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Invited Review

Interaction between thermoregulation and osmoregulation in domestic animals

Michael McKinley[1*], David Trevaks[1], Frank Weissenborn[1], Robin McAllen[1]

[1] Florey Institute of Neuroscience and Mental Health, Parkville, Victoria, Australia.

ABSTRACT - The ability to maintain core temperature as well as volume and composition of body fluids within narrow ranges is a major characteristic of mammals. Yet, the ability to maintain a stable core temperature often relies on physiological responses that perturb the stability of body fluids. A common thermoregulatory mechanism that affects body fluid homeostasis is evaporative cooling, by sweating and/or panting, to dissipate heat from the body when core temperature is elevated. However, these responses result in a reduction of total body water, thereby reducing blood volume and increasing the osmotic pressure of body fluids. While both panting and sweating are highly effective means of preventing core body temperature from increasing, unless the resultant body fluid losses are replaced (by intake of water), hypertonicity, hypovolemia, and circulatory collapse can ensue. Thus, physiological control mechanisms have evolved to limit thermoregulatory body fluid losses once they have become a liability and panting and sweating are inhibited. Thus, mammals will tolerate a higher core temperature to minimize further loss of body water. Osmoreceptors located within the lamina *terminalis* of the brain suppress panting and sweating when the effective osmotic pressure (tonicity) increases. Selective brain cooling (SBC) has been observed in several domesticated mammals when blood flowing to the brain in the carotid *rete* is cooled. Such SBC promotes reduced panting and sweating, thereby preserving body water. It is also notable that the behavioural response of drinking water can rapidly invoke panting and sweating that override osmoregulatory inhibitory influences on these responses. The preoptic region of the brain has an important role in osmoregulatory and thermoregulatory mechanisms.

Key Words: brain cooling, hypertonicity, osmoreceptors, panting, sweating

Introduction

All mammals, whether domesticated or not, are characterised by a constancy of the physical and chemical nature of their internal environments, regardless of the state of their surroundings. Claude Bernard emphasised this mammalian characteristic (Bernard, 1865) and it was termed "homeostasis" by Walter B. Cannon (Cannon, 1929). Accordingly, the constancy of the internal milieu, actively maintained by behavioural, physiological, and endocrine mechanisms in the face of perturbations allows the free movement and survival of mammals across many different external environments and conditions (Cannon, 1929). Examples of such homeostatic management are the oxygen tension of blood, plasma glucose concentration, arterial pressure, and concentrations of ions such as potassium, calcium, magnesium, chloride, phosphate, and bicarbonate as well as the pH of extracellular, intracellular, and cerebrospinal fluids (Mitruka and Rawnsley, 1981; Randall et al., 2002). Probably, the most iconic and generally well-recognized manifestations of mammalian homeostasis are the maintenance of core body temperature and extracellular fluid sodium concentration and osmolality within narrow limits (Schmidt-Neilsen et al., 1957; Schmidt-Neilsen 1983). However, homeostatic regulation of core temperature is dependent in part on mechanisms that affect body fluid and electrolyte homeostasis. This article will explore interactions between central thermoregulatory and osmoregulatory mechanisms.

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***Corresponding author:** mmck@florey.edu.au
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Regulation of plasma sodium concentration and osmolality

For all mammals, and particularly the domesticated species, plasma Na^+ concentration is normally maintained

between 140-155 mmol/L and plasma osmolality between 280-310 mosmol/kg. Because Na^+ is the largest ionic component of the plasma and extracellular fluid, its concentration and those of its associated chloride and bicarbonate anions are the main determinants of plasma osmolality and osmotic pressure (Randall et al., 2002). If the absolute volume of extracellular fluid in which these dissolved ions are either decreased (e.g. in the case of a dehydrated animal) or increased (with over-ingestion of fluid), the plasma Na^+ concentration and osmolality will correspondingly increase or decrease. Of course, if the total body content of Na^+ or the balance between extracellular and intracellular stores of Na^+ alters, these changes will also affect the level of plasma Na^+ and osmolality. Thus, it is not surprising that a number of important compensatory mechanisms are rapidly brought into operation if perturbations in plasma Na^+, osmolality, and volume arise. For instance, when body water is lost, compensatory mechanisms include the stimulation of thirst to restore lost body fluid, the secretion of vasopressin to minimise further fluid loss, and increased excretion of Na^+ in urine to ameliorate the increased plasma Na^+ concentration and osmolality (McKinley et al., 1983; Schmidt-Neilsen, 1983; Blair-West et al., 1985; Mecawi et al., 2015). If NaCl is additionally lost, increased renal sympathetic nerve activity and activation of the renin-angiotensin-aldosterone system reduces renal Na^+ loss and maintains arterial pressure, while generation of salt appetite promotes replenishment of lost sodium if it is available for ingestion (Mecawi et al., 2015).

Regulation of core temperature

In general, core body temperature is maintained within a narrow range around 36-39 °C depending on the specific mammal under consideration, e.g. marsupials, ~ 36 °C; cats and dogs, 37-38 °C; and sheep and goats, 39 °C (Baker and Doris, 1982; Baker and Dawson, 1985; Jessen et al., 1998; Randall et al., 2002; McKinley et al., 2009). This constancy of core temperature comes about because a number of homeostatic responses are engaged when core temperature changes outside the "thermoneutral range" for that species. Also, when the temperature of the environment, and therefore skin temperature, changes sufficiently, thermoregulatory mechanisms are also brought into action as anticipatory responses (Nagashima et al., 2000). Responses to cold core and skin temperatures include heat generation by shivering and/or activation of brown adipose tissue, heat conservation by skin vasoconstriction, and warmth-seeking behaviour for thermal comfort (Morrison, 2016). The temperature thresholds for these different thermoregulatory responses vary for the core and skin (McAllen et al., 2010). Conversely, when core and/or skin temperature increase, heat is actively dissipated by evaporative cooling mechanisms dependent on sweating and panting and skin vasodilatation (Nagashima et al., 2000; Nakamura and Morrison, 2010; Tan et al., 2016). Homeostatic emotions of thermal discomfort that drive animals to cooler surroundings or fatigue that induces reduced activity and heat generation from muscle are also engaged (Tan et al., 2016).

Before moving on to consideration of possible interactions between body fluid and temperature regulation, it should be noted that there are some conditions in which core body temperature is actively maintained outside the normal diurnal bounds observed in mammals. Two such examples are fever, in which core temperature is elevated by up to 4 °C (Roth and Blatteis, 2014), and hibernation, in which relatively large reductions in core temperature may be observed (Geiser, 2004). In both conditions, change in core temperature is utilised to effect a more pressing requirement for survival, such as the removal of a pathogen or the retention of nutrients. Thus, the constancy of core temperature is not absolute and there are conditions thereby temperature homeostasis may be compromised.

Competing homeostatic demands

As the defence of core temperature may be compromised under certain conditions, so too may the defence of body fluid homeostasis, for instance, when sweating, panting, or spreading of saliva on skin and fur is utilised by mammals for evaporative cooling when core temperature increases. In hot environments, the loss of body water and electrolytes by animals in sweat and evaporated respiratory fluid can be severe if they are not readily available for ingestion (Macfarlane and Howard, 1972). Camels are remarkably adapted to hot, dry conditions, losing minimal water as sweat or from panting. Yet, it has been shown that they maintain core temperature close to that in euhydrated conditions and also minimise water loss when they are in a hot environment without water to drink for periods of up to 16 days (Schmidt-Neilsen et al., 1957; Bekele et al., 2013). Camels exhibit a large diurnal variation in temperature by allowing their core temperature to fall to levels as low as 35 °C, so that the heat that accumulates in their body during the hot day is then radiated during the cooler night (Schmidt-Nielsen et al., 1957; Bekele et al., 2013). So, how do animals that utilise sweating and panting deal with minimising loss of body water at the same time as maintaining core temperature when the latter involves

further loss of body water? The objective of this short review is to give some insights into this question.

Influence of dehydration and hypertonicity on thermoregulatory panting and sweating

Investigations in several of the domesticated mammals, e.g. dogs, cats, sheep, and goats, show that when these animals are subjected to a warm environment, they engage in thermoregulatory panting and/or sweating that results in elevated plasma Na^+ concentration and osmolality if the evaporated water is not replaced (Baker and Doris, 1982; Baker and Dawson, 1985; Baker, 1989; McKinley et al., 2009). Such thermoregulatory loss of body fluids does not continue at the same rate if animals become dehydrated and many investigators have shown that dehydration, brought on usually by water deprivation, results in an attenuation of sweating and/or panting (Baker and Doris, 1982; Baker and Dawson, 1985; Baker, 1989; McKinley et al., 2009). For example, exercising cats reduce evaporative heat loss if they are deprived of water compared with those permitted to drink water (Baker and Doris, 1982). As a result, core temperature was 0.4 °C higher in dehydrated cats in that study. Exercising goats also reduce sweating (but not panting) if deprived of water to drink, with the result that core temperature increases to a greater extent in the water-deprived animals (Nijland and Baker, 1992). We observed that water-deprived sheep maintained in a relatively cool (20 °C) environment increase core temperature if they are unshorn, but not if they are shorn. Unshorn sheep are heat-stressed even at an ambient temperature of 20 °C because metabolic heat cannot be radiated adequately from their skin. Evaporative cooling by panting is necessary to dissipate excess body heat in such animals, whereas shorn sheep can radiate heat from their exposed skin. When unshorn sheep are dehydrated, panting is suppressed and core temperature increases (McKinley et al., 2009). Because the osmolality of body fluids increases with dehydration, several investigators suggested that hypertonicity of plasma is the stimulus to suppress panting and sweating in dehydrated animals (Baker and Doris, 1982; Baker and Dawson, 1985).

Experimental evidence that plasma hypertonicity is indeed the stimulus to inhibit thermoregulatory panting and sweating has been obtained in cats, dogs, and sheep. Intravenous infusion of hypertonic saline in euhydrated cats and dogs exposed to high environmental temperatures inhibits thermoregulatory sweating and panting so that evaporative heat loss fall and core temperature increases (Kozlowska et al., 1980; Doris et al., 1981). It has been also shown that infusion of hypertonic saline into the carotid artery is particularly effective in this regard and it is clear that the brain is the likely site of the sensors that detect the hypertonic plasma (Baker and Dawson, 1985; McKinley et al., 2008). To verify that it is indeed the hypertonicity and not specifically increased NaCl concentration of plasma that inhibits thermoregulatory panting, we tested the effect of another osmotic agent to increase plasma osmolality and showed that intracarotid infusion of hypertonic sorbitol is as effective as hypertonic saline in suppressing panting in over-heated sheep (McKinley and Mathai, 2014). Thus, as suggested originally by Doris and Baker (1982), it is likely that a central osmoreceptor, analogous to that which mediates thirst and vasopressin secretion, has a role in regulating thermoregulatory panting and sweating. The hypothalamus was proposed as a likely site of these osmoreceptors and this will be explored further in this review.

The abolition of suppression of sweating and panting when dehydrated animals drink water occurs rapidly before any change in systemic osmolality occurs, suggesting that the "switch-off" mechanism of panting suppression differs from its initiation. When dehydrated dogs and sheep in hot environments were rehydrated by drinking warm water, respiratory rate increased within 1-3 min, well before any change in plasma osmolality could be detected (Baker and Turlejska, 1989; McKinley et al., 2009). Heat-exposed, dehydrated goats increased sweating as well as panting within 3 min when they drank water (Baker, 1989). As a result of the increased panting and sweating, core body temperature fell rapidly in these species. To emphasise that a reduction in plasma osmolality or increase in blood volume was not the cause of the rapid increase in evaporative cooling responses, immediate sweating and panting were also observed when isotonic saline was drunk rather than water. This led to the suggestion that oropharyngeal factors or filling of the stomach associated with drinking fluid provided neural signals to influence thermoregulatory sweating and panting (Baker, 1989). Further studies in sheep showed that administration of isotonic saline directly into the rumen had no effect on thermoregulatory panting, showing that gastric distention was not a factor (McKinley et al., 2009). Administration of warm water into the rumen of dehydrated sheep caused a slow increase in panting and fall in core temperature after 30-40 min and was probably due to the slow fall in plasma osmolality that occurred. Thus, we concluded that when heat-stressed dehydrated animals rehydrate by drinking water, a rapid inhibition of the suppressive influence of dehydration on evaporative cooling responses occurs (i.e. a disinhibition of these responses), which is dependent on oropharyngeal signals

associated with drinking. In addition, as water is eventually absorbed into the systemic circulation, the reduction of plasma osmolality will further increase panting and sweating because the inhibitory influence of systemic hypertonicity on these responses wanes (McKinley et al., 2009).

Selective brain cooling as a means of conserving body fluids

Of relevance to the suppression of panting that occurs in dehydrated heat-stressed animals is the role that selective brain cooling (SBC) plays in this response. Most domesticated mammals (e.g. cats, dogs, sheep, goats, cattle, pigs, camels, but not horses) are able to reduce the temperature of the brain below that of the core body temperature when a particular threshold brain temperature is reached. This characteristic is termed selective brain cooling (Taylor, 1970). It depends on a specialised anatomical feature, the carotid rete passing through the cavernous sinus that can receive cooled venous blood coming from the nose if the hemodynamic conditions in the effluent veins are appropriate. This allows heat to be exchanged from arterial blood in the carotid rete to the cooler venous blood in the cavernous sinus, thereby cooling the carotid arterial blood before it enters the circle of Willis to ultimately supply the brain (Maloney and Mitchell, 1997; Jessen, 2001).

Originally, SBC was considered a protective mechanism whereby the brain could be shielded from excessively high core body temperatures that may occur in a dry, hot environment or in fever (Taylor, 1970; Baker and Chapman, 1977; Elkhawad, 1992). However, it has been observed that SBC often occurred during the night when ambient temperatures were not at a maximum. Also, when core and brain temperatures rose to levels as high as 42 °C during vigorous exercise, SBC was not observed (Jessen, 2001). Several investigators consider that this explanation is inadequate (Kuhnen, 1997; Fuller et al., 1999; Jessen, 2001; Mitchell et al., 2002). They propose that the function of SBC is to minimise body fluid losses when animals are dehydrated. By maintaining the brain temperature at a lower level than the rest of the body during periods of dehydration, the hypothalamic stimulus to sweating and panting would be reduced, resulting in less evaporative cooling (Kuhnen, 1997). As a result, body fluids are conserved, but core temperature increases. Evidence for this idea comes from experiments in goats in which SBC is inhibited or not and core temperature outside the brain increases by means of extracorporeal heat exchangers. Goats in which SBC is still present retain 35% more body fluid than those that do not exhibit SBC (Kuhnen, 1997). In sheep exposed to high temperatures, SBC is seldom observed if the sheep are given access to adequate water supply to drink; however, if they are deprived of water, SBC is observed more often (Fuller et al., 2007). These researchers also showed that sheep that are prone to engaging SBC maintain total body water more effectively than those that are not (Strauss et al., 2015). Also, when heat-stressed animals rehydrate as a result of drinking water, SBC ceases immediately, so that brain temperature increases rapidly; so does panting (Jessen et al., 1998). Therefore, it seems likely that abolition of SBC, by oropharyngeal signals associated with drinking, causes rapid increase in brain temperature in rehydrated animals; this may stimulate brain thermosensors to bring about the rapid panting response and drop in core temperature described above.

In summary, we propose the following sequence of responses in animals that employ selective brain cooling. When such animals are under heat stress due to a hot environment or to metabolic generation of heat, panting and sweating are engaged to dissipate excess body heat. Body fluid is lost as a result of evaporative cooling and thirst is stimulated so that water is ingested to maintain body fluid volume and composition. Vasopressin is also released into the blood stream to minimise renal urine loss. However, if water is unavailable for drinking, body fluid loss continues and hypertonicity of blood and extracellular fluid ensues. Subsequently, this systemic hypertonicity stimulates the central osmoreceptors that drive inhibition of panting and sweating, so that less heat is dissipated and core temperature increases further. When the threshold temperature for SBC is reached, this brain cooling mechanism is engaged, thereby reducing brain temperature, which further reduces the central thermal stimulus to panting and sweating. Body fluids are conserved at the expense of core temperature rising. If a cooler environment subsequently arises during the night, excess heat can be shed as a result of the thermal gradient. Whether there is also a direct osmoreceptor influence on SBC is not known at present, but panting and sweating are suppressed in two ways: directly by osmoreceptor inhibition and by SBC reducing the central thermal stimulus.

Upon rehydration by drinking, oropharyngeal signals to the brain rapidly extinguish SBC so that brain temperature rises quickly and sweating and panting increase to reduce core temperature. Oropharyngeal factors may also play a role in extinguishing central inhibitory influences on panting. As ingested water is absorbed into the systemic circulation, plasma osmolality slowly falls and the osmoreceptor-mediated inhibition of evaporative cooling subsides, allowing increased panting and sweating to be

maintained until both core and brain temperatures return to normal.

Influences of brain regions mediating osmoreceptor on thirst, vasopressin secretion, renal sodium excretion, and thermoregulatory panting

Pioneering investigations of the cerebral site of the brain osmoreceptors that regulate the secretion of the antidiuretic hormone, vasopressin, were made by E.B. Verney and P.A. Jewell in the middle decades of the 20th century (Verney, 1947; Jewell and Verney, 1957). By studying the antidiuretic responses of conscious water-loaded dogs to intracarotid or intravenous infusions of various hypertonic solutions, Verney determined that the brain was the likely site of sensors that reacted to increases in the osmotic pressure of circulating blood (Verney, 1947). Furthermore, later investigations in dogs involving the ligation of various branches of the anterior cerebral artery to prevent hypertonic infusions reaching these sensors showed that the location of the cerebral osmoreceptors was confined to an area encompassing the preoptic and hypothalamic regions (Jewell and Verney, 1957). Soon after, Bengt Andersson demonstrated that thirst and the ingestion of water in goats may also be influenced by such osmoreceptors (Andersson, 1953), although, in later investigations, Andersson and his colleagues suggested that specific Na sensors in the anterior wall of the third cerebral ventricle also played an important role (Andersson et al., 1975).

We and others focussed our attention on the exact site of cerebral osmoreceptors mediating vasopressin secretion and thirst after obtaining evidence that such sensors may be located, at least in part, in brain regions that lacked the blood-brain barrier, specifically the vascular organ of the lamina terminalis (OVLT) and the subfornical organ (McKinley et al., 1978; Thrasher et al., 1980). Subsequent studies on the effects of ablation of the OVLT in sheep and dogs showed that this circumventricular organ (CVO) is essential for normal osmoregulatory control of vasopressin secretion and thirst (McKinley et al., 1982; Thrasher et al., 1982; Thrasher and Keil, 1987).

Further studies aimed at identifying neurons in the brain that were activated in response to osmotic stimuli utilised immunohistochemical techniques to detect increased expression of the immediate early gene *c-fos* in the brain of conscious rats or calcium imaging in mice. The activity of neurons increased in response to systemic hypertonicity not only in the OVLT, but also in the adjacent median preoptic nucleus (MnPO) and subfornical organ (Oldfield et al., 1991; Zimmerman et al., 2016). Electrophysiological recordings from neurons in the MnPO of sheep showed that they were responsive to systemic hypertonicity (McAllen et al., 1990). Moreover, the neurons in these three sites in the lamina terminalis that were activated by intravenous infusion of hypertonic saline were shown to be directly connected to the vasopressin secreting neurons of the supraoptic and paraventricular nuclei (Oldfield et al., 1994; McKinley et al., 2004) and relayed via thalamic sites to cortical regions involved in the genesis of thirst (Hollis et al., 2008). Recent studies in mice using optogenetic techniques to stimulate or inhibit neuronal populations within the lamina terminalis confirm the importance of the lamina terminalis in regulating water intake (Abbott et al., 2016; Zimmerman et al., 2016).

Neuroanatomical-tracing studies have shown that neurons in the OVLT, MnPO, and subfornical organ are reciprocally connected to each other (Saper and Levisohn, 1983; Miselis et al., 1987). If both subfornical organ and OVLT are ablated in combination, then the activation of neurons within the MnPO and supraoptic nuclei in response to hypertonicity is greatly impaired (Hochstenbach and Ciriello, 1996), suggesting that, as well as direct connections from OVLT and subfornical organ, some osmoregulatory signals from these CVO to hypothalamic vasopressin secreting neurons are relayed via the MnPO. More detailed investigations of the effects of ablating the three components of the lamina terminalis in sheep, either individually or in combination, showed that sensors, i.e. osmoreceptors and possibly Na sensors (Andersson et al., 1975) within the OVLT, subfornical organ, and MnPO, likely contribute to osmoregulatory thirst (McKinley et al., 1999) and vasopressin secretion (McKinley et al., 2004).

In addition to the lamina terminalis influencing osmoregulatory thirst and vasopressin release, there is considerable evidence that this region of the brain also exerts an osmoregulatory influence on sodium excretion by the kidney. We showed that ablation of the lamina terminalis in sheep prevented the renal excretion of intravenous hypertonic (but not isotonic) saline loads (McKinley et al., 1992). The natriuresis that occurs normally in sheep and dogs in response to water deprivation (McKinley et al., 1983; Metzler et al., 1986) is also abolished by ablating the lamina terminalis, resulting in extreme hypernatremia in such lesioned animals (McKinley et al., 1983).

As mentioned previously, systemic hypertonicity, whether resulting from intracarotid infusion of hypertonic saline or from dehydration, causes a suppression of the panting response to increased core temperature. We also investigated whether this region of the forebrain plays a

role in osmotic influences on thermoregulatory panting. Sheep were exposed to an ambient temperature of 39 °C for up to 2 h and exhibited a threefold increase in respiratory frequency (i.e. panting). Intracarotid infusion of hypertonic saline was shown to cause a rapid inhibition of this panting behaviour with a subsequent increase of core body temperature. However, in four sheep in which the lamina terminalis (i.e. OVLT, MnPO, and subfornical organ) was extensively ablated, no such inhibition of panting occurred (McKinley et al., 2008). It is likely that the normal panting response to hyperthermia in these sheep was a response to increased core temperature sensed in the brain, because the afferent signals from warmth thermoreceptors in the skin are relayed via the spinal cord and midbrain parabrachial nucleus to the MnPO (Nakamura and Morrison, 2010). These afferent pathways would not have been functional in the lesioned sheep, leaving only the central warm sensors intact, which presumably were not located in the lamina terminalis. Consistent with this presumption is a recent report showing widespread distribution of warm sensitive glutamatergic neurons within the preoptic region which influence thermoregulatory cutaneous vasodilatation in mice (Song et al., 2016).

We conclude that osmoregulatory signals from the lamina terminalis have an inhibitory influence on panting initiated by increased core temperature in sheep. Inhibitory GABAergic neurons are plentiful throughout the lamina terminalis (Grob et al., 2003; Oka et al., 2015; Zimmerman et al., 2016) and these may play a role in osmoregulatory influences on panting. However, while we have rudimentary knowledge of the efferent osmoregulatory neural pathways from the lamina terminalis to vasopressin-secreting neuroendocrine cells of the hypothalamus and to cortical regions mediating thirst (Hollis et al., 2008; Mecawi et al., 2015), the efferent neural pathways from the lamina terminalis that inhibit panting and probably sweating are unknown.

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