

Drugs used for regulation of body temperature and food intake 1

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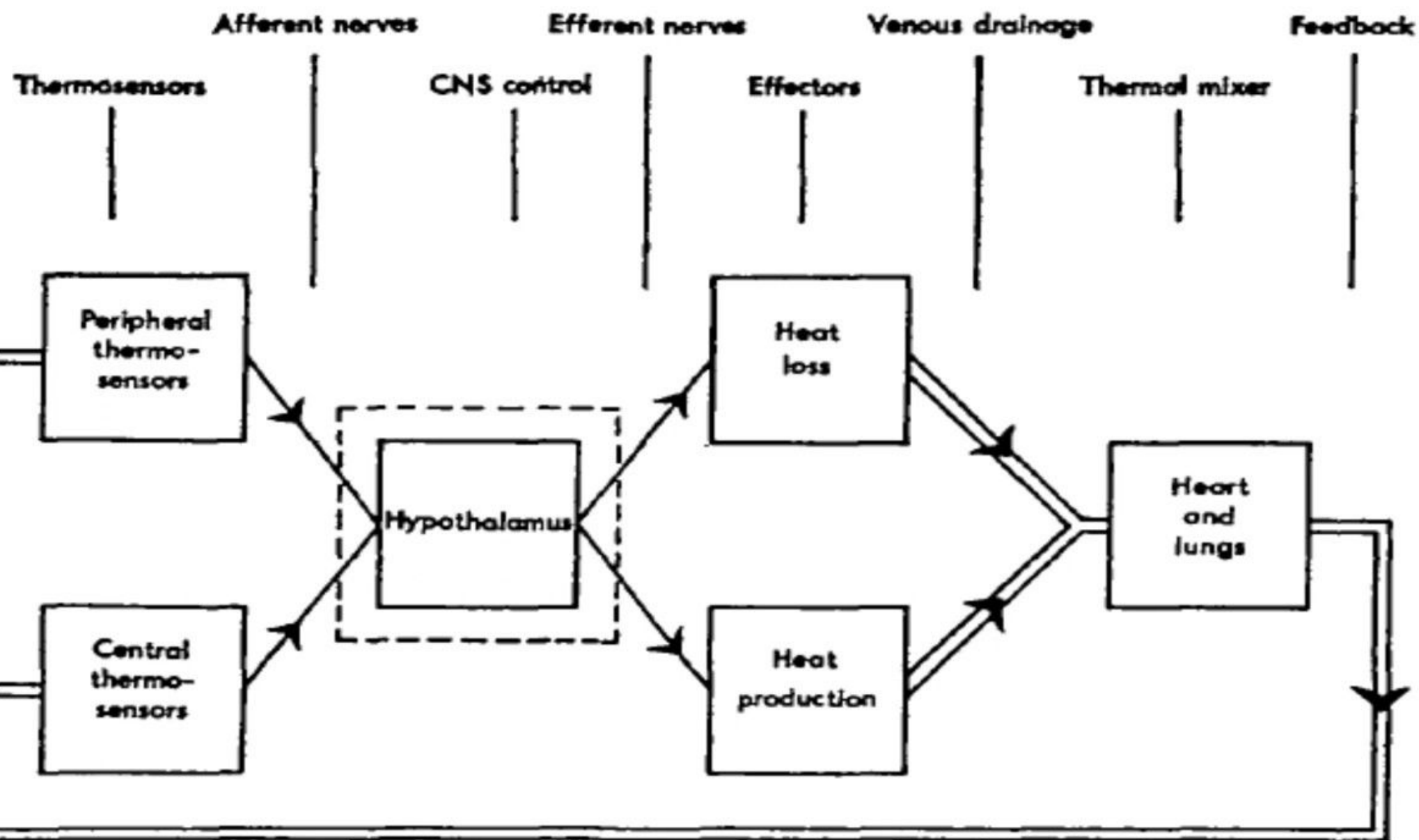
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DRUG AND HEAT

In health, the deep body-temperature of man remains relatively constant throughout his life-span. Deviations above or below a quite narrow range of body-temperature, which cannot be attributed to exposure to excessive heat or cold, are more often due to the effects of foreign substances than to idiopathic conditions. Many substances at some dose-level produce symptoms of toxicity which include a rise or fall in body temperature, but there is only incomplete understanding of the ways in which they act. There are often conflicting reports of the effects of such substances when they are administered at different dose-levels, by different routes, and to different mammalian species, but the greatest handicap in making statements about the influences of foreign substances upon thermoregulation is that the process itself is not fully understood.

The effector processes for heat production are shivering and nonshivering thermogenesis. Those for heat loss are peripheral vasomotor control, sweating, and panting

It is generally agreed that thermoregulation depends upon the integrity of the anterior hypothalamic region of the brain, into which information is fed by afferent nervous pathways from central and peripheral thermosensors, and from which appropriate control is exerted over the thermoregulatory effectors. The control of the effector organs is both neural and humoral. As with any control system, there is feedback from effectors to sensors, and this function is performed by the circulating blood. In the matter of drug action upon thermoregulation, the control system can be considered as being in two compartments, central and extra-central, separated by the blood-brain barrier. Peripheral thermosensors, the afferent pathways, the efferent pathways, and the effector organs are on the blood side of the barrier, and might be acted upon, if sensitive, by all substances entering the body enterally or parenterally. Central nervous structures, however, which may or may not include the hypothalamic thermosensors, depending on their precise location, will be affected directly only by substances which cross the blood brain barrier. The extra-central components of the thermoregulatory system may be further divided into neural, hormonal and effector structures.



Feedback to thermosensors via blood supply

In physiological terms, heat production is divided between shivering and non-shivering thermogenesis. Under usual circumstances the immediate response of a homoeotherm to a cold stress is the onset of shivering. The active translocation of monovalent and divalent cations during the muscle contraction cycle breaks down ATP to ADP and so stimulates respiration. In the absence of a cold stress, the fine balance between heat production and loss must depend on non-shivering thermogenesis, but which organs are involved is not known with certainty. Liver, kidney and intestine are important contributors. There is no evidence that the metabolic rate of the brain is under direct thermoregulatory control. Non-shivering thermogenesis gradually takes over from that of shivering during cold acclimation. It also predominates over shivering in the newborn, including the human infant. Although muscle contraction is under cholinergic control, the sympathetic nervous system has a regulatory role in both shivering and non-shivering thermogenesis. The calorogenic action of A and NA appears to be largely the result of their ability to mobilize oxidizable substrates. Free fatty acids are released from adipose tissue, and glycogen is broken down into glucose in the liver and skeletal muscle. These processes are initiated via the stimulation by the catecholamines of the formation of the enzyme modulator adenosine-3':5'-monophosphate

Theoretical Sites of Action of Drugs which Modify Thermoregulation

With this brief outline of biochemical thermoregulation several possible sites of interference by drugs can be suggested. Among these are:

- i. on mitochondria, a direct action, either on the enzymes of the respiratory chain, the supply of oxidizable substrates or the provision of ADP;
- ii. on the extra-central sympathetic nervous system, an action to block or enhance the release of catecholamines that will affect the mobilization of oxidizable substrates.
- iii. A drug that acts directly on the heat-producing organs to produce more heat will cause a rise in the temperature of the blood draining from the affected tissues. This will act upon the thermosensors and, provided that the central control processes are unaffected by the drug, the threatened rise in body temperature will be offset by an increase in heat loss through peripheral vasodilation and sweating. At high ambient temperatures, however, the remaining heat-loss potential may be inadequate to counter the elevated metabolism, and body temperature will then rise. If the central processes were also affected by the drug, compensatory heat loss might not occur and body-temperature would rise even at moderate ambient temperature.

iv. substances acting on the sensory side of the central nervous system (CNS) between the thermosensors and the hypothalamic control interfere with the sensory information upon which homoeothermy depends, and therefore have the effect of disrupting the feedback loop. This drug induced change in input signal to the hypothalamus would cause a change in the output signal to the thermoregulatory effectors, but the consequent change in blood temperature could not react upon central control. By both of these mechanisms, body-temperature would be affected even at moderate ambient temperatures.

No substance is known which interferes with both peripheral and central thermosensors. Stimulants or inhibitors of the peripheral thermosensors might be expected to cause some disturbance to the afferent input to the thermoregulatory centres.

Risk factors for heat-related illness

Poor general health and comorbidities	Cardiovascular disease Mental illness including dementia and confusion Respiratory disease Diabetes mellitus Obesity Hypertension or renal disease Substance misuse Excessive alcohol intake Neurological diseases, such as Parkinson's disease Acute illness	Socio-economic factors	Living alone Low socio-economic status with limited financial resources Poor-quality housing or homelessness Lack of use of or access to air conditioning at home Living in dense inner urban areas especially on the top floor Social isolation
Limited function, frailty and physical disabilities	Reduced mobility Confined to bed or housebound High dependency level Poor self-care or unable to care for themselves At risk of falls	Lifestyle factors	Playing outdoor sports or exercising outdoors Lack of access to health care Unnecessary outdoor excursions during the heat of the day Working outdoors

Which medicines are associated with an increased risk of dehydration or heat-related illness?

Many commonly prescribed medicines can increase the risk of heat-related illness via the following mechanisms:

- 1 Dehydration and electrolyte imbalance.
- 2 Impaired sweating.
- 3 Reduced thirst sensation.
- 4 Hypotension and reduced cardiac output, which may also increase the risk of fainting and falls.
- 5 Sedation and cognitive impairment which may reduce alertness, judgement and perception of heat and thirst.
- 6 Drug toxicity associated with reduced renal clearance of medicines in dehydrated people.
- 7 Altered central thermoregulation.

Possible effects

Antidepressants

Tricyclic antidepressants (TCAs)

For example amitriptyline

These medicines have strong anticholinergic effects

Selective serotonin reuptake inhibitors (SSRIs)

For example sertraline, citalopram and escitalopram

Serotonin and noradrenaline reuptake inhibitors (SNRIs)

For example venlafaxine, duloxetine and desvenlafaxine

Mirtazapine

Altered central thermoregulation associated with antidepressants that have anticholinergic effects

Impaired sweating – increased with SNRIs and SSRIs, decreased with TCAs

Sedation and cognitive impairment: reduced alertness, judgement and perception of hot weather

Hypotension and reduced cardiac output associated with TCAs may increase risk of fainting and falls

SSRIs commonly associated with hyponatraemia include sertraline, fluoxetine, paroxetine and citalopram^{15,16}

Venlafaxine may also contribute to hyponatraemia.^{15,16}

Anticonvulsants

For example pregabalin, gabapentin and sodium valproate

Sedation and cognitive impairment: reduced alertness, judgement and perception of hot weather

Ataxia, impaired balance, dizziness and blurred vision, especially on initiation/increase in dose: increased risk of fainting and falls.

Antipsychotics (typical and atypical)

For example risperidone, olanzapine, quetiapine and haloperidol

Impaired sweating

Altered central thermoregulation

Hypotension and reduced cardiac output may increase risk of fainting and falls

Sedation and cognitive impairment: reduced alertness, judgement and perception of hot weather

Medicines with anticholinergic effects

For individual medicines see:

www.veteransmates.net.au/TB_anticholinergic

Altered central thermoregulation

Sedation and cognitive impairment

Impaired sweating

Hypotension and reduced cardiac output may increase risk of fainting and falls

Dizziness

Diuretics, ACE inhibitors, ARBs and other medicines for hypertension

Hypovolaemia

Postural hypotension increased risk of fainting or falls

Dehydration, causing

- Reduced visceral blood flow to the liver and kidneys
- Reduced clearance of medicines and toxins electrolyte imbalances, including hyponatremia (commonly associated with indapamide, hydrochlorothiazide and furosemide)^{15,16}

Reduced thirst sensation

Renal impairment – increases risk of hyperkalaemia

Benzodiazepines and opioids

Sedation and cognitive impairment reduced alertness, judgement and perception of hot weather

Increased risk of falls

Other medicines

In dehydrated patients, drug toxicity may result from reduced renal clearance of medicines

Novel oral anticoagulants (including dabigatran, rivaroxaban and apixaban)

Oxycodone

Morphine

Gliptins and metformin

Dapagliflozin

Canagliflozin

Lithium

Digoxin