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Effects of Medications on Heat Loss Capacity in Chronic Disease Patients: Health Implications Amidst Global Warming

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Abstract—Pharmacological agents used to treat or manage diseases can modify the level of heat strain experienced by chronically ill and elderly patients via different mechanistic pathways. Human thermoregulation is a crucial homeostatic process that maintains body temperature within a narrow range during heat stress through dry (i.e., increasing skin blood flow) and evaporative (i.e., sweating) heat loss, as well as active inhibition of thermogenesis, which is crucial to avoid overheating. Medications can independently and synergistically interact with aging and chronic disease to alter homeostatic responses to rising body temperature during heat stress. This review focuses on the physiologic changes, with specific emphasis on thermolytic processes, associated with medication use during heat stress. The review begins by providing readers with a background of the global chronic disease burden. Human thermoregulation and aging effects are then summarized to give an understanding of the unique physiologic changes faced by older adults. The effects of common chronic diseases on temperature regulation are outlined in the main sections.

Physiologic impacts of common medications used to treat these diseases are reviewed in detail, with emphasis on the mechanisms by which these medications alter thermolysis during heat stress. The review concludes by providing perspectives on the need to understand the effects of medication use in hot environments, as well as a summary table of all clinical considerations and research needs of the medications included in this review.

Significance Statement—Long-term medications modulate thermoregulatory function, resulting in excess physiological strain and predisposing patients to adverse health outcomes during prolonged exposures to extreme heat during rest and physical work (e.g., exercise). Understanding the medication-specific mechanisms of altered thermoregulation has importance in both clinical and research settings, paving the way for work toward refining current medication prescription recommendations and formulating mitigation strategies for adverse drug effects in the heat in chronically ill patients.

I. Introduction

Climate change, including global warming, is a significant threat to human health. In 2020 alone, extreme temperatures resulted in an increase of 3.1 billion person-days of heatwave exposure among people older than 65 years, compared with the annual average two decades ago, while estimated heat-related mortality in this age group has increased by nearly 70% over the same period. Furthermore, under current climate policies, global temperatures are projected to increase by 2.9°C compared with preindustrial average by 2100 (<https://climateactiontracker.org/publications/global-update-climate-summit-momentum/>; Romanello et al., 2021)—this is especially concerning considering the global population will continue to age (Roth et al., 2017). Older adults and people with chronic diseases are among the most vulnerable groups susceptible to reduced human performance and adverse health consequences in the heat, given their reduced thermoregulatory capacity. Patients with chronic disease(s) often deteriorate with excess heat exposure, manifesting as increased admission and emergency presentation rates at hospitals (Kjellstrom and McMichael, 2013). Recently, a comprehensive review described the mechanisms and effects of cardiometabolic diseases, neurologic disorders, and injury on thermoregulatory responses to heat exposure and exercise heat stress (Cramer et al., 2022). While there has been more research elucidating the physiologic influence of chronic diseases on thermoregulation, less is

known about the effects of the medications used to treat these diseases. Medications prescribed for common chronic diseases can compound the severity of outcomes during heat stress (Westaway et al., 2015). In fact, recent epidemiologic evidence highlighted that even in the absence of extreme heat (e.g., heatwaves), common heat-sensitizing medications (e.g., anticholinergics and angiotensinogen-converting enzyme inhibitors (ACEIs)) increase the rate of heat-related hospitalizations during warm seasons in chronically ill older adults (Layton et al., 2020). However, there has yet to be a comprehensive review describing the effects of the medications used to treat common age-related chronic diseases on thermoregulation. Accordingly, this review serves to supplement previous reviews describing chronic diseases' influence on thermoregulation, such as the recent Cramer et al. (2022) review, by providing a much-needed summary of mechanisms underlying the effects of medications known to modify thermoregulatory responses to heat stress in clinical populations and highlighting the knowledge gaps in this lagging research field.

Type 2 diabetes (T2D), cardiovascular disease (CVD), neuropsychiatric disorders, and cancers are among the most important drivers of global health burden in older adults. Exposure to extreme heat increases the risk of morbidity in each of these conditions (Vos et al., 2020; Romanello et al., 2021). People with diabetes are at increased risk of heat-related morbidity and mortality due

ABBREVIATIONS: ACEI, angiotensin-converting enzyme inhibitors; ACh, acetylcholine; AD, Alzheimer's disease; AKI, acute kidney injury; AMPK, AMP-activated protein kinase; ARB, angiotensin II receptor blockers; BAT, brown adipose tissue; CKD, chronic kidney disease; CNS, central nervous system; COX, cyclooxygenase; CVD, cardiovascular disease; DPA, dopamine; DRG, dorsal root ganglia; GI, gastrointestinal; HbA_{1C}, hemoglobin A1C; HRT, hormone replacement therapy; L-dopa, levodopa; NO, nitric oxide; NOS, nitric oxide synthase; PD, Parkinson's disease; POA, preoptic area; RAAS, renin-angiotensin-aldosterone system; SGLT2i, sodium glucose transporter inhibitors; SkBF, skin blood flow; T1D, type 1 diabetes mellitus; T2D, type 2 diabetes mellitus.

to compromised heat dissipation resulting from diabetes-associated neuropathy (Xu et al., 2019). Globally, the estimated number of adults living with diabetes has increased by 62% in the past decade, and recent observational studies reported increased doctor consultations by diabetes patients on days of heatwaves compared with non-heatwave days (Xu et al., 2019). Alarming, besides diabetic neuropathy, diabetes medication may disrupt patients' thermoregulatory capacity and hence further exacerbate the impact of heat stress (Xu et al., 2019). Given that conservative projections see global diabetes prevalence increasing to 700 million (10.9% of the global adult population) by 2045, understanding the thermophysiological effects of commonly prescribed diabetes medication is critical to avoid unwittingly increasing diabetes patients' vulnerability to extreme heat.

CVD is the leading cause of death worldwide and contributes to significant morbidity and mortality despite advances in treatments and preventive measures (Roth et al., 2020). Like diabetes, people with CVD are at increased risk of heat-related morbidity, mortality, and hospitalization, presumably due to chronic heart insufficiency and impaired skin blood flow (SkBF), which impede effective heat dissipation (Phung et al., 2016). Further proposed mechanisms linking extreme heat to increased CVD morbidity include increases in sleep disturbance and dehydration. It is projected that 40.5% of the global population will have some form of CVD by 2030 (Heidenreich et al., 2011; Lim et al., 2015; Obradovich and Migliorini, 2018), and climate modeling studies have projected higher rates of heat-related CVD mortality in both tropical and temperate regions throughout the remainder of the century (Li et al., 2015b; Limaye et al., 2018; Silveira et al., 2021). While this projected increase is mainly attributable to increased heat exposure, it is essential to classify the potential risk due to thermoregulatory impacts of CVD medication as well, given the expected increase in the patient population who will be dependent on these medications. As covered later in this review, various pharmacological agents (e.g., aspirin, β -blockers, ACEIs, etc.) used to manage CVD can impair increases in SkBF and alter renal function during hyperthermia, predisposing patients to attenuated heat strain and possible renal injury.

Neuropsychiatric disorders encompass a range of conditions, including Parkinson's disease (PD) and Alzheimer's disease (AD), which are marked by the onset of cognitive decline typically manifesting earlier in life (Feigin et al., 2019). Neuropsychiatric disorders are the leading cause of morbidity and the second-leading (after CVD) cause of mortality worldwide (Feigin et al., 2019). In contrast to diabetes and CVD, the link between climate change and the increasing burden of neuropsychiatric disorders is less established (Bongioanni et al., 2021). Nevertheless, exposure to heat stress can lead to dysfunction of neuronal pathways, for instance via increased misfolding and

aggregation of Tau protein in the brain and altered neurotransmitter signaling (Bongioanni et al., 2021). Considering that the global burden of neuropsychiatric disorders is projected to increase significantly by 2050 and its high prevalence in older adults vulnerable to heat, it is paramount to understand the mechanisms through which medications for neuropsychiatric disorders disrupt thermoregulation (Tarawneh et al., 2022).

Cancer is often not thought of as a class of chronic diseases. However, cancer has been classified as a chronic disease by multiple health authorities (Hunter and Reddy, 2013; Bernell and Howard, 2016; <https://www.cdc.gov/chronicdisease/about/index.htm>). Indeed, survival rates of cancer have drastically improved because of advances in early diagnosis, risk stratification, and treatment options (Phillips and Currow, 2010). However, while cancer patients and survivors are living longer, there has also been an increase in morbidity associated with issues such as recurrence, secondary conditions, and long-term cancer treatment-related effects (Morgan, 2009). Additionally, emerging challenges to healthcare systems include providing support, care, and rehabilitation to patients who may experience economic burdens due to added medical expenditure and loss of productivity (Guy et al., 2013). Indeed, cancer patients receiving long-term treatment may experience limited productivity, impacted quality of life and even development of a second cancer. Cancer patients are vulnerable to extreme heat exposure, mainly due to reported secondary effects of cancer treatment (Kokolus et al., 2010; Endo, 2014; Wiśniewska et al., 2016). Furthermore, cancers such as breast cancer have been shown to enhance thermogenesis (Tsoli et al., 2012; Gandhi et al., 2021; Yin et al., 2022). Together, pathologic dysregulation of thermogenesis and thermolysis accompanied by pharmacological modulations in thermoregulation can severely impact body temperature. Understanding the impacts of chemotherapies may elucidate potential mechanisms for mitigation of thermal strain arising from cancer treatment.

This review first briefly summarizes thermoregulation, specifically thermolysis in healthy humans, and impairments associated with aging and chronic diseases (i.e., diabetes, CVD, neuropsychiatric diseases, and cancer) in the heat. We then describe in detail how common medications used to treat these diseases may impair thermoregulation. Finally, we put forth practical implications and highlight research gaps (Table 1) for consideration concerning medication use in the susceptible aging population. This review focuses on the effects of disease and medications on heat loss mechanisms during heat stress. However, it should be noted that while pathologic conditions and medications used to treat conditions may alter the inhibition of thermogenesis, these mechanisms are not discussed in specific detail in this review.

TABLE 1
Thermoregulatory considerations and research gaps involving the use of commonly prescribed medications

Drug	Physiologic Outcomes	Clinical Consideration	Research Gaps
Metformin	Gut-related changes	<ol style="list-style-type: none"> 1) Drug initiation should be conservative and progressive 2) Continually review drug tolerance and adjust doses 	<ol style="list-style-type: none"> 1) Profile short- and long-term metformin-associated gut flora changes 2) Profile biomarkers of endotoxemia and inflammation during heat stress in patients receiving metformin
SGLT2 inhibitors	Osmotic diuresis (AKI/CKD risk)	<ol style="list-style-type: none"> 1) Drug-associated diuresis may increase AKI risk 2) Monitor and report symptoms such as diuresis, postural hypotension, and excessive dizziness 3) Hydration status of susceptible patients with: <ol style="list-style-type: none"> a) Concomitant diuretic medication b) Congestive heart failure c) Prolonged heat exposure 	<ol style="list-style-type: none"> 1) Large-scale prospective studies monitoring renal injury and heat-related hospitalisations with SGLT2 inhibitor use in patients frequently exposed to prolonged exertional heat stress
Insulin	Metabolic heat production	<ol style="list-style-type: none"> 1) Insulin may raise metabolic heat production and may contribute to greater heat storage, especially in extreme heat 2) Patients should be monitored for hyperthermic responses and appropriate cooling strategies may be required, especially during exertion in the heat 	<ol style="list-style-type: none"> 1) Determine the extent of thermoeffector response to heat stress at varying insulin and glycemic levels of patients to isolate insulinemic and glycemic effects on thermoregulation
Antiplatelets	Thermoeffector response	<ol style="list-style-type: none"> 1) Caution advised for patients taking antiplatelet medications before exercise or work in extreme heat 	<ol style="list-style-type: none"> 1) Determine influence of COX inhibition by aspirin on central control of body temperature 2) Influence of antiplatelet medication on vasomotor adaptations to heat acclimation programs
ACEI and ARB	Renal changes (AKI/CKD risk)	<ol style="list-style-type: none"> 1) Hydration status of susceptible patients with: <ol style="list-style-type: none"> a) Concomitant diuretic medication b) Congestive heart failure c) Prolonged heat exposure 	<ol style="list-style-type: none"> 1) Assess the effects of ACEIs/ARBs on thirst responses in aging patients 2) Determine efficacy of fluid replenishment strategies in patients on ACEIs/ARBs
	Exercise tolerance	–	<ol style="list-style-type: none"> 1) Determine ACEI/ARBs' effects on exercise tolerance during exertional heat stress
	Thermoeffector response	–	<ol style="list-style-type: none"> 1) Determine influence of ACEIs/ARBs on sweat and skin blood flow responses
β -blockers	Thermoeffector response	<ol style="list-style-type: none"> 1) Medication effects on thermoeffector responses: <ol style="list-style-type: none"> a) Inhibited cutaneous vasodilation b) Potentiated sweat response c) Effects of selective versus nonselective β-blockers 	<ol style="list-style-type: none"> 1) Elucidate cardiovascular mechanisms underpinning suppressed SkBF during heat stress 2) Determine effects of selective and nonselective β-blockers on sweat responses across populations in different levels of heat stress 3) Elucidate the impacts of β_3 receptor activation and inhibition in BAT activated thermogenesis during heat stress
Anticholinergics and cholinesterase inhibitors	Thermoeffector response	<ol style="list-style-type: none"> 1) Medication effects on thermoeffector responses: <ol style="list-style-type: none"> a) Inhibited sweat response b) Increased rate of rise in body core temperature 	<ol style="list-style-type: none"> 1) Dose-response studies to identify the “dose threshold” at which thermoregulatory responses will be altered by ACh-modulating medications
Dopamine replacement agents and dopamine agonists	Thermoeffector response	<ol style="list-style-type: none"> 1) Potential thermoregulatory dangers of dose adjustments and withdrawal 	<ol style="list-style-type: none"> 1) Influence of L-dopa on overall thermal perception in older PD patients under resting conditions
	Perceptual	<ol style="list-style-type: none"> 1) “Dampening” effect of medication on thermal sensation and perceived exertion during exercise 	

(continued)

TABLE 1—Continued

Drug	Physiologic Outcomes	Clinical Consideration	Research Gaps
Chemotherapy (e.g., platinum analogs, taxanes, bortezomib)	CIPN	1) Hyperthermia may occur secondary to chemotherapy-induced anhidrosis	1) Health impacts of extreme or prolonged heat exposures in cancer patients
	Early menopause (Hot flashes)	1) Chemotherapy-induced early menopause risk associated with age 2) HRTs not recommended in hormone-dependent cancers (e.g., breast cancer) to treat hot flush 3) Alternative hot flush treatments: a) Paroxetine b) Fluoxetine c) Venlafaxine d) Citalopram	2) Health impacts of chemotherapy medications during extreme or prolonged heat exposures 3) Efficacy of exercise programs to mitigate chemotherapy-induced thermoregulatory perturbations

Abbreviations: ACEI, angiotensinogen converting enzyme inhibitor; ACh, acetylcholine; AKI, acute kidney injury; ARB, angiotensin receptor blocker; BAT, brown adipose tissue; CIPN, chemotherapy-induced peripheral neuropathy; CKD, chronic kidney disease; COX, cyclooxygenase; HRT, hormone replacement therapy; PD, Parkinson's disease; SGLT2, sodium-glucose cotransporter 2; SkBF, skin blood flow.

II. Thermoregulation in Health and Aging

Healthy humans are generally capable of regulating internal temperatures across a wide range of environmental conditions (Lim et al., 2008). However, high ambient temperatures and/or work intensities reduce work tolerance and increase the risk of heat-related injuries. Established evidence demonstrates impaired physical performance in the heat within exercise (Racinais et al., 2021) and occupational contexts (Flouris et al., 2018) and a greater risk of heat injuries with increasing ambient temperature (Flouris et al., 2018; Ebi et al., 2021). The functional upper limit for core temperature is approximately 40°C (Gonzalez-Alonso et al., 1999), while core temperatures beyond that, coupled with central nervous system (CNS) dysfunction (e.g., disorientation, altered consciousness, delirium, etc.) is clinically diagnosed as exertional heat stroke (Racinais et al., 2019a). Nonetheless, it has been reported that elite athletes are able to attain core temperatures of 41 to 41.5°C without adverse health consequences (Racinais et al., 2019b, 2022). Furthermore, a recent study demonstrated that the brain can function normally at temperatures 1 to 3°C above the normal body core temperatures and can attain above 40°C even in the absence of heat illness (Rzechorzek et al., 2022). Thus, substantial research has been dedicated to understanding the mechanisms underpinning human thermoregulation and health in various populations (e.g., older adults, children, chronically ill, patients with paraplegia).

A. Thermoregulation in Humans

During physical work or heat exposure, internal rates of heat production must be balanced by heat dissipation, which otherwise will result in accumulated body heat content manifesting as an increase in body core temperature (Kenny and Jay, 2013). See Fig. 1 for a detailed overview of human thermoregulation. The goal of thermoeffector responses to heat stress is to achieve thermal

balance (i.e., heat loss compensates for heat gain, resulting in stable core temperature). Central control of body temperature is primarily controlled by the preoptic area (POA) of the brain's hypothalamus via feedback and feedforward mechanisms. Sensory inputs in the brain, spinal cord, muscles, and viscera detect elevated body temperatures and feedback to the POA (Romanovsky, 2018a,b). The POA activates thermoeffector (e.g., elevating SkBF and sweating) and behavioral responses to the increasing body temperature. Furthermore, warm thermoreceptors in the skin detect increases in ambient and skin temperatures that result in reflex inhibition of cutaneous vasoconstriction and brown adipose tissue (BAT)-derived thermogenesis (Romanovsky, 2018a,b; Morrison and Nakamura, 2019).

Behavioral thermoregulation (e.g., looking for shade or water, voluntary adjustment of work rate) is considered the first line of defense in achieving heat balance during rest and exercise (Schlader et al., 2010). Autonomic thermoeffector responses include cutaneous vasodilation and eccrine sweating, which are critical to facilitate evaporative heat loss (i.e., the only means of heat loss when air temperatures exceed skin temperature) (Gisolfi and Wenger, 1984). Briefly, cutaneous vasodilation is mediated by cholinergic, nicotinic, and β -adrenergic pathways (Fujii et al., 2020b). It is well-known that eccrine sweat responses are largely modulated by cholinergic signaling (Machado-Moreira et al., 2012). However, β -adrenergic modulation of sweating through cAMP-dependent mechanisms has also been demonstrated in young healthy adults, albeit in a smaller capacity relative to cholinergic sweating (Amano et al., 2017). The concomitant redistribution of blood to the working muscles, as well as to the skin to promote dry heat loss, coupled with dehydration due to excessive sweating could determine the reduction in blood volume and arterial blood pressure (and venous return), with consequences for cardiovascular and renal function. The ensuing physiologic effects include elevated cardiovascular strain, reduced renal blood

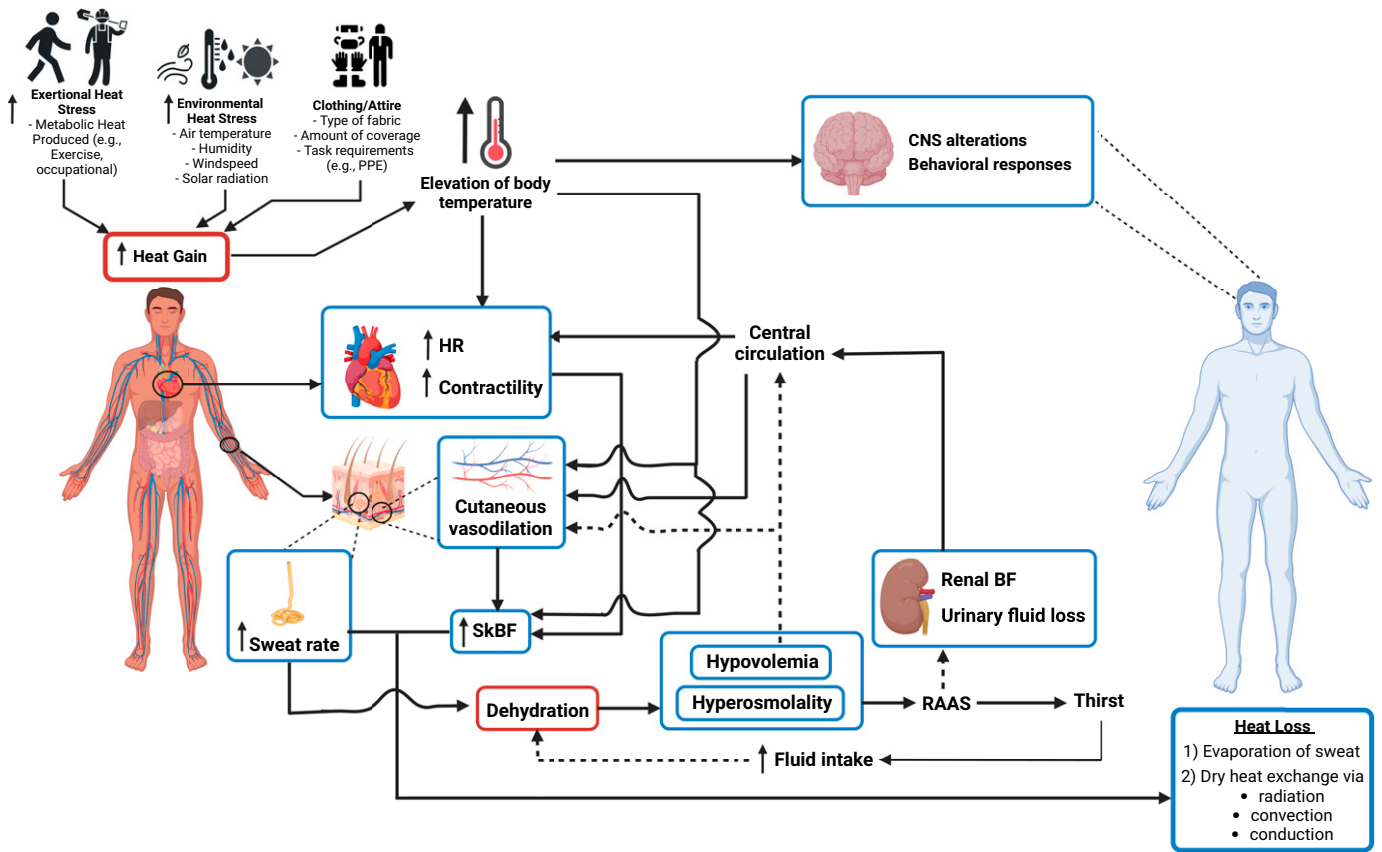


Fig. 1. Overview of physiologic responses to heat stress. Solid and dashed arrows denote a stimulation or an increase, and downregulation or decrease, respectively. Core temperature is regulated and represents the outcome of heat balance. Sources of heat gain come from environmental conditions and task-dependent factors (e.g., metabolic rate, clothing). Skin temperatures vary across the body in response to the thermal environment, providing afferent and efferent signals that drive behavioral, neural, and biophysical heat exchange mechanisms. The skin's autonomic thermoeffector responses include cutaneous active vasodilation and eccrine sweating to promote heat loss through dry (conduction, convection, and/or radiation) and wet (evaporation of sweat) heat exchanges. However, these responses decrease central blood volume, increase cardiovascular strain, and decrease renal blood flow. RAAS drives thirst responses and renal resorption to mitigate decreased central circulation and maintain blood pressure. Abbreviations: HR, heart rate; BF, blood flow; RAAS, renin-angiotensin aldosterone system; SkBF, skin blood flow. Created with BioRender.com.

flow—a key risk factor for acute kidney injury (AKI), hypovolemia, and hyperosmolality, all of which are compounded by dehydration (Chapman et al., 2020; Périard et al., 2021). Innate mechanisms such as the renin-angiotensin-aldosterone system (RAAS) function to mitigate the decline in blood volume (Fig. 1) (Périard et al., 2021).

B. Thermoregulation and Aging

Thermoregulatory function declines with age and is multifactorial, involving impairments within behavioral, cardiovascular, and sudomotor functions. Age-related thermoregulatory decline affects both thermogenic and thermolytic responses to cold and heat stress. For example, older adults experience limited cold-induced cutaneous vasoconstriction, reduced metabolism, and attenuated BAT thermogenesis that predispose them to hypothermia during cold stress (McDonald and Horwitz, 1999; Blatteis, 2012; Lettieri-Barbato and Aquilano, 2020; Bartke et al., 2021). Specific to heat stress, older adults experience suppressed heat-induced cutaneous vasodilation, thermal sweating, as

well as thermal and thirst perception (Phillips et al., 1984; Meade et al., 2020; Waldock et al., 2021). This review focuses on age-related thermoregulatory changes during heat exposure. Figure 2 provides a summary of these age-related changes in responses during heat exposure.

Age-related decrease in active cutaneous vasodilation is in part due to blunting of the skin sympathetic nerve activity (Stanhewicz et al., 2016) but works predominantly through decreased cotransmitter release and diminished nitric oxide (NO) bioavailability in humans (Holowatz et al., 2003). NO is a potent vasodilator that can induce cutaneous vasodilation to a large extent as demonstrated in healthy young adults during exertional heat stress (Fujii et al., 2014b, 2017). Nitric oxide synthase (NOS) inhibition has been shown to attenuate cutaneous vascular conductance during exercise heat stress among older adults (Fujii et al., 2015b). Cutaneous vascular conductance refers to the ratio of measured cutaneous blood flow to mean arterial blood pressure and is used as an expression of SkBF. Similar to findings

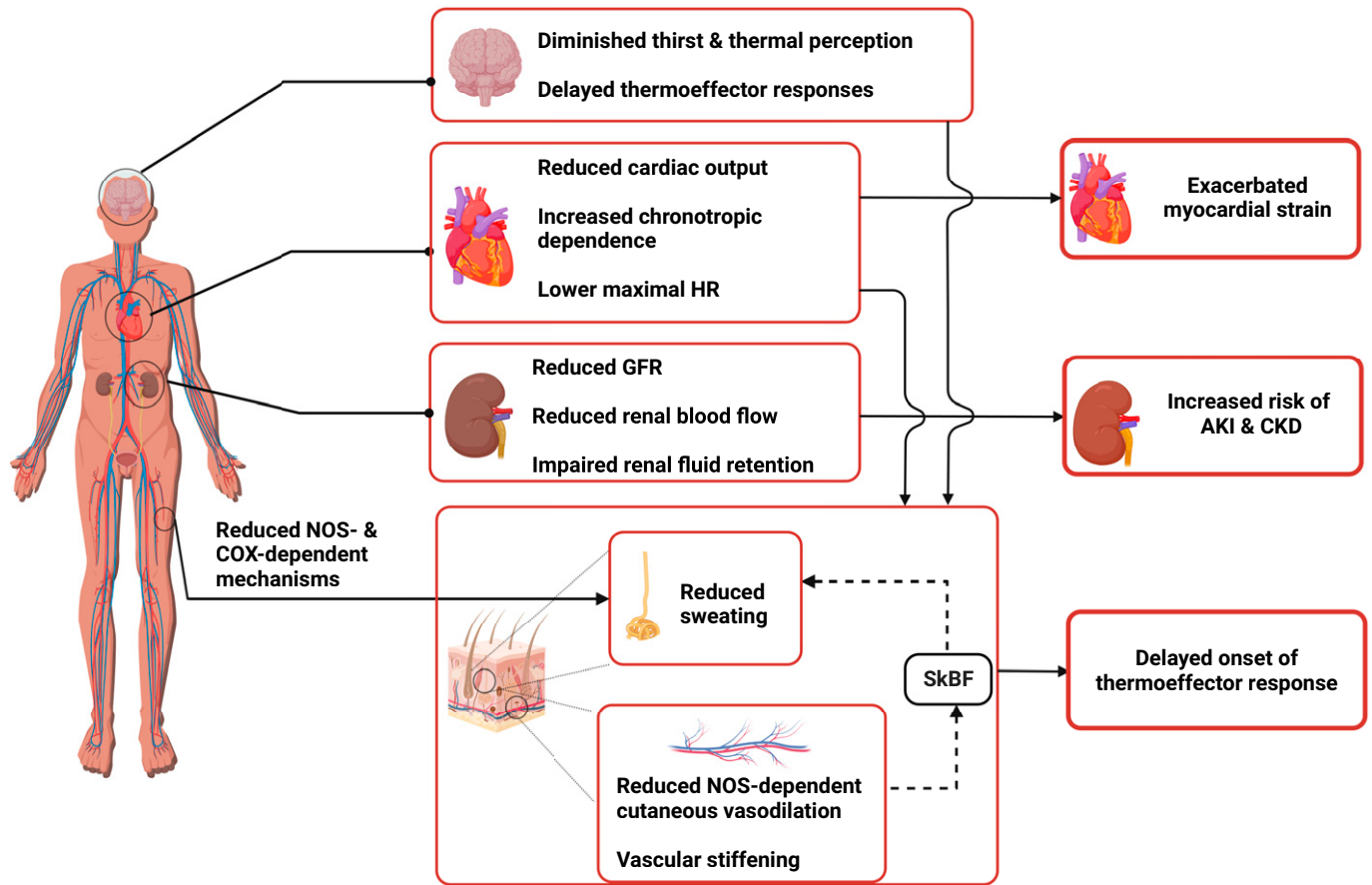


Fig. 2. Overview of the age-related impairments in thermoregulation and pathways to increased thermal strain and kidney injury. Solid and dashed arrows denote a stimulation or an increase and downregulation or decrease, respectively. Older adults exhibit reduced thirst and diminished thermal perception during dehydration and exertional heat stress, respectively. Moreover, aging is associated with reduced blood flow to the skin during exertional heat challenges, resulting in reduced convective heat transfer to the skin and environment. Decreases in skin blood flow are influenced by central mechanisms such as the decline in cardiac output and reduced visceral blood redistribution to the skin, while peripheral mechanisms include changes within the cutaneous microvascular structure and, primarily, an attenuated cutaneous vasodilatory response. Age-related decreases in cutaneous vasodilation responses are mediated by reduced circulating NO levels. Age-related decreases in eccrine sweating responses are mediated by reduced circulating NO levels and reduced NOS- and COX-dependent mechanisms. Abbreviations: HR, heart rate; GFR, glomerular filtration rate; SkBF, skin blood flow; NO, nitric oxide; NOS, nitric oxide synthase; COX, cyclooxygenase; AKI, acute kidney injury; CKD, chronic kidney disease. Created with BioRender.com.

in young adults (Fujii et al., 2018c), cutaneous microvascular cyclooxygenase (COX) pathways do not seem to be involved in the age-related decline in cutaneous vasodilation during exercise heat stress (Fujii et al., 2015b).

Although the age-related changes mentioned here appear to impair thermoregulation, there is evidence that age-related changes may induce beneficial responses to heat stress. For example, healthy older adults appear to have enhanced potassium channel-dependent endothelial vasodilatory mechanisms relative to younger adults (Serviente et al., 2020). However, the aforementioned study induced hyperemia (i.e., increased blood flow) via local administration of a pharmacological agent in normothermic conditions rather than inducing it by environmental conditions. Additionally, aging augments β -adrenergic cutaneous vasodilation in humans (Fujii et al., 2020a). Furthermore, it is worth noting that the aging effect on cutaneous vasodilation may differ between men (Fujii et al., 2018b) and women (Fujii et al., 2019c). For example, aging appears to augment only

ATP-induced increases in SkBF in older men (Fujii et al., 2018b), whereas age-related augmentation occurs only in ATP-induced and nicotinic-induced increases in SkBF in older women (Fujii et al., 2019c).

Aging also precipitates a decrease in whole-body sweat rate (Inbar et al., 2004) due to the delayed core temperature threshold for the onset of sweating (Inbar et al., 2004). When coupled with reduced sweat gland output (Inoue et al., 1999), this results in reduced potential for evaporative heat loss. In contrast to findings in young adults where local cutaneous NOS and COX pathways interact to modulate eccrine sweating (Fujii et al., 2014b), neither pathway seems to be involved in the sweat response during exertional heat stress in older adults (Fujii et al., 2015b). Indeed, separate and combined inhibition of NOS and COX demonstrated no influence on sweat rate during moderate exercise in the heat, indicating an age-related decline in NOS- and COX-dependent mechanisms of sweating in older adults during exercise in the heat (Fujii et al., 2015b). It is worth

mentioning that increases in circulating NO do not directly mediate increases in sweating as demonstrated in young men exercising in the heat (Fujii et al., 2014b). Instead, NO augments cholinergic sweating (Lee and Mack, 2006).

Impaired thirst perception in response to dehydration occurs with healthy aging (Begg, 2017). Blunted sensitivity to rising plasma osmolality, renal sensitivity to antidiuretic hormone, RAAS dysregulation, and reduced baroreflex involvement (i.e., autonomic blood pressure regulation via cardiovascular adjustments) may impair thirst (Meade et al., 2020). Considering the age-related impairments in thirst perception, elderly patients are likely to be dehydrated and may be particularly vulnerable to heat challenges (Phillips et al., 1984). Similar to SkBF responses, it should not be ignored that aging attenuates sweating differently between the sexes (Fujii et al., 2019b). Age-related attenuation in muscarinic-mediated sweating appears to occur only at high levels of local methacholine administration in older women, whereas older men experienced age-related attenuated muscarinic sweating at low to moderate levels of methacholine administration (Fujii et al., 2019b).

Age is associated with greater likelihood of chronic kidney disease (CKD), as well as AKI (Chapman et al., 2020). Age-related changes underpinning the development of AKI and CKD include attenuated thirst response to dehydration and RAAS dysregulation. This predisposes older adults to greater risk of renal complications in extreme heat (Meade et al., 2020). Indeed, AKI is one

of the leading causes of hospitalizations among older adults during extreme heat exposure (Bobb et al., 2014; Xu et al., 2020). The mechanisms underpinning this increased risk pertain to reduced kidney function involving morphologic alterations (e.g., reduced mass, increased fibrosis etc.), reduced renal blood flow, and reduced glomerular filtration rate (Chapman et al., 2020).

III. Diabetes Mellitus

Growing evidence links diabetes to impaired thermoregulatory control that may result in adverse health outcomes, particularly in extreme heat events (Kenny et al., 2016). Type 1 diabetes mellitus (T1D), T2D, and their associated thermoregulatory effects are summarized in Fig. 3, with disease- (Kenny et al., 2016; Fujii et al., 2018a, 2021a) and drug-associated modulations (Hahn et al., 2016; McCreight et al., 2016; Rodriguez et al., 2018) to physiologic responses to heat stress. In T1D and T2D, heat-induced cutaneous vasodilation and sweat responses (see *Thermoregulation in Humans*) are attenuated, resulting in increased heat strain, especially during moderate to vigorous physical activity under heat stress (Notley et al., 2019a,b). Importantly, this thermoregulatory impairment is associated with the level of glycemic control and exertional heat stress (Luo et al., 2012; Carter et al., 2014; Fuchs et al., 2017). Indeed, chronic hyperglycemia damages Schwann cells and disrupts axonal function, resulting in neuropathy (Feldman et al., 2019). Diabetic neuropathy may result in autonomic

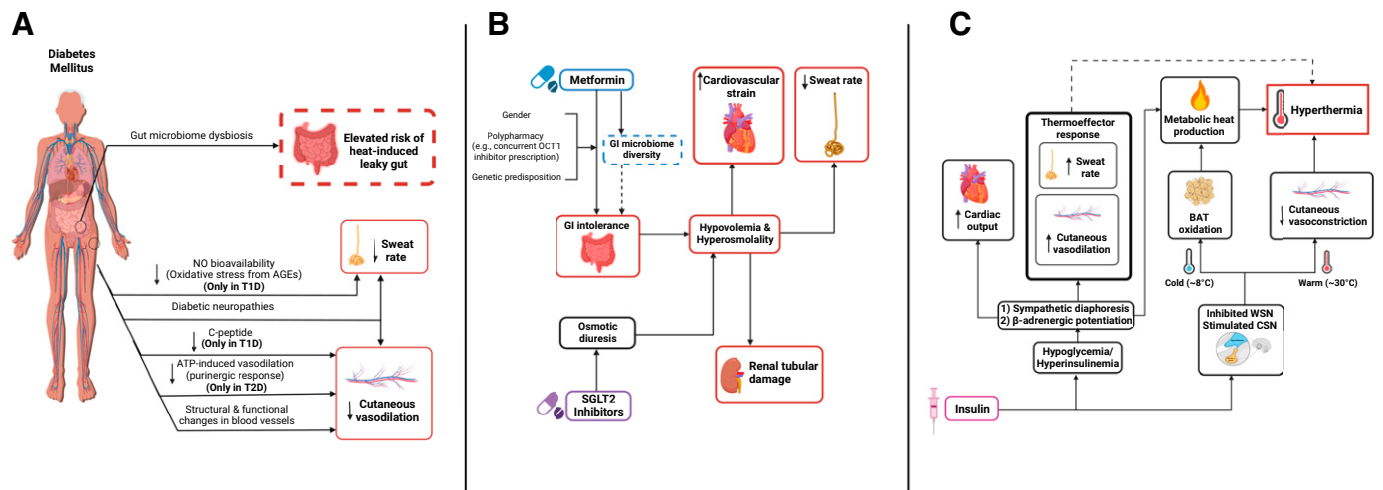


Fig. 3. (A) Impairments in thermoregulatory responses in diabetes. Solid and dashed arrows denote a stimulation or an increase and downregulation or decrease, respectively. Diabetes impairs cutaneous vasodilation by 1) neuropathy-driven denervation, 2) oxidative stress from hyperglycemic increase in advanced glycation end products, and 3) vascular function changes. Specifically, the absence of beta-cell secreted C-peptide (only in T1D) and reduced ATP-induced vasodilation (only in T2D) reduce cutaneous vasodilation. Diabetes results in nonuniform attenuations in peripheral sweating, reducing gross sweat rate. Sweat rate attenuation is associated with 1) longstanding diabetes, 2) the level of glycemic control (i.e., HbA1c), and 3) reduced NO bioavailability in T1D but not in T2D. Diabetes-related dysbiosis in the gut results in a depletion of beneficial short-chain fatty acid-producing microbiota and a concomitant increase in opportunistic pathogens that increase gut permeability and endotoxemia during exertional heat stress. (B) Metformin may lead to gastrointestinal disturbance upon drug initiation, promoting excess fluid loss. SGLT2i promotes osmotic diuresis and exacerbates the risk of dehydration if fluid intake is insufficient to maintain fluid balance. Metformin may concomitantly promote functional changes in gut microbiome, potentially protecting against heat-induced leaky gut. (C) Insulin modifies the thermoregulatory control center in the POA by concomitantly inhibiting WSN and stimulating CSN. Resultingly, an elevation in metabolic heat production occurs via oxidation of BAT (in cold conditions) or reduced SkBF (in warm conditions). Consequently, hyperthermia occurs. Insulin blunts sympathetically-mediated vasoconstriction while potentiating β -adrenergic vasodilation. On the contrary, insulin-induced hypoglycemia can result in sympathetic diaphoresis that may promote heat loss and limit body temperature rise. Abbreviations: NO, nitric oxide; ATP, adenosine tri-phosphate; OCT, organic cation transporter; BAT, brown adipose tissue; WSN, warm-sensitive neurons; CSN, cold-sensitive neurons. Created with BioRender.com.

sudomotor and microvascular dysfunction in T2D patients specifically, via purinergic-mediated (ATP-induced) cutaneous vasodilation (Fujii et al., 2018a), whereas C-peptide is absent in T1D patients, which results in reduced SkBF due to its importance in NO-dependent cutaneous vasodilation (Forst et al., 1998; Forst and Kunt, 2004). See the comprehensive reviews describing diabetes-related thermoregulatory impairments (Yardley et al., 2013; Kenny et al., 2016).

IV. Antidiabetic Medications and Heat Stress

A. Exogenous Insulin

Exogenous insulin has been used to manage patients with T1D for almost a century and is highly effective in reducing hyperglycemia. Insulin is also used as an additional therapy to intensify glycemic control in patients with T2D whose hemoglobin A1C (HbA_{1c}) is above recommended thresholds (Currie and Johnson, 2012). However, the use of insulin, specifically in patients with T2D, has been a topic of debate due to its risk profile relating to hyperinsulinemia, hypoglycemia and associated adverse events (Currie and Johnson, 2012). Evidence in both human (Maggs et al., 1994; Passias et al., 1996) and animal (Wang and Lin, 1985; Sanchez-Alavez et al., 2010) studies demonstrates how exogenous insulin administration may impair thermoregulation and increase metabolic heat production at rest and during exercise.

Animal models involving mice have demonstrated the presence of insulin receptors in the POA of the hypothalamus, which controls body temperature (Wang and Lin, 1985; Sanchez-Alavez et al., 2010). Direct insulin administration into the POA leads to dose-dependent increases in core temperature across different ambient temperatures (8–30°C) in rats (Wang and Lin, 1985). The observed hyperthermia is associated with hypothalamic-mediated increases in metabolic heat production via oxidation of BAT in cold conditions (8°C) and increased cutaneous vasoconstriction in warm conditions (30°C). Central mechanisms leading to hyperthermia appear to occur by insulin's direct inhibition of warm-sensitive neurons and stimulation of cold-responsive units of the POA that respond to temperature changes, as demonstrated in mice (Wang and Lin, 1985; Sanchez-Alavez et al., 2010).

In contrast, the findings of the effect of insulin on heat stress response in humans with diabetes remain equivocal. In one study, insulin-dependent patients were passively heated in a warm room (30°C) during a 90-minute hyperinsulinemic-hypoglycemic clamp (Maggs et al., 1994). These subjects demonstrated elevated sweat rates, peripheral blood flow, heart rate, and blood pressure, with decreased body core temperature with insulin infusion in both hypo- and euglycaemic clamps (Maggs et al., 1994). In agreement with the aforementioned mice studies by Sanchez-Alavez et al.

(2010) and Wang and Lin (1985), diabetic humans exhibited a significant rise in metabolic heat production in both hyperinsulinemic-hypoglycemic and hyperinsulinemic-euglycemic clamps (Maggs et al., 1994). These changes are associated with sympathetic activation in response to reduced blood glucose levels after insulin administration (Berne et al., 1992). Other studies have also demonstrated an increased sweating response to hyperinsulinemic hypoglycemia in both healthy and diabetic humans (Maggs et al., 1994; Elvebakk et al., 2018). An explanation is that, during hypoglycemia, there is sympathetic and adrenergic stimulation with resulting diaphoresis (profuse sweating) that may aid in evaporative heat loss from the skin (Cryer et al., 2003).

However, practitioners should caution against inferring a beneficial effect of insulin on sweat responses to heat stress during resting conditions. First, the accentuated sweating associated with hyperinsulinemic hypoglycemia may be counterbalanced by diabetes-associated autonomic impairments that lead to impaired sweating (Kenny et al., 2016). Second, accentuated sweating was only observed during 90-minute long hyperinsulinemic-hypoglycemic clamp studies designed to determine the hypoglycemic effect on thermoregulation. In practice, the effects of insulin are not long-lasting as the insulin levels are not clamped at a fixed level. Instead, the aim of insulin therapy is to maintain euglycemia. As such, insulin levels would more likely show only a “spike profile.” Consequently, thermoregulation disruptions observed in these clamp studies may not be applicable to general clinical settings since exogenous insulin is titrated and individualized to ensure optimal and safe dosing. Therefore, these findings may not be easily translated to therapeutic benefits to improve evaporative heat loss in standard care. Further research is required using clinically relevant, patient-specific doses of insulin to determine its independent effect on sweating during passive and exertional heat stress (Table 1). Practitioners and researchers should also consider the multifactorial (i.e., age, lifestyle, activity levels, etc.) nature of insulin dosing (i.e., timing, dose, administration route) that may ultimately render certain populations of patients with insulin-dependent diabetes more susceptible to elevated risk of heat strain than others (Wang and Awais, 2020).

Limited studies have investigated the impact of insulin use on thermoregulatory skin responses to heat stress and evidence remains equivocal. However, SkBF appears to be influenced by exogenous insulin administration. Under normothermic conditions, clamped hyperinsulinemia in healthy adults has been shown to increase total SkBF through NOS-mediated vasodilation and capillary recruitment (Serné et al., 2002). In insulin-dependent patients with diabetes, hyperinsulinemic hypo- and euglycemia at rest in a warm (30°C) environment resulted in increased capillary blood flow relative to

placebo (Maggs et al., 1994). However, these observed changes in SkBF did not result in changes in skin and core temperature. Possibly, hyperinsulinemia potentiates β -adrenergic vasodilation that offsets α -adrenergic vasoconstriction arising from sympathetic activation (Limberg et al., 2021). While the mechanism of β -adrenergic vasodilation is not entirely understood, β -adrenergic receptor activation may stimulate NOS-derived NO production in the human skin, as previously observed in human conduit artery in vivo (Low and Kennedy, 1997) and human skin in vivo (Fujii et al., 2017). Indeed, the increased SkBF with insulin administration may be facilitated by insulin-mediated concomitant blunting of catecholamine-mediated vasoconstriction and enhancing β -adrenergic-mediated vasodilation (Limberg et al., 2021). Taken together, clamped insulin administration may plausibly induce vasodilatory effects to improve SkBF.

However, no direct evidence is available to suggest that insulin may improve cutaneous vasodilatory function during excess heat exposure. Like insulin's effect on sweating, the current evidence from clamp studies may not represent a SkBF response to ecologically valid insulin doses. Furthermore, central, and peripheral mechanisms during hyperinsulinemia interplay dynamically with one another (Limberg et al., 2022). Therefore, further research in understanding how these complex mechanisms impact thermoregulatory responses to heat stress after insulin administration is needed. It is noteworthy that limited evidence in humans at present has shown an independent effect of different insulin dosage on thermoregulation while controlling for blood glucose levels during heat stress (Table 1). Considering the complex interplay of blood insulin and blood glucose levels, it must be acknowledged that the results presented here may be influenced by concomitant changes in blood glucose arising from insulin administration and that insulin, per se, may not directly impact thermoregulatory function.

B. Metformin

Metformin is the first-line drug prescribed by physicians in the treatment of T2D. Metformin is an insulin-sensitizing, glucose-lowering agent. Metformin opposes glucagon and activates AMP-activated protein kinase (AMPK), leading to augmented mitochondrial function and dynamics (e.g., mitochondrial fission), suppressed liver gluconeogenesis via AMPK activation, and, to a lesser extent, augmented glucose uptake in skeletal muscles. Although considered highly safe (Sanchez-Rangel and Inzucchi, 2017), nearly 30% of people with diabetes experience some form of gastrointestinal (GI) intolerance (e.g., diarrhea, nausea, and dyspepsia) to the drug upon initiation (McCreight et al., 2016). Hence, metformin may dehydrate people with diabetes (Puga et al., 2019). Consequently, there is an isotonic loss of water and sodium from extracellular fluid, without an osmotic water shift from intracellular fluid (i.e.,

isotonic hypovolemia) (Périard et al., 2021). Hypohydrated patients taking metformin, especially the elderly, are therefore at higher risk of developing early fatigue, exacerbated heat strain during exertional heat stress, and heat illness (e.g., heat syncope, heat cramps, heat stroke, etc.) (Périard et al., 2021).

Mechanisms underpinning gut intolerance induced by metformin may be explained by 1) genetic alterations in gut serotonin (Cubeddu et al., 2000; Dujic et al., 2016) and histamine transport (Yee et al., 2015), 2) high local concentration of metformin in enterocytes due to inhibition or suppressed expression of organic cation transporter 1 (Nies et al., 2011; Dujic et al., 2015), 3) bile acid pooling in the intestine (Scarpello et al., 1998; Lien et al., 2014), and 4) changes in gut microbiome during metformin treatment (Burton et al., 2015). The aforementioned mechanisms may modulate fluid balance, especially during the initial titration (i.e., dose-adjustment) phase of dosing for metformin-naive patients (Puga et al., 2019). Failure to sufficiently replace fluid loss from such GI disturbance may exacerbate dehydration-induced cardiovascular strain during exertional heat stress. Although metformin is regarded as the cornerstone of therapy for diabetes patients, to our knowledge no study has quantified the level of heat strain in metformin-naive patients receiving this medication. Considering the ill effects of metformin intolerance, clinicians should continually review adverse effects and monitor hydration strategies of patients, especially during initial metformin administration and dosage adjustment. It is highly recommended to prescribe initial doses of metformin conservatively and gradually improve tolerance (Puga et al., 2019).

Increasing evidence suggests a link between diabetes and disrupted gut microbiome homeostasis (i.e., dysbiosis) that may exacerbate gut permeability and endotoxemia, especially during exertional heat stress (Li et al., 2017). Consequently, low-grade systemic inflammation potentiates endothelial injury, cytotoxicity, ischemia, and intravascular coagulation that leads to organ failure, disability, and death in healthy populations (Mora et al., 2017; Hansson et al., 2020; Clauss et al., 2021). Some evidence indicates that metformin may confer positive changes to the gut microbiome (Rodriguez et al., 2018), which may protect against hyperthermia-induced endotoxemia during exertional heat stress (Clauss et al., 2021).

Interestingly, metformin has been shown to improve gut microbiome diversity in metformin-naive patients with T2D after two and four months of treatment. This improvement was characterized by increased short chain fatty acid metabolism and unaltered C-reactive protein (a systemic inflammatory marker), despite increases in lipopolysaccharide biosynthesis (an indicator of pathogenic Gram-negative bacteria) (Forslund et al., 2015; Wu et al., 2017). In obese mice, metformin has been shown to increase intestinal goblet cell differentiation, resulting

in increased mucin secretion and providing a physical protective barrier against pathogens (Ahmadi et al., 2020). However, it is still unknown if metformin-induced augmentation in gut microbiome may alleviate the risk or extent of hyperthermia-induced endotoxemia. Furthermore, the evidence in mouse models needs to be confirmed in human populations. Future studies should elucidate if short- and long-term metformin use alleviates the risk of heat-related endotoxemia and consequent systemic inflammatory response syndrome in patients by measuring inflammatory markers and gut flora following heat exposure (Table 1).

C. Sodium-Glucose Cotransporter 2 Inhibitors

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are another class of medications commonly prescribed for people with diabetes. SGLT2i effectively lower plasma glucose concentrations by increasing urinary glucose excretion via the proximal renal tubules, inducing an osmotic diuretic effect. Thus far, SGLT2i have demonstrated beneficial cardiometabolic effects such as reduced HbA_{1c} and improved cardiac-related risk profiles (Lupsa and Inzucchi, 2018). However, adverse effects of SGLT2i have also been reported, including volume depletion and AKI (Lu et al., 2021).

In 2016, the U.S. Food and Drug Administration issued warnings regarding the use of SGLT2i after 101 cases of AKI were reported, some requiring hospitalization and dialysis (<https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-strengthens-kidney-warnings-diabetes-medicines-canagliflozin>). A recent case report presented a patient without prior renal complications and whose prescriptions were unchanged for the past 18 months who developed AKI secondary to renal ischemia after initiation of canagliflozin (an SGLT2i) (Hassani-Ardakania et al., 2019). However, a meta-analysis has challenged these observations, suggesting that AKI risk may slightly decrease due to SGLT2i's protective renal effects (Neuen et al., 2019). As such, evidence of SGLT2i's impact on AKI risk remains equivocal, with some studies suggesting protection against AKI (Darawshi et al., 2020; Zhao et al., 2020), while others suggesting possible distal tubular injury (Menne et al., 2019; Darawshi et al., 2020). SGLT2i's associated AKI risk may be explained by hypovolemia, excessive reduction in transglomerular pressure, and renal medullary hypoxia (Hahn et al., 2016). This risk may be exacerbated by extreme heat through heat-induced hypovolemia and dehydration. SGLT2i are purported to cause tubular injury directly by increasing risk of dehydration and hyperosmolarity through osmotic diuresis (Hahn et al., 2016). Receiving multiple medications for comorbidities may significantly compound the risk of heat-related illness (Westaway et al., 2015). For instance, because of SGLT2i's osmotic diuresis effect, dehydration and symptomatic hypotension are commonly reported, especially in elderly patients or patients concurrently treated with diuretics (Vardeny and Vaduganathan, 2019). Therefore,

care should be exercised when SGLT2i are prescribed to diuretic-dependent patients (e.g., congestive heart failure patients) to avoid hypohydration, secondary cardiovascular strain and renal impairments, especially in the heat (Puga et al., 2019; Chapman et al., 2021; Periard et al., 2021).

SGLT2i should be initiated along with clear patient advice to observe for diuresis, excessive dizziness, and postural hypotension symptoms. Such complaints should be reported to the clinician-in-charge when SGLT2i are newly initiated. In occupational settings, both healthy and diabetic workers who may be repeatedly exposed to high temperatures, strenuous work, and hypohydration are at risk of CKD (Sato et al., 2019; Chapman et al., 2021). Therefore, patients who work for prolonged periods in the heat should be encouraged to discuss potential implications with respect to hydration status, especially if they have concomitant heart failure or other conditions requiring careful fluid balance. In addition, large-scale prospective studies involving outpatient populations chronically exposed to exertional heat stress (e.g., diabetic farmers and factory workers) are required to determine if SGLT2i confers protection or increases AKI risk (Table 1).

V. Cardiovascular Diseases

CVDs such as coronary heart disease, stroke, and heart failure increase patients' vulnerability to adverse cardiovascular events during heat exposure (Bunker et al., 2016; Cheng et al., 2019). The mechanisms underpinning adverse heat-related episodes in CVD patients are unclear but conceivably stem from the increased cardiac strain apparent during heat stress (Fig. 4). Indeed, tachycardia and increased contractility are typically observed during heat stress to sustain cardiac output. Interestingly, studies have reported similar increases in cardiovascular strain between individuals with CVD and healthy controls during moderate-intensity exercise in hot (30–35°C) environments (Sheldahl et al., 1992; Walsh et al., 2002). While changes in cardiac load seem similar during exercise in normothermic and warm environments, consequential increases in myocardial oxygen consumption and impaired increases in coronary blood flow have been purported to be a key stimulus triggering myocardial ischemia (Khraishah et al., 2022). In support, it has been shown that impaired coronary vasomotor function leading to reduced coronary flow is a consequence of many CVDs and traditional risk factors for adverse events (Kaski et al., 2018).

Hyperthermia-induced inflammation and hypercoagulable states may also contribute to adverse cardiovascular episodes during heat stress, especially in patients with pre-existing CVDs (Khraishah et al., 2022). These mechanisms have been implicated in the development of adverse cardiovascular events in the presence of heat stroke (Leon and Helwig, 2010). However, it is unclear if these mechanisms are also involved in cardiovascular events during heat exposure and in the absence of heat

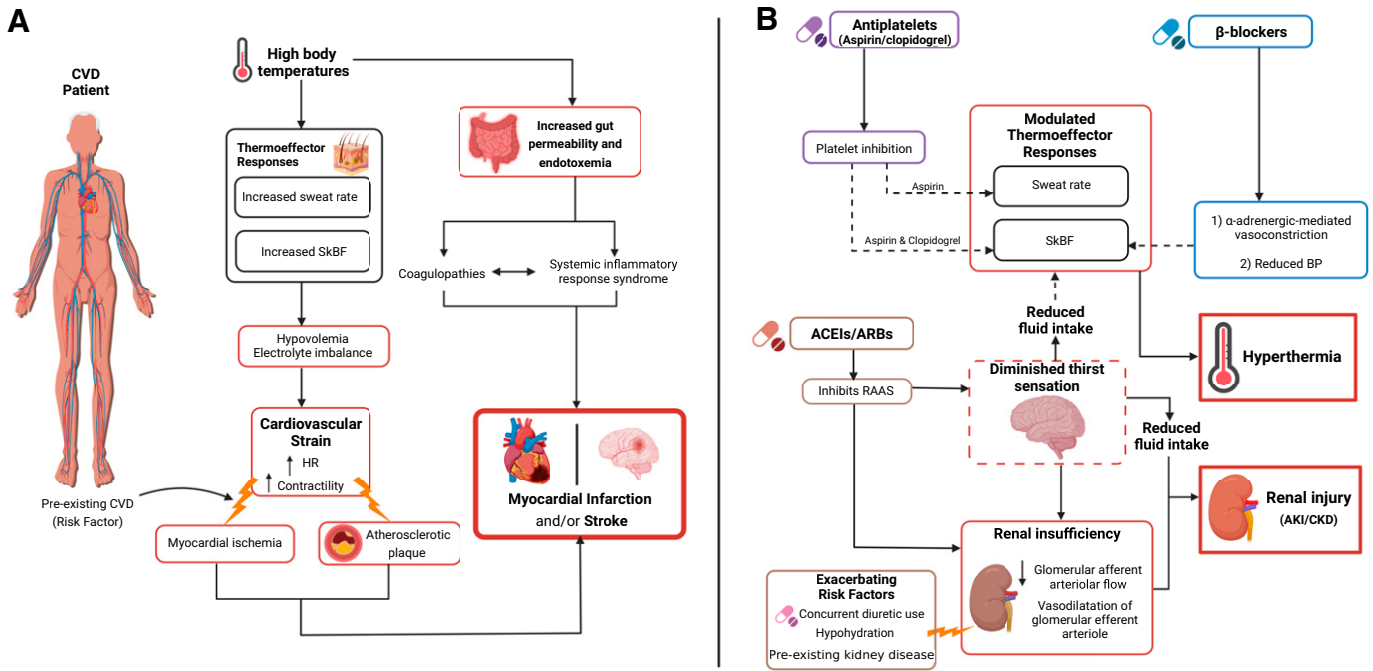


Fig. 4. (A) Impairments in thermoregulatory responses in CVD. Solid and dashed arrows denote a stimulation or an increase, and downregulation or decrease, respectively. Pre-existing CVD exacerbates the level of cardiovascular strain experienced by patients. These patients are susceptible to 1) myocardial ischemia due to increased oxygen demand to maintain cardiac output and/or 2) ruptured atherosclerotic plaque that induces a myocardial infarction and/or stroke due to arteriole blockages. Additionally, extreme heat can increase gut permeability resulting in endotoxemia. Hypercoagulability and endotoxemia-induced systemic inflammatory response syndrome may result in multiorgan failure (e.g., heart attack or stroke). (B) CVD drug modulations of thermoregulatory responses to extreme heat. Antiplatelet medications and β -blockers perturb thermoregulatory responses to heat. ACEi/ARBs inhibit RAAS signaling and may lead to renal insufficiency. Additionally, ACEi/ARBs may suppress thirst sensation and impact fluid intake behaviors. ACEi/ARBs may consequently impair fluid balance and lead to renal damage and limit thermoeffector responses. Abbreviations: HR, heart rate; RAAS, renin angiotensin aldosterone system; SkBF, skin blood flow; AKI, acute kidney injury; CKD, chronic kidney disease. Created with BioRender.com.

stroke. In support, some studies have reported young, healthy individuals exhibiting enhanced inflammatory responses during moderate hyperthermia (Laing et al., 2008; Faulkner et al., 2017), while others have reported minimal activation of coagulation during mild to moderate hyperthermia (Boldt et al., 2008; Borgman et al., 2019). However, similar studies involving older adults and CVD populations are needed to ascertain these mechanisms' involvement during heat-related cardiovascular events. See the comprehensive reviews describing CVD-related thermoregulatory impairments (Chaseling et al., 2021; Khraishah et al., 2022).

VI. Cardiovascular Disease Medications and Heat Stress

A. Antiplatelets

Antiplatelet medications are the mainstay of preventive care for individuals at risk of atherothrombotic disease and those who receive percutaneous coronary intervention with coronary artery stents (Orme et al., 2017). Antiplatelet medication inhibits the agglutination of platelets that leads to thrombi formation within blood vessels, especially the microvasculature of the heart and brain, which may lead to ischemic heart disease and stroke. Commonly prescribed antiplatelet medications include aspirin and

clopidogrel. Aspirin, a nonsteroidal anti-inflammatory drug, is usually prescribed at a low dose as primary prevention of thromboembolic events. Clopidogrel is prescribed secondary to a previous thromboembolic event. Both aspirin and clopidogrel have been shown to impair thermoregulatory responses during passive and exertional heat stress by reducing SkBF and possibly suppressing sweat responses (Holowatz and Kenney, 2009; Holowatz et al., 2010; Bruning et al., 2013).

Aspirin is a nonselective COX inhibitor that inhibits both COX isoforms (COX-1 and COX-2), which form part of the downstream mechanisms involved in cutaneous vasodilation (Fig. 2). Low-dose aspirin acetylates COX in the portal circulation and inhibits platelet COX-mediated prostaglandin and thromboxane synthesis, thereby inhibiting platelet activation and production of platelet-derived vasodilators such as NO, ATP, ADP, and 5-HT (Patrino et al., 1985; Holowatz and Kenney, 2010). Studies consistently demonstrate that low-dose aspirin therapy reduces SkBF response and delays the onset of reflex cutaneous vasodilation in healthy middle-aged adults during passive and exercise heat stress (Holowatz and Kenney, 2009; Holowatz et al., 2010; Bruning et al., 2013). Contrastingly, clopidogrel inhibits platelet activation by inhibiting the binding of ADP (a well-known platelet activator) to its platelet

receptor P_2Y_{12} . Consequently, inhibited platelet activation would result in the suppression of platelet-derived vasodilators from platelet dense core granules, thus inhibiting SkBF responses to heat exposure. Indeed, clopidogrel suppresses cutaneous vasodilation during passive heating significantly more than low-dose aspirin in middle-aged adults during whole-body passive heating (Holowatz et al., 2010). Additionally, both medications have been shown to elevate final body core temperature and increase the rate of body core temperature rise during both passive and exercise heat stress (Holowatz et al., 2010; Bruning et al., 2013).

Evidence suggests that chronic low-dose oral aspirin attenuates reflex cutaneous vasodilation through its systemic effects on platelet COX but not on vascular COX in aging adults during passive heat stress (Holowatz and Kenney, 2009). COX plays a role in synthesizing several platelet-derived vasodilator prostanoids (see *Aging Thermoregulation*) (Holowatz et al., 2010). Low-dose orally ingested aspirin does not inhibit vascular endothelium COX-1 since the drug is diluted along the GI tract before reaching the cutaneous microvasculature (Patrono et al., 1985; Bruning et al., 2013). Considering the low dosage (81 mg/d) used in human studies, it is more likely that aspirin-driven inhibition of cutaneous vasodilation is driven by systemic circulatory mechanisms (i.e., inhibition of platelets and platelet-derived cytokine and prostaglandin circulation). Furthermore, localized nonspecific COX inhibition by skin-infused ketorolac does not influence local blood flow during hyperthermia in aged skin during passive and exercise heat stress (Holowatz et al., 2009; Fujii et al., 2015b). While skin-infusion studies have concluded that vascular COX is not involved in cutaneous vasodilation responses to heat, it should be noted that orally dosed aspirin still exerts central effects on COX (Bruning et al., 2013). It is also speculated that COX inhibition by low-dose aspirin may influence thermoregulatory control in the brain by modulating the brain's preoptic area that regulates body temperature. Indeed, in mouse models, COX has previously been found in this brain region (Eskilsson et al., 2014). Notably, prostaglandin-mediated inflammatory processes are involved in exercise-induced hyperthermia resulting from heat-induced gut leakage (Cannon and Kluger, 1983; Moseley et al., 1994; Bradford et al., 2007). These prostaglandins may cross the blood-brain barrier and result in changes in the thermoregulatory setpoint in the hypothalamus for thermoeffector responses such as SkBF increases and inducing a febrile-like response (Bradford et al., 2007). Antiplatelet medications like aspirin, used to attenuate these prostaglandin effects on the hypothalamus, can cross the blood-brain barrier as well. As such, one might expect aspirin to act as an antipyrogenic, thereby reducing body temperature. However, current evidence

suggests the opposite, with aspirin increasing the body temperature setpoint threshold of onset of cutaneous vasodilation during exercise heat stress while also raising body core temperature during passive heat stress (Bruning et al., 2013). However, the mechanisms of aspirin's effect on central thermoregulatory control are not clearly understood (Table 1). Furthermore, recent evidence has highlighted the potential use of low-dose aspirin to treat mood symptoms by modulating neuroinflammation and CNS functioning (Ng et al., 2019). Further studies are warranted to determine low-dose aspirin's potential effects on centrally mediated mechanisms controlling thermoeffector responses to heat.

Clopidogrel may impair heat loss during hyperthermia by suppressing the release of platelet-derived vasodilators. P_2Y_{12} stimulation releases vasodilators such as dinucleotides, PGI_2 , and NO, which induce endothelium-dependent vasodilation (Holowatz et al., 2010; Burnstock et al., 2012). Additionally, both clopidogrel and aspirin reduce platelet aggregation and, in turn, decrease whole blood viscoelastic properties (Patrono et al., 1985; Ciuffetti et al., 2001). Both medications may decrease the shear stress associated with heat-induced hyperemia. This potentially intrudes on microvascular adaptations conferred by heat-induced shear stress (Green et al., 2010; Brunt et al., 2016). Older men on mono or dual therapy with aspirin and/or clopidogrel are thus likely to experience dampened thermoregulatory adaptations following heat acclimation/therapeutic programs. Indeed, heat acclimation and post-exercise hot water immersion have been shown to induce desirable thermoregulatory responses (e.g., improved evaporative heat loss), as well as perceptual and exercise performance improvements during heat stress compared with before heat acclimation (Fujii et al., 2021b; Waldock et al., 2021). However, COX inhibition via antiplatelet medications may offset any potential benefits through the mechanisms suggested earlier. Further research is warranted to determine how short- or long-term mono or dual therapy with clopidogrel and aspirin may impact heat acclimation protocols in patients (Table 1).

There is a scarcity of research investigating the effects of aspirin and clopidogrel on sweating. Studies on oral salicylate COX inhibitors (e.g., aspirin and sodium salicylate) have demonstrated equivocal findings (Jacobson and Bass, 1964; Bass and Jacobson, 1965; Bruning et al., 2013). At very high doses, sodium salicylate has been shown to increase sweat rate during physical activity in compensable conditions (i.e., when physiologic heat loss mechanisms can compensate for heat gain) while possibly increasing body core temperature in uncompensated conditions (i.e., heat gain overwhelms physiologic heat loss mechanisms' ability to compensate) (Jacobson and Bass, 1964). To date, the

only study to examine the effect of clopidogrel on sweating was conducted by Bruning et al. (2013), who reported no changes in whole-body sweat rate with aspirin and clopidogrel use in exercising middle-aged adults in the heat. Mechanistic studies administering COX inhibitor ketorolac via intradermal microdialysis also yielded mixed findings (Fujii et al., 2014a,b, 2015b, 2018c). Both COX-1 and COX-2 blockade contribute to decreased local sweat rate in young men undertaking moderate exercise (~400W) in the heat. Interestingly, at high heat loads (~700W), there were no differences in sweating with COX and NOS inhibition. This may be attributed to high concentrations of acetylcholine (Ach) released during high heat loads that directly upregulate muscarinic sweating and render second-messenger NO- and COX-dependent mechanisms redundant (Fujii et al., 2014b). Taken together, it is plausible that during moderate-intensity physical activity, low-dose aspirin may attenuate sweating and exacerbate heat storage, especially in environments (i.e., hot and humid) or work conditions (e.g., use of personal protection equipment or insulative clothing) that lead to uncompensated heat stress.

Future studies should investigate exercise across various populations (e.g., young versus old), exercise intensities, and ambient conditions to formulate definitive guidelines on oral antiplatelet therapy use during exertional heat stress with a specific interest in sweat responses. Furthermore, the lesser known effects of antiplatelet treatments when administering passive heat therapies and heat acclimation strategies require further understanding to ensure such strategies are safe and effective. Clinicians should consider the thermoregulatory disturbance (i.e., suppressed vasodilation and possible reduced sweating during moderate to vigorous exertional heat stress) when prescribing antiplatelet therapy to adults over 50 years old who exercise or work in a hot environment.

B. Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers

ACEIs and angiotensin II receptor blockers (ARBs) are widely used in managing cardiovascular diseases, specifically hypertension and heart failure (Laurent, 2017). ACEIs reduce plasma concentrations of angiotensin II by blocking the enzymatic conversion of angiotensin I to angiotensin II in the vascular and pulmonary endothelium. ARBs suppress end-organ responses to angiotensin II by blocking angiotensin II receptors, specifically AT₁ receptors. These receptors can be found on endothelial surfaces in kidneys, blood vessels, and the brain's POA, hypothalamus, and subfornical organ (Schiffirin et al., 2000; Leite et al., 2007; Sakai et al., 2007; Arumugam et al., 2016). Long-term ACEI/ARB use is associated with a reversal of left ventricular remodeling with improvements in contractile response to exercise (Blanchet et al., 2005). Other benefits include enhanced endothelial function and reduced arterial stiffness in patients with or

without comorbidities (e.g., heart failure, diabetes, etc.) (Agabiti-Rosei et al., 2009; Boutouyrie et al., 2011; Hao et al., 2014; Laurent, 2017).

However, it has been observed that taking ACEIs and ARBs, especially in combination with diuretics, posed the highest risk of hospitalization in seniors due to heat- and dehydration-related illnesses during extreme heat events (Kalisch Ellett et al., 2016). A recent case report described the occurrence of AKI with the use of telmisartan (an ARB), observed primarily in heart failure patients (Surendran, 2022). Similarly, ACEI use increased the risk of AKI in older adults, especially during dehydration (Chaumont et al., 2016). Angiotensin II is a powerful stimulatory signal for the renal resorption of fluid and electrolytes, blood pressure, and glomerular filtration rate maintenance during heat stress, especially in a state of dehydration. Blocking angiotensin II may exacerbate poor renal function (Laurent, 2017). Such acute renal failure with ACEIs/ARBs is further augmented by hypohydration and compounded by concurrent diuretic medication use (e.g., congestive heart failure patients) and nonsteroidal anti-inflammatory drugs (Council on the Kidney in Cardiovascular Disease and the Council for High Blood Pressure Research of the American Heart Association, 2001).

Peripherally, angiotensin II strongly mediates cutaneous vasoconstriction (Stewart et al., 2008). Exogenous administration of angiotensin II attenuates sweating and cutaneous vasodilation responses to ambient heat exposure during rest (Fujii et al., 2015a). ACEIs/ARBs may, therefore, also increase cutaneous vasodilation by inhibiting angiotensin II during passive rest in the heat. Further, these attenuations in heat loss responses were diminished during exercise in the heat (Fujii et al., 2015a). Furthermore, angiotensin II activates aldosterone, a key signal for renal reabsorption of sodium, and consequently water, to maintain blood pressure during dehydration, such as during exercise in the heat. Peripherally, aldosterone modulates sodium reabsorption and potassium excretion in the duct of human eccrine sweat glands (Sato and Dobson, 1970). Taken together, while ACEIs/ARBs may impair renal function, they may also augment peripheral heat loss responses during heat stress. However, to our knowledge no study has directly assessed the influence of ACEIs/ARBs on sweat and SkBF responses during heat stress (Table 1).

ACEIs/ARBs have been reported to diminish thirst sensation and decrease fluid intake in animal studies (Weisinger et al., 1990; Sakai et al., 2007; Begg, 2017). However, the effect of ACEI/ARB use on human thirst perception has yet to be evaluated. Reduced thirst perception and behavioral drinking occurs with aging (see *Aging Thermoregulation*) (Phillips et al., 1984, 1993; Mack et al., 1994). Therefore, it is possible that ACEI/ARB use may compound the age-related diminishment

in thirst perception and subsequently reduce fluid intake. Delayed fluid replenishment attenuates sweat responses and elevations in SkBF, increases cardiovascular strain, predisposes patients to renal injury, and increases heat strain (Periard et al., 2021). Considering all the evidence, it may be appropriate for elderly patients, particularly those receiving ACEIs/ARBs, to adopt individualized drinking strategies such as scheduled drinking rather than ad libitum drinking (Kenefick, 2018). However, future research should assess the efficacy of various drinking strategies in elderly patients and patients receiving various medications such as ACEIs/ARBs (Table 1). Clinicians should consider the fluid balance needs in ACEI/ARB-dependent patients with comorbidities such as heart failure and CKD, as well as any concurrent diuretic use.

Heat-related exercise intolerance after ACEI/ARB use has not been investigated in humans. However, angiotensin inhibition or blockade has been shown to increase the rate of rise in colonic temperature associated with delayed cutaneous vasodilation response during exercise and passive heat stress in rats (Mathai et al., 2000; Leite et al., 2007). This drug-induced exacerbated rise in heat storage and body temperature decreased exercise tolerance in these rats. The inverse relationship between the rate of core temperature rise and exercise tolerance is well documented in healthy and chronically ill (i.e., hypertension and diabetes) older adults (Notley et al., 2021a,b). Additionally, RAAS blockade impacts sodium regulation, resulting in hyponatremia, and may consequently impact fluid regulation during exercise (Puga et al., 2019). Presumably, ACEI/ARB use may limit the exercise tolerance of patients in the heat given its impacts described previously. To our knowledge, no study has directly investigated the effects of ACEI/ARBs on exercise tolerance in relation to thermoregulatory function and fluid balance during exercise heat stress in humans (Table 1). Such investigations may provide additional perspectives because ACEI/ARBs have been shown to improve exercise capacity without heat stress (von Haehling et al., 2021).

C. Beta-Blockers

β -blockers are used for multiple cardiovascular conditions such as ischemic heart disease, hypertension, and heart failure by reducing contractility of the heart and reducing myocardial oxygen demand (do Vale et al., 2019). β -blockers compete with catecholamines (e.g., epinephrine and norepinephrine) for binding sites on the β -adrenergic receptors of end organs. Skin infusion studies demonstrate that β -adrenergic cutaneous vasodilation and sweating occur in young adults (Hodges et al., 2015; Fujii et al., 2017; Amano et al., 2020). Amano et al. (2020) demonstrated that β -adrenergic sweating is augmented during exposure to a hot environment (35°C). Hodges et al. (2015) similarly demonstrated that higher skin temperatures (~39°C) elicited

by passive heating enhanced β -adrenergic cutaneous vasodilator response. Taken together, a higher environmental temperature likely amplifies the β -adrenergic thermoeffector responses to heat stress. β -adrenergic cutaneous vasodilation has been shown to be augmented and attenuated, respectively, by NOS and COX, while β -adrenergic sweating is suppressed by NOS and COX via their inhibitory effects on cAMP in young adults in a thermoneutral environment (Fujii et al., 2017). Findings by Fujii et al. (2017) suggest that NOS and COX are involved in β -adrenergic sweating and cutaneous vasodilation. There are generally two types of β -blocker medications: first generation (nonselective) and second generation (selective). Selective blockers specifically target either β_1 or β_2 receptors. β_1 receptors are exclusively found in cardiac tissue, while β_2 receptors are distributed in various end organs in central and periphery sites. As such, the respective selective β -blockers exclusively target cardiac or noncardiac tissues. Interestingly, there is another class of medications with both α - and β -adrenergic blocking (i.e., carvedilol). However, no studies have specifically studied the effects of such combination of medications on thermoregulatory responses to environmental and exertional heat stress. It should be acknowledged that certain β -blockers could also bind to β_3 receptors located on BAT, altering the thermogenic function of this tissue and compromising thermoregulation (Farzam and Jan, 2022). More recently, third-generation β -blockers like nebivolol have been developed and act as β_3 receptor agonists. β_3 receptor agonism may result in NO-mediated vasodilation (Balligand, 2016; Otljanska et al., 2016). Considering their affinity with β_3 receptors, third-generation β -blockers may also promote thermogenesis via BAT activation. However, the increased thermal dissipation (vasodilation) and increased thermogenesis arising from third-generation β -blocker-associated agonism may have compensatory effects and reduce the possibility of thermal imbalance. Contrastingly, common first- and second-generation β -blockers' affinity and action on β_3 receptors are less understood.

It is possible that nonselective β -blockers such as propranolol may inhibit the β_3 receptor and, in turn, inhibit BAT-mediated thermogenesis, possibly reducing endogenous heat gain. This reduction in thermogenesis could offset any concomitant β -blocker-induced thermoregulatory impairments from increased cutaneous vasoconstriction independent of heat stress (Gordan et al., 1985). However, evidence and understanding of β_3 receptor and third-generation β -blockers' involvement in thermoregulatory response in heat stress are in their infancy, and there remains a major research gap (Table 1). As such, this review does not provide in-depth discussion of β -blocker effects on β_3 receptor in relation to heat stress.

β -blockers may impair thermoregulatory responses. β -blockers have been shown to reduce peripheral SkBF and lower mean skin temperature during short and prolonged exercise with or without environmental heat stress in young and older adults during heat exposure at rest and during exercise (Gordon et al., 1985; Freund et al., 1987; Pescatello et al., 1987; Chaseling et al., 2022). Proposed mechanisms for shunted SkBF include 1) augmented α -adrenergic mediated vasoconstriction of the skin (Johnsson, 1975; Gordon et al., 1987; Pescatello et al., 1987), 2) reduced carotid sinus and aortic (sinoaortic) baroreceptor-mediated cutaneous vasoconstriction due to β -blocker suppression of systolic blood pressure and arterial pulse pressure (Freund et al., 1987; Pescatello et al., 1987), and 3) attenuated blood flow to cutaneous beds due to reduced arterial driving pressure (Pescatello et al., 1987).

The aforementioned studies have generally compared the effects of propranolol (nonselective β -adrenergic blocker) against selective metoprolol or atenolol (β_1 -selective adrenergic blockers). A consistent finding is that nonselective β -blockers attenuate SkBF and the rate of rise in mean skin temperature (Gordon et al., 1985; Freund et al., 1987; Pescatello et al., 1987). Several studies have demonstrated that plasma levels of epinephrine and norepinephrine were significantly elevated with propranolol use (Irving et al., 1974; Johnsson, 1975; McLeod et al., 1984). Furthermore, during peripheral β_2 -adrenergic blockade, plasma epinephrine resulted in unopposed α -adrenergic-mediated vasoconstriction (Johnsson, 1975). Alternatively, β -blockers may reduce sinoaortic baroreceptor stimulation by reducing blood pressure during exercise with and without environmental heat (Pescatello et al., 1987). Consequently, a reflex increase in skin and peripheral vascular resistance to preserve blood pressure limits dry heat dissipation. Recently, it was demonstrated in older patients with stable coronary artery disease who received cardioselective β -blockers that SkBF response in hot and humid conditions was attenuated relative to patients not receiving β -blockers (Chaseling et al., 2022). However, the suppressed vasodilatory response was not observed in hot and dry conditions and did not alter cardiovascular or thermal strain when compared with patients not receiving β -blockers (Chaseling et al., 2022). The mechanisms underlying these preliminary observations are not yet known. Although the level of thermal and cardiovascular strain remained unchanged despite β -blocker-mediated impairment of cutaneous vasodilation, caution should be exercised. Indeed, older patients often present with multiple comorbidities and polypharmacy. The combined effects of multiple medications on thermal strain are not known, warranting further investigation. Taken together, clinicians should carefully consider β -blockers' impact on attenuated SkBF responses to heat stress. Future studies should determine the exact cardiovascular

mechanism explaining β -blockers' suppression of SkBF and lowering of skin temperature to determine mitigating strategies for patients receiving these medications (Pescatello et al., 1987) (Table 1).

There is conflicting evidence of β -blockers' impact on sweating in young healthy exercising adults in various hot and normothermic conditions (Wilcox et al., 1984; Gordon, 1985, 1987; Mack et al., 1986). A likely reason for such conflicting evidence is the differing localized and systemic effects of oral β -adrenoreceptor blockers that may indirectly modulate sweating during passive and exercise-induced sweating (Buono et al., 2010, 2011). Local β -adrenergic blockade has been found to suppress local sweat rates during exercise-induced heat stress (Amano et al., 2017, 2020). Recent in vivo evidence during exercise demonstrated that locally administered propranolol attenuated local sweat response, albeit only during higher-intensity submaximal exercise (80%–90% of maximum workload) in habitually active men, with no attenuation in untrained men (Amano et al., 2017).

Contrastingly, studies investigating orally dosed nonselective β -adrenergic blockade have reported equivocal findings. Oral β -blockers have been shown to increase sweating in young, healthy, and middle-aged men exercising with and without environmental heat stress (Wilcox et al., 1984; Gordon et al., 1985, 1987; Freund et al., 1987). Cardioselective β -blockers have been shown to reduce sweating in healthy young adults (Mack et al., 1986), which can result in increased heat strain (Pescatello et al., 1987). However, recent evidence in older coronary artery disease patients showed that cardioselective β -blockers use did not alter sweat response to extreme heat in dry or humid conditions (Chaseling et al., 2022). Similarly, another study observed no difference in sweat rates during submaximal exercise between propranolol and placebo drugs (Mack et al., 1986). However, the study observed a decreased sweat sensitivity to rising esophageal temperature (Mack et al., 1986). A likely reason other studies did not observe reduced thermosensitivity of sweat response is the method of core temperature measurement (Mack et al., 1986). Considering that certain β -adrenergic blockers like propranolol may significantly reduce splanchnic (e.g., stomach, intestines, liver, etc.) blood flow and limit heat transfer from exercising muscles to the central circulation, rectal temperature and mean blood temperature may become decoupled (Trap Jensen et al., 1976). Esophageal temperature is a more sensitive proxy measure for blood temperature changes (Mack et al., 1986; Shiraki et al., 1986). Future studies should consider measuring esophageal temperature to confirm previously reported oral β -blocker-mediated sweating during hyperthermia.

While both orally dosed nonselective and β_1 -selective adrenergic blockade have been observed to increase sweating, nonselective β -adrenergic blockade with propranolol

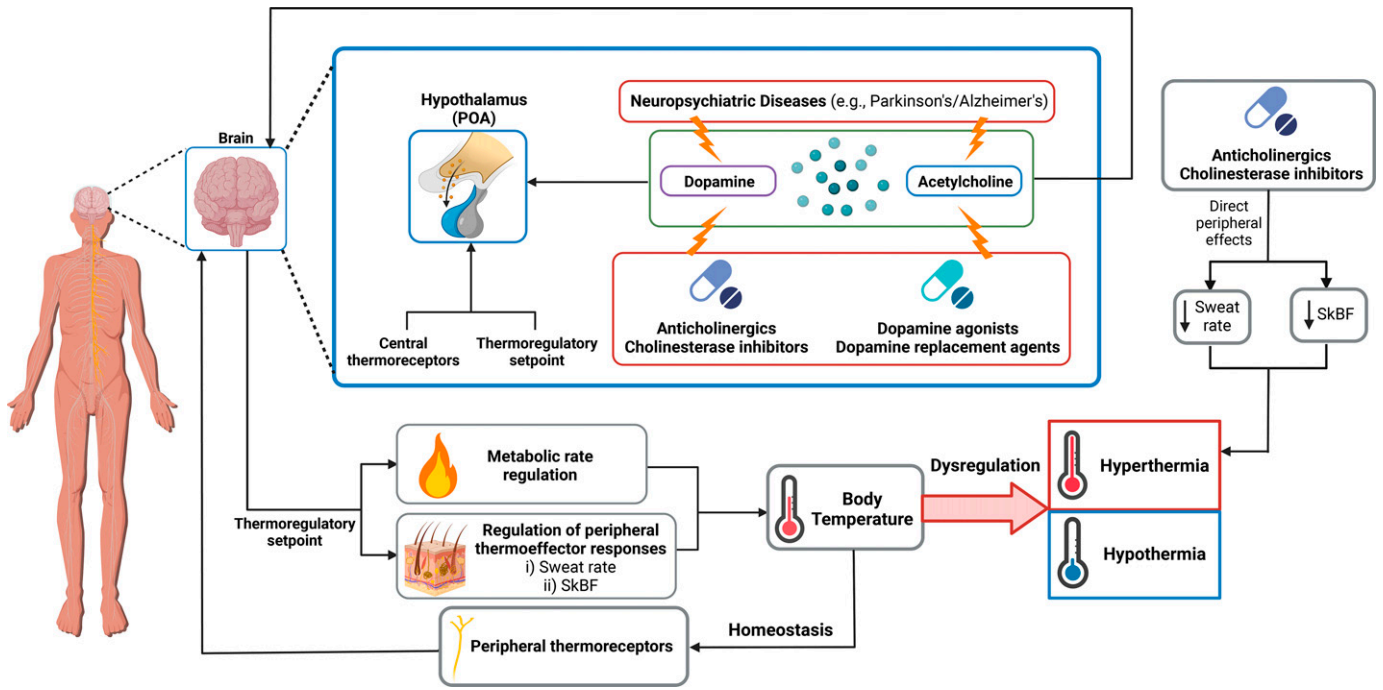


Fig. 5. Neuro-psychiatric disease (e.g., Parkinson’s and Alzheimer’s disease) and drug interactions modulate central and peripheral dopamine and Ach signaling. Given that the thermoregulatory control center resides in the POA of hypothalamus, fluctuations in global neurotransmitter levels can modify integrative inputs to POA and influence thermoregulatory setpoint. Disease and drug interactions modulate metabolic rates and thermoeffector responses to environmental and exertional stressors. Consequently, this can cause dysregulated body temperatures and disrupt negative feedback loops, thus leading to hyperthermia or hypothermia. Oral anticholinergics such as atropine can directly attenuate both sweat response and skin blood flow at the end-organ level during heat stress. Abbreviations: SkBF, skin blood flow; POA, preoptic area. Created with BioRender.com.

accentuated sweating to a greater degree (Gordon, 1985). Given the equivocal findings, further mechanistic studies are required to determine how orally dosed nonselective and selective β -blockers may affect sweating during passive heat stress and varying exercise intensities and durations across different populations (Table 1). Furthermore, greater SkBF and temperature reductions with nonselective β -adrenergic versus selective β_1 -adrenergic blockade have been observed (Gordon et al., 1985, 1987; Freund et al., 1987). Therefore, clinicians should note the potential importance of the type of β -adrenergic inhibitors prescribed to patients to minimize the perturbations to thermoregulation function. Patients receiving β -blocker treatment should be advised to consult physicians on how best to maintain fluid balance, especially during exertional heat stress and if they receive concurrent drug therapies (e.g., diuretics, SGLT2i, etc.) (Gordon et al., 1987; Puga et al., 2019).

VII. Neuro-psychiatric Disorders and Heat Stress

Thermoregulatory dysfunction is consistently reported in patients with neuro-psychiatric diseases such as PD and AD. These impairments stem from central and peripheral disruptions in autonomic responses to heat stress arising from imbalances in dopamine and ACh levels (Francis and Perry, 2007; Coon and Low, 2018). Figure 5 summarizes the effects of PD and AD and their

associated medications that alter metabolic regulation and thermoregulatory responses (i.e., eccrine sweating and cutaneous vasodilation), resulting in hyper- or hypothermia.

VIII. Neuro-psychiatric Disorders Medications and Heat Stress

A. Anticholinergics and Cholinesterase Inhibitors

The central cholinergic system is an important pharmacological target for many neurologic disorders due to its widespread involvement in physiologic functions, including learning and memory, motor coordination, thermoregulation, and autonomic function (Bertrand and Wallace, 2020). In PD and AD, drugs such as anticholinergics and cholinesterase inhibitors are prescribed to alter ACh availability in the brain to improve motor and cognitive symptoms, respectively. Nicotinic and muscarinic receptors, to which ACh binds and signals, can be found in mammalian thalamus and hypothalamus, where the central thermoregulatory centers reside (Giraldo et al., 1987; Nakayama et al., 1995). The regulation of body temperature involves cholinergic pathways in the central processing and integration of thermal information, including the control of thermoregulatory effector responses (Gordon, 1996). This indicates that medication-induced alteration of ACh levels likely induces changes in the central thermoregulatory drive.

Adverse thermoregulatory events arising, at least in part, from anticholinergic medication have been documented. Recurrent heat-related illnesses involving heat stroke and heat exhaustion have been observed in a case report of a patient using benzhexol (anticholinergic agent) and chlorpromazine (phenothiazine antipsychotic with anticholinergic effect) (Kwok and Chan, 2005). Moreover, there has been a reported case of fatal exertional heat stroke in a patient receiving benztropine (anticholinergic) and other neuroleptic drugs (Kao and Kelly, 2007). It has also been observed that exposure to environmental toxins that act as cholinesterase inhibitors manifested in febrile responses (Gordon, 1996). On the other hand, the use of anticholinergics to block the action of ACh (e.g., antimuscarinic substances such as atropine) has been shown to increase the rate of rise in core temperature under heat stress in young healthy adults (Kolka et al., 1983). This impaired thermoregulation has been attributed to the inhibited sweating response with atropine (Kolka et al., 1987). Considering that the central effect of ACh levels on thermoregulation is polarized, future research should consider dose-response studies on ACh-modulating medications to identify the “dose threshold” at which thermoregulatory responses will be altered (and how it will be altered) in passive and exertional heat settings (Table 1). This can also help avoid cholinergic insufficiency or overstimulation in patients, which leads to autonomic dysfunction and precipitates an increased risk of heat-related illnesses.

Apart from mediating central thermoregulatory drive, ACh modulates the peripheral changes in thermoeffector responses. Cutaneous active vasodilation is mediated by cholinergic nerve transmission (Kellogg et al., 1995). Interestingly, exogenous administration of systemic atropine (anticholinergic medication) induced higher cutaneous vasodilation at the same core temperature (Kolka and Stephenson, 1987), which is partly attributed to the release of vasoactive substances such as vasoactive intestinal peptide. In contrast, locally administered atropine in the skin only partially reduced active cutaneous vasodilation (Kellogg et al., 1995) and only during the initial duration of passive heating, but not any later, after substantial cutaneous vasodilation (Shibasaki et al., 2002). Taken together, evidence suggests that orally dosed atropine blunts SkBF responses to heat stress through both central and peripheral mechanisms. Atropine has been shown to reduce thermal sweating and eliminate sudomotor responses to nonthermal stimuli (Machado-Moreira et al., 2012; Suyama et al., 2016). Thus, ACh receptors located on eccrine sweat glands are essential for the induction of thermal sweating. On the other hand, eccrine sweating is stimulated by ACh released by sympathetic nerves (Shibasaki and Crandall, 2010). Notably, sweating can be initiated by an axon reflex via ACh stimulation of axonal nicotinic receptors. Anticholinergic effects of drugs such as atropine

seem to antagonize ACh at the junctions between sudomotor nerves and eccrine sweat glands (Cheshire and Fealey, 2008). Consequently, patients may experience additional thermal strain manifesting as a faster rise in core temperature (Kolka and Cadarette, 1990).

Considering the frequently reported incidence of heat-related morbidity and mortality attributed to medication-induced impaired heat dissipation, clinicians need to consider that the use of medications that alter the levels of ACh may confer an increased risk of developing heat-related illnesses in patients.

B. Dopamine Replacement Agents and Dopamine Agonists

Levodopa (L-dopa), a dopamine (DPA) precursor, increases DPA levels in the brain and is the most potent and effective medication for PD (Salat and Tolosa, 2013). In PD, movement control is impaired due to the loss of substantia nigra neurons and subsequent depletion of DPA levels available for neurotransmission in the corpus striatum (Dexter and Jenner, 2013). Central dopaminergic neurotransmission has been proposed to play an important role in thermoregulation since DPA innervation is prominent in thermoregulatory areas of the brain (Lee et al., 1985; Zheng and Hasegawa, 2016). This is indirectly evident in PD patients with autonomic dysfunction where there is high frequency of sweating dysfunction, including both hyperhidrosis (excessive sweating) and hypohidrosis (reduced sweating) (Hirayama, 2006). Notably, patients often report hyperhidrosis episodes during low dopaminergic states (Pursiainen et al., 2007; Coon and Low, 2018). The sweating dysfunctions in PD have been attributed to central mechanisms as the use of L-dopa has helped to restore normal sweating responses in PD patients (Goetz et al., 1986).

Apart from sweating responses, DPA neurotransmission may influence cutaneous vasodilation for heat dissipation, where superficial vasodilator responses have been observed to be reduced in PD patients (De Marinis et al., 1991). However, acute oral administration of L-dopa in humans resulted in a mean decrease in rectal temperature. In contrast, skin temperature did not change, suggesting that cutaneous vasodilatory response was likely unchanged (Boyd et al., 1974). This is supported by a clinical study showing that L-dopa at regular dosing did not influence PD patients' cutaneous vasomotor responses (Ludwig et al., 2007). In an exercise study, a DPA reuptake inhibitor (methylphenidate) improved cycling performance in the heat with a higher rectal temperature and heart rate, with no differences in skin temperature (Roelands et al., 2008). Both studies suggested that the increased levels of DPA could have contributed to changes in metabolic heat production and regulation, which appeared to be distinct in resting and exercise conditions. Notably, the perceptual responses (perceived exertion and thermal sensation) were not elevated by the higher rectal temperature in the latter

study. This “dampening effect” alludes to the likely danger of harmful hyperthermia development in patients taking DPA replacement agents or DPA agonists (Zheng and Hasegawa, 2016). However, it is not yet established if overall thermal perception (especially in a resting hyperthermic condition) will be influenced by taking L-dopa. This warrants more studies on the effect of L-dopa on thermal perception given that somatosensory abnormalities (e.g., pain) are known to be present in PD (Conte et al., 2013). This is critical for older PD patients on L-dopa medications, who may be inadvertently exposed to excessive heat during heat waves if their thermal perception is impaired (Table 1).

While there have been no reported cases of thermoregulatory dysfunction with use of L-dopa medication, it has been shown that L-dopa can significantly influence thermoregulation. In one case report (Renga et al., 2017), the administration of L-dopa helped to stabilize body temperature in a PD patient experiencing spontaneous periodic hypothermia, highlighting the central control of thermoregulation by DPA. More importantly, the rapid withdrawal of L-dopa medication is known to cause a rare but potentially fatal condition, parkinsonism hyperpyrexia syndrome, where body temperatures hit as high as 40°C (Sechi et al., 1984; Figà-Talamanca et al., 1985; Newman et al., 2009; Grover et al., 2018). This is not limited to L-dopa medication but also other dopamine agonists used as antiparkinsonian agents such as ropinirole (Arora and Fletcher, 2013). This shows the importance of DPA in the delicate control of the hypothalamic thermoregulatory set point. Therefore, it is prudent to note the potential thermoregulatory dangers of patients adjusting their dosage or withdrawing from DPA replacement agents or dopaminergic medications.

IX. Cancer and Heat Stress

The extent of thermoregulatory impairment in cancer patients remains largely unknown. However, thermal dysregulation has been associated with certain cancers, such as small cell lung cancers and breast cancer (Endo, 2014; Wiśniewska et al., 2016; Idiaquez et al., 2018; Adachi et al., 2020). For instance, small cell lung cancer is associated with Lambert-Eaton myasthenic syndrome, an autoimmune disorder resulting in sudomotor dysfunction (e.g., anhidrosis or hypohidrosis) (Idiaquez et al., 2018; Cheshire, 2020). This autoimmunity occurs against P/Q-type voltage-gated calcium channels on presynaptic nerve terminals that affect sweating (Zalewski et al., 2016). Furthermore, some cancers can augment thermogenesis via various mechanisms such as dysregulated activation of BAT and changes in tumor-immune microenvironment (Brooks et al., 1981; Tsoli et al., 2012; Gandhi et al., 2021). While not causative, various other cancers (e.g., prostate adenocarcinoma, serous carcinoma) besides lung cancer

have been associated with P/Q-type voltage-gated calcium channels autoimmunity (Zalewski et al., 2016).

The prevalence of hot flushes in breast cancer patients was reported to be approximately 65% (Carpenter et al., 1998). Hot flushes refer to a sudden sensation of intense warmth that begins from the chest and may progress to the neck and face (Shanafelt et al., 2002). While the pathophysiology underpinning hot flushes in breast cancer is still largely unknown, current evidence suggests a narrowing of the thermoneutral zone resulting in exaggerated vasomotor and sudomotor responses to minor increases in body temperature. Briefly, the thermoneutral zone refers to the ambient temperature range within which body temperature regulation is achieved only by nonevaporative processes, with metabolic rate remaining relatively constant without regulatory changes in heat production or evaporative heat loss (Romanovsky, 2018a). The narrowing of the thermoneutral zone occurs secondary to abrupt decreases in estrogen levels (e.g., use of estrogen antagonists, menopause) that may result from long-term use of chemotherapy drugs, such as tamoxifen, that lead to early menopause onset (Moon et al., 2017). A recent study measured the level of thermal strain and inflammatory blood markers to exertional heat stress at 4 metabolic equivalents for 30 minutes in warm (~25°C, ~50% RH) or hot (~35°C, ~50% RH) conditions in breast cancer survivors (Relf et al., 2021). The breast cancer survivors did not exhibit any differences in whole body sweat rates, heart rate, skin temperature, and rectal temperature compared with control subjects. Interestingly, the authors reported that self-paced exercise performance, measured by the 6-minute walk test, was compromised in the breast cancer survivors. There is no clear mechanism to explain this functional decline despite similar thermoregulatory capacity between groups after heat exposure. However, previous chemotherapy use may be implicated in impaired cardiovascular function (Curigliano et al., 2010; Relf et al., 2021). Further investigations are warranted, considering that chemotherapy use is associated with autonomic nervous system decline, possibly contributing to pathogenesis of CVDs (Adams et al., 2015). Furthermore, chemo- and hormonal therapies used to treat cancers are consistently reported to disrupt patients' thermoregulation (Wiśniewska et al., 2016; Adachi et al., 2020). For example, a 61-year-old woman was reported to have developed anhidrosis secondary to carboplatin and paclitaxel chemotherapies (Endo, 2014). These therapeutic complications are discussed in the subsequent section (see *Chemotherapy Medications and Heat Stress*).

X. Chemotherapy Medications and Heat Stress

Perhaps less understood than the cancers themselves are the medications used to treat them (Fig. 6). Due to the vast number of chemotherapy and hormone therapy

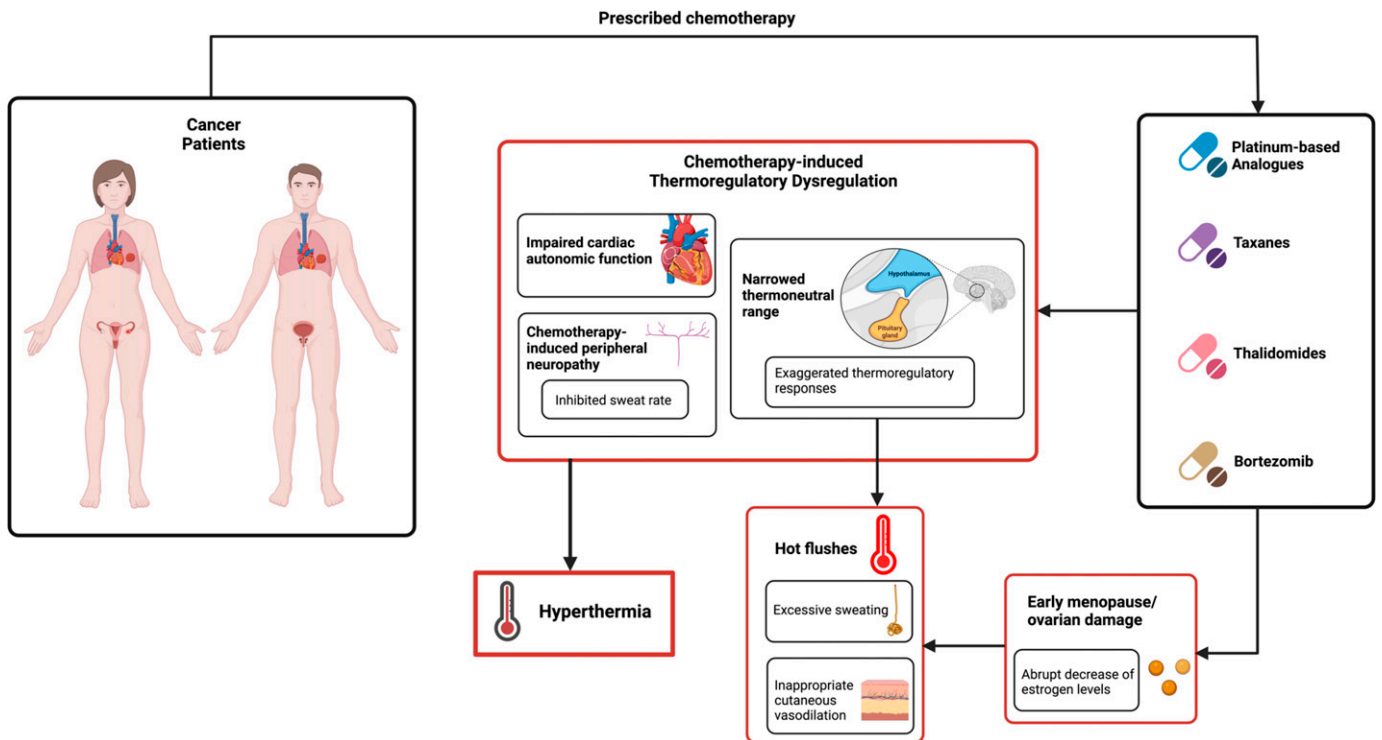


Fig. 6. Chemotherapy effects on thermoregulatory responses. Chemotherapy medications may alter onset threshold setpoints (narrowed range) for thermoregulatory response in the POA of the hypothalamus and lead to hot flushes. Chemotherapy may result in altered cardiac autonomic function that could exacerbate cardiovascular adjustments during extreme heat exposure. Chemotherapy-induced peripheral neuropathy is frequently reported during and after chemotherapy treatment, along with anhidrosis in case reports. Culminating effects may predispose cancer patients/survivors to excess thermal strain. More research focusing on the thermoregulatory effects of chemotherapy drugs is required to ascertain the impact of heat stress on cancer patients. Created with BioRender.com.

drugs on the market, and the limited number of human studies investigating thermoregulatory disruptions associated with chemo- and hormone therapy in different cancer patients, this section broadly describes case reports of patients who experienced thermoregulatory insults and, where possible, describes mechanisms of well-investigated anticancer medications.

Chemotherapies have consistently been reported to result in thermoregulatory dysfunction (Endo, 2014; Adachi et al., 2020). For example, generalized anhidrosis has been reported in young women with neurohypophyseal germinoma (Adachi et al., 2020) and a middle-aged woman with adenocarcinoma (Adachi et al., 2020) treated with combination therapy regimes with carboplatin (e.g., a platinum-based alkylating agent) and etoposide or paclitaxel. A possible mechanism of chemotherapy-induced anhidrosis is chemotherapy-induced peripheral neuropathy, as indicated by significantly reduced ACh receptors on eccrine sweat glands as observed in skin biopsies (Adachi et al., 2020), negative ACh sweat testing, and normal sweat gland structure (Adachi et al., 2020). In support of this, another case report of a 61-year-old woman who developed generalized anhidrosis after carboplatin and paclitaxel treatment highlighted that the skin biopsy presented a significantly reduced number of ACh receptors on eccrine sweat glands (Endo, 2014). In mice, both muscarinic and

nicotinic ACh receptors appear to be therapeutic sites for various therapeutic drugs designed to counteract taxane- and platinum analog-associated neuropathy (Calcutt et al., 2017; Kyte et al., 2018). Considering that there is postganglionic innervation of nicotinic and muscarinic receptors in eccrine sweat glands and the hypothalamus (Pappano, 2018), chemotherapy drug classes such as platinum analogs and taxanes may possibly attenuate ACh-mediated thermal sweating. Although the mechanisms of chemotherapy effects on cholinergic sweat signaling are not completely understood, it is important to note that any chemotherapy-induced disruption to muscarinic receptors on eccrine sweat glands may be of greater concern than nicotinic receptor disruption during hyperthermia. A recent study found that the role of nicotinic receptors is limited in thermal sweating following passive heating in humans (Fujii et al., 2019a).

Several anticancer drugs exert neurotoxic adverse effects, such as platinum analogs, antitubulins, thalidomide, and bortezomib. Platinum analogs, such as cisplatin, result in neuropathy as evidenced by a report of a 51-year-old patient who presented with polyneuropathy (Saito, 2020). After 50 minutes of passive heating (core temperature: 37.8°C), the patient was found to have regional anhidrosis on the left side of his body (Saito, 2020). Neurotoxicity of platinum analogs like cisplatin, carboplatin, and oxaliplatin is linked to their targeting of the

dorsal root ganglia (DRG), where platination of DNA occurs, resulting in structural changes in the DNA by forming interstrand crosslinks (Meijer et al., 1999). Consequently, DRG neurons prematurely undergo apoptosis while attempting to re-enter the cell cycle (Gill and Windebank, 1998). An alternative mechanism proposed is that platinum analogs exert oxidative stress and mitochondrial dysfunction, resulting in neuronal apoptosis (Yoon et al., 2009). While sweat-related dysfunction is commonly reported with platinum analog use, there is no evidence of potential impacts of these drugs on dry heat loss mechanisms.

Specific to the antitubulin taxane chemotherapy drug class, there is no report of associated thermoregulatory impairments. However, in a patient with adenocarcinoma, combination therapy of paclitaxel (a taxane) and carboplatin resulted in secondary generalized anhidrosis that was associated with high body temperatures and decreased thermoregulatory sweating (Endo, 2014). While it was not clear if paclitaxel alone resulted in sweating impairments, it may be possible that chemotherapy-induced peripheral neuropathy resulting from both the taxane and platinum analog use could be responsible for sweating impairments. Taxanes target sensory neurons as well as nerve axons (Cavaletti et al., 1997; Persohn et al., 2005). High concentrations of taxanes may result in macrophage activation in DRG and peripheral neurons resulting in microglial activation within the CNS (Cavaletti and Marmiroli, 2010).

Bortezomib has been reported to result in persistent fever and anhidrosis, relating to possible neuronal or hypothalamic damage (Liu et al., 2021). However, there have been no known reports of thalidomide-induced anhidrosis. The mechanisms of neurotoxicity of thalidomides and bortezomib in chemotherapy-induced peripheral neuropathy are largely unknown. However, bortezomib may disrupt transcription, transport, and translation processes of messenger RNA, as well as disrupt calcium regulation within DRG neurons as demonstrated in animal models, leading to neuronal damage (Landowski et al., 2005; Casafont et al., 2010). Similarly, thalidomide-induced neuropathy is not fully understood, although hypoxia of neuronal bundles appears to be responsible (Jongen et al., 2015).

Perhaps one of the most well-studied thermoregulatory side effects of chemo- and hormone therapies is hot flushes. Besides inappropriate vasodilation, sweating and increased core temperature resulting from hot flushes can impact quality of life and lead to discomfort in patients. Additionally, hot flushes may also result in night sweating and produce arousals and awakenings from sleep (Archer et al., 2011). Consequently, sleep disturbances are frequently reported with hot flushes that can result in fatigue and possibly, depression symptoms (Carpenter et al., 2004). In female cancer patients, hot flushes may occur secondary to early onset of

menopause induced by chemo- and hormone therapies (Wiśniewska et al., 2016). Chemotherapy-induced menopause may occur dependent on factors such as patient age, types, and cumulative doses of chemotherapy. In particular, older patients taking larger doses of multiple chemotherapy drugs are at higher risk of premature menopause (Morrow et al., 2011; Webber et al., 2016; Gargus et al., 2018). Short-term chemotherapy may result in amenorrhea (i.e., absent menstrual bleeding) that may be reversible (Codacci-Pisanelli et al., 2017). However, long-term use of chemotherapies, such as cisplatin and doxorubicin, are associated with irreversible ovarian follicular damage and possible premature menopause (Morgan et al., 2013). In fact, various drugs such as anthracyclines, cisplatin, cyclophosphamide, gemcitabine, mitomycin C, and taxanes are known to induce damage to DNA and vascular structures and result in DNA interstrand crosslinks in ovarian tissue (Codacci-Pisanelli et al., 2017). Tamoxifen (a selective estrogen receptor modulator) is widely used as hormone therapy in breast cancer patients and has been shown to exert antiestrogenic effects (Mourits et al., 2001), with hot flushes and night sweats being commonly reported as a side effect of long-term use (Moon et al., 2017).

Menopause and ovarian damage induced by adjuvant chemotherapies are consistently reported with low estrogen levels (Rose and Davis, 1980). The abrupt decrease in circulating estrogen levels is implicated in the increased frequency and severity of hot flushes in breast cancer patients (Carpenter et al., 1998; Fisher et al., 2013). As mentioned earlier, the pathophysiology of chemotherapy-induced hot flushes is not entirely understood. However, estrogen-mediated signaling is likely involved, as demonstrated by estrogen replacement therapy's high efficacy in managing hot flushes (North American Menopause Society, 2014). It has been shown that estrogen stabilizes thermoregulatory dysregulations and reduces sudden changes in body core temperature in animals (Bellino and Wise, 2003). Furthermore, exogenous estrogen may enhance peripheral vasomotor tone in rats (Acs et al., 2001), as well as raise sweating threshold, hence restoring the narrowed "thermoneutral zone" (see *Cancer and Heat Stress*) in women (Freedman and Blacker, 2002). Aberrant changes in estrogen may narrow the thermoneutral zone by altering norepinephrine and serotonin levels in the brain. Indeed, norepinephrine agonism has been demonstrated to alleviate hot flushes, while antagonism resulted in hot flushes (Freedman and Krell, 1999). Furthermore, serotonin is known to be a vital neurotransmitter involved in central and peripheral thermoregulation (Schwartz et al., 1995). In postmenopausal women, estrogen has been shown to increase serotonergic activity (Halbreich et al., 1995). Further supporting the close interaction between estrogen and

serotonin, women afflicted with premature menopause, and resultingly low estrogen, have been shown to have suppressed serotonin levels (Gonzales and Carrillo, 1993).

Notably, while hormone replacement therapies (HRTs) to alleviate hot flushes may be highly effective in healthy postmenopausal women, HRTs may not be appropriate in cancer patients, especially those who have hormone-dependent cancers like breast and testicular cancer. For example, in the Swedish hormonal replacement therapy after breast cancer – is it safe? (HABITS) randomized trial, HRT was ceased as initial analysis revealed that cancer relapse risk doubled after HRT in breast cancer survivors (Holmberg et al., 2008). Indeed, the risk of recurrence of cancer after HRT remains debatable, and no consensus has been reached due to a lack of large-scale randomized control trials (Li et al., 2015a; Bluming, 2022). Regardless, HRT in breast cancer patient survivors is currently contraindicated or discouraged. Instead, practitioners may consider alternative pharmacological treatments for hot flushes in cancer patients, such selective serotonin reuptake inhibitors (daily dose of 10 mg paroxetine, 20 mg fluoxetine, 37.5–75 mg venlafaxine, or 10–20mg citalopram) and norepinephrine reuptake inhibitors due to their proven efficacy, without exacerbating cancer symptoms and relapse risk (Wiśniewska et al., 2016).

Much of the literature reporting cancer treatment-related thermoregulatory dysregulation often involves case reports, such as the aforementioned. Unsurprisingly, due to ethical concerns there have been no known conventional passive and exertional heat stress studies specific to cancer treatment use. While challenges (i.e., risk to patient safety, participation) still exist in conducting thermoregulatory profiling in cancer patients, understanding the health impacts of anticancer agents, especially during prolonged and extreme heat exposures, remains a crucial gap to be filled. Novel studies in this area would highlight adverse effects during heat exposure and open new lines of research to mitigate excess heat strain in cancer patients who require these medications (Table 1). Another consideration is the importance of exercise in cancer patients and survivors in maintaining autonomic nervous system and cardiovascular function in patients (Adams et al., 2015). Chemotherapy-induced impairments in sudomotor responses and, possibly, cardiac autonomic function may limit exercise adaptations and maximal exercise performance (Hautala et al., 2009). Cardiorespiratory fitness has been shown to maintain thermoregulatory function in various populations, such as reducing the frequency of hot flushes in postmenopausal women (Bailey et al., 2016) and improving thermoregulatory responses in other chronic conditions like diabetes (Colberg et al., 2002). The maladaptive effects of chemotherapy on thermoregulatory and cardiovascular function may perpetuate a cycle of loss in exercise capacity and in turn, further

exacerbate any exercise-induced thermoregulatory adaptation. Further research is required to determine the extent of exercise's protective effect in cancer patients treated with chemotherapies during prolonged heat exposure (Table 1).

XI. Conclusion: Research Needs and Clinical Implications

Chronic illnesses can exacerbate heat strain in elderly patient populations, leading to clinical consequences. While the principles of human thermoregulation under heat stress are well-known, knowledge of heat-sensitive populations (e.g., aging populations, those living with chronic illnesses, and cancer patients) and other modifying risk factors (e.g., medication use) is still lacking. This review presented existing evidence of the interplay between heat and medications used to treat common chronic diseases.

Epidemiologic analyses amid climate change have unmasked the urgent need to address polypharmacy issues and consider heat-related risks of medication use in the elderly (Bongers et al., 2020; Layton et al., 2020). Accordingly, understanding the physiologic underpinnings of current epidemiologic observations of drug-heat interactions is instrumental in treating patients in extreme heat conditions. Surprisingly, however, the clinically relevant knowledge of medications' influence on thermoregulation is still lagging. Research gaps and clinical implications have been identified in this review pertaining to medications for common diseases of concern (diabetes, CVDs, neuropsychiatric disease, and cancer) (Table 1). Plugging knowledge gaps about what we know of individual and combined medications' effects on thermoregulation is crucial considering the propensity for multiple comorbidities, and consequently polypharmacy, increases with age (Layton et al., 2020). As climate change progresses concomitantly with an aging global population, promoting greater understanding of heat-related risks of both chronic disease and the medications used to treat them must become a priority to improve health risk assessments and provide appropriate pharmacotherapies to heat-sensitive clinical populations.

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