen synthetase system of heart, in contrast to skeletal muscle, is to increase the proportion in the more active form I (780, 784); this is seen only in the presence of glucose (784). Marked changes in carbohydrate metabolism of the heart occur after contact with adrenaline; some of these are due to the direct action of adrenaline to alter the activities of the enzymes of glycogen metabolism, but most are secondary to the changes in the concentrations of the three adenine nucleotides (ATP, ADP, AMP), which are in turn secondary to the inotropic response. The following account of these changes in carbohydrate metabolism is based on the extensive studies by Williamson of levels of glycolytic intermediates, adenine nucleotides, and other intermediates in heart (781, 783, 784, 786–788). Initially progressive decreases in ATP and creatine phosphate concentrations are accompanied by progressive increases in ADP, AMP and phosphate concentrations. The rate of glycolysis increases, probably because of increases in fructose-6-phosphate, ADP, AMP, and phosphate concentrations and a decrease in ATP concentration leading to activation of phosphofructokinase; during this period the control point of glycolysis appears to be at the glyceraldehyde-3-phosphate dehydrogenase level. Subsequently, control is re-established at the phosphofructokinase level by rising concentrations of citrate, which inhibit the phosphofructokinase. An immediate increase in the oxidation state of pyridine nucleotides (ascribed to increased respiratory activity initiated by the changed adenine nucleotide concentrations) is followed by a more prolonged reduction of pyridine nucleotides (ascribed to the increased rate of glycolysis). The source of the hexose phosphate used in glycolysis can be either glucose from the medium or both glucose from the medium and tissue glycogen. The former appears to predominate at low concentrations of adrenaline, which apparently accelerate glycolysis without altering glycogen metabolism; these low concentrations presumably do not activate phosphorylase but do, nevertheless, cause an inotropic response (198, 514–516). Higher concentrations increase both glucose utilization and glycogen disappearance; the amount of lactate produced under these conditions is approximately equal to the amount of glycogen disappearing. Increased incorporation of glucose-C^{14} into glycogen and the increased activity of glycogen synthetase I indicate an increased synthesis of glycogen despite the net breakdown. The increased utilization of medium glucose occurs despite a high intracellular concentration of glucose-6-phosphate which might be expected to inhibit hexokinase; this may be due to the simultaneous increase in phosphate concen-

tration since phosphate can antagonize the inhibition by glucose-6-phosphate of hexokinase (see 786).

Thus, although the changes in enzyme activity directly attributable to an action of adrenaline are similar in heart and skeletal muscle, the overall change in carbohydrate metabolism is entirely different in these two tissues because of their different mechanical activities. The increased mechanical activity of the heart results, *via* changes in adenine nucleotide concentrations, in altered control of glycolysis, whereas the addition of adrenaline to skeletal muscle does not appreciably alter energy utilization, and therefore there is no change in the control of glycolysis.

The early finding of a correlation between the activation of phosphorylase and the positive inotropic response to adrenaline in isolated rat heart (361) led to the suggestion that the activation of phosphorylase was in some way responsible for the increased force of contraction. A considerable amount of evidence in support of this proposal was collected subsequently and a correlation between the magnitude of the inotropic response and the activation of phosphorylase was obtained under a wide variety of conditions (see 328 for review) as well as a temporal correlation between increase in 3′5′-AMP concentration, increase in phosphorylase *a* activity and increase in force of contraction (364, 564). It was not until detailed dose-response data for each response were obtained that there was any indication that the two might be dissociated; low concentrations of adrenaline could be shown to cause a positive inotropic response without simultaneously activating phosphorylase (198, 514–516). Recent studies of the time-course of the inotropic response and phosphorylase activation have shown conclusively that these two responses can be dissociated temporally (144, 190, 563, 603, 786, 787), the inotropic response preceding the activation of phosphorylase. The difficulties in establishing such a dissociation are illustrated by the work of Øye (563), who found that the measured activity of phosphorylase *a* in the heart during the early phase of the inotropic response, when the 3′5′-AMP concentration had already increased, depended on the method of extraction; if precautions were not taken to prevent the action of the already activated phosphorylase *b* kinase, then phosphorylase *a* was formed from phosphorylase *b* during the extraction procedure and an artifactual increase in phosphorylase *a* activity at the same time as the inotropic response was observed (563). There is, therefore, considerable evidence at hand that the inotropic response cannot be a consequence of activation of phosphorylase. However, there still appears to be a close correlation between the increase in concentration of 3′5′-AMP and the inotropic response, and the suggestion has been made that 3′5′-AMP may mediate the cardiac inotropic response to adrenaline (515, 589, 603, 718; see also 721) or that 3′5′-AMP accumulation and phosphorylase *b* kinase activation may both be related in some way to the inotropic response (197). The lack of a direct correlation between total 3′5′-AMP concentration and force of contraction has led Williamson to propose that an increase in 3′5′-AMP concentration may trigger another change, such as an increase in the concentration of ionized calcium, which then regulates the force of contraction (144, 784). Extreme caution is needed in reading cause and effect

relationships into the observed changes, particularly in view of the example described above of the erroneous conclusion about a cause and effect relationship between phosphorylase activation and inotropic response derived from apparently simultaneous increases in both. There is at present insufficient evidence to either prove or disprove Williamson's suggestion, which nevertheless provides a most useful working hypothesis.

Although adrenaline has such a marked action to accelerate carbohydrate metabolism in the heart, which, considered teleologically, would be appropriate for at least supporting the increased work load also caused by adrenaline, it must be remembered that the principal fuel of the heart is neither glucose nor glycogen but lipid. In the presence of physiological concentrations of FFA, the contribution of glucose oxidation to total cardiac respiration has been calculated to be about 15% (436). Thus somewhere between 60 and 80% of the energy requirement of the heart stimulated by adrenaline is obtained from the oxidation of lipid, principally endogenous lipid (see 436). Adrenaline increases the breakdown (138, 436, 781) and turnover (436) of heart lipids. Moreover, the utilization of added FFA by heart considerably reduces the oxidation of carbohydrates (435, 436, 549, 664, 665), and cutting off the supply of FFA to the heart in the intact animal (with nicotinic acid; see section III) causes the heart to utilize its glycogen stores (610). Thus results obtained in studies of carbohydrate metabolism of hearts perfused with a FFA-free medium (144, 781, 783, 784, 786–788) cannot necessarily be applied to the heart *in vivo*. Little is known at present about the detailed sequence of events in the change of lipid metabolism induced in the heart by adrenaline, but clearly the initial attempt to correlate phosphorylase activation with the inotropic response to adrenaline was accidental in that prior discovery of an activation of a lipase would have led to a different correlation.

c. Smooth muscle. The initial changes known to occur in smooth muscle (guinea pig taenia coli) after contact with adrenaline are an increase in 3′5′-AMP concentration and relaxation (95, 192). Only later does the phosphorylase *a* activity increase (14, 192). That there is no change in the rate of glycolysis during the early phase of the relaxation is indicated by the lack of change in concentrations of glucose-6-phosphate, fructose-6-phosphate, and fructose-diphosphate (95). Early reports of phosphorylase activation during relaxation (14) and attempts to establish a cause and effect relationship between the two (14, 96) were based on the artifactual activation of phosphorylase during preparation of tissue extract of the smooth muscle (14, 94, 95). The only metabolic change apparently correlated with relaxation so far is the increase in 3′5′-AMP concentration, but it would be premature to consider 3′5′-AMP as a mediator of the relaxing action of adrenaline until more is known about the sequence of these and of other events, including for example, possible changes in lipid metabolism. The role of increased lactate production in promoting the relaxation of smooth muscle has also received considerable attention from Lundholm, Mohme-Lundholm and co-workers (see 213, 328 and 480). Again, lactate production is probably only one of many changes which might be correlated with relaxation, and more information is needed about the sequence of events that result in increased lactate production and whether

lactate production does actually occur during the first few seconds when the relaxation is taking place. By analogy with skeletal muscle and heart discussed above, it is improbable that the increased lactate production is caused by the increased rate of glycogenolysis, but no other cause is visible at present.

d. Liver. The best understood consequence of an increase in 3′5′-AMP concentration in liver is an increase in the proportion of glycogen phosphorylase in the active form (the liver enzyme differs from the muscle enzyme in that the *b* form is completely inactive even in the presence of 5′-AMP) (see 718, 719, 721); this increases the rate of glycogenolysis and the output of glucose from the cell. Another process that leads to increased production of glucose, gluconeogenesis from lactate, can also be accelerated by 3′5′-AMP and by adrenaline in perfused liver (234). The control point of gluconeogenesis altered by 3′5′-AMP appears to lie between pyruvate and phosphoenolpyruvate, and likely enzymes involved are pyruvate carboxylase, phosphoenolpyruvate carboxykinase, and pyruvate kinase. It is not known whether one of these enzymes is directly influenced by 3′5′-AMP or whether, as is more likely, the increased gluconeogenesis is secondary to changes in the concentrations of activators and inhibitors of one or more of these enzymes as a consequence of the increase in lipid metabolism also occasioned by 3′5′-AMP (see 785). The wealth of information about allosteric activation and inhibition of gluconeogenic and glycolytic enzymes and about levels of intermediates in the liver under different conditions permits almost unlimited speculation about the mechanism involved in the action of adrenaline to increase gluconeogenesis, but here we note only that a detailed analysis of the sequence of changes in levels of intermediates (*e.g.*, FFA, acetyl CoA, or $NADH_2$ as suspected activators or inhibitors and intermediates of gluconeogenesis to follow changes in regulation) is needed to establish any mechanism.

Although the action of adrenaline on glycogen synthesis in muscle has received considerable attention, little is known about the action of adrenaline or 3′5′-AMP on glycogen synthesis in liver, and there appears to be no information about a possible effect of 3′5′-AMP on glycogen synthetase in liver.

e. Adipose tissue. Adrenaline profoundly modifies carbohydrate metabolism in adipose tissue, but many of the effects result from the concurrent changes in lipid metabolism (see section II A 1). Only a few appear to be due to more direct effects of the increased 3′5′-AMP concentrations resulting from the action on adenyl cyclase. Accumulation of 3′5′-AMP activates phosphorylase in adipose tissue (257, 302, 739, 746), but it is unlikely that the minute amount of intracellular glycogen can serve as a significant source of hexose phosphate in normally fed rats (17). Only in glycogen-rich tissues (from rats re-fed after fasting) does adrenaline cause an appreciable breakdown of glycogen (17). Since, at concentrations that exert the other effects, adrenaline has no effect on glycogen synthesis (107; see 253), an action of 3′5′-AMP on the glycogen synthetase of adipose tissue is unlikely. Phosphofructokinase of adipose tissue is very sensitive to activation by 3′5′-AMP (180) and acceleration of glycolysis by adrenaline appears to be, at least in part, due to this mechanism (181). Adrenaline also increases glucose uptake, lactate formation, oxidation (in the tricarboxylic acid cycle), and the

formation and utilization of α-glycerophosphate for triglyceride synthesis (see 19, 253, 448, 659). These changes are probably due mainly to increased availability of FFA from activation of lipase. Indeed, the addition of FFA to the medium will cause similar changes in glucose metabolism (107). Excessive accumulation of FFA in the tissue, however, inhibits glucose utilization (222, 306, 483, 747), perhaps by damaging the tissue (303), since oxygen uptake is also inhibited (306). The rate of fatty acid synthesis from glucose is not directly influenced by adrenaline or 3′5′-AMP. Although high concentrations of adrenaline may inhibit it (107), possibly by raising FFA, low concentrations may enhance fatty acid synthesis when its rate is already high, as in the presence of insulin (see 252, 253). This effect is probably due to the action of adrenaline to accelerate the oxidation of reduced coenzymes produced in glycolysis; the excess of oxidized coenzymes accelerates glycolysis, no longer limited by the availability of NAD, and the formation of acetyl CoA to be used in lipogenesis (see 252, 253).

In adipose tissue in which the concentration of 3′5′-AMP has been increased by adrenaline (104, 679), insulin reduces the concentration, possibly by inhibiting adenyl cyclase (410). This observation provides an explanation for the opposing actions of adrenaline and insulin on activation of phosphorylase (410) and lipase (see 18). Despite these opposing actions, both adrenaline and insulin accelerate glucose utilization by adipose tissue. In the case of adrenaline, 3′5′-AMP appears to lift a restriction on glycolysis by activating phosphofructokinase as noted above, and the major fate of the fructose diphosphate is conversion to α-glycerophosphate to be used for esterification of FFA. In the case of insulin, the mechanism of alteration of glycolytic control is not known, but the major fate of the glycolytic products is conversion to fatty acids.

The effect of noradrenaline on metabolism of externally added glucose by rat brown adipose tissue differs from its effect on white adipose tissue in that no increase occurs in the incorporation of glucose into glyceride-glycerol or into carbon dioxide (705). This probably results from the presence of a glycerol kinase in rat brown adipose tissue (see 405) and the acceleration by noradrenaline of an almost entirely internal triglyceride cycle (406) in which re-esterification utilizes endogenous glycerol rather than external glucose.

2. INTACT ANIMALS

a. Glycerol. The injection of adrenaline or noradrenaline increases the concentration of glycerol in the blood of all species. This effect is believed to be a consequence of accelerated hydrolysis of triglycerides and has already been discussed as an aspect of lipid metabolism (section II A 2).

b. Pyruvate and lactate. The effect of adrenaline to increase blood lactate and pyruvate concentrations is usually considered to be a consequence of its glycogenolytic action in muscle (see 213); noradrenaline does not exert this effect on muscle (65, 165, 217, 254, 374, 392, 393), nor does it increase the blood lactate concentration (65, 296, 393, 478, 722, 763, 770). However, as pointed out in the discussion of the effect of adrenaline to enhance lactate production by muscle *in vitro*, an increased rate of glycogenolysis would not be expected to lead to an

increased rate of glycolysis and to an increased production of lactate unless some other change in energy utilization occurred simultaneously. An explanation for the increase in blood lactate concentration other than solely the glycogenolytic action of adrenaline on skeletal muscle must, therefore, be sought. Recent studies (763) have suggested that the increase in blood lactate is a consequence of the simultaneous increases in blood glucose and FFA concentrations brought about by adrenaline. Elevation of blood glucose concentration by administration of glucose does not by itself alter blood lactate concentration, but when the concentration of FFA in blood is already elevated, by infusion of either FFA or noradrenaline, administration of glucose greatly increases the concentration of both lactate and pyruvate in the blood. Thus the effects of adrenaline to increase blood FFA and glucose concentrations could by themselves account for the rise in blood lactate concentration; it seems likely, however, that the simultaneous increase in availability of hexose phosphates in muscle brought about by the glycogenolytic action of adrenaline also contributes. An exceptionally large rise in blood lactate concentration without a simultaneous hyperglycemia and with a decrease in the high plasma FFA concentration has been observed after administration of adrenaline to an infant with neuroblastoma and hypoglycemia (660); thus high FFA concentration and an action of adrenaline on muscle must have been sufficient to increase lactate production under these conditions. Noradrenaline usually fails to alter the blood lactate concentration because the increase in blood FFA concentration is accompanied by an increase in neither glucose concentration nor glycogenolysis in muscle; doses of noradrenaline large enough to increase both blood glucose and FFA concentrations also increase blood lactate concentrations (318). The mechanism by which increased availability of FFA increases blood pyruvate and lactate concentration in the presence of a glucose load is not completely clear. The inhibition of pyruvate utilization in muscle by FFA (270, 272) provides a partial explanation, but the role of the glucose load in this is not apparent.

c. Glucose. The hyperglycemic action of adrenaline has been considered by many authors to be one of the best understood metabolic effects of adrenaline (see 721). Recently it has become apparent that its mechanism may be exceedingly complicated, that it is not very well understood, and that increased glycogenolysis, increased gluconeogenesis, and decreased peripheral glucose utilization may all contribute to the hyperglycemia. In order to consider the roles of the relevant processes, it is first necessary to describe some of the characteristics of the hyperglycemic response to adrenaline or noradrenaline. Intravenous infusion of adrenaline causes a persistent rise in blood glucose concentration until the infusion is stopped, even after 8 hours and even in a fasting animal (242 dog). In contrast, under the same conditions noradrenaline causes only a transient and small increase in blood glucose concentration and the increase lasts only about 1 hour even if the infusion is continued for as long as 24 hours (126, 242, 503). Noradrenaline generally has a lesser hyperglycemic effect than adrenaline; the maximum obtainable increase in blood glucose concentration is smaller, and the concentration of noradrenaline needed to increase blood glucose concentration is

greater (see 65, 254, 393). Differences in the time of onset, the magnitude, and the duration of hyperglycemia after administration of adrenaline or noradrenaline, as reported in the literature, are probably due to differences in route of administration, dose, time of sampling, nutritional state of the animal, and species used. There are marked species differences in the hyperglycemic effect of noradrenaline, the rat being particularly unresponsive to this catecholamine (65, 254, 393) and the rabbit being highly responsive (307, 347, 430, 485, 722); consistent but small increases in blood glucose concentration during infusion of noradrenaline are observed in man (31, 194, 340, 390, 450, 536, 580, 700).

At least five different actions of adrenaline may be involved in its hyperglycemic effect. These actions could contribute to the hyperglycemic effect to different degrees in different circumstances. A summary is presented in figure 1.

Liver: Adrenaline (*via* 3′5′-AMP formation) activates phosphorylase and thereby causes increased glycogenolysis and increased release of glucose. Although this action of adrenaline on liver preparations is well documented (see 212, 555, 682, 718, 719, 721), there are several observations that adrenaline and noradrenaline at physiological concentrations have little, if any, direct effect on breakdown of glycogen in the isolated perfused liver (682, 684, 685; see 520, 681) or in the intact animal (235, 683), even when the amine is introduced directly into the portal vein (235, 663). Indeed, only when concentrations of adrenaline high enough to cause a marked reduction in portal blood flow are given is there appreciable glycogenolysis and any increase in glucose production in the perfused liver (520, 682, 684, 685), and the participation of a direct action of adrenaline on the liver in the production of hyperglycemia is questionable (684, 685). However, although adrenaline decreases blood flow through perfused rat liver (161) it does not have this effect in perfused rabbit liver (211). Moreover, in an intact animal (dog) adrenaline may actually increase the flow of blood through the liver when it is administered *via* a peripheral vein although when administered *via* the portal vein or hepatic artery it does decrease hepatic blood flow (642). In contrast, noradrenaline reduces hepatic blood flow regardless of the route of administration (642). Clearly, it is difficult to extrapolate these observations to what might happen in intact animals after the administration of adrenaline by various routes.

Adrenaline (*via* 3′5′-AMP formation) in some way lifts a restriction on a rate-limiting step of gluconeogenesis and permits accelerated gluconeogenesis from lactate. This action is complemented by the simultaneous rise in blood lactate concentration caused by adrenaline. Although a rise in the concentration of lactate in the blood does not by itself cause hyperglycemia (see 154), the simultaneous availability of lactate and adrenaline to the liver might permit the action of adrenaline, already documented in isolated liver, to increase lactate uptake (635) and gluconeogenesis from lactate (233, 234). From experiments in the fed rabbit it appears that a considerable portion of the lactate produced under the influence of adrenaline is oxidized (199), but the fate of this lactate in a fasting animal is unknown and may well be mainly conversion to glucose (393).

Pancreas: Adrenaline inhibits the action of glucose to stimulate the secretion of insulin by the pancreas. This has been demonstrated both *in vivo* (110, 359,

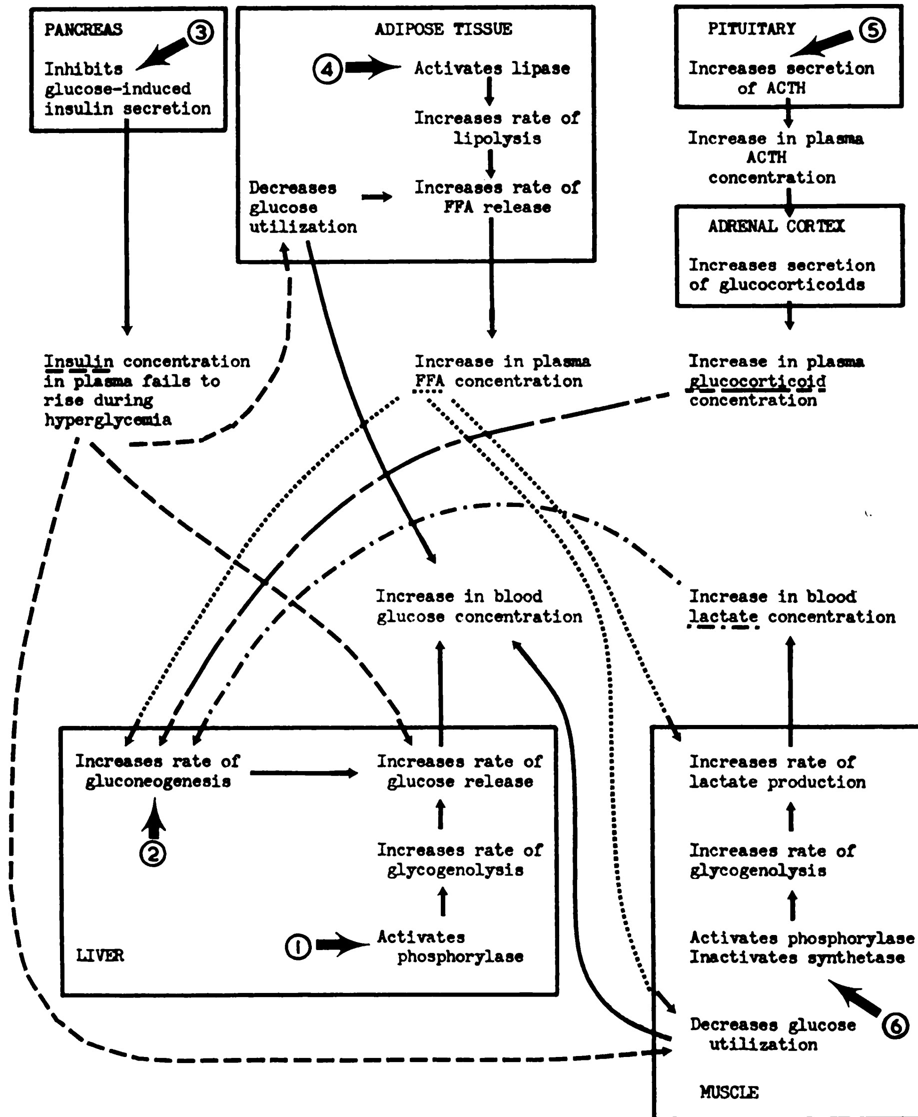


FIG. 1. Summary of possible factors involved in the hyperglycemic action of catecholamines. The extent to which each change described here contributes to the total increase in blood glucose concentration may vary according to the animal species, the nutritional state of the animal, the catecholamine used, the route of administration, and the dose administered; see text for discussion.

414, 432, 437, 580, 581) and *in vitro* (153, 502). It might at first sight appear that this inhibition could not contribute significantly to the rapid rise in blood glucose concentration that follows the intravenous injection of adrenaline. However, the sudden removal of insulin by the injection of anti-insulin serum or by the

acute removal of the pancreas produces an almost immediate increase in the output of glucose by the liver, an impairment of glucose utilization by peripheral tissues (143, 232, 799), and a rapidly increasing hyperglycemia (497, 726, 727). Moreover, inhibition of this action of adrenaline (with phentolamine in man) also markedly reduces its hyperglycemic effect (579), and infusion of adrenaline, at a concentration too low to alter systemic blood pressure, into the pancreatic artery (of dogs) causes a rapid and marked hyperglycemia (472). Dogs receiving such an infusion remain hyperglycemic for several days and may develop permanent diabetes (471, 472).

Adipose tissue: Adrenaline accelerates lipolysis and hence produces an increase in the concentration of FFA in the blood, which in turn can modify glucose utilization (571). That a high concentration of FFA in blood might lead to impaired glucose tolerance was suggested some time ago by Randle and co-workers (see 590) on the basis of evidence from experiments *in vitro*. A high concentration of FFA in the blood, brought about either by feeding a fat meal alone or by feeding a fat meal and then injecting heparin, does indeed impair glucose tolerance (244, 633). The infusion of noradrenaline also impairs glucose tolerance in man (546); this effect is probably due to the elevated concentration of FFA in the blood because glucose tolerance is not impaired when this rise is prevented with nicotinic acid (546), which does not impair the inhibition of insulin secretion by adrenaline (579). Noradrenaline also reduces the stimulation of insulin secretion caused by glucose in man (581) although this effect may not be sufficient to impair glucose tolerance. The dog differs from man in that elevation of the concentration of FFA in its blood, brought about either by infusion of palmitic acid or by the infusion of noradrenaline, does not alter glucose tolerance (763). At least in man, high concentrations of plasma FFA impair glucose utilization; yet the hyperglycemic effect of adrenaline does not appear to be significantly related to the rise in plasma FFA concentration, since inhibition of the rise in plasma FFA caused by adrenaline in man (with propranolol, nicotinic acid, or butoxamine) does not alter the hyperglycemic effect of adrenaline (579) and the rise in plasma FFA concentration caused by isopropylnoradrenaline is not accompanied by hyperglycemia (579a).

An additional effect of a high concentration of FFA in the intact animal might be to accelerate gluconeogenesis in liver, an action which has been demonstrated in liver slices and in perfused liver (716, 789).

Adenohypophysis: Adrenaline stimulates the secretion of ACTH (748) which in turn stimulates the secretion of glucocorticoids by the adrenal cortex (248, 297, 437, 749). Glucocorticoids then accelerate gluconeogenesis by the liver (538). Although this may not be a very rapid process it is undoubtedly involved in the prolonged hyperglycemia caused by infusion of adrenaline for several hours. The secretion of growth hormone also appears to be accelerated by adrenaline in rats (441, 534) but not in man (476); the extent to which this is involved in the hyperglycemic action is unknown.

It is apparent that the lesser hyperglycemic effect of noradrenaline could be due to a number of causes. Noradrenaline generally has a smaller effect than

adrenaline in the action on liver to increase the production of 3′5′-AMP (see 343, 540, 717, 719, 721) although there are marked species differences in this response. It inhibits the secretion of insulin by the pancreas less than adrenaline (437, 502, 581) and stimulates secretion of ACTH less than adrenaline (297, 495). In addition, the failure of noradrenaline to increase blood lactate concentration in conjunction with the lesser direct effect on the liver to increase 3′5′-AMP production would be expected to lead to a lesser effect on gluconeogenesis from lactate. The only action of these five in which the effect of noradrenaline equals or is greater than that of adrenaline is the one on adipose tissue, which results in an increase in the concentration of FFA in the blood. Although noradrenaline does impair the disposal of an administered glucose load in man (546), the increase in plasma FFA alone is apparently insufficient to impair glucose utilization at normal blood glucose concentrations. Moreover, noradrenaline does not exert this effect in the dog (763). It should be noted also that the relative hyperglycemic effects of adrenaline and noradrenaline vary according to the nutritional state of the animal and the dose employed (254). Such variation might indeed be expected for a response which is the sum of a multiplicity of actions on physiological functions operating at different levels in fed and fasting animals.

Since the extent to which each of the several actions of adrenaline or noradrenaline contributes to the overall hyperglycemia is unknown, the scheme illustrated in figure 1 and discussed above should be regarded as tentative. The complexity of the hyperglycemic action of adrenaline becomes more understandable if this effect is considered teleologically from the viewpoint of its function in the intact animal. The fight-or-flight situation described by Cannon (111, 112) requires the mobilization of substrates for all tissues of the body. The simultaneous mobilization of FFA and glucose by adrenaline ensures a supply of substrates. The inhibition of insulin secretion by adrenaline could have a 2-fold function. Firstly, it ensures that the mobilized substrates are not immediately stored again, an energy-consuming process that would presumably be disadvantageous when the metabolism should be geared to energy production for flight or fight. Secondly, it ensures that glucose is conserved for utilization by the brain, since in the absence of insulin the utilization of glucose by most peripheral tissues (muscle, adipose tissue) is restricted. The alternative substrate made available to these tissues, the FFA, itself imposes a secondary regulation which also results in conservation of glucose; FFA act upon muscle to divert any glucose used back to the liver in the form of lactate, and in addition they act on the liver to divert the incoming lactate back to glucose again.

C. *Protein metabolism*

Studies of the actions of adrenaline and noradrenaline on protein metabolism have been much more limited than those of the actions on lipid and carbohydrate metabolism and interpretation of the known effects is complicated by the apparently opposite actions of adrenaline *in vivo* and *in vitro*.

The principal action reported from studies *in vitro* is an inhibition of the incorporation of amino acids or other precursors into protein (798 muscle; 586, 587

liver; 358, 595, 668 adipose tissue). 3′5′-AMP appears to exert the same effect (587 liver). In contrast, in an intact animal adrenaline decreases the concentration of amino acids in the blood (92, 299); noradrenaline does not have this effect. This effect of adrenaline is not dependent on the presence of the pituitary or the adrenal (299), nor is it mediated by increased secretion of insulin (622), now known to be inhibited by the adrenaline in any case. Accelerated gluconeogenesis from amino acids would be a logical explanation but there is no direct evidence for this at present. Adrenaline does not alter gluconeogenesis from amino acids by perfused liver as indicated by unchanged urea production (520).

The secretion of proteins by cells may also be influenced by catecholamines. Inhibition of the secretion of insulin by the pancreas has already been discussed. The secretion of amylase by salivary glands *in vitro* is accelerated by adrenaline (28, 29, 305, 644), an effect apparently mediated by 3′5′-AMP (30). This effect of catecholamines, particularly isopropylnoradrenaline, on salivary glands in the intact animal (rat or mouse) is associated with hypertrophy and hyperplasia of the gland (21, 141, 577, 638, 652, 655). In contrast, the direct action of adrenaline on the pancreatic islets may even be associated with destruction of the cells (472).

D. *Metabolic rate: a new hypothesis of the calorigenic effect of catecholamines*

The increase in metabolic rate produced by the catecholamines is usually referred to as their calorigenic effect. During the last 40 years there has been much controversy about whether they have this effect at all. This has arisen from what might at first sight appear to be conflicting results obtained by different workers. Some of these arose from differences in the age of the experimental animal, the species studied, the dose and route of administration of the catecholamines, and the previous environmental history of the animal. The earlier literature on this subject has been reviewed (300, 212, 480) and will not be considered in detail here. The mechanism of the calorigenic effect of catecholamines is still not understood. An attempt is made here to analyze its characteristics and to assess the contributions of the better understood metabolic actions of the catecholamines to the increase in metabolic rate.

The magnitude of the calorigenic effect of noradrenaline in the rat depends on the age of the rat, the dose of noradrenaline used, the route of administration, and the temperature at which the rat has been living. The role of age is illustrated in figure 2, which includes data from several different studies. Whereas noradrenaline can tremendously increase the metabolic rate of the rat shortly after birth, its effect decreases progressively until by the time the rat weighs 400 g little or no calorigenic response is obtainable. The dose-response curves have different shapes at different ages and larger doses of noradrenaline are needed to produce lower maximum calorigenic responses in older rats (8). In old rats, doses of noradrenaline slightly larger than those which produce a maximum effect have a smaller effect and still larger doses may actually inhibit the basal oxygen uptake, whereas in young rats a maximum response is still produced by doses several times larger than the smallest dose that produces a maximum response and no inhibition of oxygen uptake is observed with high doses (5, 8). Noradrenaline has

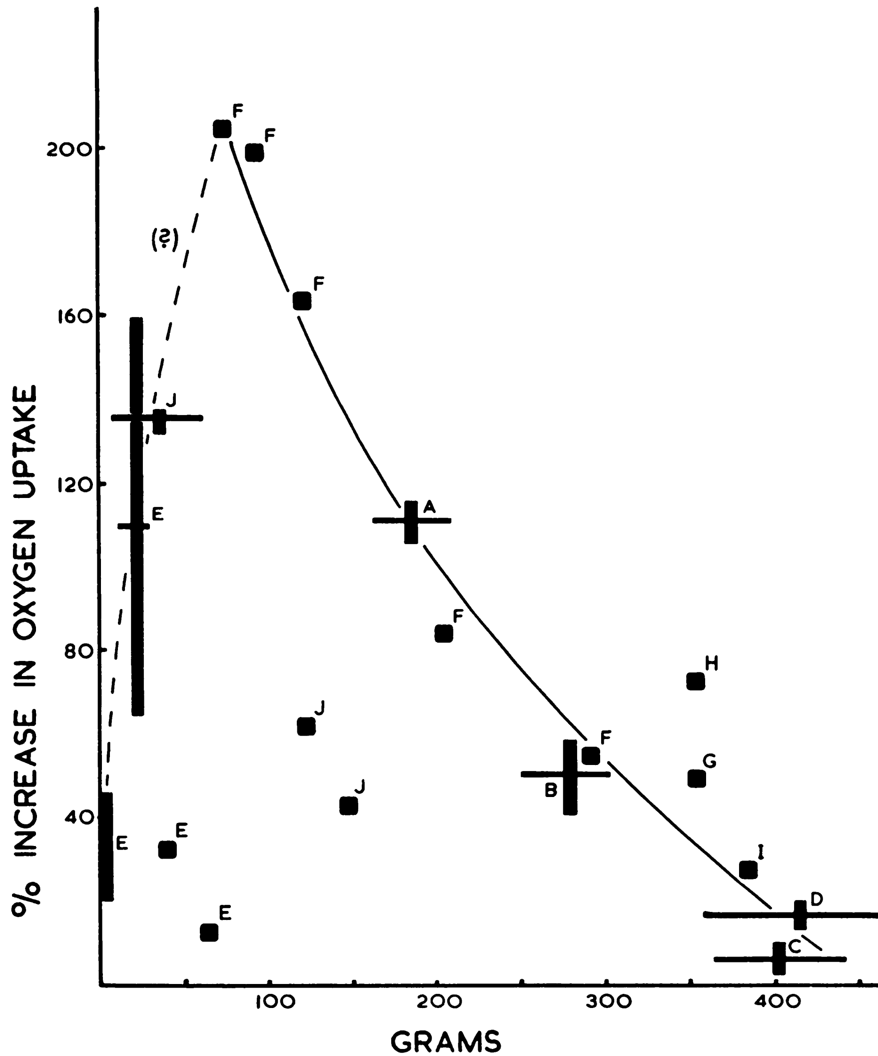


FIG. 2. The effect of the age of the rat on the calorigenic response to noradrenaline. The percent increase in oxygen uptake is plotted against the weight of the rat. The initial oxygen uptakes varied from 1.3 to 4.0 ml per 100 g per minute; they were greatest in the newborn rats and decreased progressively with age. Values are calculated from the following reports: A (7); B (184); C (184); D (378); E (527); F (8); G (229); H (231); I (454); J (524). The doses of noradrenaline used were: A, 1.05 μg per 100 g per minute, intravenously; B, C, 0.25 to 0.75 μg per 100 g per minute, intravenously; D, 20 μg per 100 g, intramuscularly; E, 40 μg per 100 g, subcutaneously; F, 1.0 μg per 100 g per minute, intravenously; G, 0.57 μg per 100 g per minute, intravenously; H, 0.57 μg per 100 g per minute, intravenously; I, 20 μg per 100 g, subcutaneously; J, 5 to 100 μg per 100 g, subcutaneously. Approximate ranges of weights and increases in oxygen uptake are indicated.

It should be noted that the different doses and routes of administration used make these data not strictly comparable, and this graph should be regarded as providing only a general idea of the change in the calorigenic response to noradrenaline with age.

less effect when given intramuscularly or subcutaneously than by intravenous infusion; it should be noted that the values for very small rats in figure 2 were obtained by the intramuscular or subcutaneous administration (524, 527) and larger responses could possibly have been obtained by intravenous infusion. No systematic studies of the calorigenic effect of adrenaline in rats of different ages have been made, but age seems to have less influence than in the case of noradrenaline. In adult animals adrenaline has a greater effect than noradrenaline in some species (378 rat; 159, 478 rabbit; 90, 477 guinea pig; 523, 527 cat) and an equal effect in others (207, 324, 340, 700 man; 79, 334 dog) whereas in newborn animals noradrenaline usually has the greater calorigenic effect (523, 527 cat; 173 rabbit; 90,171 guinea pig).

Rats that have lived in the cold for 3 weeks or longer develop an accentuated calorigenic response to noradrenaline (184, 378): such rats will be referred to here as *cold-acclimated* rats. The magnitude of this accentuated response in an old rat may be almost as great [up to 150% increase (184)] as that in a young rat that has not been kept in the cold. Thus, after living in the cold for a short time the old rat either develops or regains some characteristic that permits it to respond to noradrenaline like a young rat. The role of cold-acclimation and the sympathetic nervous sytem in the regulation of body temperature in the cold is discussed in section IV E 2. Here the change in calorigenic response of the cold-acclimated rat to noradrenaline is considered simply as another peculiarity of this calorigenic effect that must be taken into account in considering the mechanism by which the catecholamines raise the metabolic rate.

In attempts to understand the mechanism of the calorigenic effect of adrenaline and noradrenaline in intact animals, investigators have looked for a similar action of these two amines on isolated tissues in the hope of finding a system in which this effect could be more readily analyzed *in vitro*. Under appropriate conditions *in vitro* adrenaline, or noradrenaline, or both, can increase the oxygen uptake of liver (226, 227, 367), muscle (205, 276, 367), heart (249, 331, 784, 788), white adipose tissue (16, 17, 251, 306, 370, 483, 562), and brown adipose tissue (405, 406). Unfortunately many studies have produced conflicting results, because of such differences as those in the species, age, and tissue studied, the concentration of catecholamines used (usually only very low concentrations are needed and high concentrations either have no effect or inhibit oxygen uptake), the substrate supplied, and the composition of the incubation medium. The effect of catecholamines *in vitro* is usually very small (only about a 20% increase in oxygen uptake in liver and muscle) compared with the very large changes often demonstrable *in vivo* [for example, a 200% increase with noradrenaline in young rats (8)]. The only exception to this is adipose tissue (white or brown); under certain conditions adrenaline or noradrenaline can increase its oxygen uptake 3- to 5-fold (306, 406). With the possible exception of the adipose tissues, the biochemical mechanism of the calorigenic effect in any of these tissues is unknown. Indeed, it is rather surprising that any calorigenic effect is observed *in vitro* since much of the calorigenic action of the catecholamines in the intact animal might well be due to the other effects they produce: redistribution of substrates (glucose, FFA,

lactate, pyruvate, amino acids), changes in the secretion of other hormones (glucocorticoids, insulin), and redistribution of blood flow. It is clear that tissues of the intact animal may change their metabolism in response to administration of catecholamines in a way not reproducible *in vitro*.

Before considering the mechanism of the calorigenic effect of adrenaline and noradrenaline, one should first examine the basic regulation of the final steps involved in the increase in metabolic rate, namely, the utilization of oxygen by cells. The rate at which the electron transport system operates and, therefore, the rate at which oxygen is consumed, depends primarily on the availability of one substrate (ADP) for oxidative phosphorylation and is normally restricted by its availability. It can be postulated that an increase in the rate of operation of the electron transport system might be brought about in either of two different ways:

I: An increase in the supply of ADP and phosphate. This implies an accelerated breakdown of ATP to ADP and phosphate since each cell contains a relatively fixed amount of total ATP plus ADP.

II: An increased role of nonphosphorylating pathways. This increase might occur in 4 different ways: 1. A switch from entry of electrons into the electron transport system *via* NAD to entry *via* FAD or a cytochrome, *i.e.*, a bypassing of one or both of the first two steps of oxidative phosphorylation. 2. Uncoupling of oxidative phosphorylation. 3. An increase in the utilization of high-energy intermediates (nonphosphorylated) produced during normal electron transport. This bypasses the formation of ATP since these intermediates would otherwise be used to make ATP from ADP and phosphate. 4. Use of a different pathway of electron transport in which no high-energy intermediates are produced or, if they are made, in which the high-energy intermediates are immediately broken down and their energy not utilized in any other reaction.

Current biochemical thinking recognizes the first process (I: an increase in the supply of ADP) as the primary regulatory factor determining the changes in oxygen consumption that accompany the changes in work of various kinds taking place continuously in cells. The most obvious example of this is the increase in oxygen consumption during exercise; this is ultimately determined by the provision of large amounts of ADP to the muscle mitochondria through the rapid hydrolysis of ATP during muscle contraction. In order to find out whether the increase in oxygen uptake produced by the catecholamines results from an acceleration of the hydrolysis of ATP, one must consider the action of catecholamines on metabolic pathways in which ATP is known to be hydrolyzed. These pathways include those for the synthesis of triglycerides, glycogen, urea, and glucose. In each the acceleration is due, not to a direct action of the catecholamines on the pathway, but to a greater delivery of substrate to the pathway, caused by the catecholamines.

The accelerated synthesis of triglyceride in muscle, liver, and heart that follows the administration of noradrenaline to the intact animal (see section II A) results from the increased availability to these tissues of FFA derived from adipose tissue

and must involve the formation of considerable ADP (from ATP), which in turn leads to a higher oxygen uptake. The release of storage fat by catecholamines results in the need to store it again (at least under laboratory conditions when the catecholamines are injected) in the same or other tissues. This may be likened to the consequence of a fat meal, which also results in storing the fat in excess of immediate energy requirements. In both phenomena, oxygen consumption rises as a result of the increased ATP hydrolysis for the triglyceride synthesis during fat storage. This aspect of the calorigenic effect of catecholamines is like the specific dynamic action of ingested fat.

It should be possible to estimate from published data on the increased turnover of plasma FFA and the accompanying increase in oxygen uptake brought about by the infusion of noradrenaline (207, 700) the proportion of the total calorigenic effect caused by this "specific dynamic action." In normal human subjects in whom the total oxygen uptake has been elevated by about 18% by noradrenaline, only about 5% of the elevation (range 0.3 to 23%) would appear to be due to increased turnover of FFA; thus the specific dynamic action of the mobilized FFA could account for an increase of only about 1% in the total oxygen uptake. Curiously, in the one hyperthyroid subject studied in this way (207) the specific dynamic action of the increased supply of FFA (much larger than normal in this subject) could account for 52% of the 16% increase in oxygen uptake observed. Unfortunately, nothing is known about the effect of noradrenaline on the turnover of FFA in young rats or in cold-acclimated rats, which show the large calorigenic response to noradrenaline. It is possible that some of the increase in the turnover of the FFA may be entirely intracellular, *e.g.*, in adipose tissue, and, therefore, not included in measurements of turnover of plasma FFA; indeed catecholamines do increase the oxygen uptake of adipose tissue *in vitro* (306, 406). Since adipose tissue comprises only a small part of the total metabolizing tissues of the body, even a 5-fold increase in its oxygen uptake would contribute little to the total increase in oxygen uptake produced by noradrenaline.

Although on theoretical grounds, the above calculations of the increase in oxygen uptake appear entirely justified, direct experimental support has not been obtained *in vitro*. Indeed, attempts to produce an increase in metabolic rate in rats by the infusion of FFA have not been successful (187). Perfusion of hearts with solutions of high FFA concentration increases the oxygen uptake not only beyond that required to supply the energy for esterification but beyond that needed for the oxidation of the FFA taken up (139, 140). Yet attempts to find an increase in the oxygen consumption of isolated tissues have not always been successful. The oxygen uptake of the perfused liver is accentuated by the triglyceride synthesis that follows the addition of FFA to the perfusion fluid (697), but in experiments with isolated liver (611) or diaphragm (206, 696) the rate of esterification is so low that any attendant increase in oxygen uptake would have been unmeasurable. Only a very high concentration of FFA (10^{-1} M) increases the oxygen uptake of diaphragm (26). The theory that a high concentration of FFA in the intact animal can elevate the metabolic rate (137) is not in keeping with these observations. Moreover, the calorigenic action of catecholamines is

not inhibited by agents that inhibit their effect to raise FFA concentration in the blood (see section III and table 1).

The increase in blood glucose concentration that is produced by adrenaline and, to a much lesser extent, by noradrenaline, would also be expected to lead to an increase in the oxygen uptake of those tissues disposing of the glucose as glycogen. This increase should represent about 5% of the caloric value of the glucose mobilized and would probably contribute only slightly to the total calorigenic effect.

The increase in oxygen uptake that would result from the action of adrenaline to increase gluconeogenesis from amino acids may be likened to the specific dynamic action of ingested protein, the increase in energy expenditure being that required to dispose of the amino groups as urea and to synthesize glucose (or fat) from the residual carbon skeleton of the amino acids. An estimate of the rate of gluconeogenesis from amino acids after adrenaline administration in rats can be obtained from values for urea excretion under these conditions (220, 221). The amount of oxygen needed to regenerate the ATP split in making urea and glucose from the amino acids is less than 1% of the calorigenic effect of adrenaline in rats.

It may be concluded that the increase in oxygen uptake of the whole animal caused by the action of adrenaline or noradrenaline to shift storage material around can represent only a very small proportion of the calorigenic effect.

Process II:1 could theoretically occur. Two examples will be given to clarify the proposal. A switch to the use of the α-glycerophosphate shuttle has been proposed to explain the hypermetabolism seen under the influence of excess thyroid hormone (673). If, for example, complete oxidation of glucose *via* glycolysis and the tricarboxylic acid cycle uses a shuttle with a P:O ratio of 3 (such as the β-hydroxybutyrate shuttle) to shift the hydrogen of extramitochondrial pyridine nucleotides into the mitochondria, then the overall P:O ratio of the mitochondrial oxidations would be 2.83. If the extramitochondrial $NADH_2$ were instead to be oxidized *via* the α-glycerophosphate shuttle with a P:O ratio of 1 (or 2, the acceptor status of the mitochondrial L-α-glycerophosphate dehydrogenase being still uncertain) the overall P:O ratio would change to 2.5. This means that, per mole of ADP phosphorylated, the oxygen uptake could be increased by only 13%. Since it is unlikely that most cells oxidize solely glucose, the contribution of this switch to total oxygen uptake would be smaller than this. Another example of such a switch would be a change in the liver from complete oxidation of FFA to their oxidation to the ketone body level. The average P:O ratio of oxidation of reduced coenzymes produced in the complete oxidation of the FFA would be 2.68 whereas the P:O ratio for their oxidation to the ketone body level would be 2.5. This switch could lead to an increase in oxygen uptake in the particular tissue by up to 7%.

Whether any of the other processes listed in II (2 to 4) can be switched on in response to noradrenaline or adrenaline is unknown. The excessive use of nonphosphorylating (oligomycin-insensitive) pathways of electron transport as a basis for the increased metabolic rate of phaeochromocytoma, hyperthyroidism, diabetic ketosis, or nonshivering thermogenesis, as well as the calorigenic effect

of noradrenaline, has been postulated to be initiated simply by excessive FFA concentrations induced by noradrenaline or the sympathetic nervous system (137). However, as has been pointed out above, there is no direct evidence that a high concentration of FFA can appreciably alter the oxygen consumption of the bulk of body tissues *in vitro* (liver, muscle). Only in heart (140, 139) and possibly in adipose tissue (367) has an appreciable increase in oxygen uptake caused by a surfeit of FFA been demonstrated.

In conclusion, the nature of the calorigenic action of catecholamines is poorly understood and cannot be explained by present knowledge of the operation of metabolic pathways during this action. In fact, attempts to study the calorigenic effect of adrenaline and noradrenaline by examining the changes in metabolism of fats, carbohydrates, and amino acids in the intact animal may be a little like trying to find out why the metabolic rate is increased during exercise by examining the changes in the metabolism of fats, carbohydrates and amino acids. A large amount of information about turnover of metabolites and functioning of the sympathetic nervous system in the regulation of metabolism would be obtained if this approach were taken, but from such studies alone the investigator would gain no inkling whatever that a mechanical process in muscle was involved. Starting from the supposition that a process inaccessible to conventional tracer studies, like muscle contraction only not so visible, is activated by catecholamines to bring about their calorigenic action, the conclusion is reached that a reversible, energy-using, structural change must be involved. If the contraction and relaxation of mitochondria (459) or the movement of mitochondria such as that seen in tissue culture (255) required as an energy source the high-energy nonphosphorylated intermediates of electron transport and if such movement could be either initiated or accentuated by catecholamines (or 3′5′-AMP), an increased rate of oxygen uptake would result. A precedent for an action of a catecholamine to accentuate a contractile response is provided by its inotropic action on the heart, for which no convincing biochemical explanation is available. At the moment there is little or no evidence for this supposition. The finding of a decreased P:O ratio in heart mitochondria from catecholamine-treated rats in the absence of an increase in ATPase activity (680) would be compatible with such a mechanism. Catecholamines can modify the structure and function of heart and muscle myofibrils (243, 291, 694), possibly indirectly (418), but their effects on the contractile elements of mitochondria (459) is unknown. The movement of mitochondria intended here is probably akin to the swelling and contraction seen in isolated mitochondria and known to be associated with respiratory activity (303, 795), but movements comparable to those seen in intact cells do not seem to occur in isolated mitochondria. Although this hypothesis is in fact saying, in other words, that electron transport *via* nonphosphorylating pathways is increased, which has been suggested before (46), it is not simply describing the process but is attempting to approach the fundamental mechanism by which the process might be switched on and off. If the postulated increase in mitochondrial movement used ATP as an energy source rather than high-energy nonphosphorylated intermediates, the net effect would be the same as an uncoupling of oxidative phosphorylation.

The extension of this hypothesis to the production of the elevated metabolic rate of cold-acclimated rats living in the cold is discussed further in section IV E 1.

III. BLOCKING AGENTS AND THE METABOLIC EFFECTS OF CATECHOLAMINES: THE CLASSIFICATION OF RECEPTORS

A. Introduction

Adrenergic blocking agents are often used in attempts to decide whether responses to particular metabolic stimuli are mediated by the sympathetic nervous system. In recent years many papers have dealt with the effects of different blocking agents on the various metabolic actions of adrenaline and noradrenaline. The aim of much of this work has been to classify particular metabolic actions of catecholamines into those exerted *via* α-receptors and those exerted *via* β-receptors and to extend to the metabolic actions of the catecholamines the scheme proposed originally by Ahlquist (1) for other actions of these compounds. As originally proposed, this classification is based on the relative potencies of adrenaline, noradrenaline, and isopropylnoradrenaline in producing a particular response. Noradrenaline stimulates principally α-receptors, isopropylnoradrenaline stimulates principally β-receptors and adrenaline stimulates both α- and β-receptors. The effects of catecholamines on α-receptors are inhibited by a group of drugs referred to as α-adrenergic blocking agents (*e.g.*, Dibenamine, dibenzyline, phentolamine, and tolazoline) whereas the effects on β-receptors are inhibited by another group of compounds, the β-adrenergic blocking agents, *e.g.*, DCI [1-(3,4-dichlorophenyl)-1-hydroxy-2-isopropylaminoethane, dichloroisoproterenol], DCB [1-(2,4-dichlorophenyl)-1-hydroxy-2-*t*-butylaminoethane], pronethalol [nethalide, Alderlin], propranolol [Inderal], MJ1999 [1-(4-mesylaminophenyl)-1-hydroxy-2-isopropylaminoethane], Kö-592 [1-(3-methylphenoxy)-2-hydroxy-3-isopropylaminopropane], and INPEA [1-(4-nitrophenyl)-1-hydroxy-2-isopropylaminoethane]. The identification of a response as being due to stimulation of a particular type of receptor depends, therefore, on a knowledge of the relative activities of adrenaline, noradrenaline, and isopropylnoradrenaline to produce the response and of the effects of the different types of blocking agents upon these activities. The following discussion will be concerned mainly with the reasons why this aim has not been achieved and with the general conclusions that may be obtained from the results of such experiments. Instead of a complete review of the effects of blocking agents, several illustrative examples are selected.

Tables 1 to 4 contain a compilation of the effects of the more important blocking agents on four metabolic actions of catecholamines in intact animals of five species. The responses were chosen because they are those usually measured in studies of intact animals subjected to stimuli thought to activate the sympathetic nervous system (they will be discussed from this aspect in section IV). It is apparent that knowledge of the effects of blocking agents on many metabolic effects of adrenaline and noradrenaline in most species is lacking. Most available information applies to the dog.

Major problems in arriving at any general scheme for the inhibition of meta-

bolic effects of catecholamines in intact animals are that species vary in susceptibility to inhibition of a metabolic effect by a given compound, that similar agents have different effects, and that the same blocking agents exert different effects in the hands of different investigators.

Many of the contradictory or negative results of experiments with blocking agents are due to failure to realize pitfalls inherent in the design and interpretation of such experiments. Those which are most frequently overlooked follow. (i) A metabolic change that is the sum of several actions of a catecholamine may never be completely inhibited at any dose and may be inhibited to different degrees in different species, in which the relative contribution of each participating action differs. In studies in the same species the inhibition depends on whether the animal is fed or fasting. (ii) Inhibition unrelated to inhibition of catecholamine action may occur, particularly when large doses or high concentrations of the blocking agent are employed (see 552, 729). (iii) Rapid metabolism of an agent in some species may prevent a blocking action except at very high doses. (iv) The degree of blockade varies with the dose of the blocking agent and the duration of its action before administration of a catecholamine. The frequently used hit-and-miss approach (a single dose of blocking agent, a single dose of catecholamine at a single time thereafter, and subsequent removal of a sample at a single time) often yields negative results or even results that are positive but misleading. (v) The blockade exerted by a compound with intrinsic activity cannot be assessed. If for example, the concentration of FFA in blood is already elevated by the administration of a blocking agent, it may be impossible to find out whether the effect of a catecholamine to increase blood FFA concentration is blocked or not. (vi) Studies of the actions of blocking agents in man are hampered by the impossibility of giving very large doses. Although blockade of some of the nonmetabolic physical actions of catecholamines is achieved in man, as in experimental animals, with low doses of blocking agents, larger doses are often needed in experimental animals to block their metabolic effects, and it seems likely from the number of negative results listed in tables 1 to 4 that the same is true of man. This may of course indicate that the results with man are the more valuable and that the results with large doses in experimental animals are due to nonspecific actions of the blocking agents.

The following are the only general conclusions that may be drawn from the results of experiments listed in tables 1 to 4.

B. Effect on changes in blood metabolites

1. GLUCOSE (table 1). α-Adrenergic blocking agents block the hyperglycemic effect of adrenaline in rats and rabbits, have a variable effect in cats, and do not block in dogs or man. The β-adrenergic blocking agents block the hyperglycemic effect of adrenaline fairly consistently in rats, dogs, and cats; propranolol and pronethalol do not do so in man whereas MJ1999 does. Another inhibitor (butoxamine) blocks the hyperglycemic effect of adrenaline in dogs and rats but not in man. If the commonly used criteria for deciding whether α- or β-receptors are involved were followed, then the receptors stimulated by adrenaline in the production of its hyperglycemic effect would be β in the dog, α and β

in the rat and neither α nor β in man. Consideration of the relative potencies of adrenaline, noradrenaline, and isopropylnoradrenaline often does not contribute greatly to this decision. The relative hyperglycemic potencies in the fasting

TABLE 1

Effects of blocking agents on hyperglycemia produced by catecholamines

Blocking agent	Rat			Dog			Man		Cat	Rabbit
	A[a]	NA	IPNA	A	NA	IPNA	A	NA	A	A
Dibenamine				−341[a]	−341				−216	+327
				−490	−490				−162	
									−327	
Dibenzyline	+647			−505	−490		−575		−210	+327
				−517	−506				+327	
GD121	+142								+327	
Phentolamine							+579			
Tolazoline									+327	
Dibozane									−228	
Azapetine				−486	−486	−486			+327	+327
DCI	+146	−146	+146	+517	−486	+486			+210	
	+473			+486	−517	+517				
	+554									
Pronethalol	+444	−444	+444	−99		+444	−575			
				+444		−802				
Propranolol	+269			+511		+542	−324			
				+695		+695	−579			
						−802				
MJ1999	+444	−444	+444	+444	+444	+444	+725		+210	
	+422									
Ergotamine	+609			+490 +517	−505				+327	+327
Dihydroergota-	+422								+162	+215
mine	+554								+327	+327
	+573									
Nicotinic acid		−749				−422	−724	−340		
							−579			
Methoxamine				+99 +626					+218	
				+149						
Isopropyl-				+99	+506				+218	
methoxamine				+626					+228	
Butoxamine	+624		+624	+98 +624		+624	−390	−390		
				+100 +627			−579			
Dimethylpyra-	−50			−269						
zole	−269									
Prostaglandins				−40						
				−698						
				−704						

[a] The numbers refer to items in the reference list. Abbreviations and code names are A, adrenaline; NA, noradrenaline; IPNA, isopropylnoradrenaline; +, inhibition; −, no effect; ±, variable effect; ?, doubtful effect (includes those agents that themselves bring about the effect); GD121, N-(α-naphthyl)-N-ethyl-β-chloroethylamine; DCI, dichloroisoproterenol or 1-(3,4-dichlorophenyl)-1-hydroxy-2-isopropylaminoethane; MJ1999, 1-(4-mesylaminophenyl)-1-hydroxy-2-isopropylaminoethane.

rat are adrenaline > isopropylnoradrenaline ≫ noradrenaline, typical of β-receptor stimulation (254, 444). In man, adrenaline and to a lesser extent noradrenaline (31, 194, 390, 536) exert hyperglycemic effects whereas isopropylnoradrenaline does not (87, 273, 390, 536); this is typical of α-receptor stimulation, but α-adrenergic blocking agents do not inhibit this effect of adrenaline. In the dog, isopropylnoradrenaline is the most potent (487, 802) while noradrenaline has little hyperglycemic effect except in fed dogs (444, 487). This is in keeping with the actions of the blocking agents except that the small effect of noradrenaline in fed dogs is not blocked by the α-receptor blocking agents. Since the hyperglycemic effect of adrenaline appears to be the resultant of several different and independent actions of adrenaline, each of which may participate to a different extent in different species, or under different conditions in the same species, it is perhaps not surprising that blocking agents do not completely block the hyperglycemia and that species differences exist. It is indeed rather more surprising that in many instances a single agent can in fact block completely the hyperglycemic effect of adrenaline. The effect of blocking agents on the various actions of adrenaline which contribute to its hyperglycemic effect will be discussed later.

2. LACTATE (table 2). Since the increase in blood lactate concentration is probably a consequence of simultaneous increases in plasma FFA concentration and in glucose concentration or increased glycogenolysis in muscle, or both, it might be expected that inhibition of any one of these responses would also reduce the increase in blood lactate concentration (see tables 1, 2 and 3). Findings compatible with this expectation are: the inhibition of hyperglycemic, lacticacidemic, and plasma FFA responses in the dog by butoxamine, DCI, and isopropylmethoxamine and, in man, by MJ1999; inhibition of none of these responses by dibenzyline in man and by dibozane in the cat; inhibition of lacticacidemic and plasma FFA responses but not of the hyperglycemic response by propranolol in man; inhibition of the hyperglycemic and lacticacidemic responses but not the plasma FFA response by MJ1999 in the rat. There are also observations which are not compatible with this expectation: nicotinic acid inhibits the plasma FFA response to adrenaline or to isopropylnoradrenaline in man or dog but does not alter the lacticacidemic or hyperglycemic responses; dihydroergotamine inhibits both the hyperglycemic and plasma FFA responses without altering the lacticacidemic response in the rat. The meaning of these inconsistencies is not clear. The lacticacidemic effect of the catecholamines fits into the classification as an effect on β-receptors, both in its susceptibility to inhibition by blocking agents and in its production by the three catecholamines.

3. FFA (table 3). Like the hyperglycemic action, this action of the catecholamines cannot be readily fitted into either the α- or β-category on the basis of the effects of blocking agents.

C. Effect on calorigenic action (see table 4)

On the basis of reported information about the relative activities of the blocking agents in any single species, the calorigenic action of the catecholamines

TABLE 2

Effects of blocking agents on the lacticacidemia produced by catecholamines

Blocking agent	Rat		Dog		Man	Cat	Rabbit	
	A[a]	IPNA	A	IPNA	A	A	A	IPNA
Dibenzyline			−517[a]		−3			
Dibozane						−228		
DCI			+517				+481	+481
Propranolol					+324			
MJ1999	+422				+725	+228		
Ergotamine			−517			+282		
Dihydroergotamine	−422							
Nicotinic acid				−422	−724			
Isopropylmethoxamine			+99			+228		
Butoxamine	+624	+624	+624	+624				

[a] The numbers refer to items in the list of references. Abbreviations and code names are A, adrenaline; NA, noradrenaline; IPNA, isopropylnoradrenaline; +, inhibition; −, no effect; ±, variable effect; ?, doubtful effect (includes those agents that themselves raise the lactate concentration); DCI, and MJ1999 as in table 1.

does not fall into either the α- or the β-category. Since it is inhibited neither by an agent that inhibits the plasma FFA effect of catecholamines in man or dogs (nicotinic acid), nor by agents that inhibit one or more of the hyperglycemic, plasma FFA, and lacticacidemic effects of adrenaline in the rat (MJ1999, dihydroergotamine, dibenzyline), it cannot readily be related to any of the other metabolic effects of catecholamines considered here. The observations that the calorigenic effects of adrenaline and noradrenaline in man are inhibited by an agent that also blocks their effects on plasma FFA (pronethalol) and that the calorigenic, hyperglycemic, lacticacidemic, and plasma FFA effects of adrenaline in man are inhibited by MJ1999 may be fortuitous, but they have been interpreted as an indication that the one is causally related to the other (700, 725).

D. Effect on changes in individual tissues

Consideration of the effects of blocking agents on the actions of catecholamines on metabolic processes in individual tissues believed to participate in the production of a change in the concentration of a compound in the blood of an intact animal should help to decide to what extent each of the several actions contributes to the overall response. This is not always possible, largely because the relevant information for the species in question is lacking or because of contradictory results (see tables 5, 6A, 6B). However, I shall attempt to relate the actions of blocking agents on individual tissues to their actions in the intact animal.

1. PANCREAS (table 5). Inhibition by adrenaline of the secretion of insulin (as measured by the concentration of insulin in the blood) is not altered by butoxamine, propranolol, or nicotinic acid in man; these agents also do not block the hyperglycemic effect of adrenaline in man although they do block the effect on plasma FFA (see table 3). Thus this effect of adrenaline to inhibit

TABLE 3

Effects of blocking agents on the rise in plasma FFA produced by catecholamines

Blocking agent	Rat			Dog			Man			Cat
	A[a]	NA	IPNA	A	NA	IPNA	A	NA	IPNA	A
Dibenamine				+341[a] −490 −802	+341	−802				
Dibenzyline		+710			−490 −506		−575	−574		
Phentolamine					−71 −263		−578 −579			
Dibozane	−219									−228
DCI				?99 +517	?517	+12 ?517				
Pronethalol		+269 +444 +777		−99 ?263	?263	?802	+575	+700		
Propranolol		+241		+511		+802 +542	+324 +578 +579	+574 +732	+790	
INPEA		+241								
MJ1999	−219 −422 −444	+269 −444	−444	+147 +444	+147 +443 +422 +444	+147 −444	+725			+228
Kö-592		+710 +712								
Ergotamine	+287			±490						
Dihydro-ergotamine	+219 +422									
Nicotinic acid		+710 −749			+124 +263 +127 +443	+422	+207 +579 +724	+128 +340 +200 +545 +207 +546		
Methoxamine				+99 +149						
Isopropyl-methoxamine	−422			+99 +626	+99 +506					+228
Butoxamine		+50 +269 +52		+100 +627 +147	−147	−147	+390 +578 +579		+390	
Dimethylpyrazole	+50 +52 +269									
Salicylic acid		+48 +49								
Prostaglandins				+40 +704 +41 +701	+40 +41	+41		−38 −39		
Lactic acid					+518					
Insulin				+691	−179 −691					

TABLE 3—*Continued*

[a] The numbers refer to items in the reference list. Abbreviations and code names are A, adrenaline; NA, noradrenaline; IPNA, isopropylnoradrenaline; +, inhibition; −, no effect; ±, variable effect; ?, doubtful effect (includes those agents that themselves raise plasma FFA concentration); DCI, dichloroisoproterenol or 1-(3,4-dichlorophenyl)-1-hydroxy-2-isopropylaminoethane; INPEA, 1-(4-nitrophenyl)-1-hydroxy-2-isopropylaminoethane; MJ1999, 1-(4-mesylaminophenyl)-1-hydroxy-2-isopropylaminoethane; Kö-592, 1-(3-methylphenoxy)-2-hydroxy-3-isopropylaminopropane.

TABLE 4

Effects of blocking agents on the rise in metabolic rate produced by catecholamines

Blocking agent	Rat			Dog		Man		Cat		Rabbit		
	A[a]	NA	IPNA	NA	IPNA	A	NA	A	NA	A	NA	IPNA
Dibenzyline	+409 −647	−27 −647						−27	−27			
Phentolamine		−6										
DCI										?481		?481
Pronethalol						+324	+700			+383		+383
Propranolol	+714	+714	+714							+350	+350	+350
MJ1999	−422			+422		+725						
Ergotamine								+479				
Dihydro-ergotamine	−422	−395										
Nicotinic acid					−422	±725 ±207	±340 ±207					
Prostaglandins							−38					

[a] The numbers refer to items in the list of references. Abbreviations and code names are A, adrenaline; NA, noradrenaline; IPNA, isopropylnoradrenaline; +, inhibition; −, no effect; ±, variable effect; ?, doubtful effect (includes those agents that themselves raise metabolic rate); DCI and MJ1999 as in tables 1 and 3.

insulin secretion could conceivably be one of the causes of the hyperglycemic effect of adrenaline in man but could not be a cause of the effect on plasma FFA. Phentolamine does inhibit both the action of adrenaline to inhibit insulin secretion and the hyperglycemic effect but does not inhibit the effect on plasma FFA. These findings are also consistent with the lack of causal relationship between inhibition of insulin secretion and increase in plasma FFA concentration. The effect of adrenaline to inhibit insulin secretion *in vivo* would be classified as on an α-receptor on the basis of these effects of blocking agents. This is consistent with the somewhat smaller effect exerted by noradrenaline (581). The stimulation by isopropylnoradrenaline of insulin secretion in man, an action inhibited by β-adrenergic blocking agents (579a), may be one reason for the lack of hyperglycemic effect (578, 579). The relative potencies of the three catecholamines may, however, reflect their action to alter blood flow rather than their direct metabolic effects; adrenaline reduces pancreatic blood flow in dogs whereas noradrenaline increases it (178). The rat is like man in that the effect of adrenaline (to inhibit insulin secretion by isolated pancreas; table 6A)

TABLE 5

Effects of blocking agents in vivo on actions of catecholamines believed to be associated with their actions on plasma glucose, lactate and FFA and with their metabolic action

Blocking agent	Decrease in liver glycogen		Increase in muscle glycogen		Phosphorylase activation			Inhibition of insulin secretion
					in liver	in muscle		
	Rat	Dog	Rat		Rat	Rat		Man
	A[a]	NA	A	IPNA	A	A	IPNA	A
Dibenzyline		−506[a]	−374	−374		−374		
Phentolamine	+421		−421					+579 +578
Dibozane	−421		−421					
DCI	−421		+421	+392				
Pronethalol				+392	+588	+588		
Propranolol								−579 −578
Dihydroergota-amine	+421		?421					
Nicotinic acid								−579 −578
Isopropylmethox-amine		−506			+588	+588		
Butoxamine						+624	+624	−579 −578

[a] The numbers refer to items in the list of references. Abbreviations are A, adrenaline; NA, noradrenaline; IPNA, isopropylnoradrenaline; +, inhibition; −, no effect; DCI as in tables 1 and 3.

is blocked by the α-adrenergic agents phentolamine (502) and dibenzyline (501, 502) but not by the β-adrenergic agents pronethalol and propranolol (502). However, the secretion of insulin is inhibited by all three catecholamines in the rat (502). In the rat, in contrast to man, the hyperglycemic effect of adrenaline is inhibited by agents [propranolol (269); pronethalol (444)] that do not block the effect of adrenaline to inhibit insulin secretion. Since phentolamine itself produces hyperglycemia in the rat (70), the possible blocking action cannot be evaluated; dibenzyline blocks both the hyperglycemia (647) and the inhibition of insulin secretion caused by adrenaline. These differences between man and rat might indicate that in man the inhibition of insulin secretion is of greater significance in the hyperglycemic action of adrenaline than it is in the rat, but there is really too little evidence to permit any definitive conclusion.

2. LIVER (tables 5 and 6B). Other actions of adrenaline that may contribute to its hyperglycemic action are activation of liver phosphorylase and increased release of glucose by the liver. In the intact rat activation of phosphorylase is inhibited by pronethalol (588), an agent which also inhibits the hyperglycemic effect. *In vitro* this effect is inhibited by phentolamine, DCI, dihydroergotamine, and methoxamine; the increased release of glucose from liver slices

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caused by adrenaline is also inhibited by DCI and dihydroergotamine. DCI and phentolamine both inhibit the hyperglycemic action of adrenaline in the intact animal, and phentolamine inhibits the decrease in liver glycogen that follows the administration of adrenaline. These findings are all consistent with the hypothesis that an action of adrenaline on liver to activate phosphorylase is a cause of its hyperglycemic effect. Yet contradictory reports inconsistent with this hypothesis exist. Firstly, there is a report that DCI does not inhibit the decrease in liver glycogen caused by adrenaline in the intact rat (421) although it inhibits the hyperglycemia, the activation of liver phosphorylase, and the increased release of glucose by liver. Secondly, there is another report that phentolamine does not inhibit the effect of adrenaline to increase glucose release by liver. In the experiments on which this report was based phentolamine was in fact used to permit this effect since it inhibited the vasoconstriction, which would otherwise reduce the effect of adrenaline (684). Phentolamine does, however, inhibit activation of phosphorylase by adrenaline in liver slices. In these contradictory reports the concentrations of the drug in question may have been too low even though other blocking actions were evident in both studies.

3. ADIPOSE TISSUE (table 6A). During the last few years considerable effort has gone into the study of the effect of blocking agents on catecholamine-induced lipolysis in isolated adipose tissue. The results apply almost entirely to the rat. As most information about intact animals applies to dogs and men, comparison of effects *in vitro* and *in vivo* is therefore difficult. Despite a few negative reports in table 6A, it seems safe to say that all blocking agents studied inhibit the lipolytic effect of catecholamines *in vitro* on rat adipose tissue. The correlation between inhibition *in vitro* and *in vivo* of the FFA-mobilizing effect is fairly good although much information is lacking. There are two exceptions. Isopropylmethoxamine is not a good inhibitor in intact rats because it is metabolized very rapidly (625); accordingly, it caused no inhibition of the plasma FFA effect of adrenaline in intact rats (228). Also MJ1999, which inhibits *in vitro*, does not inhibit the effect of any of the catecholamines *in vivo* in the rat. The multiplicity of agents that inhibit the stimulation by catecholamines of lipolysis *in vitro* and the finding that many of these agents also inhibit not only the lipolytic actions of other hormones such as ACTH, TSH, glucagon and growth hormone, but also the effect of insulin on adipose tissue, suggest that the action of some of these agents *in vitro* may be not specifically anticatecholamine but rather antilipolytic or even more generally antimetabolic. Compounds with a general antilipolytic effect rather than a specific anti-catecholamine action include the α-adrenergic blocking agents, nicotinic acid, 3,5-dimethylpyrazole, salicylic acid, various purines, purine nucleotides, purine nucleosides, the ergotamines, and the prostaglandins (see also 52, 269). The β-adrenergic blocking agents seem to act more specifically to prevent any stimulation of lipolysis by catecholamines or other hormones. The site of action of some of these inhibitory agents is known. For example, phentolamine inhibits the effect of already formed 3′5′-AMP rather than the effect of noradrenaline to increase 3′5′-AMP formation (438, 711), whereas DCI or Kö-592 inhibits the latter (81, 438, 711). This con-

TABLE 6A

Effects of blocking agents in vitro on actions of catecholamines believed to be associated with their actions on plasma glucose, lactate and FFA and with their metabolic action (for further effects see table 6B)

Blocking agent	FFA release: adipose tissue				Glycerol release: adipose tissue		Inhibition of insulin secretion: pancreas
	Rat			Man	Rat		Rat
	A[a]	NA	IPNA	NA	A	NA	A
Dibenamine	+643[a]						
Dibenzyline	+85				−237		+502
	+643						+501
	−77						
	−237						
Phentolamine	−78	+643	+771			+711	+502
	+531	+771	+772				
	+442	+533					
	+643	+772					
	+771						
	+772						
DCI	+771	+771	+771				
	+473	+772	+533				
	+99	+646	+772				
	+12	+533					
	+149						
	+772						
	+474						
Pronethalol	+99	+444	+444		+53		−502
	+149	+646					
	+53						
	+444						
Propranolol	+77	+241			+237	+711	−502
	+78	+769					
	+237						
INPEA	+531	+241					
		+456					
MJ1999	+444	+444	+444				
Kö-592						+711	
Dihydro-ergotamine	+531						
Nicotinic acid	+237	+55			+237	+55	
		+24				+117	
		+117				+56	
		+204				+204	
Methoxamine	+99						
	+149						
Isopropyl-methoxamine	+99					+711	
Butoxamine	+100				?237	+711	
	?237						

TABLE 6A—*Continued*

Blocking agent	FFA release: adipose tissue				Glycerol release: adipose tissue		Inhibition of insulin secretion: pancreas
	Rat			Man	Rat		Rat
	A	NA	IPNA	NA	A	NA	A
Prostaglandins				−37 −118	+703 +704	+703 +704 +711	
Lactic acid		+54				+56	
β-Hydroxybutyric acid		+57				+58	
Insulin	+411 +531 +497 +455 +292 +572				+455 +412 +497 +411 −411	+497	

[a] The numbers refer to items in the list of references. Abbreviations and code names are A, adrenaline; NA, noradrenaline; IPNA, isopropylnoradrenaline; +, inhibition; −, no effect; ?, doubtful effect (includes those agents that themselves have the effect); DCI, dichloroisoproterenol or 1-(3,4-dichlorophenyl)-1-hydroxy-2-isopropylaminoethane; INPEA, 1-(4-nitrophenyl)-1-hydroxy-2-isopropylaminoethane; MJ1999, 1-(4-mesylaminophenyl)-1-hydroxy-2-isopropylaminoethane; Kö-592, 1-(3-methylphenoxy)-2-hydroxy-3-isopropylaminopropane.

clusion is drawn from the relative activities of the compounds to inhibit the effect of theophylline to accelerate lipolysis (81, 438, 711) [theophylline inhibits the phosphodiesterase that hydrolyzes 3′5′-AMP, an action which results in accumulation of 3′5′-AMP (391, 766)]. Consistent with this conclusion is the competitive inhibition of the action of noradrenaline by the β-adrenergic blocking agents (DCI 533; Kö-592 and propranolol 711; INPEA 241, 456) and the noncompetitive inhibition by the α-adrenergic blocking agents (phentolamine 533, 711). Nicotinic acid acts by activating the phosphodiesterase that hydrolyzes 3′5′-AMP (439). The site of action of the other blocking agents is unknown.

The inhibitory action of insulin to decrease the stimulation by adrenaline of the release of FFA in the absence of glucose (411, 412, 497, 531, 572) is probably mediated by a decrease in the concentration of 3′5′-AMP (104, 679) due to inhibition by insulin of adenyl cyclase (410). When glucose is available to the cells, the effect of insulin to accelerate glucose utilization supervenes, and, although this may result in an even greater decrease in FFA release because of accelerated esterification of the FFA (292, 455), the rate of lipolysis (as indicated by the release of glycerol) can actually be increased under these conditions (411), presumably because of the lifting of the usual restriction on lipolysis imposed by the high internal FFA concentration (411, 606).

TABLE 6B

Effects of blocking agents in vitro on actions of catecholamines believed to be associated with their actions on plasma glucose, lactate and FFA and with their metabolic action
(for further effects see table 6A)

Blocking agent	Liver phosphorylase activation		Muscle phosphorylase activation	3′5′-AMP synthesis in liver	Glucose release liver				
	Rat	Rabbit	Rat	Dog	Rat				Rabbit
	A[a]	A	A	A	A	NA	IPNA	3′5′-AMP	A
Dibenzyline						−351[a]			
Phentolamine	+2		−2		−684				
DCI	+2		+2	+540	+553		+753	−553	
Pronethalol			+2				+753		
Propranolol			+360						
Ergotamine				+540					
Dihydroergotamine	+2		−2		+553			+553	+215
Methoxamine	+2								
Isopropyl-methoxamine		+99							

[a] The numbers refer to items in the list of references. Abbreviations are A, adrenaline; NA, noradrenaline; IPNA, isopropylnoradrenaline; +, inhibition; −, no effect; DCI as in tables 1, 3, and 6A.

E. Classification of "receptors" for the metabolic effects of adrenaline and noradrenaline

The information available about the effects of blocking agents on metabolic effects of catecholamines does not permit a general classification of these effects into those exerted at α- and β-receptors. The reasons for this are species differences, contradictory reports, failure of blocking agents within one group to exert similar effects, and lack of the relevant information. In view of the composite nature of a metabolic response to a catecholamine in an intact animal, since many actions on different tissues are involved, and, therefore, different receptors, the total response cannot itself be classified as either α or β.

Consideration of the relative effects of the three catecholamines, adrenaline, noradrenaline, and isopropylnoradrenaline, also does not help in this attempt to classify the receptors involved. Their relative potencies in producing a particular response may vary from one tissue to another in one species, or from one species to another for one tissue (see 308). For example, in a single species, the rat, the three catecholamines have a number of different metabolic actions in different tissues, but they have in common an effect of the catecholamine to increase 3′5′-AMP production. The effect of the increased 3′5′-AMP concentration depends on the metabolic composition of the tissue in question. A comparison of the potencies of the three catecholamines in producing this common effect in a number of different tissues would therefore seem useful. Despite this

TABLE 7

Relative potencies of noradrenaline (NA), isopropylnoradrenaline (IPNA) and adrenaline (A) on metabolic processes in isolated tissues of the rat

Tissue	Effect on	Relative Potency	References
Liver	Glucose release	NA ≪ A; IPNA = 0	212, 465, 616
Heart	Phosphorylase activation	NA = A ≪ IPNA	330
	Glucose uptake		330, 781
	Glycogenolysis		781
Muscle	Glycogenolysis	NA = 0; A ≪ IPNA	217, 392, 393, 421, 755
Adipose tissue	FFA release		
	(i) intact tissue	NA = A = IPNA	771, 772
	(i) isolated cells	A < NA ≪ IPNA	237
	(iii) minced tissue	A = NA ≪ IPNA	247
Pancreas	Insulin secretion	A > IPNA = NA	502

common response in four different tissues (liver, muscle, heart, adipose tissue) the relative potencies of the three amines are different for each tissue (see table 7), and the obvious conclusion is that the receptor is different for each tissue. The relative potencies of the catecholamines to inhibit secretion of insulin by the pancreas (table 7) are again different; moreover, this effect is probably mediated by inhibition of 3′5′-AMP formation (732a), and an increase in 3′5′-AMP formation [caused by caffeine (447a) or theophylline (732a)] actually stimulates insulin secretion. Suggestions that the receptor is 3′5′-AMP (33) or a specific enzyme-substrate complex of adenyl cyclase and ATP (64) are not compatible with the observed differences; it would be necessary to postulate that the adenyl cyclase is a different enzyme in each of the different tissues. Although this is quite likely it is nevertheless of little help in arriving at a molecular description of the mechanism of action of catecholamines.

The marked species differences also necessitate the assumption that adenyl cyclase differs markedly in the same tissue of different species. For example, in most species, including the rat, the relative potencies to activate phosphorylase and increase glycogenolysis in liver are isopropylnoradrenaline = 0; noradrenaline ≪ adrenaline. In contrast, the relative potencies in dog liver to increase 3′5′-AMP formation (540) and in the intact dog to increase blood glucose concentration (444, 460, 487, 517) are isopropylnoradrenaline = adrenaline ≫ noradrenaline.

In recent years much effort has gone into the attempt to force the metabolic actions of catecholamines into the α- and β-receptor system or some modification of it. It is worth while at this point therefore to question the usefulness of such a classification if it could be achieved. The classification of the "nonmetabolic" physical effects of the catecholamines was necessitated by ignorance of the chemical nature of the underlying processes involved. Although nothing is known about the chemical nature of the receptors that participate in the

metabolic effects, more is known about the chemistry of the processes involved subsequent to the initial reaction or reactions, and these processes and their relation to the initial reaction seem more amenable to study by biochemical techniques that are the physical changes involved in the nonmetabolic actions of the catecholamines, which are for the most part observable only in intact tissues. At the moment, attempts to impose an inappropriate classification might possibly retard progress rather than aid it.

In the case of AMP, a compound of primary importance in intracellular regulatory mechanisms (see 13), the multiplicity of "receptors" within a single cell and differences between enzymes of different tissues in its regulatory effects (see 13, 475, 494), permit us to suppose that more than two types of receptor for the catecholamines might exist. These several receptors might simply be different adenyl cyclases (isoenzymes) and the mixture of adenyl cyclases present in a tissue would determine the response to a catecholamine.

When the chemistry of the receptor and the nature of the reactions by which it is linked to the currently known earliest effects become known, in some detail for several tissues in each of several species, a new and useful classification of receptors may become apparent. It seems likely that the classification would be based on the amino acid sequence and tertiary structure of the protein, perhaps adenyl cyclase itself, that would be the primary site of binding of the catecholamine, although the assumption that a receptor is a protein (see also 34) is not necessarily correct.

IV. ROLE OF THE SYMPATHETIC NERVOUS SYSTEM IN THE REGULATION OF METABOLISM: THE USE OF DRUGS THAT MODIFY SYMPATHETIC ACTIVITY IN THE STUDY OF THIS ROLE

A. Introduction

The role of the sympathetic nervous system in regulating a particular metabolic function may be studied either by stimulating the activity of the sympathetic nervous system and comparing the effect with that of administered noradrenaline or adrenaline, or by inhibiting the activity of the sympathetic nervous system and comparing the effect of stimulation after inhibition with the effect obtained before inhibition. In both cases, interpretation is complicated by the lack of specificity of the stimulation or inhibition. In an intact animal, stimulatory procedures usually modify other regulatory processes; and inhibitory agents do not always cause complete inhibition and may also inhibit other regulatory processes. The conclusion that a particular metabolic function is regulated primarily by the sympathetic nervous system must usually be derived from several different approaches.

Agencies known to activate the sympathetic nervous system in an intact animal include exposure to cold or heat, emotional stress, trauma, tilting, hypotension, exercise, birth, hypoxia and anoxia, hypercapnia, and arousal from hibernation. Many of these stimuli may occur simultaneously in any given

experimental situation; for example, exposure to cold also involves exercise (shivering) while birth involves cold exposure, exercise, and trauma. The best known metabolic stimulus is hypoglycemia. Increased or accentuated activity of the sympathetic nervous system has been postulated to occur in fasting, diabetes, and hyperthyroidism. A particular form of overactivity occurs in phaeochromocytoma. Many compounds can stimulate sympathetic nervous activity in various ways. Thus some agents stimulate ganglia (including the nicotine from cigarette smoking, which perhaps should be considered among the naturally occurring events listed above), others liberate catecholamines from storage sites, while others prevent the destruction of 3′5′-AMP and thereby enhance the action of the catecholamines.

Procedures to reduce the activity of the sympathetic nervous system can be classified into three groups: (a) surgical, (b) immunological, and (c) pharmacological. All of these may suffer from either lack of completeness or lack of specificity or both. Compounds that interfere with the functioning of sympathetic regulation are of four types: (1) ganglion blocking agents, which, by inhibiting transmission in sympathetic ganglia, prevent release of noradrenaline from nerve endings and of adrenaline and noradrenaline from the adrenal medulla; (2) agents that prevent release of noradrenaline from nerve endings (but usually not the adrenal medulla) either by prior depletion of the noradrenaline (*e.g.*, reserpine) or by blocking its release (*e.g.*, bretylium); (3) adrenergic blocking agents, which inhibit the actions of the catecholamines fairly specifically (see Section III); and (4) a wide variety of compounds whose principal action is inhibition of some metabolic process that is also indirectly influenced by the catecholamines. These agents are not specific anticatecholamine agents since they exert many of their effects in the absence of the catecholamines. For want of a more specific name this group of compounds is referred to here as "metabolic inhibitors," but this is not meant to imply that they have a common mechanism of action. Such diverse compounds as nicotinic acid, methoxamine and its derivatives, 3,5-dimethylisoxazole and its derivatives, 3,5-dimethylpyrazole and its derivatives, the ergot alkaloids, and some compounds normally present in the body such as insulin, lactic acid, β-hydroxybutyric acid, and purine nucleotides are included in this group.

B. *Lipid metabolism*

Since the role of the sympathetic nervous system in the regulation of lipid metabolism has been reviewed several times recently (81, 83, 334, 335, 337, 698) emphasis here will be placed on more recent studies and on aspects not stressed by previous reviewers.

The sympathetic nervous innervation of adipose tissue and the metabolic effects of stimulation of these nerves indicate a major role of the sympathetic nervous system in the control of lipid metabolism. Both brown and white adipose tissues contain noradrenaline (570, 708, 765) in nerve endings around arteries and arterioles (793, 794) and lose this noradrenaline after denervation (667, 765).

Although nerve endings on adipose cells have been seen both with the light (67, 332, 544, 666) and the electron (543) microscope, these do not appear to contain noradrenaline (793, 794) and their origin is unknown. Suggestions that they are cholinergic nerve endings (see 150, 333, 628) have not been established. However, stimulation of the nerves to isolated, incubated epididymal fat pad does lead to increased release of FFA (44, 155, 157, 767) and of glycerol (767) into the incubation medium, and the release can be inhibited by adrenergic blocking agents (155, 157, 498, 767) and by prior sympathectomy of the rat (157). It seems reasonable to conclude, therefore, that this metabolic change is mediated by noradrenaline released from sympathetic nerve endings. Unfortunately, attempts to demonstrate this phenomenon in an intact animal have been hampered by the intense vasoconstriction that occurs during the stimulation. In a number of experiments no rise in the output of FFA into the perfusate occurs during rapid stimulation of the nerve to white adipose tissue perfused in whole animal, although an increase in the output of FFA does occur when the stimulation is stopped (561), and a lower frequency of stimulation does permit some FFA release during the stimulation (551, 612). This suggests that the noradrenaline released from the stimulated nerves brings about an increased rate of lipolysis, but the FFA produced do not escape during the stimulation *via* the tightly constricted vessels and appear in the perfusate only when the circulation to all cells is again established. Although in this type of experiment the total blood flow through the tissue has been maintained by raising the perfusion pressure (561, 612), the constancy of blood flow was probably due to the opening up of arteriovenous shunts rather than to the maintenance of flow through the smaller vessels closely associated with the adipose cells; the observation that FFA release increased at a time when the resistance to flow of the perfusion fluid decreased (561) is compatible with this interpretation. That vasoconstriction is not a necessary accompaniment of accelerated lipolysis is indicated by the dissociation of these two effects of catecholamines in isolated perfused epididymal fat pad, by the use of very low concentrations of noradrenaline (650) or by the use of papaverine to block the vasoconstriction (650), and *in vivo* by the use of blocking agents (551, 612). The major difference between the response of incubated and perfused adipose tissue to nerve stimulation is that in the former the products of lipolysis can diffuse directly into the incubation medium whereas in the latter the only available exit for these products, the blood stream, is closed during the stimulation. It is probably unrealistic to apply results of experiments in which electrical stimulation is applied to the nerves of adipose tissue to the situation in which normal physiological impulses pass down these nerves to the white adipose tissue in the intact animal. Yet it is clear that circulatory adjustments could well modify an action of increased sympathetic activity to increase mobilization of lipid in the intact animal.

The circulation of brown adipose tissue appears to differ from that of white adipose tissue in its response to catecholamines. The brown adipose tissue of the rat (230), newborn guinea pig (90) and newborn rabbit (349, 350) responds to the intravenous infusion of catecholamines by a very large increase in blood

flow. The receptors for vasodilation in the brown adipose tissue differ from those in muscle in that they respond in this way to noradrenaline as well as to adrenaline and isopropylnoradrenaline (90, 350), and the vasodilator action of all three catecholamines is inhibited by propranolol (90, 350). The receptors are, therefore, not typical β-receptors.

Changes in lipid metabolism in the intact animal subjected to stimuli that activate the sympathetic nervous system are usually measured by following the increase in concentration of FFA in plasma. This technique has certain limitations. Although the increase in the plasma FFA almost always indicates an increased liberation of FFA, the reverse is not necessarily true since many stimuli increase both utilization and production simultaneously and may, therefore, cause no change in the concentration despite an increased turnover. Stimuli that increase the concentration of FFA in plasma include electrical stimulation of the hypothalamus (156, 560), emotional stress (see 68, 630), trauma of various kinds (47, 123, 310, 521, 756), noxious stimuli such as noise (376) or electric shocks (376, 424), tilting (312, 559), hypercapnia (490, 491), hypoxia (492), hypotension (541), birth (172, 420, 556, 557, 736–738), exercise (25, 121, 258, 404, 645, 800), smoking (389, 423, 686), cold exposure (279, 316, 317, 376, 466, 499, 500, 507, 625, 627), and hypoglycemia (10, 119, 158, 262, 762, 774). The increased secretory activity of phaeochromocytoma is also associated with very high concentrations of plasma FFA (145, 224, 322). There are some reports in which a few of the stimuli noted above did not increase the plasma FFA concentration. In most cases an explanation for the discrepancy can be found. For example, in young rats (up to 300 g) the concentration of plasma FFA increases considerably during exposure to cold for 1 to 24 hours (279, 499, 500, 507, 625, 709) whereas in old rats (360 to 408 g) there is no change during shorter exposures (up to 4 hours) (366, 512) and very little change in FFA or glycerol concentrations during a longer exposure lasting 20 hours (366). The most probable explanation for this discrepancy is that an increased rate of mobilization is more closely balanced by an increased rate of utilization in the older rats than in the younger rats since the turnover of FFA is increased in the older rats (512) despite the unchanged FFA concentration in the blood. Exercise also alters the rates of both mobilization and utilization of FFA; since the activation of each process is sometimes equal and sometimes unequal, exercise may decrease, not alter, or increase the concentration of FFA in plasma. During exercise in man an initial decrease in plasma FFA concentration (121, 132, 135, 258, 323, 342, 428) may be followed by a further decrease (132, 258, 428, 604), a return to normal (342), or an increase above normal (25, 121, 258, 404, 537, 645, 800) depending upon the severity of the exercise (604); after the exercise the concentration always increases (132, 258, 323, 339, 342, 404, 537, 604) because the increase rate of utilization is reduced before the increased rate of output decreases. A progressive increase in blood glycerol concentration is consistently observed during exercise in man (121, 122, 323, 339, 342). Only a decrease in plasma FFA concentration in dogs has been observed during exercise (396, 397, 518, 519), but the exercise was of the type that increased blood lactate

concentration in the dogs, and this type of exercise is also associated with a decrease in plasma FFA concentration in man (604). Several observations suggest that lactate itself may participate in the regulation of lipid mobilization during exercise: 1) the inverse relationships between FFA and lactate concentrations during exercise (397), 2) the decrease in FFA concentration caused by infusion of lactate into resting dogs (396, 518, 519), 3) the reduction by lactate of the elevated plasma FFA concentration during infusion of noradrenaline (518), and 4) the inhibition by lactate of the action of noradrenaline to increase release of FFA from incubated adipose tissue (54). Presumably increased lactate production by muscle is a signal that aerobic oxidations have reached an upper limit and that no additional supply of FFA can be used.

Several studies designed to show selective activation of certain portions of the sympathetic nervous system have yielded results contradictory to those listed above. Hypercapnia may (491) or may not (558, 585) increase the plasma FFA concentration despite evidence of increased sympathetic activity. This results from the different degrees of acidosis produced in the different experiments. Acidosis inhibits the action of infused noradrenaline or adrenaline to increase plasma FFA or glycerol concentrations (585), an effect in keeping with the known pH-dependence of the lipolytic action of the catecholamines *in vitro* (531, 730, 773). When the blood pH returns to normal after a period of hypercapnic acidosis the concentration of FFA does rise (558, 585) or rises even further if it has already increased during the hypercapnia (491). Likewise the acidosis that develops during hemorrhagic hypotension appears to prevent the increase in plasma FFA concentration that occurs if the pH is maintained at a normal level (541). Hypoxia increases plasma FFA concentrations in man (470) and rats (735). In the three contradictory reports of the effect of hypoxia on lipid mobilization in dogs (62, 492, 558), the experimental conditions differed in the degree of hypoxia attained. Those dogs that were the most hypoxic (558) did not respond by an increase in plasma FFA concentration, whereas the less hypoxic dogs did (492) and the least hypoxic dogs did not (62). The effects of administered catecholamines on plasma FFA concentration in severe hypoxia are not known, but it is reasonable to suppose that the observed inhibition of the lipolytic action of noradrenaline by anaerobiosis *in vitro* (17) would also obtain to some extent *in vivo*. In the least hypoxic dogs, the effect of injected adrenaline or noradrenaline was not inhibited (62).

It is clear, therefore, that the failure to observe a metabolic effect (in this case an increase in plasma FFA concentration) during a stimulus known from other measurements such as heart rate, blood pressure, *etc.*, to activate the sympathetic nervous system, does not necessarily mean that a portion of the sympathetic system is not activated by the stimulus but may mean that the noradrenaline liberated from the nerve endings does not exert its usual metabolic effect. One can check this possibility by infusion of noradrenaline under the same conditions. The one good example of selective activation of certain portions of the sympathetic nervous system is the finding of no increase in plasma FFA concentration (264) and no vasoconstriction in adipose tissue (551) during carotid

occlusion in dogs, despite the increased sympathetic activity indicated by the rise in blood pressure (264). Infused noradrenaline does still increase plasma FFA concentration during the carotid occlusion (264).

The participation of the sympathetic nervous system in the increased lipid mobilization that occurs in response to most of the stimuli mentioned so far has been confirmed by the use of ganglion blocking agents, adrenergic neurone blocking agents, or adrenergic blocking agents and by removal of the adrenal medulla. A few examples will be presented. The increase in plasma FFA concentration caused by insulin-induced hypoglycemia (10, 119, 158, 262, 762, 774) is considered to be mediated by the sympathetic nerves since it is not altered by removal of the adrenal medulla (158, 262), although the adrenal medulla does normally secrete more adrenaline under these conditions (762). The increase is inhibited by ganglion blocking agents (469 chlorisondamine; 262 azamethonium; 774 hexamethonium), adrenergic neurone blocking agents (10 guanethidine; 262 reserpine), and an adrenergic blocking agent (10 dibenzyline) as well as by a metabolic inhibitor (119, 262 nicotinic acid). In dogs a decrease in glucose utilization induced by 2-deoxyglucose causes an increase in plasma FFA concentration (283, 284); this is not dependent on the presence of the adrenal medulla (284), although increased secretion of adrenaline does occur if the adrenal is intact, but is considered to be mediated by sympathetic nerves since it is inhibited by hexamethonium (283, 284). In contrast, the rat requires an intact adrenal to respond to 2-deoxyglucose by an increase in lipid mobilization (598). The fact that in man the effect of 2-deoxyglucose is associated with a large increase in adrenaline secretion and little or no change in noradrenaline secretion suggests that man behaves like the rats thi in response (372, 449). The increased lipid mobilization in rats in response to cold exposure does not require the adrenal medulla (82, 279, 709) but is considered to require functioning sympathetic nerves since it is inhibited by ganglionic blockade (82, 279, 709 chlorisondamine), by adrenergic neurone blocking agents in adreno-demedullated rats (82, 279, 568), by adrenergic blocking agents (82 dibenamine; 712 Kö-592)) and by metabolic inhibitors (625 isopropylmethoxamine; 50, 269 dimethylpyrazole; 48, 49 salicylic acid; 712, 749 nicotinic acid). The observation that syrosingopine inhibits lipid mobilization in response to cold exposure in normal rats as well as in adreno-demedullated rats (709) suggests that the role of the adrenal medulla in this response is not important even when it is the only functioning portion of the sympathetic nervous system available. The function of the sympathetic nerves in this response is further indicated by the enhanced response seen in rats treated with nialamid or pargyline to increase the noradrenaline content of their nerves (709). Smoking appears to cause lipid mobilization by stimulation of the adrenal medulla in man (423, 778), since it is ineffective in adrenalectomized subjects (423) and after ganglionic blockade (423).

The role of the sympathetic nervous system in the mobilization of FFA from adipose tissue during fasting has received considerable attention during the past few years. The divergence of opinions is illustrated by two recent reviews, which present entirely different conclusions (83, 337). There are three main

lines of evidence. The first is that a variety of blocking agents do not alter the increase in plasma FFA concentration during fasting (ergotamine, dibenzyline, hexamethonium, dibenamine, propranolol, 287, 576, 706). Although hexamethonium does sometimes decrease the concentration of plasma FFA in fasting dogs (341) and men (289), it does not always have this effect (135, 774), and other ganglion blocking agents do not have this effect. For example, pentolinium does not alter the concentration of FFA in the plasma of man (289), and trimethaphan camphorsulfonate does not do so in the dog (490) and may (135) or may not (69) in man. Azamethonium may or may not decrease plasma FFA concentration in dogs (262). Chlorisondamine does not alter plasma FFA concentration in rats (82, 279, 709). It is not known whether the progressive increase in plasma FFA concentration that occurs during fasting would be prevented by ganglionic blockade in dogs or man, but it is clearly not altered in the rat (287, 706). Depletion of nerve endings with reserpine or prevention of noradrenaline release with adrenergic neurone blocking agents, with or without simultaneous removal of the adrenal medulla, also does not abolish the rise in plasma FFA concentration in fasting rats (208, 240, 706). The conclusion to be drawn from these studies is that the sympathetic nervous system is not essential for FFA mobilization during fasting.

A second line of evidence is the effect of denervation to inhibit the mobilization of fat from brown (152) or white (115) adipose tissue during fasting. Since lack of sympathetic innervation prevents the fat mobilization induced by fasting the conclusion is usually drawn that sympathetic stimulation must be responsible for this mobilization. Another possibility is that the denervated tissue *in vivo* lacks adequate blood supply and is therefore unable to respond to blood-borne factors with an alteration in lipid metabolism (115).

The third line of evidence comes from the known participation of the sympathetic nervous system in other conditions of glucose deprivation such as insulin-induced hypoglycemia (10, 262, 469, 774) and treatment with 2-deoxyglucose (283, 284). It is often assumed that the decreased availability of glucose during fasting is likewise responsible for the rise in the plasma FFA concentration (283, 284), but there is reason to doubt the validity of this assumption because the decreased availability of glucose during fasting (normal blood glucose concentration, lack of insulin) differs from that during insulin hypoglycemia (low blood glucose, high insulin concentration) or during 2-deoxyglucose treatment (hyperglycemia but decreased glucose utilization, low insulin concentration).

There is then little or no evidence that the sympathetic nervous system does initiate lipid mobilization during fasting and considerable evidence that it does not. The stimulus to the mobilization of FFA from adipose tissue is probably diminished secretion of insulin (see 106, 288). The remarkable sensitivity of the lipolytic system of adipose tissue to inhibition by insulin (238, 425) indicates that this system is normally inhibited and that this inhibition is removed during fasting. The recent finding that insulin may exert its antilipolytic effect by reducing the 3′5′-AMP concentration of the adipose tissue (104, 410) and the

suggestion that the noradrenaline-activated lipase is the same as the fasting-activated lipase (83) indicates that the increased mobilization of lipid during fasting is brought about by the same 3′5′-AMP activated lipase system as that involved in the action of the sympathetic nervous system but that noradrenaline is not an essential component of this system. The inhibition of fasting-induced increase in plasma FFA concentration by metabolic inhibitors such as nicotinic acid (51, 127, 240, 269, 712), methoxamine and derivatives (100, 147, 390, 625), salicylic acid (48, 49), and 3,5-dimethylpyrazole (50, 51, 269, 277) is explained by their interference with the lipolytic process in some way, other than by inhibition of the action of noradrenaline. Nicotinic acid, for example, activates the phosphodiesterase (439) and thereby decreases the availability of 3′5′-AMP. The finding of a reduction in plasma FFA concentration after ganglionic blockade in some species does not, therefore, prove that the sympathetic nerves provided the stimulus for the fasting-induced increase in FFA concentration but may simply reflect removal of one of the several small, normally occurring stimuli to lipolysis.

It has been suggested that the sympathetic nervous system has a role in the increase in concentration and in turnover of FFA that occurs in hyperthyroidism (207). This increase appears to be due to an augmentation by thyroid hormone of one part of the lipolytic system of adipose tissue such as to cause an increase in the total adenyl cyclase activity of the adipose tissue (81). This results in an increased capacity of the tissue to respond to agents that stimulate adenyl cyclase, such as adrenaline and noradrenaline (81, 176, 189, 285), although the lipolytic capacity, as determined by the total lipase present, is unchanged, as judged by the unaltered effect of theophylline (81). There is no convincing evidence that noradrenaline release plays any part in the increase in blood FFA concentration in hyperthyroidism. The finding of a reduction in plasma con-concentration of FFA after treatment with metabolic inhibitors (nicotinic acid 207; butoxamine 147, 148, 627) does not establish that the release of noradrenaline is involved, since these agents interfere with lipolysis at a site other than that stimulated by noradrenaline. The reduction in plasma FFA concentration after ganglionic blockade (699 hexamethonium) or adrenergic neurone blockade (84) also does not prove that noradrenaline secretion is the only stimulus to lipolysis. Since, however, noradrenaline secretion at sympathetic nerve endings is one of the factors involved in the continuous maintenance of the level of lipase activity, inhibition of its release would inevitably diminish lipolysis. The increased mobilization of lipid in hyperthyroidism can therefore be regarded primarily as a defect of the lipase activation system leading to increased lipase activity; the sympathetic nervous system probably normally participates in this system, and, under conditions that increase sympathetic activity, such as any of those discussed above, it is the response of the adipose tissue lipolytic system which is exaggerated.

It has also been suggested that the sympathetic nervous system has a role in the increased lipid mobilization in diabetes (627). Since diabetes may be regarded as an exaggerated form of fasting, in which insulin lack is more complete, the

role of the sympathetic nervous system would be expected to be similar to its role in fasting, that is, the sympathetic would not be expected to provide the stimulus for increased lipid mobilization in diabetes. This stimulus would be rather the withdrawal of insulin, exerting its effect *via* the same lipase system that is activated by sympathetic stimulation. A reduction of plasma FFA concentration in diabetes by metabolic inhibitors (627 butoxamine in dogs; 280, 336 nicotinic acid in dogs; 120, 131, 522 nicotinic acid in man; 129, 131 salicylic acid in man; 623 butoxamine in rats; 50, 269, 277 dimethylpyrazole in rats; 130, 712 nicotinic acid in rats) would therefore be expected, and the finding of no change in plasma FFA concentration of diabetic rats after a β-adrenergic blocking agent (710, 712 Kö-592) but a decrease after an α-adrenergic blocking agent (710 dibenzyline) is in keeping with this interpretation.

C. *Carbohydrate metabolism*

The hyperglycemic effect of catecholamines is contributed to by several different actions of these compounds (see section II B). The hyperglycemia that accompanies sympathetic nervous system activation might be due to several different effects of sympathetic activity, some produced principally by circulating adrenaline liberated from the adrenal medulla and others produced primarily by noradrenaline liberated at nerve endings in adipose tissue, liver, and pancreas. In assessing the function of the sympathetic nervous system in carbohydrate mobilization, it should be remembered that the concentration of glucose in the blood is not always a good index of the rate of glucose production. Some stimuli that activate the sympathetic nervous system, *e.g.*, exercise or exposure to cold, also increase the rate of glucose utilization directly. Simultaneous increases in the rates of production and utilization may cause no change or even a decrease in the concentration of glucose in the blood. Moreover, hyperglycemia due to increased sympathetic activity will presumably be modified by the counter-regulatory effect of high blood glucose concentrations to diminish sympathetic tone (201, 289); on the other hand, when there is no hyperglycemia despite an adrenaline-induced increase in glucose production, this counter-regulatory mechanism would not be brought into play. Exposure of a fed rat to cold causes a mild, transient hyperglycemia (188, 274, 279, 366); that this does not occur in a fasting rat (186) or in an adrenodemedullated rat (274, 279) suggests that an action of adrenaline on the liver is involved. Rats that have become acclimated to cold do not develop any hyperglycemia when returned to the cold after a short period in a warm environment (378). These observations alone might be taken to indicate that little or no change in carbohydrate metabolism occurred, but there is about 60% increase in the rate of glucose turnover in these rats (188). The decrease in liver glycogen is compatible with an effect of adrenaline on the liver (188), but the finding of a similar increase in glucose turnover in fasting rats exposed to cold (186) indicates accelerated gluconeogenesis. This increased gluconeogenesis could be due, at least in part, to an action of glucocorticoids, whose secretion is increased at the same time. It is not known whether increased glucose turnover and increased gluconeogenesis occur in the absence of the adrenal medulla.

In exercise both increased glucose turnover and increased sympathetic activity occur; a possible role of the sympathetic nervous system in the increased glucose production must therefore be considered. During the exercise the concentration of glucose in the blood may remain fairly constant (532, 604; see 275), slowly decrease (404, 604), or increase (707). There are, however, increases in peripheral glucose utilization (394, 532, 629) and in hepatic glucose output (615), reflecting an increased turnover of glucose (398). Since these changes can occur in fasting subjects (615), the glucose must be formed by gluconeogenesis, a supposition supported by the increased nitrogen excretion during and after exercise (see 275). The role of the sympathetic nervous system in the mobilization of glucose during exercise is uncertain. Surgically sympathectomized dogs are stated to be able to exercise normally and to maintain normal blood glucose concentrations during exercise (86), but in rats the ability to exercise is reduced by adrenergic blockade (693), adrenergic neurone blockade in adrenodemedullated rats (83, 504), or adrenodemedullation (504); and sympathectomized cats have a reduced capacity for exercise (371). Of these observations, that on the effect of adrenodemedullation (504) is the most informative since this prevents the hyperglycemia but not the increased concentration of FFA caused by exercise; this suggests that curtailment of the accelerated glucose mobilization caused by adrenaline reduces the capacity for exercise. As pointed out above, it is not known whether adrenodemedullation completely abolishes the increased glucose production but it clearly abolishes at least that portion responsible for the mobilization in excess of utilization. Adrenergic neurone blockade accentuates the exhaustion of adrenodemedullated rats during exercise (504). This is probably due to the inhibition of mobilization of both glucose and FFA. FFA mobilization is not essential for continuing exercise providing that glucose is available (122, 537) and conversely, glucose is not essential provided that FFA are available (504), but the absence of both substrates leads to very rapid exhaustion (504).

Hypoxia or hypercapnia, which both increase sympathetic activity, cause hyperglycemia (245, 491, 492, 733) by liberation of adrenaline from the adrenal medulla (491, 492). It is worth noting that hyperglycemia does not occur in the rat if alkalosis develops during the hypoxia because the hyperglycemic effect of adrenaline is inhibited by alkalosis (733). One contradictory report of no hyperglycemia in severely hypoxic dogs (558) may be due to alkalosis. Another contradictory report of no hyperglycemia in mildly hypoxic dogs (62) may be due to insufficient activation of the sympathetic nervous system; the hyperglycemic effects of adrenaline and noradrenaline were not altered under these conditions (62).

The marked increase in the rate of glucose production that occurs in response to hypoglycemia is associated with an increase in sympathetic activity (113); receptors for hypoglycemia appear to be located both in the hypothalamus (201) and in the lower cervical and upper thoracic regions of the spinal cord (116, 283, 284). Surgical sympathectomy (488, 636), ganglionic blockade with hexamethonium (194, 451, 632), or adrenergic blockade with propranolol (105) accentuate insulin-induced hypoglycemia. There is a condition in man, idiopathic hypoglycemia, in which failure to secrete adrenaline after insulin-induced

hypoglycemia is associated with marked sensitivity to the hypoglycemic action of insulin (80, 496). However, the fact that blood glucose concentration does eventually return to normal despite ganglionic blockade (774) or despite failure to secrete adrenaline (80) indicates that other regulatory mechanisms are involved in addition to adrenaline secretion. The lack of effect of removal of the adrenal medulla on the extent and duration of the hypoglycemic effect of insulin (65, 262) suggests that noradrenaline liberated at nerve endings may be more important for the rapid recovery of normal blood glucose concentrations. The site of this action of noradrenaline is uncertain.

The overproduction of adrenaline in subjects with phaeochromocytoma causes decreased glucose tolerance (145, 779) apparently due to inhibition of insulin secretion by the adrenaline (779); the glucose tolerance returns to normal after surgical removal of the tumor (145, 779).

The role of the sympathetic nervous system in the regulation of glycogenolysis in skeletal muscle is uncertain. Since only adrenaline, and not noradrenaline, has this effect, any noradrenaline liberated from the nerve endings in muscle (651) would not be expected to exert this metabolic effect. Adrenaline is, of course, not the only stimulus that increases muscle phosphorylase activity. Electrical stimulation of muscle leads to exceedingly rapid activation by a mechanism different from that involved in the slower action of adrenaline (170). Thus the increased rate of muscle glycogenolysis known to occur during exercise is most probably not brought about by adrenaline. The concentration of adrenaline in the blood during exercise is in any case not high enough to have this effect (135). During insulin-induced hypoglycemia the increased glycogenolysis and lactate production by muscle do appear to result from an action of adrenaline since they do not occur in adrenodemedullated rats (65).

The role of the sympathetic nervous system in the regulation of glycogenolysis in heart by activation of phosphorylase has received an amount of attention in recent years which probably is out of proportion to its importance in normal cardiac metabolism. Since the action of many drugs on cardiac phosphorylase has been reviewed recently (328) it will not be discussed in detail here. Stimulation of the sympathetic nerves to the heart results in an increase in phosphorylase *a* activity (365, 516); this effect is blocked by β-adrenergic blockade (DCI), does not appear in hearts depleted of their noradrenaline (with reserpine), and is in keeping with the effect on the heart of administered noradrenaline (516). Increased sympathetic activity brought about by anoxia in intact animals causes activation of cardiac phosphorylase (670, 796) and also leads to a decrease in cardiac glycogen (715); this increase in phosphorylase activity is delayed by pronethalol (670), and the decrease in glycogen content is delayed by propranolol (715). However, for purposes of this discussion, anoxia is not a good example of a stimulus to the heart *via* the sympathetic nervous system since anoxia also activates phosphorylase (670, 797) and inactivates glycogen synthetase (687) in a way which is independent of the sympathtice nervous system. The role of cardiac glycogenolysis and phosphorylase activation in an intact animal subjected to sympathetic stimulation is uncertain since the simultaneous

increase in plasma FFA concentration would be expected to exert a glycogen-sparing action on the heart (75). Another way of assessing the role of the sympathetic activation of phosphorylase in the normal functioning of the heart is to remove the mediator, noradrenaline. Sympathetic denervation of the heart leads to an accumulation of glycogen (403). The hearts of immunosympathectomized rats also contain larger than usual amounts of glycogen (464) but nevertheless appear to function normally (43) despite the complete absence of noradrenaline from the heart (311). The hearts of reserpine-treated animals also contain more glycogen than usual (374, 379) but there is no change in the proportion of phosphorylase in the active form.

Some confusion has arisen in the literature over the effect of reserpine-induced depletion of cardiac noradrenaline on the proportion of cardiac phosphorylase in the *a* form, some authors reporting a decrease (32, 191, 363, 447) and other authors reporting little or no change (362, 374, 375, 493, 516). These differences become more explicable when the so-called "basal" level of phosphorylase *a* in the different experiments is taken into account. In animals killed by decapitation or by stunning (32, 191, 363, 447) the basal level of phosphorylase *a* is very high (51.4 to 89.0%) and is reduced in reserpine-pretreated animals (30.9 to 54.8%). In rats or dogs anesthetized before the heart is removed (362, 374, 375 493, 516), the basal level is much lower (4.0 to 37.6%) and is not different in reserpine-pretreated animals. More than one interpretation of these results is possible, but the most likely explanation is that the animals that are decapitated or stunned are subjected to a brief sympathetic discharge resulting in activation of cardiac phosphorylase by noradrenaline liberated within the heart and by adrenaline liberated from the adrenal medulla and circulating in the blood. The cardiac phosphorylase of the reserpine-treated animals would probably be subjected to the latter stimulus, but not to the former, and would therefore be activated to a lesser extent. Hearts removed from anesthetized animals would probably not be subjected to either of these stimuli, and the presence or absence of noradrenaline in them would therefore be expected to have little influence on the proportion of phosphorylase in the *a* form. The large variation of the basal level of phosphorylase even in the anesthetized animals is most likely due to differences in the technique of freezing and preparation for assay; it is in fact possible to obtain a basal level of zero phosphorylase *a* when the heart is frozen very rapidly (796). The significance of these observations for the normal functioning of the heart in an intact unanesthetized animal is not clear; it is not even known whether the proportion of phosphorylase in the *a* form fluctuates during the spontaneous rhythmic cardiac contractions as it does in uterine muscle (193). Similar contradictory observations are available concerning the modification by hyperthyroidism of the proportion of cardiac phosphorylase in the *a* form. Most workers have reported an increase in the proportion of phosphorylase *a* in the heart in hyperthyroidism (329, 362, 374, 375) and this has been attributed to an enhancement of the action of noradrenaline released from nerve endings in the heart in the hyperthyroid state. Values for the proportion of phosphorylase in the heart in the *a* form reported by different workers for hyperthyroid animals are zero (796), 38.0 (374), 32.8 (375), and 50.5 (329, 362); the corresponding values in euthyroid animals are zero (796), 14.2 (375), 20.3 (374), 30.1 (362), and 28 (329). In view of these differences the question arises: what is the actual concentration of phosphorylase *a* in the heart of the intact animal before removal and preparation for assay, and to what extent does the technique of removal and preparation influence the observed results? The exceedingly rapid activation of phosphorylase by anoxia (796) indicates that the time lag between removal of the heart and complete freezing may be critical in determining the proportion of phosphorylase found in the *a* form. The initial activation of heart phosphorylase by anoxia is sensitive to pronethalol and may be attributed to the release of endogenous noradrenaline (796, 797). Moreover, since this rapid activation is accelerated by hy-

perthyroidism (796) the reported different degrees of activation in hyperthyroidism quoted above may depend on difference in the time of freezing. If this interpretation were correct, then agents that remove the noradrenaline from the heart and agents that inhibit the action of noradrenaline on the heart should prevent the apparent activation of phosphorylase by hyperthyroidism, whereas agents that prevent the release of noradrenaline in the intact animal would be without effect. This is indeed so, since reserpine-pretreatment (362, 375) and pronethalol (362, 375) reduce or abolish the apparent thyroid hormone-induced increase in phosphorylase *a* activity, whereas ganglionic blockade with trimethidinium does not alter it (375). Moreover, exceedingly rapid freezing results in practically zero phosphorylase *a* activity in the hearts of both normal and hyperthyroid dogs (796). In summary, thyroid hormone probably does not alter the basal level of phosphorylase *a* in the heart but may increase the capacity of the heart to respond to noradrenaline by an increase in phosphorylase *a* activity (375). By analogy with the observation of an increase in adenyl cyclase activity in adipose tissue of hyperthyroid rats, it would be of interest to know whether the adenyl cyclase activity of heart is increased in hyperthyroidism.

D. Protein metabolism

Little is known about the effects of adrenaline and noradrenaline on protein and amino acid metabolism although they do seem to influence it in some way. Nothing is known about the possible physiological significance of the observed effects of catecholamines, such as the decrease in amino acid concentration in blood and the increase in urea excretion and the inhibition of protein synthesis (see section II C), or whether the sympathetic nervous system can produce such effects.

E. Metabolic rate

There is an increase in metabolic rate during exposure to cold, during arousal from hibernation, and during exercise. Nonphysiological factors that increase metabolic rate include hyperthyroidism and phaeochromocytoma. Since the mechanism of the increase in heat production in each of these conditions may be different, the extent to which the sympathetic nervous system is involved in the increase in metabolic rate in each condition will be discussed separately. For this reason, too, the metabolic response to exposure to cold of warm-acclimated animals, of cold-acclimated animals, and of newborn animals will be discussed separately.

1. EXPOSURE TO COLD[4]

a. Warm-acclimated animals. The sympathetic nervous system is activated in warm-acclimated animals exposed to cold, as indicated by an increase in the urinary excretion of adrenaline and noradrenaline (453, 457), and the liberated adrenaline and noradrenaline would be expected to exert a calorigenic effect,

[4] In this discussion animals kept at low temperatures for long periods of time, several weeks or months, will be referred to as "cold-acclimated" animals, while the term "cold-exposure" is restricted to the acute exposure of animals to low temperature for relatively brief periods (up to 48 hours), whether they had been previously cold-acclimated or not; animals kept at usual room temperature will be referred to as "warm-acclimated" animals. To investigate the effect of cold-exposure on cold-acclimated animals, the animals are first removed from the cold and allowed to recover at room temperature for several hours.

whose extent would depend on the age of the animal (see section II D). In warm-acclimated animals the increase in metabolic rate produced by the secretion of noradrenaline and adrenaline is overshadowed by the much greater increase due to shivering (326, 357), and in the studies reported the increase has been insufficient to maintain body temperature in the cold when shivering is prevented by tubocurarine (160, 379). The lack of marked increase in metabolic rate in the cold not due to shivering (nonshivering thermogenesis) may, in part, have been due to the use of older rats. In the two published studies the increase in oxygen uptake of curarized rats exposed to cold was greater in the younger rats [230- to 300-g rats had a 28% increase (379)] than in the older rats [300- to 400-g rats had a 14% increase (160)]. The size of these increases is difficult to assess because they are superimposed on a decrease in oxygen uptake due to the developing hypothermia of the animals and they are, therefore, only approximate. They do, however, correspond to the increases obtained after administration of noradrenaline to rats of these size ranges at room temperature (see fig. 2, section II D).

Although the increase in metabolic rate possibly attributable to an action of the sympathetic nervous system is relatively minor in these warm-acclimated rats it could nevertheless be important. One might determine the requirement for sympathetic activity in this response by inactivating the sympathetic nervous system in some way. This approach generates two new problems. Firstly, the sympathetic nervous system is essential for the mobilization of substrates during cold-exposure (glucose and FFA, section IV B and C), and inactivating the sympathetic nervous system will prevent this mobilization. Lack of substrate will adversely affect the metabolism of the shivering muscles (just as it adversely affects muscle metabolism in exercise, section IV B and C) and may also influence adversely the metabolic process involved in the calorigenic action of the catecholamines (it is assumed that this process is, for the most part, not the same as, nor a consequence of, the mobilization of substrate, section II D). Secondly, when the sympathetic nervous system is inactivated, the usual circulatory adjustments that reduce heat loss may be impaired. This would aggravate the hypothermia and complicate the interpretation of studies in which the sympathetic nervous system is inactivated.

Ganglion blocking agents prevent the small rise in oxygen uptake seen in curarized rats during cold-exposure (hexamethonium, 379) and cause death in hypothermia of normal rats exposed to cold (mecamylamine, 457) despite their very marked shivering. The probable lack of substrate mobilization, calorigenic action, and circulatory adjustments is deleterious to survival under these conditions. With chlorisondamine, rats exposed to cold also fail to shiver and die (279), and lack of shivering alone (curarized rats) causes death in hypothermia (160, 379). Administration of adrenaline, but not noradrenaline, can protect mecamylamine-treated rats against hypothermia caused by cold-exposure (457); this finding suggests that the adrenal medulla might play a more important role than the sympathetic nerves in these animals.

Reserpine and adrenergic neurone blocking agents [guanethidine and BW-

392C60 (N-*o*-chlorobenzyl-N′, N″-dimethylguanidine)] have been used extensively to study the role of the sympathetic nervous system in the metabolic response to cold-exposure (279, 457, 569; see 81 and 83). The multiplicity of actions of reserpine makes the interpretation of its effect on metabolic responses to cold-exposure difficult. Although reserpine does indeed cause prolonged depletion of noradrenaline in sympathetic nerve endings and also of adrenaline and noradrenaline in the adrenal medulla if the dose is large enough, at first it causes excessive release of these compounds from their storage sites, and it also modifies the functioning of the central nervous system and of the pituitary gland (see 776). Hence one cannot attribute the lack of particular response after reserpine solely to the absence of a functioning sympathetic nervous system. If rats are exposed to cold shortly after a large dose of reserpine they die in hypothermia (167, 279, 457, 500, 641, 768, 801), but as reserpine inhibits their shivering (279), this alone could account for their death in hypothermia. Moreover, the initial massive release of adrenaline and noradrenaline, together with the accentuation of their toxicity by cold (461, 641) and by reserpine itself (452), may contribute to their dying. Other responses lacking in adrenodemedullated rats exposed to cold shortly after reserpine treatment include increases in plasma glucose (279), FFA (279, 500), and corticosterone concentrations (279). Rats exposed to cold only 24 to 48 hours after a large dose of reserpine do not become hypothermic or die (457, 641) although the tissue contents of adrenaline and noradrenaline are at a minimum at this time. Their ability to survive is due to the incomplete depletion of the adrenal medulla (457); they can still increase their secretion of adrenaline during cold-exposure (457), whereas adrenalectomized rats (maintained on deoxycorticosterone) die in hypothermia during cold-exposure 48 hours after only a small dose of reserpine (457; see also 407). Thus the initial effect of reserpine differs from its later effects, and it may be concluded that the initial effects are not due to interference with sympathetic functioning but to some other action of the reserpine.

The adrenergic neurone blocking agents also interfere with shivering in adrenodemedullated rats exposed to cold (81, 83, 279, 569). This may be due to the curare-like action at the neuromuscular junction that they have at high doses (see 74, 225) or to some other action, but this action makes them less valuable in studies of the metabolic responses to cold mediated by the sympathetic nervous system. Prolonged treatment of rats with guanethidine does not alter their resistance to very low temperatures (−35°C) (356), but such rats would have a normally functioning adrenal medulla.

Inhibition of dopa decarboxylase [with Ro4-4602, N-(*dl*-seryl)-N′-(2,3,4-trihydroxybenzyl)hydrazine] to prevent noradrenaline synthesis does not by itself prevent the usual metabolic response to exposure to cold, since the store of adrenaline in the adrenal medulla appears to be adequate to permit a response under these conditions; removal of the adrenal medulla together with inhibition of dopa decarboxylase causes death in hypothermia early in cold exposure (408).

Blocking of the actions of adrenaline and noradrenaline (with dibenzyline) during cold-exposure also leads to death in hypothermia (457). From available

information about its inhibition of metabolic effects of adrenaline and noradrenaline, dibenzyline would be expected to inhibit the increases in blood glucose (647), FFA (710), and oxygen uptake (409) as well as some of the circulatory adjustments. Hence, such studies would not assist greatly in analysis of the role of the sympathetic nervous system in cold-exposure.

Surgical, immunological, and some pharmacological procedures do allow a differentiation to be made between the relative importance of adrenal medulla and sympathetic nerves in cold-exposure. Removal of the adrenal medulla alone from rats leads to some impairment of the ability to maintain body temperature during cold-exposure. Young rats (less than 200 g) become mildly hypothermic during 6 to 8 hours of cold-exposure (43, 279) whereas older rats (more than 200 g) are better able to maintain their body temperature under these conditions (43). Removal of the adrenal medulla does not alter the small increase in metabolic rate seen in curarized rats (300 to 400 g) exposed to cold (160). Immunological sympathectomy (see 462, 463) results in lack of the adrenergic nerve endings in those organs normally innervated by the superior cervical and paravertebral ganglia, *e.g.*, the heart and blood vessels of skeletal muscle (311), but leaves intact the prevertebral ganglia (coeliac, inferior mesenteric, and superior mesenteric) (754) and the nerve endings on intestine and reproductive organs (311); the noradrenaline content of the brain is unchanged (752) and the adrenal medulla continues to function normally (752). Immunosympathectomy alone (43) or dopa decarboxylase inhibition alone (408) does not alter the ability of young adult rats (about 200 to 300 g) to maintain their body temperature in the cold. Clearly a rat of this age can survive in the cold without either its adrenal medulla or most of its sympathetic nerves, but young rats both immunosympathectomized and adrenodemedullated become hypothermic very rapidly in the cold (43), as also do adrenalectomized rats whose dopa decarboxylase is inhibited (408). Older rats survive in the cold even when immunosympathectomized and adrenodemedullated (639). This appears to be due to the remnant of the sympathetic nervous system still functioning in these rats since their excretion of noradrenaline is similar to that in control rats although their excretion of adrenaline is reduced (639). Only in their ability to survive a more severe cold stress (shaving at 4°C) do these rats differ from the controls (639). The extent to which the two major divisions of the sympathetic nervous system participate in the reactions involved in survival in the cold differs then in rats of different ages. Young adult rats depend more on the adrenal medulla than do older rats. All rats, nevertheless, can substitute one part of the sympathetic for the other according to circumstances. Moreover, when deprived of the adrenal medulla and most of the sympathetic nerves, a rat can still use the remaining sympathetic nerves to counteract hypothermia. The sympathetic nervous system is clearly a highly efficient emergency mechanism in that although, to the best of our knowledge, the functions of its parts are normally well integrated, a small part can nevertheless take over the functions of the other parts when necessary. This substitution of functions indeed complicates the study of the normal functioning of the sympathetic nervous system;

the observation that removal of the adrenal medulla does not lead to a change in a particular metabolic response does not necessarily mean that the adrenal medulla played no part in the production of that response when it was present. In fact, it might normally play the major role, and, once removed, its function may simply be replaced by that of another part of the sympathetic nervous system.

The old observation of Cannon that surgically sympathectomized cats cannot maintain their body temperature when exposed to cold despite marked shivering (114, 631) is in keeping with the concept that the sympathetic nervous system is essential for the metabolic response to cold and was one of the observations which led Cannon to the conclusion that, although the sympathetic nervous system was not necessary for survival under well regulated laboratory conditions, it was nevertheless of prime importance in the maintenance of homeostasis under a variety of adverse conditions (114). The recent suggestion (81, 83) that, because the surgical procedure used left some portions of the sympathetic nervous system intact, Cannon's original conclusion is incorrect is based on a misquotation of the original conclusion. The finding that a supposedly more complete sympathectomy of cats by chemical and surgical means (adrenodemedullation plus an adrenergic neurone blocking agent) leads to a more marked impairment in response to cold is not surprising in view of the inability of these animals to shiver (81, 83); whether the lack of shivering is due to impairment of sympathetic function, as suggested, or whether some other action of the drugs is responsible remains to be established.

b. Cold-acclimated animals. In contrast to warm-acclimated rats, cold-acclimated rats do not shiver when exposed to cold but increase their heat production by another means, usually referred to as *nonshivering thermogenesis.* During the acclimation the extent of shivering during cold-exposure gradually decreases over a period of about 3 weeks, and the contribution of the nonshivering process gradually increases. Two types of evidence support this. One comes from experiments in which shivering has been measured directly by recording the electrical activity of the muscles (326, 357, 653), the other from experiments in which shivering has been prevented by tubocurarine (160, 182, 379). The nonshivering thermogenesis in the cold acclimated rat is believed to be due to an action of noradrenaline liberated from the nerves of the sympathetic nervous system. The evidence for this has been reviewed (see 133, 134, 183, 308, 457) and will only be summarized here: (i) the effect of cold-exposure to increase oxygen uptake can be mimicked by the administration of noradrenaline (184, 378); (ii) the increase in the capacity for nonshivering thermogenesis during the first few weeks in the cold is paralleled by an increase in the capacity to respond to noradrenaline by an increase in metabolic rate (184); (iii) nonshivering thermogenesis is inhibited by inactivation of the sympathetic nervous system with hexamethonium or piperoxane in cold-acclimated curarized rats exposed to cold (379) and is inhibited by propranolol in cold-acclimated rats exposed to cold (640); (iv) the involvement primarily of noradrenaline liberated from sympathetic nerves rather than adrenaline liberated from the adrenal medulla is suggested by the lack of effect of adrenodemedullation on nonshivering thermo-

genesis (160) and by the ability of noradrenaline but not adrenaline to increase oxygen uptake and maintain body temperature in cold-exposed, curarized rats treated with hexamethonium (379). The metabolic effects of infused noradrenaline do not mimic exactly the metabolic effect of cold-exposure (315), but it would not be reasonable to expect that they should, since noradrenaline administered *via* the blood stream would reach tissues not involved in the sympathetic response and infusion of noradrenaline causes hyperthermia in the cold-acclimated rat at room temperature (315) but not when the rat is exposed to cold.

Nonshivering thermogenesis then appears to be a particular manifestation of the calorigenic effect of noradrenaline. Since the magnitude of this effect of noradrenaline is age-dependent (see section II D), the capacity for nonshivering thermogenesis should also be age-dependent as well as cold-dependent. Unfortunately, the rats used in studies in cold acclimation have been usually old (300 g or more), mainly because of the time needed for acclimation and of the convenience of working with larger animals. However, the re-appearance of a response to noradrenaline that was already possessed by these animals in their youth suggests that cold-acclimation simply reactivates some dormant process. Since species other than the rat show a similar decline in calorigenic response to noradrenaline during early life (section II D), the question arises whether the supposedly dormant process might be activated in the other species if they were to be put into the cold at a growth phase corresponding to that at which the rat is put in the cold, *i.e.*, while they are still growing. A failure to carry out the cold exposure at the appropriate growth phase might explain the usual failure to demonstrate appreciable nonshivering thermogenesis in species other than the rat. The finding of a prolongation of the nonshivering thermogenesis of the newborn guinea pig by rearing the guinea pigs at low temperatures (91) supports this suggestion.

The primary process of nonshivering thermogenesis has been the subject of much study in the last 10 years (see 513, 676, 803–806). Three distinct experimental approaches have been used. The first is the search for differences in concentrations of substrates, cofactors, or enzymes, or differences in metabolism *in vitro* between tissues of warm-acclimated rats and cold-acclimated rats (see 671, 672, 676). This approach is based on the assumption that the difference in metabolic response to cold or to noradrenaline must be reflected in a difference in composition or in metabolism *in vitro*. However, reflection on the nature of the nonshivering process suggests that this approach is unlikely to yield useful results. Although it may be of use in establishing changes in the capacity of the various tissues for certain metabolic processes, it could hardly elucidate the nature of the nonshivering process, since this process obviously should not operate *in vitro* in an isolated system removed from the source of stimulation, just as it does not operate *in vivo* except when stimulated. Whatever the nature of the system or systems switched on or off in the cold-acclimated animal in response to changes in external temperature, it is most likely that this system would be switched off in the isolated system.

The second approach is measurement of heat production by various organs

in the cold-acclimated rat exposed to cold, or the measurement of heat production by cold-acclimated rats subjected to removal of various organs. The main conclusion derived from this approach is that all major organs participate in the increased oxygen uptake (see 182, 183, 399, 400).

The third approach is the study, by means of the administration of radioactive compounds, of the metabolic processes occurring in the intact animals in the cold. This approach is based on the assumption that the primary process of nonshivering thermogenesis is a metabolic one, accessible to such biochemical measurements. While this approach certainly yields more meaningful information about metabolic processes than can be obtained by merely measuring changes in the concentrations of substrates in the blood, the only conclusion possible from the results of these studies is that these metabolic processes are very similar in cold-acclimated rats exposed to cold and in warm-acclimated rats exposed to cold. This type of investigation has shown that there is a marked increase in the turnover and oxidation of plasma FFA (512), which is accompanied by a small decrease in the concentration of FFA in the plasma (366, 512) [a report that plasma FFA levels are higher in cold-acclimated rats probably refers to cold-acclimated rats at room temperature (315), a suggestion in keeping with other measurements in such animals (366, 512)]. There is also a marked increase in the turnover of plasma glucose and its oxidation in both fed (185, 188) and fasting (186) cold-acclimated rats exposed to cold. The increases in turnover and oxidation of substrates are very similar in cold-acclimated rats in the cold and in warm-acclimated rats in the cold (185, 188, 512). There is evidence that the triglyceride cycle is not accelerated in most tissues of the warm-acclimated or the cold-acclimated rat in the cold (liver, muscle, white adipose tissue, heart) (366, see 513). This is in agreement with the finding that most (about 60%) of the FFA turning over under these conditions are oxidized rather than re-esterified (512). It should be emphasized that there is no direct relationship between the concentration of FFA in plasma and the increase in oxygen uptake during infusion of noradrenaline into cold-acclimated rats (380). The operation of a glucose-glycerol cycle is greater in cold-acclimated rats in the cold than in warm-acclimated rats in the cold (177), but the amount of oxygen uptake that can be attributed to this cycle is only a minute part of the total.

The brown adipose tissue differs from other tissues of the cold-acclimated rat in that the rate of operation of the triglyceride cycle in it is increased relative to the increase in rate in warm-acclimated rats exposed to cold (366). In newborn animals and hibernators the brown adipose tissue is believed to play a prominent role in heat production during exposure to cold or during arousal from hibernation (section IV E, 3 and 4) and a similar role has been proposed for the brown adipose tissue of the cold-acclimated rat. Heat production in brown adipose tissue of the cold-acclimated rat increases during exposure of the rat to cold (674). Moreover, the brown adipose tissue shows marked changes during the development of acclimation; initially there is edema (366, 654), which is followed by an increase in total mass (an increase in lipid content,

protein content and water content) (366, 567, 677) associated with a hyperplasia (109). An increase in the activity of nonphosphorylating pathways of electron transport in mitochondria of brown adipose tissue of cold-acclimated rats is in keeping with this proposal; but the mechanism by which the activity of these pathways is regulated has not been considered (678). The report of greater oxygen uptake *in vitro* by slices of brown adipose tissue from cold-acclimated rats than in that from warm-acclimated rats has also been taken to support this hypothesis (601a, 677), but attempts to confirm this report have not been successful (405), and it is apparent that there are technical difficulties in measuring the exceedingly high oxygen uptake of brown adipose tissue *in vitro* (405). Noradrenaline does have a marked calorigenic effect on brown adipose tissue *in vitro* (405, 406). The particular anatomical location of the brown adipose tissue (particularly the interscapular tissue) and of its venous effluent has led to the suggestion (109, 677) that heat production by the brown adipose tissue is of special importance in maintaining the temperature of the spinal cord and heart of the cold-exposed rat. There are, however, two reasons why the brown adipose tissue cannot be a major site of nonshivering thermogenesis in cold-acclimated rats. First, it is small, of the order or 1% of body weight. If the value from studies *in vitro* of an average oxygen uptake by brown adipose tissue in presence of noradrenaline of 0.07 to 0.23 ml of oxygen per g per minute (405, 677) is taken, then the 4 g of this tissue in a cold-acclimated rat might be expected to consume 0.3 to 0.9 ml of oxygen per minute. Even if this value is underestimated several-fold it is still very small compared with the 18 ml per minute an intact rat would use. Second, the increase in heat production during cold-exposure is nonspecific. It occurs in both cold-acclimated (674) and warm-acclimated (195) rats. Thus, although the brown adipose tissue may well play a special role in nonshivering thermogenesis in both warm-acclimated and cold-acclimated rats by virtue of its anatomical position, it is not likely to be appreciably involved in nonshivering thermogenesis in the cold-acclimated rat.

The primary difference in the response of the warm-acclimated rat (mainly shivering thermogenesis) and the cold-acclimated rat (nonshivering thermogenesis) in the cold does not, therefore, reside in the degree of substrate mobilization, in the nature of the substrates mobilized, or in the pathways by which these substances are utilized. This is perhaps not surprising since the cold-induced increases in metabolic rate are very similar in cold-acclimated and in warm-acclimated rats (326) and must represent similar increases in the oxidation of substrates in response to an increased demand. Just as it would be impossible by any of the experimental approaches outlined above to pinpoint shivering (which has been recognized because it is so visible) as the mechanism by which warm-acclimated animals increase their heat production in the cold, so it would seem improbable that the mechanism of heat production in nonshivering thermogenesis could be established by this type of approach either. The primary difference in the responses of warm-acclimated and cold-acclimated rats exposed to cold must be the way in which the signal for increased oxidation of substrates is expressed. In the warm-acclimated rat the signal is undoubtedly a rise in

ADP production in the shivering muscles as a result of the utilization of ATP for the contractile process. The nature of the signal in the cold-acclimated animals is unknown. If the mechanism proposed for the calorigenic action of catecholamines (section II D) is extended to nonshivering thermogenesis, then it might be postulated that the mitochondria of various tissues of the cold-acclimated animals differ from those of warm-acclimated animals in responding to noradrenaline by an increase in force or rate of contraction; nonshivering thermogenesis then could be regarded as a shift of the shivering process from the whole muscle cells entirely to the mitochondria that frees the contractile fibers of the muscle for their normal function.

The sympathetic nervous system not only operates the switching on and off of nonshivering thermogenesis in the cold-acclimated rat but also participates in the development by the rat living in the cold of the capacity for nonshivering thermogenesis. The principal evidence for this is that frequent administration of noradrenaline (daily subcutaneous injection in oil) for several weeks causes the development of an increased capacity of rats to respond to injected noradrenaline by an increase in oxygen uptake and in a prolongation of the survival time of rats exposed to a temperature of −20°C (454); both of these changes are characteristic of cold-acclimated rats. Most blocking agents are of little use in the study of the role of the sympathetic nervous system in the development of cold-acclimation since they cause the death of the animals during the initial cold-exposure (section IV D 1). The finding that treatment of rats with guanethidine over a long time (intraperitoneal injection every third day for 6 weeks) increases their metabolic responses to noradrenaline while not altering their ability to survive in the cold has been interpreted as indicating that an increased metabolic response to noradrenaline is not sufficient to explain cold-acclimation (356). However, the repeated administration of guanethidine may be like the repeated administration of noradrenaline in that it causes repeated liberation of noradrenaline from nerve endings; an increased metabolic response to noradrenaline would then be expected, as with repeated administration of noradrenaline itself. However, since the sympathetic nervous system would not be functioning normally in the guanethidine-treated rat, it is not surprising that the response to cold is impaired by this treatment. Out of keeping with this proposal is the finding that repeated treatment of rats with guanethidine during acclimation to cold slightly increases their subsequent ability to survive extreme cold (584). The response of these rats to injected noradrenaline is unknown; the possibility that their response to noradrenaline would be greater than that of the cold-acclimated control rats and that the adrenal medulla would furnish enough noradrenaline to maintain body temperature cannot be excluded. Also out of keeping with this hypothesis is the observation that immunosympathectomized and adrenodemedullated rats can become cold-acclimated (639) but since these animals do possess some functioning sympathetic nervous tissue and do increase their urinary excretion of noradrenaline in the cold to the same extent as normal rats, a role of secreted noradrenaline in the production of cold-acclimation cannot be excluded.

The hyperplasia of the brown adipose tissue during cold-acclimation (109) may also be brought about by the sympathetic nervous system. A similar increase in size is observed in a number of other conditions [hyperthyroid rats (445, 446); cortisone-treated rats (445); ACTH-treated rats (445); exercise-stressed rats (654); altitude-adapted rats (63); rats with cut spinal cords (654)] all of which are associated with enhanced sympathetic activity. A precedent for an effect of the sympathetic nervous activity on growth of a tissue is provided by the salivary gland hypertrophy and hyperplasia caused by catecholamines (21, 141, 655). However, no increase in salivary gland size is apparent in cold-acclimated rats (367).

c. Newborn animals. Newborn mammals resemble cold-acclimated rats in that they can exhibit nonshivering thermogenesis. Exposure of a newborn mammal to a temperature lower than that to which it is accustomed (this may be as low as 20° or as high as 30°C) leads to an increase in oxygen uptake [rabbits (171, 173, 384, 648); guinea pigs (88–91, 171); kittens (384, 527, 648); rats (728); man (175)] which is not accompanied by shivering [guinea pigs (88–91); rats (728)] and which occurs in paralyzed animals (171). Several lines of evidence indicate that the sympathetic nervous system participates in this calorigenic response to cold. The large calorigenic effect of noradrenaline in newborn animals [rabbits (61, 173, 383, 388, 525, 527, 648); guinea pigs (90, 171); kittens (525, 527, 648); rats (527); man (415, 416)] and the increased excretion of noradrenaline during exposure of newborn babies to cold (634) indicate that the mediator, noradrenaline, does have the required effect and is secreted in response to cold. Procedures that inactivate the sympathetic have been useful in determining the role of the sympathetic in this response. Immunosympathectomy prevents the calorigenic response to cold-exposure in newborn rats and causes hypothermia (768). These rats cannot shiver, an ability which develops only at about 3 weeks of age, their adrenal medulla is still immature and does not function at this age (see 151), and they have no alternative calorigenic mechanism to the nonshivering thermogenesis mediated by the sympathetic nerve endings. Ganglionic blockade inhibits the calorigenic response to cold in newborn kittens (525–527, 648), rats (768) and sometimes also in guinea pigs (89). The variability of inhibition in guinea pigs is due to the replacement of nonshivering thermogenesis by shivering thermogenesis in some animals and the apparent inhibition of shivering by hexamethonium in the others (89). Propranolol inhibits the calorigenic response to cold-exposure in newborn rabbits (350), and pronethalol inhibits the increase in nonshivering thermogenesis caused by cold-exposure of newborn guinea pigs and usually induces shivering thermogenesis (89). The total increase in oxygen uptake may, therefore, be rather similar in the presence and absence of pronethalol when the animal is able to use shivering thermogenesis as an alternative mechanism of heat production. The contribution of nonshivering thermogenesis, as estimated by the effect of pronethalol and the production of shivering, decreases rapidly with age in guinea pigs from 90% at 1 to 2 days to 26% at 3 weeks (89). This decrease is paralleled by a decrease in the calorigenic response to injected noradrenaline (90). The finding that

pronethalol does not inhibit the calorigenic response to cold-exposure of newborn rabbits, although it does inhibit the calorigenic response to injected noradrenaline (173, 383), is probably explained by a switch from nonshivering thermogenesis (inhibited by pronethalol) to shivering thermogenesis.

Brown adipose tissue, which may comprise up to 5% of the body weight at birth, is usually considered to be a major site of nonshivering thermogenesis in the newborn (174). Three lines of evidence implicate it in this response. (i) This tissue is the warmest region in the newborn rabbit (173) and guinea pig (90) during cold-exposure. Stimulation of the sympathetic nerves to the brown adipose tissue also increases its temperature (387), and pronethalol prevents the maintenance of the temperature of the brown adipose tissue above that of the other tissues during cold-exposure (90). (ii) Removal of the brown adipose tissue abolishes the calorigenic response of the newborn rabbit to cold-exposure (386), depletion of the lipid content of the brown adipose tissue by fasting prevents the calorigenic response to cold-exposure (388), and babies that died in hypothermia have lipid-depleted brown adipose tissues (385). (iii) Injected noradrenaline can bring about the same changes in brown adipose tissue as those caused by cold-exposure. Infusion of noradrenaline into a newborn rabbit causes a marked rise in the temperature of the brown adipose tissue and a lesser rise in other tissues (173) and also increases the blood flow (349, 350) and oxygen consumption (349, 350) of this tissue. Removal of the brown adipose tissue (386) or depletion of the brown adipose tissue lipid by fasting (388) abolishes the calorigenic response of the newborn rabbit to noradrenaline. Pronethalol inhibits the effect of noradrenaline to increase the temperature of the brown adipose tissue (173), and propranolol inhibits the effect of noradrenaline to increase the oxygen uptake and blood flow of the brown adipose tissue (350). Calculations based on the measured oxygen uptake of brown adipose tissue during infusion of noradrenaline into newborn rabbits and the observed increase in total oxygen uptake of the whole animal show that up to three quarters of the increase in oxygen uptake during infusion of noradrenaline occurs in the brown adipose tissue itself (349, 350); probably the same is true of the cold-exposed rabbit. In the newborn rabbit at room temperature, the brown adipose tissue consumes about 17% of the total oxygen uptake but during infusion of noradrenaline this proportion increases to 52%. It is worth noting that the oxygen uptake by brown adipose tissue stimulated by noradrenaline in the intact newborn rabbit (349) is about three times greater than the maximum possible rate which can be calculated from measurements *in vitro* (173, 405); this shows the fallacy of the extrapolation of results of studies of this type *in vitro* to what might happen *in vivo*, an extrapolation often made because of lack of appropriate information from studies with intact animals.

From the evidence cited above there can be little doubt that brown adipose tissue has an important role in the increase in metabolic rate during exposure to cold of newborn animals, and it has become widely accepted that the increased heat production on exposure to cold occurs there (90, 173, 386–388). However, clearly a portion of the increase in oxygen uptake occurs in other

tissues. Which tissues are involved and what substrate supports this increase in metabolic rate is unknown. The finding of no increase in plasma FFA concentration in the newborn rabbit during exposure to cold (173) has been taken to indicate that the FFA produced and re-esterified within the brown adipose tissue are retained there for oxidation, but, in the absence of information about the turnover of plasma FFA, this conclusion is not justified, and the brown adipose tissue may well supply substrate to other tissues in the newborn rabbit. No information is available about the turnover of plasma glucose nor about the possible significance of liver lipid stores at birth (468) for the provision of substrate for other tissues. The mechanism of the accelerated metabolism in the brown adipose tissue is most probably the accelerated operation of the triglyceride cycle (429), stimulated by noradrenaline and resulting in an increased rate of ATP hydrolysis (173, 308), but in the absence of measurements of the rate of operation of this cycle in this tissue *in vivo* this suggestion cannot be regarded as conclusive.

Newborn chicks differ from mammals in that their nonshivering thermogenesis is neither mediated by the sympathetic nervous system nor attributable to brown adipose tissue metabolism (256).

2. AROUSAL FROM HIBERNATION. Hibernating animals resemble newborn animals in their ability to use nonshivering thermogenesis, in this case for warming up the body during arousal from hibernation, and in their possession of a relatively large mass of brown adipose tissue which appears to be of prime importance in heat production.

The brown adipose tissue is the warmest part of the body during the arousal of marmots (674, 675) and bats (345, 346, 669) and has a markedly increased blood flow under these conditions (97). The venous drainage of the large interscapular brown adipose tissue has led to the suggestion that it is most important in rewarming the nervous system and thoracic region (674). Ball (15) has aptly described this role of the brown adipose tissue as serving "to breathe warmth into the heart, lungs and brain of the awakening animal and so kindle the whole animal into respiratory activity and thermogenesis." Calculations of the contribution of the oxygen uptake of the brown adipose tissue (as estimated from measurements *in vitro*) to the increased oxygen uptake of the intact animal during arousal (15, 344) are not in keeping with its major role in this process suggested by other evidence. This may simply be because estimates *in vitro* are unreliable as an index of the maximum attainable rate *in vivo* (344), a conclusion which is in keeping with the recently observed 3-fold discrepancy between measurements of oxygen consumption by brown adipose tissue of newborn rabbits *in vitro* and the observed rates *in vivo* (section IV E 1). No other thermogenic process is apparent in bats, which can rewarm almost normally even when curarized (345), but they do shiver to some extent normally (345, 482). Shivering appears to play a greater role in the rewarming process in dormice and hamsters (15, 345).

3. HYPERTHYROIDISM. Many manifestations of hyperthyroidism could possibly be attributed to actions of catecholamines, and there has been considerable

interest in the role of the sympathetic nervous system in their production (see 325, 760). However, most sympathetic blocking agents do not alter the elevated metabolic rate in human hyperthyroidism [trimethaphan camphorsulfonate (325); pronethalol (791); propranolol (792); nicotinic acid (207)], although there is one report of a decreased metabolic rate in triiodothyronine treated subjects after ganglionic blockade [hexamethonium (699)]. Guanethidine does reduce the elevated metabolic rate of hyperthyroid patients (458, 761) or of subjects treated with triiodothyronine (267), but it also reduces the tachycardia and tremor associated with the increased metabolic rate, and it is not known to what extent this reduced activity causes the reduction in metabolic rate. That butoxamine decreases the metabolic rate of hyperthyroid rats (148) is probably due to some action other than inhibition of an action of noradrenaline, and it also reduces the basal metabolic rate of normal rats (148). The evidence available indicates that the sympathetic nervous system is not responsible for the elevated basal metabolic rate seen in hyperthyroidism. This does not of course exclude its participation in thyroid "storm."

4. PHAEOCHROMOCYTOMA. An elevated metabolic rate occurs in association with phaeochromocytoma in man (224, 266). This is clearly due to the action of adrenaline or noradrenaline secreted in excess by the tumor because it is inhibited by dibenzyline (224) and disappears after surgical removal of the tumor (224).

V. CONCLUDING REMARKS

The sympathetic nervous system regulates metabolic functions mainly in accordance with changes in the activity of the whole animal. This contrasts with the continual regulation, principally by insulin, of many of the same metabolic functions in accordance with changes in the availability of substrates derived from ingested food. The hormones of the sympathetic nervous system, adrenaline and noradrenaline, have widespread effects upon metabolic processes in the intact animal. These are of two main types: those modifying the supply of oxidizable substrates to tissues and those modifying the metabolic rate of tissues. Some of these actions, particularly of the first type, are exerted to some extent continuously. Tonic stimulation of lipid mobilization (337) by the sympathetic nervous system probably provides a background against which lipid metabolism is further modified by other hormones such as insulin and probably provides a mechanism by which lipid mobilization can be switched to a lower level during periods of almost complete inactivity (*e.g.*, sleep) and to higher levels in response to increased activity (*e.g.*, exercise or shivering) or to stresses of various kinds, which may or may not be followed by increased activity. In contrast, adrenaline is not normally considered to be a glucoregulatory hormone (734), and the sympathetic nervous system does not appear to exert a tonic stimulatory action on glucose mobilization. Only during actual activity or as a reaction to external stress does the sympathetic nervous system effect the mobilization of carbohydrate substrates. Integration of the activity-determined sympathetic regulation and the substrate-determined insulin regulation can

occur. A high concentration of glucose reduces the activity of the sympathetic nervous system and stimulates the secretion of insulin. However, in an emergency the sympathetic nervous system appears to be able to override the regulation by insulin in that it can promote mobilization of glucose and fat and reduce insulin secretion so that substrates are made available for actual or potential energy needs instead of being stored.

In the regulation of metabolic rate the role of the sympathetic nervous system is of prime importance in cold-acclimated animals but its significance in normal animals is poorly understood. The mechanism by which the sympathetic nervous system produces this regulation is not at all understood.

Future work will probably proceed along two main routes. Firstly, the detailed study of the metabolic changes induced by catecholamines and by increased sympathetic nervous activity in the intact animal should help to elucidate the relative participation of processes occurring in different tissues during an overall metabolic change, such as hyperglycemia or increased turnover of plasma FFA, and to elucidate the role of the different components of the sympathetic nervous system in bringing about such changes. Secondly, the study of the chemistry of the reactions of catecholamines with subcellular preparations of a variety of tissues from a variety of species to produce the activation of adenyl cyclase may provide a better understanding of the nature of a receptor and may in turn provide information of use in the study of the physicochemical changes in membrane and protein structure involved in the nonmetabolic as well as the metabolic actions of catecholamines. It is not possible to make the metabolic actions of the catecholamines fit into the α-receptor and β-receptor classification. Indeed, attempts to classify the metabolic actions of the catecholamines in terms of this system may hamper our understanding of the nature of adrenergic receptors.

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