Humoral Thermogenesis and Its Role in Maintaining Energy Balance

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I. INTRODUCTION

Maintaining energy balance and generation of heat have been central interests of physiologists since the time of Lavoisier. In spite of that, the physiological mechanisms by which various neural and humoral substances liberate heat have not been satisfactorily clarified. The thermogenic effect of a humoral substance prepared from the adrenals of the dog was described almost a century ago (251). Even earlier, Claude Bernard (34) reported data that he interpreted to indicate that in cold-exposed animals other sources of heat exist in addition to shivering. In 1923, Boothby and Sandiford (40) summarized the first evidence about thermogenic action of epinephrine, and Cannon et al. (58) concluded that heat production due to hormones forms the first line of defense against cold. Numerous authors described the occurrence of cold thermogenesis after elimination of shivering or after application of mild cold stimuli, which were not capable of inducing muscular tremor. This heat production was denoted as chemical thermoregulation in the strict sense of the word (433) and was supposed to be based on the thermogenic action of epinephrine. In the 1950s, a substantial amount of evidence accumulated about hormonal thermogenesis, and several review papers were published on the subject (see Refs. 20, 118, 154, 290, 291). Interest in the physiology of heat-producing mechanisms participating in thermoregulation was renewed in 1954, when Sellers et al. (397) showed that, in spite of a similar high oxygen consumption in the cold, shivering was less in rats that had been acclimated to cold than in those previously acclimated to higher temperatures. Later, Hsieh and Carlson (205) demonstrated a marked thermogenic effect of norepinephrine in cold-adapted rats and postulated that norepinephrine was the mediator of nonshivering heat production. The term nonshivering thermogenesis was used for the first time in the paper of Cottle and Carlson (79). In 1961, Smith (416) noted that brown adipose tissue may be important for nonshivering thermogenesis. The detailed mode of norepinephrine action in mitochondria of the brown adipose tissue was described by Nicholls (338). Jansky (227) concluded that thermogenic actions of other hormones may also be of thermoregulatory significance. Kuroshima and Doi (268) drew attention to the possible role of glucagon in cold acclimation. Although most studies have been performed on mammals, Barré (21) described nonshivering thermogenesis in birds. Attempts have been also made to clarify the mode of cellular action of norepinephrine in organs other than in the brown adipose tissue, particularly in skeletal muscles (67, 74, 243, 309). Finally, Rothwell and Stock (376) drew attention to diet-induced thermogenesis.
They proposed that diet-induced thermogenesis could be utilized also for maintaining energy balance and preventing obesity in overfed individuals. Thus there are many sites and mechanisms whereby heat production can be mobilized in homeotherm species, including humans. The purpose of this paper is to draw attention to the possible physiological role of the thermogenesis that is not dependent on norepinephrine or brown fat.

II. DEFINITIONS

To avoid confusion, it should be stated that the terms heat production, thermogenesis, energy expenditure, and metabolic rate are used synonymously in this paper.

Humoral thermogenesis is identified as a heat producing mechanism activated due to action of hormones and/or neurotransmitters. It is related to nonshivering thermogenesis but may not always be equivalent to it. Various humoral substances may induce this metabolic response.

Nonshivering thermogenesis is defined as “heat production due to metabolic energy transformation by processes that do not involve contraction of skeletal muscles, i.e., tone, microvibrations tremor (shivering), or tonic or voluntary contractions. Nonshivering thermogenesis increases in response to acute cold exposure. The principal effector organ is the brown adipose tissue, which may adaptively increase its capacity for production in the course of acclimatization and adaptation to cold stress” (see glossary of terms for thermal physiology; Ref. 406). This definition can be expanded by stating that nonshivering thermogenesis is an effector thermoregulatory mechanism based on thermogenic action of neuronally released norepinephrine. The physiological background of nonshivering thermogenesis may not be uniform. Various mechanisms and effectors may be involved.

For the sake of clarity, it is convenient to distinguish between obligatory and facultative (regulatory, adaptive) nonshivering thermogenesis. In both cases, heat is generated as a product of metabolic reactions. However, obligatory thermogenesis refers only to the basal heat production at thermoneutrality, i.e., to the energy required to maintain the integrity of the cell and the steady-state condition of the animal. All tissues contribute to obligatory thermogenesis. Facultative nonshivering thermogenesis, on the other hand, is superimposed on obligatory thermogenesis and occurs when the animal is exposed to cold.

In the past, nonshivering thermogenesis has also been called cold-induced thermogenesis, or chemical thermoregulation. These terms are not accurate for a variety of reasons. For example, cold-induced thermogenesis may also involve shivering, in addition to nonshivering thermogenesis. The term chemical thermoregulation, in addition to heat-producing mechanisms (nonshivering thermogenesis and shivering), also involves afferent, central, and efferent components of thermoregulation and is considered obsolete.

Hormonal thermogenesis, the heat produced in response to various hormones, may not be used to maintain constant body temperature alone; it may also be used to maintain energy balance at thermoneutral conditions and may serve to control body weight.

Other heat-producing mechanisms may be related to humoral thermogenesis. Diet-induced thermogenesis is defined as “nonshivering thermogenesis occurring especially in rodents when transferred from standard food to a highly palatable cafeteria diet, of which the animals consume more but dissipate part of the surplus caloric (energy) intake by enhanced heat production. The brown adipose tissue is considered as the main effector organ of diet-induced thermogenesis” (406). Adaptive diet-induced thermogenesis and facultative diet-induced thermogenesis are terms that are also used. Postprandial (excess) heat production is defined as an “increase in metabolic heat production, relative to the postabsorptive resting level, in the hours following food intake. It comprises, but is not identical to, the specific dynamic effect of food” (note that “while the term postprandial heat production is coming into use, it is recommended to include the specification excess, because the definition means heat production in excess of basal metabolic rate”) (406). The specific dynamic effect of food is specified as a temporary increase in metabolic energy transformation following food intake. The phenomenon is assumed to be related to the catabolism of foodstuff, particularly proteins. This term is becoming obsolete.

The terms obligatory diet-induced thermogenesis or heat increment of feeding are also used for postprandial heat production.

III. NONSHIVERING THERMOGENESIS AND THERMOREGULATION

A. Mammalian Nonshivering Thermogenesis

1. Occurrence and physiological significance

Nonshivering thermogenesis is a heat-generating mechanism that, in addition to shivering, helps to maintain thermal homeostasis in cold-exposed homeotherms. When the environmental temperature falls, the temperature gradient between the body and its environment increases. As a consequence, heat loss from the body increases. In homeotherms, the increased heat loss from the body must be compensated by the increased heat production within the body by shivering and nonshivering means. Thus the physiological role of nonshivering thermogenesis is to prevent hypothermia in cold-exposed homeotherms. Nonshivering thermogenesis should be classified, therefore, as an effector thermoregulatory mechanism. The details about the physiological role of the nonshivering thermogenesis have been extensively reviewed (52, 65, 178, 179, 182, 183, 186, 201, 226). Three books were published on this topics (141, 224, 443).

Nonshivering thermogenesis is based on the thermogenic action of norepinephrine, which was first described in rats (205). It is common to all homeotherms to some
extent. In adult animals, the magnitude of the norepinephrine nonshivering thermogenesis depends on body size, being greatest in small mammals, where it may exceed the basal metabolic rate by almost 800%. Species that weigh more than 10 kg usually do not exhibit much norepinephrine nonshivering thermogenesis (165, 166).

Norepinephrine nonshivering thermogenesis plays the most significant role in newborn mammals, including neonates (226). It has been described in all species studied thus far, except for the pygmy pig, pig, and calf (48, 247, 256, 284, 355). Data of Mount (322), Dauncey and Ingram (86), Kaciuba-Uscilko and Poczopko (256), Kaciuba-Uscilko and Ingram (253), Heath and Ingram (163), and Jamieson et al. (220) indicated the existence of some kind of nonshivering thermogenesis in young pigs, however. In species that are born immature (rats), the amount of nonshivering thermogenesis initially increases after birth, then decreases slowly. In guinea pigs, which are born relatively mature, the amount of nonshivering thermogenesis decreases immediately after birth (16, 226).

In adults, norepinephrine nonshivering thermogenesis is usually negligible, but it may develop again following long-term cold exposure. In individuals adapted to different temperatures, the extent to which nonshivering thermogenesis develops depends on the temperature of adaptation and duration of cold exposure. In rats, there is an inverse relation between the temperature of adaptation and the magnitude of norepinephrine nonshivering thermogenesis: the lower the adaptation temperature, the higher the magnitude of nonshivering thermogenesis (32, 241). Therefore, the magnitude of norepinephrine nonshivering thermogenesis can be used as an indicator of the level of cold adaptation in rats. At all temperatures it takes ~3–4 wk of continuous cold exposure to induce an adequate amount of nonshivering thermogenesis. After transferring cold-adapted animals back to a thermoneutral environment, the nonshivering thermogenesis slowly disappears.

The intensity of the cold stimulus plays an important role in inducing cold adaptation and the quantity of nonshivering thermogenesis. There are species differences, and in general, smaller species (e.g., mice), because of their greater surface area-to-volume ratio, need milder cold stimulus to induce maximum nonshivering thermogenesis (308). In contrast, larger species are less sensitive to low temperatures of adaptation. Indeed, furred species (rabbit) may preferentially adapt to cold by improving body surface insulation (fur) and expanding the thermoneutral zone. Consequently, mild cold exposures may not be sufficient to induce nonshivering thermogenesis (263) in furred animals.

Intermittent cold exposures also lead to the development of nonshivering thermogenesis but to a smaller extent (167, 173, 281, 462). Nonspecific stressors, such as physical training (188, 282, 319), immobilization stress (274, 345), short photoperiod (168, 169), abnormal food intake (377), or repeated injections of norepinephrine (207, 285, 325) may also induce a certain amount of nonshivering thermogenesis.

2. Methods for estimating the magnitude of nonshivering thermogenesis

Estimation of the magnitude of nonshivering thermogenesis is difficult, since there is no method available to measure it directly and quantitatively (226, 229). In general, cold thermogenesis that is not accompanied by an increase in muscle electrical activity due to shivering can be denoted as nonshivering thermogenesis. Therefore, nonshivering thermogenesis can be estimated by simultaneous measurement of total oxygen consumption and of muscle electrical activity in cold-exposed individuals. The magnitude of nonshivering thermogenesis is then given by the highest level of oxygen consumption in the cold that is not accompanied by shivering. The main difficulty of this method is that the transition from nonshivering thermogenesis to shivering is not clearly defined. Consequently, the amount of nonshivering thermogenesis estimated by this method may not be maximal.

Comparable results can be obtained by using sympathetic blocking agents and curare and measuring subsequent decrease in total metabolism in animals previously exposed to a mild cold stimulus (206). The disadvantage of this method is that it induces hypothermia, and thus it can hardly be used for quantitative studies.

Thermogenin (uncoupling protein in the inner mitochondrial membrane) content in the brown adipose tissue was used as an indicator of the brown adipose tissue activity and, hence, the intensity of nonshivering thermogenesis. In rats (95, 426), the relative concentration of thermogenin reaches a peak after ~3 wk, and after ~10 wk in the cold, it has almost returned to initial values. Thus, at first sight, it does not seem reasonable to use the relative thermogenin concentration (per milligram of mitochondrial protein) as a measure of recruitment. However, the mitochondrial content of brown adipose tissue continues to increase even after 3 wk in the cold (426, 437), and the total amount of thermogenin in a rat is actually constant after full acclimation is achieved (i.e., after 3 wk). This indicator, however, does not include the proportion of nonshivering thermogenesis located in organs other than brown fat, nor does it give information about the capacity of the total nonshivering thermogenesis.

The most suitable method for measuring the magnitude of nonshivering thermogenesis depends on the close association between nonshivering thermogenesis and the thermogenic action of norepinephrine. Thus the magnitude of nonshivering thermogenesis can be measured as the metabolic increase after intravenous infusions of different concentrations of norepinephrine under thermoneutral conditions. A dose response curve can be obtained, and the highest value of the metabolic rate induced by norepinephrine indicates the capacity of nonshivering thermogenesis (306). The concentration of norepinephrine needed to induce maximal nonshivering thermogenesis seems to increase with decreasing body weight (165, 166).

Intramuscular, intraperitoneal, or subcutaneous injections of norepinephrine may also induce nonshivering thermogenesis. However, the responses are only transient and may not correspond to maximal values.
Using microspheres, Foster and Frydman (129) have shown that the brown adipose tissue is a dominant site of norepinephrine thermogenesis in rats, contributing ~60% of the total heat production. Measurements of total cytochrome oxidase activity revealed that in adult rats this organ could not account for the whole metabolic increase during nonshivering thermogenesis (245). Bourhim et al. (42) also concluded that the oxidative capacity of the brown fat in gerbils cannot account for the whole nonshivering thermogenesis. In other species, the brown fat contributes even less to the total metabolic increase in the cold (~40% in mice) (228, 358). Rafael et al. (362) suggested that in Eungarian hamsters brown fat may contribute ~20% to the whole body nonshivering thermogenesis in warm adapted animals and 45% in cold-adapted animals, while Puchalski et al. (359) calculated that 28 and 61% of total nonshivering thermogenesis were due to the brown adipose tissue of 23°C acclimated or outdoor-acclimated hamsters, respectively.

The significance of the brown adipose tissue thermogenesis for the cold-induced thermogenesis differed in species adapted to different environmental temperatures (228). Furthermore, it was shown clearly that the brown adipose tissue is of minimal size, or even absent, in larger species, although they may increase their metabolic rate due to action of catecholamines. The physiological role of brown adipose tissue has been reviewed several times (see Refs. 184, 185, 381). In conclusion, we can say that brown adipose tissue is an important, but not the only, organ participating in nonshivering thermogenesis. The role of some other organs must also be considered.

The role of skeletal muscles in nonshivering thermogenesis has been studied thoroughly. Many years ago, Mansfeld and Lukács (301), Freund and co-workers (134, 135), and Isserkszt (214) observed in dogs and cats that denervated muscles could increase their metabolic rate after exposure of animals to cold. Furthermore, oxygen consumption of leg muscles was more than doubled during infusion of norepinephrine or during exposure to cold as did the total metabolism of the curarized rat (243, 225). Similar data were obtained on muscles of dogs (80, 112, 142, 369, 390) and rats (77, 156, 157, 265, 266, 307, 309–311, 404, 439, 465, 466). Nonshivering thermogenesis of muscular origin has been demonstrated also in cold-acclimated white mice (415) and in fur seal pups (147). Some authors, however, were not able to demonstrate the thermogenic effect of norepinephrine in muscles (51, 63, 72, 460). It should be kept in mind, however, that infusions of norepinephrine may not mimic nonshivering thermogenesis precisely. Very high plasma concentrations may be achieved during infusions, which may stimulate oxygen consumption in organs that do not normally exhibit nonshivering thermogenesis.

Nevertheless, the balance of evidence suggests that skeletal muscles participate in nonshivering thermogenesis, although their relative contribution has not been specified exactly. An indirect method based on measurements of the cytochrome oxidase activity and blood flow values indicated that ~50% of nonshivering thermogenesis could be produced in muscles of cold-acclimated rats (222, 225,
244), while Foster and Frydman (129) found a 30% increase in muscle blood flow and a 60% increase in oxygen consumption after norepinephrine administration in warm-adapted rats. Chinet and Mejsnar (68) concluded that skeletal muscles could contribute to 25% of the regulatory nonshivering thermogenesis by increasing oxygen availability to cells.

4. Cellular mechanisms of norepinephrine nonshivering thermogenesis

Norepinephrine is thought to be the primary physiological activator of nonshivering thermogenesis due to its interaction with both \( \beta \) and \( \alpha \)-receptors. Stimulation of \( \beta \)-receptors and the resulting activation of the adenylate cyclase-adenosine 3',5'-cyclic monophosphate (cAMP) system then stimulation of lipolysis and enhancement of substrate oxidation in the brown fat is the primary thermogenic pathway.

The thermogenic response to norepinephrine in the brown fat cell is mediated mostly by \( \beta \)-adrenergic receptors (314). The \( \beta_1 \) and \( \beta_2 \)-adrenergic receptors are particularly involved in the thermogenic response (8). There are indications that the \( \alpha \)-adrenergically mediated processes in the brown adipose tissue also exist (125), and pharmacological studies (315) have shown that \( \alpha \)-adrenergic processes contribute \( \sim 20\% \) of the total heat production.

Enormous effort has been made to study and clarify the mode of action of norepinephrine in the brown adipose tissue, and many of the details of cellular mechanisms have been reviewed (53–57, 178–180, 186, 187, 208, 288, 329–334, 339, 340, 417).

There are two mechanisms that may be responsible for the high metabolic rate in the brown adipose tissue, one involving uncoupling of oxidative phosphorylation and the other involving increased utilization of ATP.

Originally, Horwitz (200) and Horwitz and Eaton (202) proposed that increased activity of Na\(^+\)-K\(^+\)-adenosinetriphosphatase (ATPase) contributed to brown adipose tissue thermogenesis in cold-adapted animals. Later, Nicholls (337) suggested that brown adipose tissue mitochondrial membranes possess a proton conductance pathway that allows protons to “leak” back across the inner mitochondrial membranes without obligatory synthesis of ATP. Under these conditions, due to action of fatty acids and acyl CoA, oxygen consumption is effectively uncoupled from oxidative phosphorylation, with a resultant increase in heat production. This pathway can be inhibited by purine nucleotides, which bind to a protein of molecular mass 32 kDa, called “thermogenin” or “uncoupling protein” (see reviews mentioned above). Several groups have reported that the activity of the proton conductance pathway is elevated in cold-adapted animals (94, 338, 426). The uncoupled oxidation due to thermogenin results fully from the stimulation of the \( \beta \)-adrenergic receptors.

The relative importance of the proton conductance pathway and the Na\(^+\)-K\(^+\)-ATPase to in vivo metabolic rates is unknown. The contribution of the ATPase mechanism is likely to be small. Indeed, it might be considered that these two mechanisms are mutually exclusive, since one involves reduced production of ATP and the other increased utilization. However, it is possible that both mechanisms could act simultaneously because even in active brown adipose tissue, mitochondrial respiration may still be partially coupled so that some ATP is synthesized and ATP could also be derived from other substrates.

Electrophysiological studies on brown fat slices show that addition of norepinephrine leads to a plasma membrane depolarization (125, 140). This phenomenon, which is mediated by the \( \alpha \)-adrenergic pathways, does not produce a measured metabolic effect, however (928).

Several mechanisms have been suggested to explain cellular processes regulating nonshivering thermogenesis in muscles.

Many data indicate that the metabolic rate of skeletal muscles increases with an increase in perfusion pressure or blood flow. This relationship has been reported for rat gracilis muscle (109), dog hindlimb with (72) or without (353) norepinephrine infusion, isolated autoperfused preparations of the cat soleus and gracilis muscles (459), resting and isolated gracilis muscles of rats (264), and hindlimbs of lemmings (158) and rats (100, 156, 310, 311, 405). While this relationship appears to exist in all rat muscle preparations without exception, it is not always apparent in dogs (61, 111, 112, 190).

The dependence of muscle oxygen consumption on blood flow has been interpreted as a physiological limitation of oxygen consumption by oxygen transport, owing to the inhomogeneity of capillary functions (289), uneven distribution of oxygen within the organ, and heterogeneity of oxygen delivery to cells (67, 68, 100, 405). Granger and Shepherd (146) suggested that diffusion parameters (e.g., capillary surface area and mean capillary-to-cell diffusion distance) could limit the organ metabolic rate.

Coulson (80) complemented this view by stating that the relationship between the rate of blood flow and the rate of chemical reaction seems to be a function of the amount of substrate available for diffusion in a given time. The greater is the blood flow, the greater the number of molecules passing the region of the enzymes and the greater the likelihood of reactions. In his recent paper, Mejsnar (304) suggested that the increased oxygen consumption due to increased perfusion rate is a consequence of the effects of the perfusion rate on all the reactions of oxidative phosphorylation.

Data showing that the metabolic rate of muscles can be stimulated by norepinephrine even under constant blood flow (243) indicate a direct thermogenic effect of norepinephrine in skeletal muscles and are not consistent with the above theories. Furthermore, Mejsnar and Pacha (311) have shown that both the direct effect of norepinephrine on thermogenesis in skeletal muscles and the indirect effect mediated by changes in blood flow take place in isolated hindlimbs of cold-adapted rats. Evidently, the metabolic rate was not limited by oxygen supply under these conditions. Koláf and Jansky (265) concluded that the metabolic rate of muscles after norepinephrine depended on rates of oxygen delivery (product of blood flow and arterial oxygen content) rather than on the blood flow.
Experiments with isolated perfused muscle preparations may help to explain the above findings and the apparently contradicting observations that isolated muscles when incubated or perfused in vitro with norepinephrine failed to respond with an increase in oxygen uptake or heat production (100, 177). In recent works using the constant-flow perfused rat hindlimb (75, 76), evidence was obtained (70, 465, 466) that the oxygen uptake and metabolism of resting muscle is controlled by vasomodulators. Hormones, nerves, and drugs that cause vasoconstriction in the perfused rat hindlimb were found to fall into two categories: those that stimulated oxygen uptake [type A: norepinephrine, epinephrine, phenylephrine, methoxamine, amidephrine, norephedrine, angiotensin, vasopressin, capsaicin, gingerols, shogaols, and low-frequency sympathetic nerve stimulation (0.5-4 Hz)] and those that inhibited oxygen uptake [type B: serotonin, norepinephrine at high doses, high-frequency sympathetic nerve stimulation (6-20 Hz), high-dose capsaicin, gingerol, and shogaol]. Vasoconstriction by type A constrictors was associated with increased lactate (177), glycercol (70), urate (71), and uracil (1971) efflux from the muscle, together with an increased perfusate distribution volume (70). Vasoconstriction in the hindlimb required external calcium and oxygen, and in the absence of either moiety or with respiratory poisons present, the pressor effect of type A vasoconstrictors did not occur (98). In addition, vasodilators with differing modes of action blocked the type A vasoconstrictors, inhibiting the increases in perfusion pressure and oxygen uptake as well as the metabolic changes (70). Furthermore, the effect of type A vasoconstrictors to increase oxygen uptake was additional to the increased oxygen uptake due to skeletal muscle contraction. Nitrovasodilators reduced the vasoconstriction but had no effect on the oxygen uptake (70). In all respects, the metabolic effects of the type B vasoconstrictors were the opposite of type A. Type B vasoconstrictors are, therefore, potentially negatively thermogenic and are proposed to result in functional vascular shunting with reduced nutritive flow even though overall flow through the hindlimb remained unaltered (98). The sites or vessels responsible for vascular shunting are distinguishable in terms of their fuel and oxygen uptake and metabolism.

Skeletal muscles may also produce heat by nonshivering means in poikilotherms. In billfish (marlin, swordfish), ocular muscles are transformed into specialized heater tissue. In muscles associated with thermogenesis, contractile myofilaments are absent, and the cells have densely packed mitochondria, an extensive sarcoplasmic reticulum, and some transverse tubules. The sarcoplasmic reticulum membranes are rich in Ca"^2+ -ATPase, and the inner membranes of the mitochondria area are a source of ATP. Heater organ mitochondria are tightly coupled. However, calcium continuously leaks across the sarcoplasmic reticulum membrane in ocular muscles, inducing higher rates of ATP hydrolysis. Mitochondrial respiration is then stimulated by cytosolic ADP generated by the Ca"^2+ -ATPase, the result being an increased heat production. An alternative explanation might be that the heat is generated as a result of calcium ions short-circuiting the mitochondrial proton gradient (38).

Thus it can be seen that there is no consensus about the means whereby norepinephrine increases thermogenesis in muscles.

It should be kept in mind that the role of norepinephrine in nonshivering thermogenesis is very complex. Norepinephrine not only activates the heat production in body organs of cold-exposed animals, but it also stimulates the growth of the brown adipose tissue, changes the blood distribution within the body, and influences neural activity of thermoregulatory control centers (187). It is of interest that at various adaptational temperatures different mechanisms regulating the protein synthesis and the growth of the brown adipose tissue take place. Mild cold stimuli induce hypertrophy of adipocytes and activation of oxidative enzymes, while more intensive cold stimuli induce proliferation of adipocytes and the "de novo" synthesis of oxidative enzymes (259).

One aspect should be particularly emphasized. Cold exposure also induces profound changes in the humoral status of the organism. Kuroshima et al. (280) studied the
effect of norepinephrine on plasma hormones in cold-acclimated rats. They found that plasma glucagon, corticosterone, and deoxycorticosterone levels increased significantly. Evidently, the hypothalamo-pituitary-adrenal stress axis is strongly activated to ensure the supply of substrates for heat generation.

5. Central regulation of nonshivering thermogenesis and its modulation by humoral substances

Cold-induced nonshivering thermogenesis is mediated primarily by the sympathetic nervous system. Immediately upon cold exposure, the activity of sympathetic nerves that innervate brown adipose tissue and vascular smooth muscles is increased (197, 210, 217, 312, 354, 387, 444), due to increased input from the thermosensitive elements in the skin and in the preoptic region of the hypothalamus (46, 47, 137), with the result being increased neural signaling and release of norepinephrine (41) to nonshivering effectors. Epinephrine is also released from the adrenals and is capable of interacting with adrenergic receptors on the membranes of target tissues.

Brick (46) presented evidence that the threshold temperatures at which nonshivering thermogenesis is activated in cold-adapted guinea pigs are shifted to lower body temperatures. This downward shift of the thermoregulatory threshold may be due to increased levels of norepinephrine in the peripheral blood (469). Zeisberger and Roth (471) and Roth et al. (371) suggested, however, that the activity of the noradrenergic pathways in the brain stem, and hence the concentration of the endogenous transmitter at postsynaptic sites in the hypothalamus, is higher in warm-adapted than in cold-adapted or newborn animals. Because in the peripheral circulation the concentration of norepinephrine is much higher in cold-adapted animals, this can be taken to mean that the extensive stimulation of the peripheral sympathetic nervous system inhibits, by feedback signals arriving at the brain stem, the thermointegrative area in the hypothalamus. This may lower the thermoregulatory threshold for shivering. This demonstrates that peripheral catecholamines levels may influence central structures controlling regulatory set point. On the other hand, stimulation of central adrenergic pathways projecting to the hypothalamus raises the shivering threshold (470).

There are numerous other substances in addition to catecholamines that can modulate the central nervous control of thermogenesis. In the hypothalamus, the activity of neural components involved in body temperature control can be modulated significantly by intrahypothalamic or intracerebroventricular administration of peptidergic substances. Neuropeptides are present in considerable quantities in the preoptic area of the anterior hypothalamus, strengthening the view that neuropeptides may be involved in controlling thermogenesis.

Some neuropeptides, mostly those of opioid character (β-endorphin, enkephalins), when applied centrally, tend to increase body temperature (230). Cytokines [tumor necrosis factor, interleukin (IL)-1, IL-6, IL-8, and interferon] and prostaglandins also increase body temperature (373). Their action may be associated with the increased activity of the brown fat (374). On the other hand, nonopiod peptides [adrenocorticotropic hormone (ACTH), α-melanocyte stimulating hormone, arginine vasopressin, somatostatin, cholecystokinin, calcitonin, and bombesin] usually induce hypothermia (230). Some peptides, namely neurotensin, thyrotropin-releasing hormone, and Met-enkephalin, may elicit both hyper- and hypothermic effects, depending both on experimental conditions and on the species used. All effects of neuropeptides are mediated through the preoptic area of the anterior hypothalamus.

The data strongly suggest that neuropeptides specifically influence activity of centers controlling body temperature and thus may act as neuromodulators under physiological conditions and during fever (230). There is evidence for the increased production of some neuropeptides (β-endorphin) during cold stress in humans (447).

B. Avian Nonshivering Thermogenesis

It is well documented that catecholamines have a negligible effect on thermogenesis in birds (60, 130, 131, 161, 190, 357, 458). Indeed, catecholamines may even induce hypothermia at the thermoneutral zone or below it (4–6, 189, 191, 192). These findings are not surprising, since the brown adipose tissue is absent in birds (25, 249, 347).

On the other hand, the impairment of thermoregulation after administration of a β-blocker, propranolol, in neonatal and adult birds (360, 386) suggested the existence of some kind of nonshivering thermogenesis in birds too. Further experiments (193), however, demonstrated that in pigeons propranolol inhibits shivering.

The first clear demonstration of the presence of nonshivering thermogenesis in birds was made in cold-acclimated chickens (117). This was reinforced when Berré and co-workers (21, 22, 31, 105) presented data showing a powerful thermogenic action of glucagon in king penguin chicks. The thermogenic action of glucagon was found to be potentiated by cold acclimation (102, 103) or by chronic glucagon treatment (26). Nonshivering thermogenesis in response to glucagon was also described in cold-acclimated ducklings (23, 25, 27). Glucagon thermogenesis could replace cold thermogenesis in intact cold-exposed birds, suggesting that the thermogenic actions of glucagon may be of thermoregulatory significance. In pigeons, however, glucagon inhibited thermogenesis (196).

It has been clearly demonstrated that avian nonshivering thermogenesis occurs mostly in skeletal muscles and in the liver (101, 104, 106, 107). The oxidative capacity of muscles increased after cold adaptation (23). Muscle nonshivering thermogenesis in birds may be based on cold-induced modifications of the calcium transport in skeletal muscle mitochondria (29) and on activation of the Ca2+-ATPase in the sarcoplasmic reticulum (108, 110). A potential role of palmitoyl carnitine in modulation of the calcium channels in avian muscles has also been suggested (109).

In addition to glucagon, other hormones may partici-
pate in avian thermogenesis. Freeman (130) described a small thermogenic effect of epinephrine and of 3,5,3'-triiodothyronine and thyroxine (T₄) in chicks, while in the tinamou and in the young laughing gull, total metabolism can be increased by application of corticosterone (190, 352).

IV. HORMONAL THERMOGENESIS AND ENERGY BALANCE

Evidence that injected hormones can increase thermogenesis has been available for many years, but the physiological significance of these observations and the role of various hormones and other humoral agents has remained equivocal. Reluctance to accept a role for different hormones in maintaining energy balance appears to stem from reservations that the observed thermogenic effects may be a pharmacological phenomenon without relevance to normal physiology. Cannon and Nedergaard (56) suggested that the thermogenesis in brown adipose tissue in vivo is activated neurally and not hormonally. They claim that hormonal substances other than norepinephrine act by inducing the release of norepinephrine from nerve vesicles. Hormones may also affect cold thermogenesis indirectly, by influencing the oxidative capacity and the growth of the brown adipose tissue and of other organs.

Data in the literature strongly suggest that there are several hormones that may be thermogenic, namely epinephrine, glucagon, thyroid hormones, corticosteroids, and neuropeptides. The mere fact that an injection of a hormone induces an increase in metabolic rate does not necessarily mean that such thermogenesis is of physiological significance; under conditions of cold exposure, the hormonal thermogenesis evidently substitutes for the increased heat production induced by cold. On the other hand, if hormonal thermogenesis is additional to thermogenesis induced by the cold, then it is of no thermoregulatory use, because the heat produced due to the action of a hormone would be eliminated from the body by increased peripheral vasodilation and thus wasted. It was found that the norepinephrine nonshivering thermogenesis substituted for cold thermogenesis in Djungarian hamsters, rats, guinea pigs, and rabbits (39, 240, 263, 306); epinephrine thermogenesis substituted for cold thermogenesis in guinea pigs (242) and in dogs (318); and glucagon thermogenesis substituted for cold thermogenesis in birds (31). On the other hand, norepinephrine thermogenesis is additional to cold thermogenesis in mice and hedgehogs (240), suggesting an important role of the nonnorepinephrine thermogenesis in thermoregulation of these species.

B. Epinephrine Thermogenesis

1. Occurrence and physiological significance

In the 1950s to 1960s, there were several reviews of epinephrine thermogenesis (118, 154, 290, 292–294). From the data available, it is evident that epinephrine induces a thermogenic effect in most species of vertebrates ranging from frogs (162, 452) to humans. In humans, subcutaneous or intravenous injections of epinephrine increase the total metabolic rate by 20% on average, with the limits ranging from 2 to 77%. The increase reaches a maximum 15–30 min after administration of the hormone and persists for a period of 2.5 h (for recent data, see Refs. 300, 413, 421).

According to Blaak et al. (37), in healthy lean men both β₁ and β₂-adrenoceptors are involved in sympathetically mediated thermogenesis, whereas α-adrenoceptors probably do not play an important role. Although there are no firm data to support the involvement of β₂-adrenoceptors in human energy metabolism, there is conclusive evidence to exclude their role in human thermogenesis.

A stimulatory effect of epinephrine of the same magnitude as in humans has been demonstrated in the following mammalian species: sheep, newborn pig, dog, rabbit, cat, guinea pig, white rat, and mouse. Epinephrine also stimulates metabolic rate in newborn birds (31, 130).

To complete the picture, it should be noted that in some experiments there was no effect of epinephrine on metabolic rate, or even a reduction. In adult rabbits and guinea pigs, low doses of epinephrine only induce a small thermogenic effect (10–17%); higher doses induce bradycardia and hypometabolism (S. Vybril, unpublished data). This may be due to suppression of metabolism (326, 402) via the baroreceptor reflex.

A. Methods to Establish the Thermoregulatory Role of Hormonal Thermogenesis

Heat produced due to thermogenic action of hormones may be used in the maintenance of thermal homeostasis in cold-exposed homeotherms. There is only one indirect method capable of establishing the thermoregulatory role of hormonal thermogenesis, however. This involves measuring metabolic response to an infused hormone at both thermoneutral temperature and in the cold. The assumption is that if the extra heat production due to a hormone infused at a thermoneutral temperature is not manifested in cold-exposed animals, then it is of thermoregulatory significance; under conditions of cold exposure, the hormonal thermogenesis evidently substitutes for the increased heat production induced by cold. On the other hand, if hormonal thermogenesis is additional to thermogenesis induced by the cold, then it is of no thermoregulatory use, because the heat produced due to the action of a hormone would be eliminated from the body by increased peripheral vasodilation and thus wasted. It was found that the norepinephrine nonshivering thermogenesis substituted for cold thermogenesis in Djungarian hamsters, rats, guinea pigs, and rabbits (39, 240, 263, 306); epinephrine thermogenesis substituted for cold thermogenesis in guinea pigs (242) and in dogs (318); and glucagon thermogenesis substituted for cold thermogenesis in birds (31). On the other hand, norepinephrine thermogenesis is additional to cold thermogenesis in mice and hedgehogs (240), suggesting an important role of the nonnorepinephrine thermogenesis in thermoregulation of these species.
2. Site of epinephrine thermogenesis

Epinephrine has a major influence on metabolism in individual organs both in vivo and in vitro. Many years ago it was noted that the oxygen consumption of the heart increases by 200–300% after administration of epinephrine (19). Similar increases have been seen both in beating or arrested hearts by many authors (61, 62, 121, 122, 144, 152, 209, 286, 369, 420). Epinephrine also seems to have an effect on cardiac efficiency (150), since in some conditions oxygen consumption increased far more than work output (159).

In many studies epinephrine was shown to exert a strong thermogenic effect in striated muscles in vivo or in vitro (3, 10, 15, 16, 49, 119, 138, 155, 160, 215, 262, 295, 365–367, 369, 370, 408, 409). Although some authors observed that the metabolic rate of isolated incubated diaphragms was not influenced by epinephrine (350, 451), Issekutz et al. (215) concluded that epinephrine only increased oxygen consumption of muscles when vasoconstriction was prevented. As discussed in section III.A, control of thermogenic reactions in resting muscle by catecholamines is dose dependent (e.g., see Ref. 98) and linked to the vasoconstrictor effects. It was calculated that at least 40% of the enhanced metabolic rate induced by epinephrine in humans is taking place in skeletal muscles (408, 409). Few data are available on the effect of epinephrine on metabolic rate of smooth muscles (50, 91).

Epinephrine also increases metabolic rate of the brain (59, 82, 260, 313), of the adipose tissue (127, 298, 349, 408), and of the gastrointestinal tract (198, 400); in some cases, oxygen utilization by the dog kidney was increased due to epinephrine (297). Evidence based on evisceration studies indicated a positive influence of epinephrine on liver metabolism (38, 414), but other authors did not observe stimulation of liver metabolic rate by epinephrine (82, 160, 296, 302, 419). A small role of the brown adipose tissue in epinephrine thermogenesis was documented by Vybral and Andrews (448). In humans, only ~5% of the whole body thermogenesis induced by epinephrine is located in adipose tissue (409).

Evidently, epinephrine thermogenesis involves many different organs. Epinephrine thermogenesis may be of thermoregulatory significance. In rats exposed to cold, epinephrine level in the blood is much higher than that of norepinephrine (~2.5 ng/ml compared with ~0.5 ng/ml) (41). Furthermore, Morin (318) presented evidence that epinephrine thermogenesis could substitute for cold thermogenesis in dogs, and similar effects were observed in rabbits (283, 449) and in rats (240). Epinephrine thermogenesis may be potentiated by cold acclimation in rats (305), guinea pigs (240), and sheep (145). In contrast, in king penguin chicks, the epinephrine thermogenesis is additional to the cold thermogenesis (31).

Another role of epinephrine thermogenesis may be in influencing energy balance and controlling body weight at thermoneutrality. Evidently, all stressors activate the sympathetic nervous system and release of epinephrine from adrenals. Increased heat production due to thermogenic action of epinephrine uses metabolic fuels and may counteract anabolic processes during excess food supply and contribute to preventing obesity.

3. Mode of action

Several possible ways have been suggested by which epinephrine could exert its thermogenic action (154), namely, 1) specific stimulation of the metabolism at the cellular level, 2) specific dynamic action of carbohydrates resulting from epinephrine hyperglycemia, 3) extra expenditure of oxidative metabolism involved in the removal or resynthesis of lactic acid, 4) increase in cardiac activity, 5) peripheral vasoconstriction reducing heat loss and raising body temperature, 6) an effect on tissue oxygen supply and utilization, and 7) activation of skeletal muscle activity. In addition, in spite of a relatively weak lipolytic action of epinephrine, the possible effect of free fatty acids on brown adipose tissue metabolism should be also considered, although Vybral and Andrews (448) have shown that the brown adipose tissue thermogenesis contributes to the total heat production after epinephrine only by 40%. Selberg et al. (396) concluded that the energy-consuming processes contributing to epinephrine-induced thermogenesis include alterations in respiratory and heart work, hepatic glucose production, lipolysis, substrate cycling, and changes in the endogenous fuel mixtures. Stimulation of futile cycles such as substrate cycling between glucose and glucose 1-phosphate or fructose 6-phosphate and fructose 1,6-diphosphate by epinephrine was suggested by Newsholme and Crabtree (336). Lundholm et al. (294) stressed the importance of the increased lactate metabolism, the reesterification of free fatty acids to triglycerides, and the direct stimulation of ATP hydrolysis in muscles and adipose tissue for epinephrine thermogenesis.

It may be that the thermogenic action of epinephrine is not based on a simple unitary reaction but rather on the integral sum of several effects. In other words, all the possible modes of action may contribute to the epinephrine thermogenesis.

C. Glucagon Thermogenesis

The thermogenic action of glucagon was first reported in adult rats by Davidson et al. (87), who observed a 50% increase in the total oxygen consumption 1 h after a subcutaneous injection of glucagon (1 mg). The response was independent of the hyperglycemic action of the hormone. In newborn rabbits, the metabolic rate almost doubled after administration of this hormone together with a simultaneous increase in blood flow and temperature of the brown adipose tissue; the effect was not blocked by propranolol (164). In dogs, glucagon has a greater thermogenic effect than epinephrine (453, 454) and is not related to free fatty acid mobilization. Glucagon also produced a significant elevation of oxygen consumption, body temperature, and brown adipose tissue temperature in rats and mice, an effect potentiated by cold acclimation (96, 97, 203). Furthermore, it was demonstrated...
that glucagon increases the total metabolic rate of pigs (211), birds (21, 22, 25, 26, 28, 31, 267), and humans (327).

Hohtola et al. (190), on the other hand, were not able to demonstrate glucagon thermogenesis in adult pigeons after intramuscular injections of 100 µg/kg glucagon, in spite of the increase in free fatty acid levels.

Cold exposure and cold adaptation result in increased levels of glucagon in the plasma (116, 170, 268, 279) and in the brown adipose tissue of rats (159) and raises plasma glucagon concentration in humans (272, 365). This suggests that glucagon thermogenesis is induced by physiological stimuli. Recent experiments (36) showed that brown adipose tissue thermogenesis in vivo can be activated by physiological concentrations of the hormone. Furthermore, it was shown that glucagon treatment improves cold tolerance in rats (463).

It was shown that norepinephrine stimulates secretion of glucagon (273), and this may suggest that these thermogenic hormones act synergistically in cold-exposed individuals.

In birds, glucagon thermogenesis occurs in skeletal muscles (101, 104, 106, 107). In ducklings, the liver cannot be excluded as a source of glucagon thermogenesis, since an increase in oxidative capacity of this organ was reported in chronically glucagon-treated birds, and hepatic mitochondria were found to be loosely coupled (24).

Several papers presented indirect or direct evidence that in mammals the thermogenic effect of glucagon depends on brown adipose tissue. Glucagon stimulates thermogenesis in the brown adipose tissue (136, 164) and in isolated brown fat cells (248, 277). Repeated glucagon injections increased the brown adipose tissue weight, protein content, DNA content, cytochrome oxidase activity, free fatty acids, and GDP binding in mitochondria. The changes were of lesser magnitude than those after norepinephrine, however (35). Glucagon also increased heat production in rat white adipocytes (275), and cold acclimation increases the number of glucagon receptors in epididymal white adipocytes (445).

The precise way in which glucagon produces its thermogenic action at a cellular level has not yet been fully clarified. The uncoupling effect of free fatty acids, which are released due to lipolytic action of glucagon in loosely coupled liver mitochondria, may be responsible for glucagon thermogenic effect (24, 30, 108). The similarity of the cellular and tissue events that follow both glucagon and norepinephrine stimulation of metabolism implies that stimulation by both these hormones shares a final common pathway; this may involve the activation of adenylate cyclase with a subsequent increase in cAMP levels and activity of a cAMP-dependent protein kinase (55). Among the actions that may also occur in adipose tissues is the activation of the hormone-sensitive lipase (334). Glucagon infusions provoke an immediate rise of blood free fatty acids and glucose concentrations (269, 276, 287). These originate mostly from the brown adipose tissue (248, 278).

The extent of the free fatty acid increase from the brown adipose tissue was smaller in cold-adapted rats, and the response to glucagon was unchanged after administration of the β-adrenergic blocker propranolol (270). Thermogenic response to this hormone is abolished by thyroid and adrenocortical deficiency (88, 271).

Glucagon and norepinephrine actions in the brown fat may thus be additive or synergistic. This makes complete separation of their physiological roles very difficult.

D. Thyroid Thermogenesis

Production of thyroid hormones increases due to cold exposure, indicating their role in thermoregulation (78, 133, 450, 460a). This may reflect an increased resting metabolism (obligatory thermogenesis) of cold-adapted animals. It has been known for many years that administration of thyroid hormones increases the resting metabolic rate by ~10-50% (for review, see Refs. 20, 114). This thermogenesis is slow and usually appears after several hours or days of administration of the hormone. Thyroidectomy, on the other hand, attenuates the basal metabolic rate and the metabolic response to cold (204).

An immediate thermogenic response to thyroid hormones has also been described after more physiological doses of hormones (7, 254, 255, 316). This transient stimulation of oxygen consumption can be linked with the "loosening" of oxidative phosphorylation in hepatocytes.

Additionally, thyroid hormones generally stimulate growth and development (126) of the brown adipose tissue (172). Thyroid hormones also potentiate the thermogenic effects of other humoral substances, namely, catecholamines (428, 429), by increasing the number of β-adrenergic receptors on cell membranes (see sect. IVF).

The effects of thyroid hormones are widespread. They have a major influence on obligatory thermogenesis in most organs of the body with the exception of the brain (418). It was suggested that thyroid hormones act as an anti-brown fat hormone by increasing thermogenesis in the rest of the body and thus diminishing the demand on brown fat. Hyperthyroid rats have less thermogenin in the mitochondria of the brown fat (425).

During facultative thermogenesis, thyroid hormones predominantly influence the brown adipose tissue and skeletal muscles, and its principal role appears to be a permissive one. The importance of the permissive effects of thyroid hormones is illustrated by the fact that thyroidectomized animals die when exposed to cold and that the genetic obesity in mice depends on thyroid deficiency (for review, see Ref. 181).

There is no general agreement about the precise mechanisms of action of thyroid hormones and the extent to which they participate in cold-induced or diet-induced thermogenesis. A major difficulty in interpreting results so far obtained is that thyroid hormones may not only influence the action of other hormones in target organs but also modulate the secretory activity of other endocrine glands and of the sympathetic nervous system.

At a cellular level, thyroid hormones obviously have multiple mechanisms of action (194, 212, 348, 431). The old explanation of thyroid thermogenesis based on partial uncoupling of oxidative phosphorylation has been rejected because of the huge doses of hormones required
In preparations of liver mitochondria, only pharmacological doses of T₃ can "uncouple" oxidative phosphorylation. Skeletal muscle mitochondria are not affected. The "uncoupling" has little connection with normal thyroid hormone functions under physiological conditions. Thus thyroid hormones may be essential for normal function of enzymes and may have a permissive action. Thyroid hormones may, however, change the properties of the mitochondria such that their metabolic rate increases even though oxidative phosphorylation remains coupled (194, 398, 399). They also may increase the protein synthesis (403) and the total mitochondrial content of tissues (81, 90, 343).

Finally, thyroid hormones may increase the Na⁺-K⁺-ATPase activity in tissues (9, 115, 212, 213, 418). Rothwell et al. (384) have found that the Na⁺-K⁺-ATPase in brown fat cells may be involved in the thermogenic response to thyroid hormones and catecholamines. The concept that the thermogenic activity of thyroid hormones is directly linked to Na⁺-K⁺-ATPase activation is not universally accepted (423). Folke and Sestoft (128) concluded that the energy expenditure due to Na⁺-K⁺ transport is too small to make significant contribution to thyroid thermogenesis in the liver. Thyroid hormones have little effect on sodium transport-dependent respiration in either brown adipose tissue or liver (261). An activation on the Ca²⁺-ATPase by thyroid hormones may also occur (407, 446). A spontaneous leak of protons across the mitochondrial inner membrane is stimulated by thyroid hormones (13), so it is suggested that the essential mechanism stimulated by the thyroid hormones is a loose coupling in liver mitochondria (151).

These mechanisms are not mutually exclusive and may all be involved. There is no agreement as to their relative contributions. It is outside the scope of this paper to review all aspects of thyroid thermogenesis. Nevertheless, it is evident that thyroid hormones contribute to the catabolic state of an organism and may maintain stable body weight under conditions of an increased energy intake.

F. Peptide and Steroid Thermogenesis

The first evidence that administration of peptidergic substances other than glucagon induces a thermogenic effect comes from the paper of Evans et al. (123), who demonstrated a thermogenic effect of growth hormone in rats. This effect was confirmed by Yousef and Johnson (467) on cattle.

Heim and Hull (164) have shown a thermogenic effect of pharmacological doses of ACTH in newborn rabbits. In our laboratory, Boštík (unpublished data) also demonstrated that intravenous infusions of 33 mg·kg⁻¹·min⁻¹ ACTH increased the metabolic rate of warm- or cold-adapted rats by 15.7% or 24%, respectively. This effect was not mediated by adrenal steroids, since adrenalectomy did not influence the responses, and peripheral administration of deoxycorticosterone was without effect on metabolic rate.

The effects of corticosteroids are very variable. In birds and hibernators, corticosteroids may be thermogenic; Illsza and Palokangas (190) have shown that corticosterone had a stimulating effect on the oxygen consumption in the titmouse but could not demonstrate the effect of corticosterone on body temperature of the pigeon (189). Deoxycorticosterone may be related to nonshivering thermogenesis in the hedgehog (461, 456, 457). Ohno and Kuroshima (346) suggested that metapyrone, an inhibitor of adrenal 11β-hydroxylase, causes an increase in oxygen consumption of rats. Finally, Freeman et al. (132) demonstrated a thermogenic effect of progesterone in the rat.

The thermogenic effect of insulin in physiological concentrations is probably small (69). It is not directly involved in the activation of the brown adipose tissue thermogenesis, but it is essential for the maintenance of a metabolic capacity of this organ (403). Therninarias et al. (434), however, showed that insulin has a thermogenic effect and improved resistance to cold in dogs. Felig (124), Ravussin and Bogardus (363), and Ravussin et al. (364) have also found that in humans an insulin infusion increases the metabolic rate, but part of this response (24–35%) was due to increased activity of the sympathetic nervous system.

Insulin stimulates the metabolic rate of the liver and muscles (99, 148, 199) and enhances thermogenesis in perfused rat muscle, following intensive exercise (18). Recent observations that insulin increases leg blood flow leading to capillary recruitment may explain this effect and would be consistent with the theory of vascular control of resting muscle thermogenesis (Ref. 70; see sect. IIIA4).

F. Mutual Interactions Among Thermogenic Hormones and Their Role in Maintaining Energy Balance and Thermal Homeostasis

There exists a substantial amount of evidence that the thermogenic effect of catecholamines, and of epinephrine in particular, can be influenced by other hormones, namely by insulin and thyroid hormones.

Epinephrine thermogenesis is inhibited by hyperinsulinemia (323, 396, 411) and potentiated by hypoinsulinemia and starvation (300, 323, 324), indicating a competition for substrates between these hormones. Thus hyperinsulinemia may contribute to energy retention and weight gain, while hypoinsulinemia may lead to heat loss. Although insulin, per se, does not affect energy expenditure in humans, basal plasma insulin concentration affects epinephrine-induced thermogenesis and, consequently, energy balance. In contrast, Staten et al. (422) demonstrated that the effect of epinephrine on metabolic rate is independent of changes in plasma insulin and glucagon.

Thyroid hormones, on the other hand, potentiate epinephrine and norepinephrine thermogenesis (85, 356, 440). This effect was originally described by Schaeffer and Thibault (388, 389) and confirmed in a series of other papers (45, 252, 427–429, 435). The mechanism is not fully
understood, but it may involve altered balance between α- and β-adrenergic receptors (139).

The problem of interaction between thermogenesis due to epinephrine and norepinephrine has not been discussed in detail thus far. Mejšnar et al. (305) found that epinephrine thermogenesis can fully substitute for norepinephrine thermogenesis, providing that higher concentrations of epinephrine are being used.

The physiological conditions under which the thermogenesis due to hormones other than catecholamines is manifested are not known.

V. DIET-INDUCED THERMOGENESIS

A large amount of data (372, 378–380, 382–385) indicates that the leanness or obesity of mammals depends on the capacity of the diet-induced thermogenesis in brown adipose tissue. Thus this organ plays the role of an energy buffer (84, 176, 183, 184, 218, 219, 441, 442).

Obese subjects show a reduced response to norepinephrine (250). In some types of obese animals, a defective brown adipose tissue thermogenesis occurs (181). The possibility that impaired thermogenesis is associated with some types of human obesity has been extensively investigated. Several studies have shown that the rise in metabolic rate after ingestion of a meal or after the combination of a meal and physical exercise is significantly smaller in obese than lean humans (392–394, 401). Controversy still exists, however (176, 283, 380).

There are similarities between diet-induced and cold-induced thermogenesis. Both are mediated by norepinephrine; they act at a common site, the brown adipose tissue; and they have a common metabolic background. This suggests that diet induced thermogenesis may be important not only for regulation of energy balance under different feeding regimes but also for maintenance of constant body temperature in the cold (377). Thus humoral thermogenesis induced either by cold or other types of stressors may be used both for thermoregulation and for body weight control.

In the early 1980s, several authors (1, 2, 143, 391, 410, 430, 436, 455) described a thermogenic effect of carbohydrates. This effect is not due entirely to the energy requirements for digestion, absorption, conversion, and storage of substrates. The facilitative component of this thermogenesis is supposed to be at least partly due to insulin-mediated activation of the sympathetic nervous system, which in turn exerts its thermogenic effect via release of catecholamines stimulating β₁-adrenergoreceptors (1, 361, 438). More recent work on humans (10, 14–16) indicates that a major part of this thermogenesis occurs in skeletal muscles and not in the brown adipose tissue (83). Subgroups of obese and reduced obese patients, a decreased glucose-induced thermogenesis has been reported that is thought to contribute to a positive energy balance and weight gain (11–13, 412). The concept of defective thermogenesis in obesity is supported by the finding of an impaired reactivity of the sympathetic nervous system in some obese humans (11–13) and a decreased thermogenic sensitivity to β-adrenergic stimulation (317).

A. Humoral Modulation of Food Intake and Its Possible Implications for Diet Induced Thermogenesis

It has been suggested that the control of food intake depends on a delicate balance of noradrenergic and serotonergic pathways projecting to sites close to those regulating thermal homeostasis in the anterior hypothalamus (195, 320). Depletion of serotonin stores in the brain induces hyperphagia and obesity, while activation of serotonergic pathways evokes anorexia (44). Recently, it was found that hypothalamic control of food intake can be modulated by peptidergic substances. Opioid peptides, pancreatic polypeptides (neuropeptide Y and human pancreatic polypeptide), growth hormone-releasing factor, and calmodulin stimulate food intake when administered centrally, whereas nonopioid peptides usually inhibit food intake (for review, see Ref. 321).

There appears to be a correlation between the effect of peptides on control of food intake and on control of body temperature. Opioid peptides, which increase food intake, usually induce hyperthermia, whereas nonopioid peptides, which inhibit appetite, induce hypothermia (230). It is tempting to speculate that under stressful conditions the balance among hypothalamic neurons is influenced by humoral factors. These processes could contribute to regulation of thermal homeostasis and energy balance.

VI. CONCLUSIONS

The aim of this review is to point out that in addition to norepinephrine nonshivering thermogenesis, the energy balance and, consequently, the body weight of homeotherms depends on different types of hormonal thermogenesis originating not only in the brown adipose tissue, but also in other tissues. The nonnorepinephrine and non-brown fat thermogenesis may become very important in adult and large mammals, where the amount of brown adipose tissue is very small or even nonexistent.

A distinction has been made, therefore, between nonshivering and hormonal thermogenesis. Nonshivering thermogenesis is based on thermogenic action of norepinephrine. Hormonal thermogenesis may be induced by substances other than norepinephrine (epinephrine, glucagon, thyroid hormones, peptidergic hormones, steroid hormones). In birds, glucagon thermogenesis located mostly in muscles, or in the liver, is of particular importance. While nonshivering thermogenesis is important in cold-exposed animals, hormonal thermogenesis may be induced by other types of stress. Hormonal thermogenesis influences energy balance within the thermoneutral zone and in this way contributes to maintaining the constant body weight in overfed individuals. In general, humoral thermogenesis (comprising nonshivering thermogenesis
and hormonal thermogenesis) represents an adaptive mechanism enabling adjusting of animals to various environmental stressors. It is evident that there is no single mechanism responsible for humoral thermogenesis. Several substances are involved, and each substance may have several modes of action. Humoral substances affect not only the target thermogenic organs but also influence several mechanisms, such as stimulation of the growth of thermogenic organs, activation of enzyme activities, and modulation of nervous activity that indirectly alters thermogenesis.

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