The Autonomic Nervous System and Regulation of Body Temperature

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EVER SINCE the initial recognition of homeothermy, physiologists have been fascinated with the processes that regulate body temperature and have been seeking to identify the details of the physiological mechanisms involved. It was discovered early that maintenance of body temperatures is under control of the nervous system and that the sympathetic nervous system plays a major role. This relationship was brought to attention by two prominent physiologists, Claude Bernard and W. B. Cannon.

The physiologic processes which maintain normal body temperature include the following:

SHIVERING

A rhythmic contraction of voluntary muscle, shivering is involuntarily induced. Activated as a response to cold, it produces additional metabolic heat, as much as five times the resting non-shivering heat production rate.[1] Shivering is not a function of the sympathetic nervous system; a totally sympathectomized animal can protect against coldness by shivering.

NON-SHIVERING THERMOGENESIS

With increased metabolism not due to shivering, a homeotherm, adapted to cold, can increase its heat production rate to about double the value in a comfortable environment. This non-shivering thermogenesis is controlled, or influenced, by the sympathetic nervous system.

CUTANEOUS VASO-ACTIVITY

The blood vessels of the skin dilate in a warm environment or constrict in the cold, thus controlling the flow of blood and regulating skin temperature. The control of cutaneous vasoactivity is a function of the sympathetic nervous system.

SWEATING

In a warm environment the sweat glands are stimulated to secrete sweat, which evaporates from the skin, causing cooling. Sweating is a special activity of the sympathetic nervous system.

PILOERECTION

This fluffing of the fur in animals increases insulation and reduces heat loss. Piloerection is a function of the sympathetic nervous system.

PANTING

In a warm environment, in order to prevent body hyperthermia, warm-blooded animals (and reptiles) can pant. The rapid, shallow breaths of panting produce maximum evaporation from mouth, tongue and upper airways, but with minimal alveolar ventilation for maintenance of normal arterial CO_2 tension. Panting is not a function of the sympathetic nervous system.

Thus, the everyday routine of body temperature adjustment requiring precise control is a function of the sympathetic nervous system. A totally sympathectomized animal resorting to shivering and panting can regulate body temperature with a control resembling that produced by a coarse thermostat. The fine adjustment, operating continuously through 24 hours of the day, belongs to the sympathetic nervous system. Man, the animal with which we are most concerned, does not pant; but he does have an effective sweat mechanism. Generally, animals that pant have poorly developed sweating processes and *vice versa;* those that sweat do not rely on panting.

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The following pages contain a brief description of the basic physiology and anatomy of the sympathetic nervous system as it functions in temperature regulation, and sections on the mechanisms listed above and the role of the sympathetic nervous system, as defined in the recent literature. The parasympathetic nervous system plays no direct role in regulation of body temperature.

Anatomy, Hormones, Alpha and Beta Receptors

The factors controlling body temperature, activating the processes listed, can be considered to consist of reflexes of the Sherrington type, with receptors stimulated by heat or cold, afferent pathways to a reflex center and efferent pathways for activation of the responses. The receptors are distributed mainly in the skin; when they are stimulated, afferent impulses travel to the central nervous system via the dorsal roots of spinal nerves and the cranial nerves. Impulses are relayed within the spinal cord to neurons which ascend to the thalamus, considered to be the distributing center. From the thalamus impulses are transmitted to the cerebral cortex for sensation; others are transmitted to the hypothalamus for temperature control. The hypothalamus can be considered the main temperature-regulating center, "center" used in its loose sense, since many details of its function are lacking.

In addition to this classical reflex control, another system exists. In the rostral hypothalamus, medial between the optic chiasma and anterior commissure, there is a temperature-sensitive region, discovered in the brain of rabbits by Barbour,[2] and localized in the rostral hypothalamus of the cat by Magoun *et al.*[3] Hemingway and co-workers[4] and Hammel *et al.*,[5] found a similar center in dogs. A thermosensitive center in the same region was found by Andersson and co-workers[6] in the goat. Hardy *et al.*,[7] have obtained nerve action potentials associated with warming of this region. This thermally-sensitive region functions like the cutaneous receptors. The afferent information from both thermosensitive regions is modulated in the brain centers and the appropriate efferent response made. The two sources of afferent input act together as a dual control. In the rostral hypothalamus there is no distinguishing characteristic anatomical feature which enables the thermally-sensitive cells to be differentiated from other neurons.

If the control of body temperature be considered a complex reflex with a dual afferent system and a reflex center in the hypothalamus, the efferent arm of the reflex system next needs consideration. There are three or more neurons in the pathway from center to sympathetic effector organs. These are: (1) a descending pathway in the brain stem and spinal cord, from the hypothalamus to preganglionic neurons in the gray matter of the spinal cord; (2) preganglionic sympathetic fibers in the ventral roots of the spinal nerves, terminating in sympathetic ganglia; and (3) postganglionic fibers to end organs. Of special interest are the chemical nature and sensitivity of the terminal endings of this efferent pathway. Although the pathways outside the central nervous system is well-defined, more information about the pathways and their distribution in the cord is needed.

A few years ago, it was believed that the sympathetic nervous system discharged as a unit when danger threatened (Cannon's emergency theory). It is now known that its action can be divided into parts, each with a specific activity in non-emergency control of function. Temperature regulation is one of these; in this, the role of the sympathetic system can be subdivided into the four categories: (1) cutaneous vasoactivity, (2) sweating, (3) pilo-erection and (4) non-shivering thermogenesis. Before further description of these activities, the chemical mediation at sympathetic postganglionic nerve terminals will be discussed briefly.

The reaction of smooth muscle to naturally-occurring and synthetic catecholamines has long interested pharmacologists, since some muscle (cutaneous arterioles) is constricted while other muscle (*e.g.*, bronchioles) is relaxed by these substances. Supposedly, there are two types of "receptors," designated alpha and beta, for catecholamines, in addition to the cholinergic receptors for sweating, giving three end-receptor types. The concept of two receptors has aroused controversy,[8] because there are no well-defined anatomical features and proof of their existence is purely pharma-

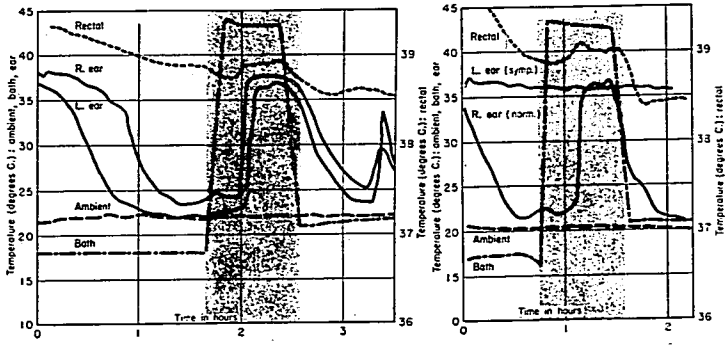

FIG. 1. Role of the sympathetic nerves in temperature regulation.

cological.[9] There are two types of experimental evidence: (1) a difference in the graded response to a series of catecholamines; (2) effects of a variety of blocking agents. Furchgott[10] proposes as a method of recognition of alpha receptors the decreasing graded responses to the sequence: phenylephrine > epinephrine, norepinephrine > isopropylnorepinephrine. If beta activity is involved, the order is reversed. Phenylephrine is a potent alpha stimulator, isopropylnorepinephrine a potent beta stimulator, propranolol a beta inhibitor, and dibenamine an alpha blocker. The further identification of these receptors is discussed by Nickerson[11] and by Braunwald.[12] Alpha receptors function in the contraction of smooth muscle of cutaneous arterioles, beta receptors in metabolic stimulation induced by cold.[9]

Cutaneous Vasomotor Control

The thermal cutaneous response is a change in diameter of the arterioles, with a high degree of contractility. Blood flow determines skin temperature, which in turn determines heat loss to the surroundings, the flow being about 1–3 per cent of the total cardiac output in a comfortable environment.[13] It is of major importance in the fine control of body temperature.

The role of the sympathetic nerves in temperature regulation is illustrated in figure 1. A trained dog stood in a water bath with head protruding, bath temperature near the ambient (about 20° C.). Rectal and aural temperatures were measured with thermocouples, the ear thermocouple being taped to the skin. When the bath temperature was changed from cold (about 20° C.) to warm (about 40° C.), after a latent period there was a sudden rise in aural temperature (left, fig. 1). After left-sided sympathectomy the response was different; in the cold there was no vasoconstriction of the sympathectomized ear; while the normally-innervated ear had a temperature near the ambient value; when the animal was warmed the temperature in the normal ear rose to that of the sympathectomized ear.[14]

Celander and Folkow[15] measured blood flow in the veins of the hind limbs of cats anesthetized with chloralose and urethane. With the sympathetic nerves cut and the distal ends stimulated, blood flow rate in the saphenous vein, draining the skin, was reduced to about one per cent of the pre-stimulation value; blood flow in the femoral vein, draining muscle, was doubled. These results indicate striking differences in the control of blood vessels of skin and muscle.

When sympathetic function is reduced or blocked, there is impaired ability to adjust to cold. Leduc[16] noted that after administration of phenoxybenzamine (an alpha and beta blocking agent) the survival periods of rats exposed to cold were reduced, and excessive

quantities of the now-ineffective catecholamines appeared in the urine. The production rates of the sympathetic hormones, measured by urinary excretion, are increased when the cold-response mechanisms are stimulated.[17] With thermode cooling of the hypothalamus of the goat, which caused cutaneous vasoconstriction sufficient to elevate rectal temperature about 2° C. at a room temperature of 18° C., urinary epinephrine and norepinephrine both increased significantly. The excretion rate of epinephrine increased from 1.7 to 3.7 mμg./min., an increase of 117 per cent, while norepinephrine increased from 6.3 to 9.3 mμg. (48 per cent increase). Honda *et al.*,[18] found that cutaneous vasoconstriction, caused by perfusing a rabbit's ear with epinephrine or norepinephrine, was similar for both catecholamines.

Sweating and Piloerection

Current knowledge of the nervous control of sweating is contained in abundant and controversial literature. Only a superficial review will be given here, the older work having been reviewed by Rothman[19] and Kuno,[20] more recent work by Randall.[21]

Most of the information about sweating has been obtained from studies on man, who differs in this respect from other animals. Man has two types of sweat glands, eccrine and apocrine. The eccrine glands, widely scattered over the surface of the body, are mainly responsible for the excessive thermal sweating which can reach as much as one liter of sweat per hour, in a hot environment or with severe exercise.[22] All sweat glands are innervated by postganglionic sympathetic fibers and most eccrine glands are thermally activated. However, an unusual feature is that the chemical mediator is acetylcholine, rather than a catecholamine. Hence, thermal sweating is inhibited by sympathectomy and atropine but stimulated by pilocarpine. The eccrine glands in the distal extremities, especially the palms and soles, seem to be an exception. They respond more to mental than to thermal stress.[20]

The apocrine glands are restricted to certain regions such as the axilla, mammary areolae, anogenital region, ear canal and eyelids. In general, their locations parallel the regression of terminal body hair for the glands secrete into the hair follicles. Function and structure are described by Hurley and Shelley.[23] Apocrine sweat is viscid and cloudy and less profuse than eccrine sweat. The apocrine glands are involved mainly in emotional sweating. Their activity is also controlled by the sympathetic system; the postganglionic chemical mediators are the catecholamines. In man, these glands can be stimulated thermally, but only as a secondary defense against excessive heating. Emotional states and epinephrine can also stimulate sweat secretion in the distal portions of the extremities where there are few hairs and eccrine glands are most abundant.[24, 25]

The secretion of sweat is controlled as a thermal reflex similar to that of cutaneous vasoactivity; warmth receptors in skin and brain, when stimulated, activate the reflex. Benzinger *et al.*,[26] have proposed that the temperature of the tympanic membrane is representative of brain temperature, with a sharp, well-defined threshold above which sweating is elicited. However, Hammel *et al.*,[27] Hayward and co-workers,[28] and McCook *et al.*,[29] found that spontaneous or induced temperature changes in the hypothalamus do not activate thermoregulatory processes. Hammel *et al.*,[27] believe that all afferent impulses subserving warmth are integrated in the hypothalamic center and that the thresholds of both skin and brain temperature are variable. Hypothalamic tumors interfere with thermal sweating and cutaneous vasodilation.[30, 31]

In addition to activation of sweating by the hypothalamic reflex center, sweating has other controls. In a spinal animal sweating can be initiated by a spinal reflex through noxious stimulation to the skin, induced as an axon reflex, or elicited by heat applied to the skin. These mechanisms which do not involve the hypothalamus are crude in comparison with normal control.[19]

Sweating control in animals differs from that in man. In animals the glands are mostly apocrine. In the horse and ox they are widely distributed in the skin.[23, 32] Hypothalamic heating does not cause sweating in horse or ox.[33, 34] The glands of the ox are innervated by sympathetic adrenergic nerves and activated thermally.[32] The horse may not have sudomotor nerves,[34] and sweating may be acti-

vated by circulating catecholamines. The cat has apocrine glands which are thermally-activated and cholinergic in the footpad,[35] while the dog has apocrine glands which are emotionally, rather than thermally, activated, distributed widely over the skin. However, dogs in a hot environment leave moist footprints; this does not occur in a cooler environment. Sheep have widely distributed apocrine glands apparently activated by a hot environment.[23] One may question the usefulness of sweat glands in a sheep, with its thick moisture-repelling fleece. In primates there are interesting differences. A lower primate, the lemur, has apocrine glands only. Macaques have both types, the apocrine being more numerous. Baboons have both types in about equal numbers. The gorilla has eccrine glands on palms and soles but apocrine glands over the rest of the body.[23]

Piloerection on "fluffing" of body hair can be an effective means of increasing the surface insulation because air is "trapped" between the skin surface and the surroundings. Air thus trapped between the body hairs is a much more effective insulator than a similar layer of air over hairless skin.

The smooth muscle fibers which upon contraction cause the body hairs to become more vertical to the surface are innervated by adrenergic fibers.[19, 35] Electrical stimulation of the anterior and posterior hypothalamus may evoke piloerection.[37] Piloerection persists vestigially in man as "goose bumps," but has no thermoregulatory importance.

Non-shivering Thermogenesis: Role of Sympathetic and Thyroid Hormones

In the physiologic response to cold there is an increase in oxygen consumption and associated heat production which can arise from two sources: (1) shivering, and (2) non-shivering thermogenesis. It is difficult physiologically to separate these two sources of extra body heat, *i.e.*, to determine when elevated oxygen consumption in a cold environment is the result of shivering or a non-shivering source, because when the animal is exposed to cold there can be slight or unrecognized shivering movements which may elevate oxygen consumption without visible shivering. However, shivering can be suppressed by neuromuscular blockers and if, under conditions of complete muscle paralysis, oxygen consumption rate is elevated, it can be attributed to non-shivering thermogenesis. Studies of this response in recent years have involved two phenomena: (1) cold adaptation; and (2) the role of catecholamines.

As a result of prolonged exposure to cold not severe enough to cause freezing, there are adaptive changes such as (1) growth of hair; (2) increased thyroid activity with associated metabolic changes; (3) increased ability to tolerate cold without apparent discomfort; (4) reduction in visible shivering. These processes, collectively designated "cold acclimatization" or "cold adaptation," have been studied most extensively in rats, but similar adaptive changes occur in other animals.

It has been known for years that epinephrine exerts a stimulating effect on energy metabolism as measured by oxygen consumption rate.[38, 39] Ring[39] found that previous thyroxine treatment increased the metabolic response to epinephrine, causing oxygen consumption to increase about 90 per cent. Cold adaptation increased the metabolic response to epinephrine, which led Ring to revive an old theory called the "Goetsch effect," which proposed that the metabolic role of the thyroid was to sensitize the animal to epinephrine (and now, norepinephrine).

Since the discovery that there are two sympathetic hormones, the direction of research has been to evaluate the roles of epinephrine and norepinephrine in the physiologic reaction to cold, particularly in cold adaption.[40] When animals become adapted to cold, calorigenic sensitivity to catecholamines is increased; the conclusions of Ring have been confirmed. Evonuk and Hannon[41] measured oxygen consumption of warm- and cold-adapted anesthetized rats and noted that while norepinephrine infusion increased oxygen consumption rate about 50 per cent in warm-adapted rats the increase was about 100 per cent in cold-adapted rats. Depocas[42] noted that oxygen consumption rate rose to two to three times the pre-injection value when norepinephrine was infused into cold-adapted rats. Earlier, Hsieh and Carlson[42] had given single injections of catecholamines to rats almost completely paralyzed by high cervical transection

or by curarization. Their results summarized in table 1, demonstrated the following: (1) cold adaptation elevates non-shivering oxygen consumption rate in a warm environment; (2) thyroidectomy lowers non-shivering oxygen consumption; (3) norepinephrine and epinephrine elevate oxygen consumption of both cold-adapted and warm-adapted animals, but norepinephrine has the greater effect; (4) exposure to cold elevates the oxygen consumption of curarized animals about 80 per cent; (5) epinephrine elevates blood sugar level of cold-adapted animals, but norepinephrine is without effect; (6) exposure of cold-adapted animals to cold raises blood sugar levels slightly, about 10 per cent.

In comparative tests of the potencies of the catecholamines, norepinephrine has been found to be the more potent stimulator of oxygen consumption in rats (table 1) and in cats.[44] The cat has a metabolic response to catecholamines lower than that of the rat. The source of the extra oxygen consumption generated by norepinephrine has been shown to be muscle rather than viscera by Depocas[42] in eviscerated rats, and by Jansky and Hart[45] using perfusion of a hind limb. The role of the sympathetic nervous system in the metabolic response to cold is further shown by the striking reduction in oxygen consumption rate caused by hexamethonium, a ganglionic blocking agent, and by piperoxan, an adrenolytic drug, in cold-adapted curarized rats.[46]

Both epinephrine and norepinephrine are effective metabolic stimulators but it is believed that norepinephrine causes the elevated oxygen consumption rate of non-shivering thermogenesis. Evidence for this is based on two observations. The first is the analysis of nervous tissue by von Euler,[47] who found that peripheral nerves have a much higher content of norepinephrine than epinephrine. The second is the classical work of Leduc,[15] who measured urinary excretion of epinephrine and norepinephrine in rats exposed to cold. After exposure, urinary norepinephrine increased from about 5 μg./day to 16–20 μg. The high excretion rate with continued exposure to cold was not maintained; a decline to 7 to 8 μg. occurred after three months in the cold. Adrenalectomy with adequate adrenal corticoid therapy had no appreciable effect on the excretion pattern of norepinephrine. Urinary epinephrine excretion rose from 0.5–1.0 μg. /day to a peak of 4–5 μg. after which there was a slow decline to a final value of about 1.5 μg., two times the pre-cold exposure value. After adrenalectomy urinary epinephrine excretion in the cold was below that of sham-operated controls. Leduc[15] proposes that norepinephrine in peripheral nerve functions in non-shivering thermogenesis and that cold acclimatization is a process whereby the organs functioning in cold adaptation become hypersensitive to the hormone. Epinephrine formed mainly in the adrenal gland, functions as the last line of defense against cold and is brought into action only in an extreme emergency such as cold sufficient to cause freezing of tissues. Under these conditions urinary epinephrine rises to a value of 12 μg./day.

There is evidence of a relationship between the thyroid hormone and the catecholamines in controlling energy metabolism in the control of non-shivering thermogenesis, but exact details of this relationship have not been elucidated. However, sufficient information is available to support the Goetsch effect mentioned above. As shown in table 1, thyroidectomy significantly reduces heat production and its stimulation by cold. Hsieh and Carlson[48] removed the thyroid glands from cold-adapted rats and measured oxygen consumption at intervals for 24 days postoperatively. The caloric response to cold decreased progressively for 12 days before reaching a low value characteristic of the thyroidectomized animal; apparently the hormone stores decline in this period. Andersson *et al.*[49] measured urinary excretion of epinephrine and norepinephrine in normal and thyroidectomized goats. In animals with intact thyroids exposure to cold resulted in only a slight increase in urinary epinephrine but a threefold increase in norepinephrine. After thyroidectomy, urinary norepinephrine increased at room temperature; during exposure to cold both catecholamines were increased, with epinephrine elevated to about five times the pre-cooling value and about eight times the preoperative pre-cooling value. Rectal temperatures of the thyroidectomized animals were maintained in the cold.

TABLE 1. Oxygen Consumption Rates and Blood Sugar Levels of Non-shivering Rats Given Single Doses of Epinephrine and Norepinephrine*

	Oxygen Consumption Rate (ml./kg.$^{3/4}$/hour)		Ratio	Blood Sugar Level (mg./100 ml.)		Ratio
	Before Injection of Catecholamine	Maximum		Before Injection of Catecholamine	Maximum	
Rats with spinal transection at C2, response to epinephrine						
Warmth-adapted rats	640	950	1:5	158	340	2:1
Cold-adapted rats	950	1,710	1:8	157	287	1:8
Warmth adapted rats, thyroidectomized	370	490	1:3	196	303	1:5
Cold-adapted rats, thyroidectomized	490	660	1:3	156	283	1:8
Cold-adapted Rats paralyzed with *d*-tubocurarine						
Response to epinephrine	1,200	1,560	1:3	280	415	2:5
Response to norepinephrine	1,250	2,410	1:8	268	269	1:0
In cold environment	1,250	2,300	1:8	284	307	1:1

* Hsieh and Carlson.[43]

Two other effects were noted in the hypothyroid goats: (1) earlier and more intense shivering; and (2) elevated blood sugar levels. In the cold, blood sugar levels of euthyroid goats increased only 10–20 per cent, but in the thyroidectomized goats blood glucose increased from 40–50 to 150–180 mg./100 ml. blood. After adrenalectomy there was no significant rise in blood sugar or urinary epinephrine. These results support the view of Leduc that the hormone for non-shivering thermogenesis is norepinephrine. Epinephrine stored in chromaffin tissue can function as a second line of defense during severe-cold stress. The thyroid hormone sensitizes the muscle to norepinephrine thermogenesis. Thyroid insufficiency results in lowered efficiency of the norepinephrine-induced muscle thermogenesis; when this occurs, the stores of epinephrine in the adrenal medulla are utilized.

Results of recent investigations by Smith [50, 51, 52] have shown that multilocular brown adipose tissue plays an active part in non-shivering thermogenesis. This tissue, the "hibernating gland" originally discovered in the interscapular region of hibernating rodents, is found in a variety of mammals including non-hibernating rodents, cats, man and other primates.[53] In addition to the interscapular region, brown fat is found in the mid-dorsal cervical area, axillary region, and at numerous sites in the abdomen. Acute exposure of non-hibernating animals to cold initiates an immediate thermogenic response from brown fat. Prolonged exposure results in hyperplasia of tissue and in an increased metabolic rate per gram of tissue. Thus, the oxygen consumption of brown fat deposits may increase three- to six-fold in cold-acclimatized animals.[52]

The sympathetic nervous system innervates brown adipose tissue. The interscapular gland is innervated bilaterally; denervation on one side leads to vascular stasis of that side.[54] Norepinephrine infused into a cold acclimatized rat increases the blood flow to brown fat.[55]

Smith and Hock [50] have found that when an animal with brown fat is exposed to cold there is an immediate rise in temperature of the fat and the thoracic cage, before warming of other parts of the body. Smith [52] proposes that: (1) a portion of the increased metabolism of non-shivering thermogenesis is due to brown fat; and (2) cold-induced arousal from hibernation is caused by sympathetic stimulation of metabolism of brown fat.

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Anesthesia

Rh SENSITIZATION It has been speculated that administration of plasma containing anti-D antibody to Rh-negative sensitized women might prevent further production of anti-D antibodies with resultant fetal loss. Of 500 mothers passively immunized with anti-D plasma, 74 have been observed through the delivery of a subsequent Rh-positive baby. In none of these were antibodies present in the next observed pregnancy. In a series of 88 controls, 16 of the women became sensitized in the second observed pregnancy. It is believed that passively supplied anti-D plasma can prevent sensitization of D-negative mothers following the delivery of an Rh-positive baby. (*Hamilton, E. G.: Prevention of Rh Isoimmunization by Injection of Anti-D Antibody, Obstet. Gynec. 30: 812 (Dec.) 1967.*)