Endocrine effects of heat exposure: Is it relevant to climate change?

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Abstract

Climate change is causing higher seasonal temperatures and more frequent and severe heat extremes. As the endocrine system facilitates physiological adaptations to temperature changes, diseases with an endocrinological basis have the potential to affect thermoregulation and increase the risk of heat injuries. The impact of climate change and chronic high temperature exposure on endocrine axis development and function, and on the prevalence and severity of diseases associated with hormone deficiency or excess, is unclear. This Perspective a) summarises current knowledge relating to the hormonal effects of heat exposure in species ranging from rodents to humans; b) describes the potential impact of high temperature exposures on patients with endocrine diseases; and c) highlights the need for more basic science, clinical and epidemiological research into the effects of heat on endocrine function and health so that interventions can be developed for people most at risk, in the context of rising environmental temperatures.

Introduction

Global mean surface temperatures are rising by 0.2°C per decade because of climate change[1]. Consequently, seasonal temperatures are higher, heatwaves more frequent, prolonged and intense, and daily temperatures higher in most countries[1,2]. Hormones are involved in mediating physiological adaptation to temperature changes, which is likely impaired by endocrine diseases leading to increased risk of heat injury or heat-related health effects in patients[3]. However, the effect of high temperatures, particularly in the context of climate change, on endocrine function, disease progression and population health are unclear. This Perspective addresses the hormonal consequences of heat exposure with a focus on key stages of the life course and potential impact on patients with endocrine diseases. Furthermore, we highlight the paucity of knowledge in this area and emphasise the need for more research, education and healthcare provision relating to the impact of climate warming on endocrine health.

Endocrine adaptions to heat

Humans have a core temperature of ~37°C, mainly achieved through metabolic processes generating heat. The range of ambient temperatures at which the body can maintain this core temperature solely through dry (non-sweating) heat loss is known as the thermoneutral zone[4]. Physiological adaptation to heat involves activation of thermoreceptors mainly in the skin, muscle, viscera and brain, which relay sensory inputs to the preoptic area (POA) of the anterior hypothalamus[5,6]. In rodents, the POA triggers autonomic responses that suppress brown adipose tissue (BAT) thermogenesis and promote heat loss by stimulating cutaneous vasodilation to restore thermoneutrality[5-7]. In humans, POA activation is associated with autonomic responses inducing sweating in response to heat[8].

Thermodysregulation may cause heat stress, which if prolonged or excessive leads to core temperatures above the thermoneutral zone and cause heat injuries such as heat exhaustion or life-threatening heat stroke, or have other health effects ranging from sports injuries to exacerbations of pre-existing chronic cardiac, renal or metabolic diseases[2,9]. Physical exertion and exercise exacerbate thermodysregulation and cause heat stress, which arises when metabolic heat from muscle activity exceeds

the capacity for heat dissipation[10]. The ability to cope with exertional heat stress is influenced by the cardiovascular system's capacity to dissipate heat through increased skin blood flow whilst maintaining adequate tissue perfusion to support metabolic demands during exercise[10]. Sweating is the primary heat-loss mechanism during exercise and results in high rates of fluid loss. Inadequate fluid replacement may decrease plasma volume which further exacerbates exertional heat stress and causes cardiovascular strain[10].

The role of the endocrine system in facilitating adaptation to heat during rest and exercise is not fully elucidated. Studies in many species have demonstrated that acute and chronic heat exposure affects numerous hormones (Table 1). Hormones with possible roles in adapting to heat include cortisol, thyroid hormones, arginine vasopressin (AVP), prolactin, growth hormone (GH), insulin and adipokines (Figure 1). Their roles are described below.

Heat induces a stress hormone response

Exposure to heat induces a stress response characterised by activation of the autonomic nervous system and hypothalamic-pituitary-adrenal axis which in healthy humans acutely increases noradrenaline and cortisol secretion[11-13]. Plasma cortisol, which is mainly bound to corticosteroid binding globulin (CBG) is a sensitive heat stress marker with values correlating with acute elevations in core temperature and body heat storage in healthy humans[11]. A rise in temperature within the clinically relevant range of 35-42℃ may also cause free cortisol concentrations to increase due to release of cortisol from CBG[14]. Prolonged heat exposure in rats (32℃ for 7 days) additionally led to pituitary and adrenal gland enlargement in association with increased serum adrenocorticotropic hormone (ACTH) and cortisol concentrations compared to rats at 24℃[15].

The influence of cortisol and catecholamines on thermoregulation is unclear. In rabbits and rats, these hormones may induce physiological adaptation to heat by acting directly on the POA (Figure 1)[16,17]. Other hormones involved in the stress response include AVP, prolactin and GH (described below).

Suppression of thyroid axis activity may decrease thermogenesis and increase heat loss

Thyroid hormones regulate metabolism and their secretion is influenced by changes in ambient temperature[18]. Indeed, direct cooling of the POA is reported to increase TSH secretion in rats[19]. Thyroid hormones increase core temperature by promoting obligatory thermogenesis through effects on cell metabolism and mitochondrial activity, which in turn elevate basal metabolic rate[20]. When this is insufficient, thyroid hormones will stimulate adaptive thermogenesis, mainly mediated by BAT in small mammals, and decrease blood flow-mediated heat dissipation[20]. Heat stress can suppress plasma TSH, T_4 and T_3 concentrations as shown in cattle exposed to daily temperatures of 32-40°C compared to cattle maintained at 19°C[21]. Suppression of the thyroid axis also occurs in humans: exertional heat stroke in military recruits, which was associated with a decrease in serum T_3, reciprocal increase in reverse T_3 and inappropriately normal serum TSH concentrations[22]. These findings indicate that heat injury may have caused non-thyroidal illness syndrome and impaired peripheral conversion of T_4 to T_3. The low T_3 state may aid thermoregulation by decreasing metabolic heat generation; hence, exogenous T_3 administration to chickens shortens the duration of survival during heat exposure[23].

Heat also promotes the release of T_4 from thyroxine binding globulin (TBG), which is likely beneficial for increasing metabolism in response to fevers induced by infection and inflammation[24]. However, this response may be detrimental to individuals living with high temperature exposures. Intriguingly, two missense TBG variants, p.Ala191Thr and p.Leu283Phe, which are co-expressed in aboriginal Australians are reported to confer thermal protection by reducing the release of T_4 in response to heat whilst maintaining TBG storage and carrier functions[24].

Arginine vasopressin and aldosterone regulate water balance in response to heat

In individuals with adequate fluid and electrolyte intake, circulating plasma volume and total body water increase after heat acclimation or acclimatization[25]. These adaptations support thermoregulation by increasing the capacity for heat loss. However, the elderly, patients with chronic diseases, and people working in hot environments are often dehydrated and may therefore have limited ability to dissipate heat by increased blood flow or sweating.

Regulation of water balance in response to heat is likely mediated by increased secretion of AVP and aldosterone, which decrease water and sodium excretion, respectively[25]. In humans, activation of the renin-angiotensin-aldosterone axis occurs within minutes of acute heat stress as shown in healthy young men exposed to sauna heat (85-90℃), and may be mediated by increased circulating catecholamines or decreased renal blood flow, both of which increase renin secretion (Figure 1)[26]. AVP may be released as part of the stress response to heat exposure and its secretion is sensitive to changes in core temperature in humans. A small (≤1°C) elevation potentiates AVP secretion and increases thirst and water intake following hypertonic saline infusion[27]. Heat-induced AVP secretion may also contribute to exercise-associated hyponatraemia in endurance athletes[28].

Rat studies suggest a thermoregulatory role for AVP: intravenous AVP injection acutely decreased,, and a vasopressin V1 receptor antagonist increased, body temperature[29]. AVP functions as a neurotransmitter acting on the rat POA, likely via the vasopressin V1a receptor, to excite warm-sensitive neurons that inhibit BAT thermogenesis and promote heat loss (Figure 1), whilst inhibiting cold-sensitive neurons that promote thermogenesis and heat retention[30].

Prolactin and GH secretion may promote heat loss via sweating

Prolactin and GH are homologous peptides that exert hormonal and cytokine effects[31]. Prolactin facilitates maternal adaptation during pregnancy and stimulates lactation postnatally, whilst GH promotes linear growth in childhood and may also increase cellular senescence in adulthood[32,33]. In sauna and warm water immersion studies, exposure to temperatures ranging from 44-85℃ acutely increased plasma prolactin in healthy humans, whereas increases in plasma GH occurred in younger, but not older, men[34-36]. Increases in prolactin and GH may form part of the stress response to heat exposure. Indeed, prolactin acts directly on the hypothalamus, pituitary and adrenal glands and stimulates the secretion of corticotropin-releasing hormone, ACTH and cortisol[37,38].In addition, these hormones may have thermoregulatory roles. In an exercise-heat stress study involving healthy young men, serum GH levels were positively correlated with whole body sweat production, highlighting that GH and/or its downstream mediator, IGF-1, may act on

sweat glands to promote evaporative heat loss (Figure 1)[39]. In keeping with this, adult GH deficient patients have a decreased density of acetylcholinesterase- and vasoactive intestinal peptide-positive nerves supplying sweat glands, which significantly increased following recombinant human GH treatment[40]. Prolactin may also promote sweating (Figure 1) as a dopamine receptor agonist, which inhibits prolactin secretion, significantly decreased sweating and plasma prolactin concentrations in healthy young men during an exercise-heat stress study[41]. Furthermore, dairy cattle harbouring a germline *PRL* mutation, p.Cys221Gly, had decreased sweating associated with higher rectal temperatures and a heat stress response characterised by increases in respiration rate[42].

Insulin sensitivity may increase or decrease in response to heat

Insulin regulates post-prandial tissue uptake, storage and metabolism of glucose, lipids and amino acids[43]. Heat exposure may influence the responsiveness of target tissues to insulin. However, the evidence is conflicting. In aged rats, acute heat exposure, which raised core temperature to 41℃ for 20 minutes, increased insulin-stimulated glucose uptake in skeletal muscle consistent with increased insulin sensitivity[44]. The effect was associated with induction of heat shock protein expression that may enhance insulin signalling, and protect against insulin resistance by maintaining mitochondrial function and decreasing reactive oxygen species[45,46]. Increased insulin sensitivity leading to utilisation of glucose as an energy substrate may help adapt to heat exposure as conversion of glucose to ATP is associated with less metabolic heat generation compared to fatty acid oxidation[47]. However, a study involving overweight men showed no effect of ~34℃ heat exposure over 10 days on insulin sensitivity as assessed by hyperinsulinaemic euglycaemic clamp, although fasting plasma glucose and insulin concentrations were decreased[48].

Higher ambient temperatures have also been associated with insulin resistance in humans as evidenced by a population-based study which showed that insulin resistance, measured by the homeostasis model assessment, was positively correlated with mean annual temperature, with the association persisting after adjusting for physical activity[49]. Heat-induced insulin resistance may be caused by dehydration, which

impairs insulin signalling[3,50], or by decreased BAT activity which increases fatty acid flux to metabolically active tissues such as skeletal muscle, thereby decreasing insulin-mediated glucose uptake by these tissues[51].

Heat affects adipose tissue and promotes adipokine secretion

Adipose tissue is involved in energy storage and release, thermal insulation and hormone secretion[52]. Heat exposure affects brown and white adipose tissue (WAT). In rodents, BAT rapidly becomes deactivated following an increase in ambient temperature, thereby reducing excess heat generated by thermogenesis[6]. In mice, heat also affects WAT and activates heat shock factor-1, which triggers WAT browning to beige fat[53]. This may have anti-obesogenic effects and local hyperthermia administered to mouse inguinal WAT over 10 weeks reduced fat mass and body weight[53]. Reduction of total body WAT may promote heat adaptation by reducing insulation and enhancing heat dissipation.

In addition, exposure to 35°C heat over 5 days in mice increased adipose tissue expression of adiponectin and leptin, hormones that sensitise peripheral tissues to insulin and promote insulin-mediated glucose uptake[47]. Plasma leptin concentrations were also increased in military recruits exercising in 30°C heat compared to those exercising in temperate (21°C) or cold (-10°C) conditions[54]. Heat-induced leptin secretion, in addition to increasing insulin sensitivity, may decrease metabolic heat production by acting centrally to reduce appetite and food intake and suppress BAT thermogenesis (Figure 1)[55]. This may explain why activation of leptin receptor-expressing POA warm-sensitive neurons in mice decreased core temperature in association with decreases in energy expenditure and food intake[55]. However, increased plasma leptin in humans exercising in heat was not associated with changes in appetite or dietary intake[54]. In addition, gut hormones do not mediate heat-related appetite suppression[56]. A study involving healthy men at rest showed that exposure to 30°C heat for 5.5 hours significantly decreased *ad libitum* energy intake without altering the plasma concentrations of acylated ghrelin, an orexigenic hormone, or peptide tyrosine-tyrosine (PYY) and glucagon-like peptide 1 (GLP1), which are anti-orexigenic hormones[56].

In summary, these studies indicate that hormones may mediate adaptation to heat by exerting central or peripheral effects to suppress thermogenesis, or may act peripherally to increase cutaneous heat dissipation or decrease the renal excretion of water and electrolytes (Figure 1). However, many of these studies were performed in non-human animal models, and the influence of hormones on human thermoregulation remains to be elucidated.

Effects of heat on endocrine development and hormones mediating key stages of the life course

Hormones play essential roles in key life stages such as childhood growth, puberty, reproduction and pregnancy, lactation and the menopause. Here, we summarise evidence for the potential effects of heat exposure on the endocrine regulation of these processes.

In utero, childhood and puberty

Early life exposure to high temperatures may have adverse effects on child health[57]. However, it is unclear if heat exposure affects *in utero* or postnatal endocrine axis development in humans. Limited data from rodents indicate that intrauterine heat exposure may affect fetal endocrine development. Pregnant rats exposed to 43°C heat for 15 minutes had pups with brain malformations in association with decreased adrenal size and reduced numbers of pituitary somatotrophs[58]. Moreover, pre-pubertal rats acutely exposed to heat had pituitary and adrenal degeneration with decreased serum corticosterone concentrations[59].

Pubertal timing in girls and boys is progressively occurring earlier due to multiple putative causes including metabolic disorders such as obesity and environmental exposures such as endocrine disrupting chemicals[60-62]. However, it is unknown if heat exposure influences the onset of puberty, which is regulated by hypothalamic kisspeptin-expressing neurons that activate gonadotrophin releasing hormone (GnRH) neurons[60,63]. In pigs, persistently increased ambient temperatures during the summer decreased hypothalamic kisspeptin expression, associated with reduced serum concentrations of GnRH, luteinising

hormone and follicular stimulating hormone[64]. These findings highlight a potential mechanism by which heat could influence pubertal onset via effects on hypothalamic kisspeptin.

Reproduction, pregnancy and birth outcomes

The hypothalamic-pituitary-gonadal axis regulates cyclical changes of the female reproductive tract, including ovulation and endometrial development for embryo implantation[65]. Heat affects the rodent reproductive cycle, which lasts 4-5 days and is associated with endometrial resorption in the absence of fertilisation[66]. Female rats repeatedly exposed to 38°C heat had decreased serum oestradiol and progesterone concentrations, and prolonged dioestrus (luteal phase)[67]. However, it is unclear if heat exposure affects the human menstrual cycle with lasts around 28 days and is associated with endometrial shedding[66]. A retrospective study involving >300,000 women showed no substantial effect of ambient temperature on menstrual cycle length[68]. Moreover, menstrual cycle phase appears not to affect heat tolerance: a direct calorimetry study involving healthy exercising women showed no effect of the menstrual cycle phase on heat production or loss[69].

Heat exposure transiently decreases plasma testosterone and spermatogenesis in bulls and rats and impairs fertility in men[70-72]. However, the evidence is less clear for effects on fertility in women. A prospective study of women evaluated for infertility showed that exposure to higher ambient temperatures in the 90 days preceding a pelvic ultrasound scan was associated with a decreased antral follicular count, an indicator of ovarian reserve[73]. The underlying cause is unclear although cultured ovarian follicles from dairy cattle exposed to 41°C heat over 48 hours showed decreased steroid hormone synthesis and premature luteinisation of follicular cells, which is associated with reduced fertility[74].

Pregnancy affects maternal thermoregulation and pregnant women persistently exposed to increased temperatures may have an increased risk of maternal complications such as gestational diabetes mellitus (described below)[75,76]. Epidemiological evidence indicates that heat exposure during pregnancy is teratogenic and increases risk of adverse birth outcomes such as preterm birth, stillbirth and low birth weight[76], that can be manifestations of poor placentation. It is unknown whether pregnancy hormones

influence these adverse outcomes although exposure to 40°C heat for 7 days during early pregnancy in mice caused autophagy of steroidogenic cells within the corpus luteum, which was associated with decreased serum progesterone concentrations and impaired embryo implantation[77].

Lactation

Lactation is regulated by prolactin and oxytocin, which promote milk synthesis and let-down, respectively[33]. Human data are lacking on how heat affects lactation although the time spent breastfeeding decreases during periods of high ambient temperature[78]. In contrast, decreased milk yield is the most recognised consequence of heat exposure in dairy cows and occurs despite heat causing a paradoxical increase in circulating prolactin concentrations[79,80]. Heat-related decreased milk yield in livestock has multiple causes including reduced food intake and direct effects of heat on mammary cells, which alter the expression of genes involved in prolactin and oestrogen signalling and impair metabolic processes mediating milk synthesis[80,81]. Moreover, in hypothalamic, pituitary and mammary gland tissues from heat-stressed cows, there was altered expression of long noncoding RNAs regulating target genes involved in pituitary secretion of thyroid and growth hormones and mammary oxytocin and prolactin signalling pathways[82].

Menopause

Menopause is characterised by neuronal and hormonal changes, including oestrogen deficiency, that impair thermoregulation mediated by the POA[83], leading to increased heat dissipation manifesting as hot flushes affecting around 80% of postmenopausal women[83,84]. However, it is unclear whether changes in ambient temperature exacerbate menopausal symptoms. Although one study found no association between hot flushes and season or temperature[85], the effect of rising temperatures on menopausal symptoms warrants further investigation. It also remains to be determined if menopause-related thermodysregulation increase the risk of heat injuries.

In summary, a small number of studies, mainly involving rats, have shown that heat exposure affects fetal and pre-pubertal pituitary and adrenal glands, alters the reproductive cycle and may reduce fertility. Heat is also recognised to impair lactation in cows, perhaps in part due to effects on mammary hormone signalling. The effect of heat on puberty and the menopause is unknown.

Effects of heat on chronic endocrine diseases

Evidence is emerging that rising global temperatures may be linked to an increase in diabetes mellitus cases. Some endocrine diseases have the potential to cause maladaptive thermoregulatory responses and increase the risk of heat injury by either impairing heat dissipation due to sweat gland dysfunction or reduced cutaneous blood flow, or causing increased renal water excretion and dehydration. This is discussed below.

Diabetes mellitus

Diabetes mellitus affects around 530 million people worldwide with type 2 diabetes mellitus (T2DM) accounting for 96% of all cases[86]. The prevalence of T2DM is expected to increase as a consequence of obesity and demographic shifts with around 1.3 billion people predicted to be affected by 2050[86]. Meta-regression analysis has demonstrated an association with higher mean annual outdoor temperatures and increasing diabetes incidence in the USA and prevalence of glucose intolerance worldwide[51]. The prevalence of gestational diabetes mellitus may also be associated with higher temperature[75]. These epidemiological studies are supported by passive heating experiments involving human subjects, which showed that short-term exposure (≤4hrs) to elevated ambient temperatures increases glucose intolerance in diabetic and non-diabetic subjects[87].

Diabetes is a risk factor for heat-related mortality and heat-related hospital admissions[88]. In a US study, diabetic patients had a 17% increased risk of dying on hot days than other subjects[89]. The increase in heat-related morbidity and mortality may be due to a range of possible causes. For example, diabetic patients are susceptible to water loss and dehydration, which may increase the risk of hospitalisation due to renal complications or hyperosmolar hyperglycaemic state[90]. Diabetes is also associated with decreases in dermal

blood flow and heat dissipation[91]. In men with T2DM, reduced sweat evaporation during exercise was associated with increases in body temperature and cardiovascular strain[92]. In addition, diabetes and heat exposure are both coronary artery disease risk factors, and so diabetic patients exposed to heat extremes may potentially have a higher cardiovascular event burden.

Endocrine disorders with potential effects on thermoregulation

Thyroid disorders are associated with impaired thermoregulation. Although hyperthyroidism is characterised by heat intolerance, which likely exacerbates heat injuries, the consequences of heat exposure at the population level on thyroid disorders are largely unknown and clinical data are restricted to individual case reports. In one case, heat stroke was the presenting feature of hypothyroidism[93]; in another, fatal heat stroke was associated with Hashimoto's thyroiditis, a common cause of hypothyroidism[94]. This suggests that while hypothyroidism is typically characterised by cold intolerance, it might paradoxically predispose to heat injuries by impairing sweating.

Adrenal insufficiency and hypocortisolaemia may also impair thermoregulation as some patients with adrenal insufficiency have low or high body temperatures[95,96]. Rats with adrenal insufficiency have decreased resistance to 37-40°C heat and exhibit a higher colonic temperature when exposed to heat compared to healthy controls[97]. These findings suggest a decreased ability to dissipate heat[97].

GH deficiency may impair thermoregulation due to decreased sweating[98], as evidenced by a study of young affected adults, who exercised in heat and developed hyperthermia in association with decreases in sweat secretion rate and sweat gland sensitivity to core temperature[98].

Arginine vasopressin deficiency, a disorder of water regulation associated with hypohydration and impaired heat dissipation[99], is reported to cause increased body temperature and has been diagnosed in a patient with heat stroke[100,101].

In summary, diabetes is a risk factor for heat-related morbidity and mortality. Case reports and small studies indicate that thyroid disorders, adrenal insufficiency, and deficiencies of GH or AVP may also increase

susceptibility to heat injuries. Large-scale epidemiological studies are required to determine the impact of higher environmental temperatures on endocrine patients.

Managing heat exposure in endocrine patients

Managing heat exposure in chronic endocrine conditions requires the involvement of patients, physicians, health services, community health workers and social services, and professional organisations (Figure 2)[3]. Detailed assessment of endocrine patients allows clinicians to provide targeted advice on heat avoidance and personal cooling strategies. Screening tools can also be used in primary care to identify patients at high risk of heat injuries, other health events or death. One reported tool incorporates quantitative environmental data such as ambient temperature and humidity, and physiological measures such as heart rate and core temperature into a heat stress risk formula, whilst another tool employs a qualitative assessment of environmental, physical and social risk factors[102,103]. These screening tools require careful evaluation and have limited use without social information, such as housing type that is a major determinant of heat-related mortality.

Patients should be encouraged to take individual measures during hot weather such as maintaining adequate fluid intake, consuming cold drinks, using cooling vests and incorporating periods of rest in cooled environments. Hydration is essential as water deficits impair thermoregulation and are associated with increased core temperature, particularly during physical exertion[104]. Adopting healthy lifestyle measures such as regular aerobic exercise will improve cardiovascular fitness and help acclimatise to higher temperatures[104].

Physicians should be aware that drugs affecting endocrine systems or used to treat diabetes may affect thermoregulation and exacerbate heat injury and heat-related health events. For example, one study involving patients aged ≥65 years with chronic conditions showed that treatment with ACE inhibitors, angiotensin receptor blockers or loop diuretics, which have the potential to cause dehydration (Table 2), increased the risk of heat-related hospitalisations[105]. In addition, oxybutynin which is used to treat diabetic overactive bladder, and may also suppress sweating, has caused heat stroke in elderly patients[106,107]. Other

drugs that may affect thermoregulation include exogenous T_4 and T_3; β3 adrenergic receptor agonists that may increase metabolic heat generation, whilst non-selective β-blockers such as propranolol may impair cutaneous vasodilation and the capacity for heat dissipation, and sodium-glucose co-transporter-2 (SGLT2) inhibitors, which are used to treat T2DM, that may cause polyuria and dehydration (Table 2)[6,108].

Injectable hormone replacement therapies ranging from insulin to parathyroid hormone are used to manage endocrine conditions. These biologics are sensitive to temperature extremes and physicians should educate patients about the effect of heat on peptide stability and absorption, and provide guidance on the correct storage of medications during hot weather[3]. Pharmacies and other health facilities should store drugs in air-conditioned environments, where possible, and monitor the temperature of refrigerators containing drug stocks.

Improving education about the risks of heat

Health services and professional organisations such as endocrine societies can support physicians and patients by developing educational programmes and patient-based information on the risks of heat (Figure 2). In particular, greater awareness is required about endocrine conditions such as diabetes, hypothyroidism or hyperthyroidism, and adrenal insufficiency impairing thermoregulation and potentially increasing susceptibility to heat injuries. Heat exposure is an environmental and occupational health hazard that should be included on medical school curricula and training provided to clinical trainees, nursing staff and endocrinologists on how to integrate heat prevention and mitigation measures into the clinical care of high-risk endocrine patients[3,104]. Endocrine societies and physician organisations also have a role to play in advocating for policies to tackle global warming such as promoting energy efficiency and shifting energy production from fossil fuels to renewable sources.

The need for further research

It is currently unclear whether increased heat exposure as a consequence of climate change has adverse effects on endocrine health. Epidemiological data are lacking for endocrine patients living in hot climates,

and the impact of age, sex, pregnancy, comorbidities and medications on heat-related clinical outcomes in these patients is unknown. Multi-disciplinary research involving the endocrine and global health research communities is required to evaluate the impact of rising temperatures and heatwaves on endocrine patients and efforts should be focused on populations living in low- and middle-income countries with limited access to space cooling, which have the greatest health burden. Research efforts should also prioritise establishing heat thresholds for adverse endocrine effects and developing low-cost interventions to facilitate heat acclimatisation and prevent heat injuries and other heat-related health events in endocrine patients (Box 1).

A combination of basic science and clinical research is also required to assess the effects of acute and chronic heat exposure on hormone secretion and action, and determine whether hormonal changes occur as a direct consequence of heat exposure or arise secondary to pathophysiological changes such as hypovolaemia or cardiovascular strain (Box 1). Endocrine adaptation to heat has been incompletely characterised and data are lacking for a range of endocrine axes such as parathyroid-kidney-bone. Furthermore, there is a paucity of research involving humans, with studies largely historical and generally limited to acute heat exposure in healthy male volunteers, military recruits and athletes[104]. Despite substantial insights into thermoregulation being generated from non-human animal models, there are limitations with translating findings from these models to the human setting. This is particular apparent for small mammals such as mice which have a greater surface area-to-volume ratio, higher basal metabolic rate and a higher thermoneutral zone of around 30°C compared to 20-22°C for clothed humans[109,110]. In addition, there are differences between humans and other large mammals. For example, heat generation from microbial fermentation of feed contributes to thermoregulation in cows, whilst pigs lack functional sweat glands and instead dissipate heat through respiration and changes in body posture[111,112].

Moreover, the influence of genetics and epigenetics on endocrine adaptation to extreme heat remains to be elucidated. Whole genome and epigenome profiling of populations acclimatised to hot climates may yield insights into genetic variants and epigenetic alterations protecting against heat injuries.

Climate change is also causing higher levels of humidity, worsening air pollution, increased environmental chemical contamination, and affecting water supplies[2,57]. These hazards can exacerbate heat-

related health outcomes[2], and should be considered when developing studies to assess the impact of rising temperatures on endocrine patients.

Concluding statement

Climate change is likely to accelerate without significant action on decarbonisation, leading to increased heat exposure in the coming decades. A greater understanding of the impact of heat on endocrine health is required so that effective interventions can be developed for patients most at risk from rising environmental temperatures.

Glossary

Adipokine: hormone secreted by adipose tissue.

Ambient temperature: Average temperature of a gaseous or liquid environment, usually air or water, surrounding a body[9].

Heatwave: Period of extreme high temperature lasting several days or longer[113].

Heat (or thermal) stress: Ineffective dissipation of metabolic heat in hot environments and/or during physical exertion or exercise[113].

Heat acclimation: Repeated periods of heat exposure conducted in artificial or laboratory settings[25].

Heat acclimatisation: Repeated periods of heat exposure in natural environments[25].

Heat injury: Adverse health outcome, usually heat exhaustion or heat stroke, caused by increased core temperature due to sustained or excessive heat stress.

Heat exhaustion: Characterised by hyperthermia during exercise or exposure to environmental heat. Symptoms include fatigue, muscular weakness and dizziness[9]. Can progress to heat stroke if untreated.

Classic heat stroke: Characterised by central nervous system dysfunction and hyperthermia due to heat exposure while at rest.

Exertional heat stroke: Characterised by central nervous system dysfunction and hyperthermia caused by physical exertion or exercise.

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Competing interests

None

Author contributions

F.M.H., M.K.S.L., J.K.W.L., S.K., and T.E. researched data for the article and wrote the manuscript. S.H.K. and R.V.T. reviewed and edited the manuscript. All authors made substantial contributions to discussion of the content.

Table 1. Reported effects of heat exposure on hormone secretion or expression.

Endocrine axis or pathway	Type of heat exposure	Effect on hormone[a]	Species[b]	References
Stress hormone response				
CRH	Acute[c]	↑	Chicks	114
ACTH	Chronic[d]	↑	Rats	15
Cortisol	Acute (climatic chamber)[e]	↑	Humans	11
	Chronic[d]	↑	Rats	15
Adrenaline	Acute (water bath)[f]	↔	Humans	34
	Acute, exercise-heat stress[g]	↔	Humans	12
Noradrenaline	Acute (water bath)[f]	↑	Humans	34
	Acute, exercise-heat stress[g]	↑	Humans	12
Water balance				
AVP	Acute (water bath)[h]	↑	Humans	27
	Acute[i]	↑	Sheep	115
Aldosterone	Acute (sauna)[j]	↑	Humans	26
Growth hormone				
GHRH	Acute (sauna)[k]	↑	Humans	36
Growth hormone	Acute (sauna)[k]	↑	Humans	36
	Acute, exercise-heat stress[l]	↑	Humans	39
Thyroid				
TSH	Acute, exertional heat stroke[m]	↔	Humans	22
	Chronic (climatic chamber)[n]	↓	Steers	21
T4	Acute, exertional heat stroke[m]	↓	Humans	22
	Chronic (climatic chamber)[n]	↓	Steers	21
T3	Acute, exertional heat stroke[m]	↓	Humans	22
	Chronic (climatic chamber)[n]	↓	Steers	21
Hypothalamic-pituitary-gonadal				
Kisspeptin	Chronic, seasonal[o]	↓[p]	Pigs	64
GnRH	Chronic, seasonal[o]	↓	Pigs	64
LH	Chronic, seasonal[o]	↓	Pigs	64
FSH	Chronic, seasonal[o]	↓	Pigs	64
Oestradiol	Chronic, seasonal[o]	↓	Pigs	64
	Chronic (climatic chamber)[q]	↓	Rats	67
Testosterone	Acute, exertional heat stroke[r]	↓	Rats	71
	Chronic[s]	↓	Bulls	70
Pregnancy and lactation				
Progesterone	Acute (water bath)[f]	↑	Humans	34
	Chronic (climatic chamber)[q]	↓	Rats	67
Prolactin	Acute (water bath)[f]	↑	Humans	34
	Acute (sauna)[j]	↑	Humans	35
	Chronic	↑	Cows	79
Oxytocin	Acute[i]	↑	Sheep	115
Pancreas and gut				
Insulin	Chronic (climatic facility)[t]	↑	Cows	116
	Chronic (climatic chamber)[u]	↑	Mice	47
Ghrelin	Acute (climatic chamber)[v]	↔	Humans	56
PYY	Acute (climatic chamber)[v]	↔	Humans	56

Glucagon-like peptide 1	Acute (climatic chamber)[v]	↔	Humans	[56]
Adipose tissue				
Leptin	Acute, exercise-heat stress[w]	↑	Humans	[54]
	Chronic (climatic chamber)[u]	↑	Mice	[47]
Adiponectin	Chronic (climatic chamber)[u]	↑	Mice	[47]

Acute refers to sustained or intermittent heat exposure lasting <24hr. Chronic refers to sustained or intermittent heat exposure lasting >24hr.

[a]↑, increased; ↓, decreased; ↔, no effect.

[b]Reported thermoneutral zones: chicks 29-30°C[117]; mice 29-31°C[110]; rats 29-31°C[118]; dairy cows 0.5-20°C[119]; pigs <18-27°C[120]; sheep 12-27°C[121]; clothed humans 20-22°C[110].

[c]40°C for 6 hours.

[d]32°C for 8 hours daily over 7 days.

[e]48-55°C for ≤3hr with vapour pressure ranging between 15-34 Torr.

[f]Lower body warming in 44°C water bath for ~60min.

[g]Subjects exercised on cycle ergometer for ~45min at 19-21°C and 35-45% relative humidity with or without excess clothing.

[h]Lower body warming in 41°C water bath for 120 min.

[i]48°C for ~120 min.

[j]80-90°C for 20min in a sauna.

[k]72°C for 15 min in a sauna.

[l]Treadmill walking until volitional exhaustion at 42°C and 18% relative humidity.

[m]Reported in military recruits.

[n]Cyclical daily temperatures of 32-40°C at 20% humidity for 9 days.

[o]Hormonal values in summer season (~29-33°C) compared with spring season (18-21°C).

[p]Decreased hypothalamic expression of kisspeptin.

[q]38°C for 120min daily for two weeks in in climatic chamber with 45-60% humidity.

[r]Treadmill exercise at 38°C in climatic chamber with ~50% relative humidity.

[s]Daily heat exposure (34.5°C for 8hr and 31°C for 16hr) for 14 days.

[t]28°C for 13 days with ~60% relative humidity.

[u]35°C for 5 days.

[v]30°C for 5.5hr.

[w]Military personnel conducted 2hr bouts of physical activities at ~30°C in climatic chamber with ~31% relative humidity.

GHRH, growth hormone-releasing hormone.

Table 2. Drugs prescribed for the treatment of endocrine and metabolic conditions which may affect thermoregulation.

Drug	Treatment indications	Mechanism of adverse thermoregulatory effects
Drugs impairing sweating or heat dissipation		
SGLT2 inhibitors Lithium Loop diuretics	Type 2 diabetes Thionamide-resistant hyperthyroidism Hypercalcaemia Diabetes with heart failure	Polyuria-induced dehydration
Metformin	Type 2 diabetes	Diarrhoea-induced dehydration during treatment initiation phase[6]
ACE inhibitors ARBs	Diabetic nephropathy Diabetes with hypertension	Impaired thirst and fluid intake causing dehydration

Oxybutynin	Diabetes with detrusor overactivity	Suppression of sweating
Topiramate	Metabolic syndrome and obesity	Suppression of sweating
Non-selective β-blockers e.g. propanolol	Hyperthyroidism	Impaired cutaneous vasodilation
Drugs increasing heat production		
Thyroxine Triiodothyronine	Hypothyroidism	Increased basal metabolic rate
Mirabegron	Diabetes with bladder overactivity	Increased brown adipose tissue metabolic activity[108]
Testosterone	Hypogonadism	Increased heat stress susceptibility[122]. Potentially mediated by etiocholanolone, a testosterone metabolite with pyrogenic actions[123]
Progesterone and progestogens	Assisted reproduction and gynaecological disorders	Pyrogenic action mediated by direct effects on hypothalamus or via indirect effects on cytokine production[124].

ARB, angiotensin receptor blockers; ACE, angiotensin converting enzyme; SGLT2, sodium-glucose co-transporter-2.

Figure legends

Figure 1. Possible involvement of hormones in thermoregulatory adaptation to heat. Changes in temperature affect a range of endocrine systems including: the hypothalamic-pituitary-adrenal axis and autonomic nervous system, which are involved in the stress response and produce hormones such as cortisol, arginine vasopressin (AVP), prolactin, growth hormone (GH), and noradrenaline; the thyroid axis, which involves hormones such as TSH, T_4 and T_3; the renin-angiotensin-aldosterone axis, which involves the kidneys, lungs and adrenal glands and regulates sodium and water balance; and white adipose tissue (WAT) which produces hormones such as leptin which affect appetite and food intake. Heat-induced secretion of hormones such as cortisol, noradrenaline (NA), leptin and AVP may influence the central thermoregulatory network by acting on the hypothalamic pre-optic area (POA)[11,12,27,47]. The POA activates autonomic responses (yellow arrows) which lower core temperature by decreasing brown adipose tissue (BAT) thermogenesis and by promoting heat loss via sweating and increased cutaneous blood flow[5,6]. Heat-induced hormonal changes also affect peripheral thermoregulatory processes. Suppression of the thyroid axis may decrease BAT thermogenesis and obligatory thermogenesis whilst increasing cutaneous blood flow[20,22]. Increased pituitary secretion of growth hormone (GH), which induces insulin-like growth factor-1 (IGF-1) secretion, and pituitary secretion of prolactin may increase sweating from eccrine glands[40,42]. Increased AVP secretion decreases renal excretion of H_2O, and heat-induced NA secretion and decreased renal blood flow leads to activation of the renin-angiotensin system resulting in decreased renal excretion of Na^+ and H_2O[26,27]. Possible hormone actions in response to heat exposure are represented by dashed arrows.

Figure 2. Strategies involving patients, healthcare professionals and organisations for improving the care of endocrine patients at risk of heat injuries and other health events.

Adapted from Ratter-Rieck et al. Diabetologica 2023 Jun;66(6):1003-1015[3].

Box 1. Recommendations for research relating to the endocrine effects of heat.

Basic science research

- *In vitro* studies required to assess how heat influences:
  - Hormone expression and secretion in endocrine cells and tissues.
  - Hormone receptor expression, activation, recycling, signalling and biological actions in target cells and tissues.
- Utilisation of *in-vivo* models to investigate:
  - The range of hormones influencing central and peripheral thermoregulatory processes.
  - Effects of chronic heat exposure on fetal and postnatal endocrine axis development.
  - The epigenetic and transgenerational endocrine effects of heat exposure.
  - How heat affects the pharmacokinetics and pharmacodynamics of exogenously administered hormones and other endocrine-targeted drugs.
  - The effects of heat on morbidity and mortality in models of endocrine disorders such as hypothyroidism and adrenal insufficiency, and evaluate strategies such as heat acclimatisation for minimising adverse health outcomes.

Clinical and epidemiological research

- Conduct passive heating and exercise-heat stress studies to characterise how endocrine axes change in response to acute heat exposure.
- Use retrospective data or establish prospective cohorts in countries or populations that are most exposed to high temperatures for the following research:
  - Examine effects of high temperatures and extreme heat events on hormonal changes at key stages of the life course such as infancy, puberty, pregnancy, lactation and menopause.
  - Identify how individual characteristics such as age, sex and genetic polymorphisms may affect endocrine adaptions to heat.
  - Improved description of heat exposures (thresholds, magnitude and duration and timing of exposures) mediating adverse endocrine effects.
  - Assess clinical outcomes in patients with endocrine disorders with a focus on vulnerable groups such as children, pregnant women, the elderly and different types of workers with high heat exposures.
  - Characterise behavioural responses to heat in patients with endocrine disorders.
- Clinical and epidemiological research on effects of drugs on thermoregulation.
- Evaluate heat risk screening tools for use with endocrine patients.
- Develop and evaluate low-cost interventions and practical heat management strategies to prevent adverse endocrine effects of heat.

Figure 1

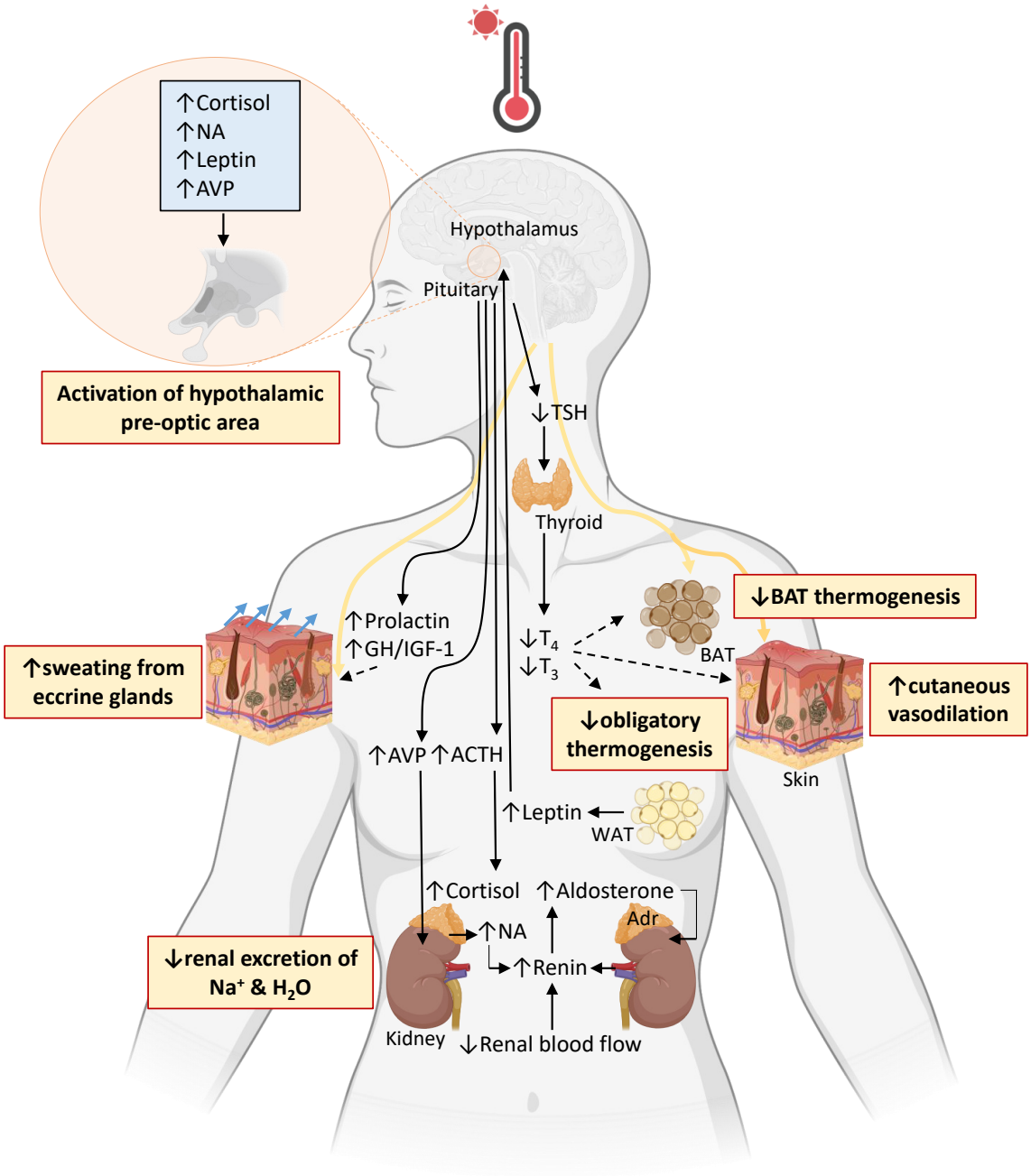
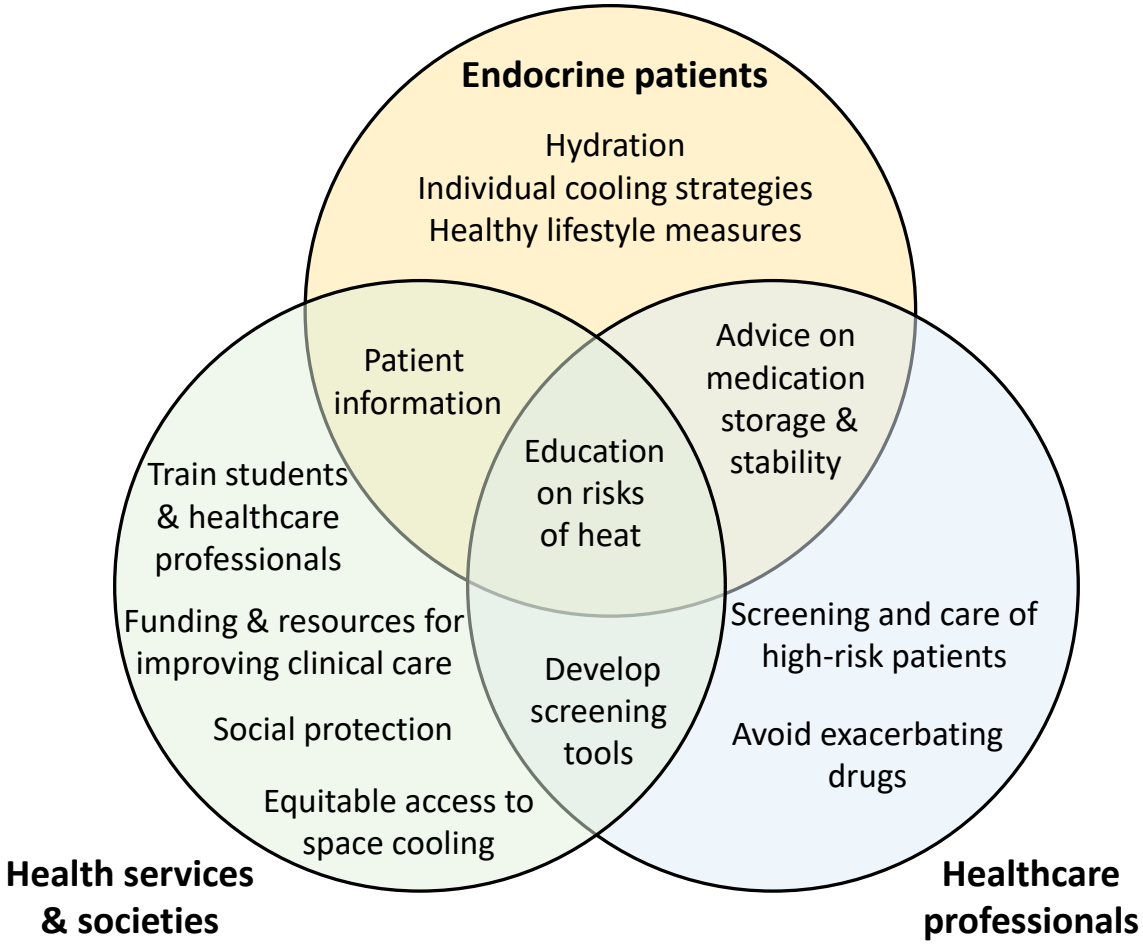

↑Cortisol
↑NA
↑Leptin
↑AVP
Activation of hypothalamic pre-optic area
Hypothalamus
Pituitary
↓TSH
Thyroid
↑Prolactin
↑GH/IGF-1
↓T4
↓T3
BAT
↓BAT thermogenesis
↑sweating from eccrine glands
↓obligatory thermogenesis
↑cutaneous vasodilation
Skin
↑AVP ↑ACTH
↑Leptin
WAT
↑Cortisol
↑Aldosterone
Adr
↑NA
↑Renin
↓renal excretion of Na+ & H2O
Kidney
↓Renal blood flow

Figure 2


Endocrine patients
Hydration
Individual cooling strategies
Healthy lifestyle measures
Patient information
Advice on medication storage & stability
Education on risks of heat
Train students & healthcare professionals
Funding & resources for improving clinical care
Social protection
Equitable access to space cooling
Develop screening tools
Screening and care of high-risk patients
Avoid exacerbating drugs
Health services & societies
Healthcare professionals