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CONTROL OF EVAPORATIVE HEAT LOSS DURING CHANGES IN PLASMA OSMOLALITY IN THE CAT

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SUMMARY

1. The effects of intravenous infusion of hypertonic saline and distilled water into normally hydrated and dehydrated cats have been examined at both high and neutral ambient temperatures.

2. In hydrated cats measurements of body temperature (T_b) and evaporative heat loss (e.h.l.) show that infusion of 30% saline (1·5 ml./kg) at an ambient temperature of 38 °C, lowers e.h.l. by an average of 0·21 W/kg ($P < 0·001$) and elevates T_b by 0·43 °C ($P < 0·01$).

3. At 25 °C alterations in these two parameters were in the same direction, though not statistically different from pre-infusion levels ($P > 0·05$).

4. Infusion of distilled water (15 ml./kg) into dehydrated animals produced significant increases in e.h.l. (+0·35 W/kg, $P < 0·001$) and reductions in T_b (−0·45 °C, $P < 0·001$) at 38 °C. No significant effects were observed at 25 °C.

5. Infusion of water into normally hydrated animals at 38 °C also significantly increased e.h.l. (+0·13 W/kg, $P < 0·05$) and insignificantly lowered T_b (−0·03 °C, $P > 0·05$).

6. Local heating of the preoptic hypothalamic area in four animals indicated that hypertonic saline infusion into normally hydrated animals caused a reduction in the slope and displacement to the right of the relationship between hypothalamic temperature and e.h.l.

7. Conversely, water infusion into dehydrated animals increased the slope and shifted this relationship to the left.

8. These experiments provide evidence for an osmotic interaction in body temperature regulation which acts to alter the responsiveness of the hypothalamus to increasing temperature. This osmotic component may be an important factor in the alterations in thermoregulation seen in dehydrated animals.

INTRODUCTION

A persistent relationship between the electrolyte and osmotic content of plasma and the level at which body temperature is regulated during thermal stress has been reported (Nielsen & Greenleaf, 1977; Greenleaf, 1979; Senay, 1979). In man, heat

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stress from both ambient and exercise heat loads results in higher equilibrium rectal temperatures and suppressed evaporative responses in dehydrated compared to normally hydrated subjects (Senay, 1968; Hertzman & Ferguson, 1960; Greenleaf & Castle, 1971). Similar elevations in deep body temperature and inhibition of evaporation occur in most other mammals examined under these conditions (Taylor, 1970; Turlejska-Stelmasiak, 1974; Doris & Baker, 1981). Ingestion or infusion of hypertonic fluids has been associated similarly with the changes in temperature regulation observed in dehydrated subjects (Nielsen, Hansen, Jorgenson & Nielsen, 1971; Nielsen, 1974; Greenleaf, Kozlowski, Nazar, Kacuiba-Uscilko, Brzezinska & Ziemba, 1976; Kozlowski, Greenleaf, Turlejska & Nazar, 1980). Replacement of water losses reverses these changes in dehydrated subjects (Senay & Christensen, 1965) as does water consumption in animals made hyperosmotic by hypertonic saline infusion (Greenleaf *et al.* 1976). Prior hyperhydration is associated with lower levels of equilibrium rectal temperature and higher evaporative heat loss during exercise than if water losses are replaced (Moroff & Bass, 1965; Nielsen *et al.* 1971).

Another dimension has been added to the study of mechanisms of temperature regulation in dehydration by the finding that the regulated level of body temperature can be modified by alterations in the ratio of ionized sodium to ionized calcium in the hypothalamus (Myers & Veale, 1971; Myers & Yaksh, 1971). Much of the investigation of temperature regulation in hyperosmotic states has relied on alterations in circulating fluid osmolality by infusion or ingestion of hypertonic saline, this achieving both plasma osmolalities and Na^+ concentrations approximating those found in varying degrees of dehydration. Since it is possible that the excess Na^+ infused might alter the ionic ratios in the hypothalamus it is difficult to distinguish which effects are the consequence of changes in osmolality and which might be related to ionic ratios.

Our previous work with the cat has shown that there are several fundamental changes in the characteristics of the thermoregulatory system in this animal when dehydration, achieved by removal of drinking water, is accompanied by moderate ambient heat stress. Not only are body temperatures elevated and evaporation inhibited (Doris & Baker, 1981), but the thermosensitivity of the hypothalamus, as measured by evaporative responses to local hypothalamic heating, is reduced (Baker & Doris, 1982). The present experiments were designed to determine whether the same pattern of thermoregulatory changes occurring during dehydration can be achieved by hypertonic saline infusion into normally hydrated cats in warm environments. We also wished to examine whether hypertonic saline infusions produced similar changes in evaporative responses to hypothalamic heating as have been demonstrated in dehydrated animals. Furthermore, to exclude possible consequences of altered ionic ratios subsequent to hypertonic saline infusion the reverse approach was used, in which animals dehydrated by removal of drinking water were infused with water only and the effects on evaporative heat loss, body temperature and hypothalamic thermosensitivity were observed.

METHODS

Surgical preparation of animals

Experiments were conducted on eight cats (*Felis domesticus*) ranging in body weight from 2·5 to 4·5 kg.

All animals were implanted with a Silastic cannula (o.d. 0·06 in.) passed from the external jugular vein to the right atrium. A copper–constantan thermocouple, sealed within polythene tubing (PE50) was implanted with the cannula into the right atrium and was used for measuring deep body temperature (T_{ra}). The thermocouple and the cannula were led subcutaneously from the jugular vein to emerge at the top of the head where they were stabilized on a platform mounted above the scalp on stainless-steel bolts fastened to the skull.

Four cats were additionally implanted with radio-frequency thermodes in the preoptic area of the hypothalamus. An array of four stainless steel thermodes (0·6 mm diameter) was implanted in each animal. The thermodes were insulated except over the final 2 mm of their tips with several coatings of baked epoxy resin. The tips of the thermodes were stereotaxically implanted 2 mm lateral to the mid line, with two thermodes on either side of it. The anterior two thermodes were placed in front of the anterior commissure and the posterior pair at about the frontal level of the optic chiasm, corresponding to the frontal planes of A16·5 and A13·5 using the co-ordinates of Snider & Niemer (1961). The vertical position of the lowest part of the tips was 6 mm above the interaural line. A copper–constantan thermocouple bonded to a tungsten wire was placed between the uninsulated tips of the thermodes in order to measure hypothalamic temperature (T_{hyp}). Animals were allowed 1–2 weeks for recovery before experiments were begun.

Both groups of animals were used in the experiments described below under *Saline and water infusions*. In some animals, the right atrial thermocouple leads were broken before the series of experiments was completed. When this occurred in the animals with hypothalamic thermocouples, the temperature of the hypothalamus was used as an index of body temperature. When we compared the temperature changes produced in the right atrium and in the hypothalamus by saline and water infusions, we found no difference between the two sites.

Measurements

During experimentation, animals were housed individually in a metabolism chamber (volume, 35 l.) placed within a temperature-controlled room. Air was passed through the metabolism chamber at a rate of 20 l./min. Evaporative heat loss (e.h.l.) derived from the difference in relative humidity of air entering and leaving the chamber was recorded simultaneously with either T_{ra} or T_{hyp} on a polygraph. Ambient temperature (T_a) was measured inside the chamber with a thermocouple suspended above the animal. Experiments were conducted at ambient temperatures of 25 and 38 °C. Intravenous infusions were made through an extension attached at the head platform and led through a small port in the metabolism chamber to the outside of the temperature-controlled room, permitting all observations and infusions to be made without disturbing the animal. Water was infused at a rate of 1·9 ml./min and saline at 0·5 ml./min.

Saline and water infusions

In one series of experiments, saline was infused into normally hydrated animals which had drinking water available *ad lib* before the beginning of the experiment. Saline infusions consisted of 30 % NaCl (1·5 ml./kg) made up in sterile, pyrogen-free water and autoclaved. In a second series of experiments sterile, pyrogen-free water (15 ml./kg) was infused into both normally hydrated animals and animals dehydrated for 1–2 days by removal of drinking water and exposure to a T_a of 38 °C for 12 hr per day, the remaining 12 hr being spent at 25 °C.

During experiments, animals were allowed 90 min in the metabolism chamber before measurements were made. Five measurements of e.h.l. and of T_b, either in the right atrium or the hypothalamus, were made at 6 min intervals during the next 30 min. Infusion was then begun. The length of the infusion varied with the size of the animal and ranged from 8 to 14 min for saline and 20 to 36 min for water. Beginning 30 min after the end of the infusion, five measurements of T_b and e.h.l. were made at 6 min intervals. By this time, T_b and e.h.l. were usually stable. In the final calculations, the mean of the five pre-infusion measurements was subtrated from the mean of the five post-infusion measurements.

Plasma osmolalities were measured before and after infusion in most experiments. Blood samples were withdrawn through the jugular cannula into heparinized syringes and centrifuged. Osmolality

was measured by vapour pressure osmometry (Model 5100B, Wescor, Logan, Utah). Manufacturer's stated precision for this instrument is ±3 m-osmole/kg. Plasma samples were always clear and there was no visible indication of haemolysis consequent to infusion.

Thermode experiments

All thermode experiments were conducted at T_a of 38 °C. Animals were in the metabolism chamber for at least 1 hr before any measurements were made. In three animals, hypothalamic heating lasting 15–20 min was then begun and the evaporative response to heating was assessed by measuring T_{hyp} and e.h.l. every 2·5 min during the last 10 min of heating. After heating, T_{hyp} and e.h.l. were allowed to re-equilibrate, at which time infusion (30 % NaCl in hydrated animals and water in dehydrated animals) was begun. Another period of hypothalamic heating followed re-equilibration of T_{hyp} and e.h.l. after infusion. In a fourth animal, several periods of hypothalamic heating were performed before and after infusion. This enabled statistical evaluation of the relationship between T_{hyp} and e.h.l. and the changes in this relationship after infusion. Best fit by the method of least squares was used to test linearity of this relationship before and after infusion, and analysis of covariance was used to test for changes in the T_{hyp}: e.h.l. relationship consequent to infusion (null hypothesis rejected at $P < 0·05$).

RESULTS

Saline and water infusions

Effects of hypertonic saline infusion on T_b and e.h.l. are shown in Table 1. At 38 °C, hypertonic saline infusion into normally hydrated animals inhibited evaporation and elevated body temperature in every case. At 25 °C, hypertonic saline infusion produced small and statistically insignificant changes in body temperature and evaporative heat loss in normally hydrated animals. Table 2 shows that infusion of water into dehydrated animals at 38 °C resulted in a decrease in body temperature and substantial increases in e.h.l. Water infusions in normally hydrated animals at 38 °C also produced significantly increased e.h.l. and an insignificant lowering of T_b. These responses were smaller than those occurring in dehydrated animals. In three experiments water was infused into dehydrated animals at a T_a of 25 °C, without significant effect on either T_b or e.h.l.

Infusion of 30 % saline (1·5 ml./kg) into hydrated animals resulted in an elevation of plasma osmolality from 306·1 ± 1·6 m-osmole/kg (mean ± S.E. of mean, $n = 15$) to 344·4 ± 3·5 m-osmole/kg ($n = 15$). Infusion of water (15 ml./kg) into dehydrated animals lowered it from 323·0 ± 2·4 ($n = 12$) to 315·3 ± 2·9 m-osmole/kg ($n = 12$).

TABLE 1. Effect of intravenous infusion of 30 % NaCl in normally hydrated cats at high and low ambient temperatures (T_a)

	ΔT_b (°C)	P	ΔE.h.l. (W/kg)	P	n_1	n_2
T_a 38 °C	+0·43 ± 0·06	< 0·01	−0·21 ± 0·03	< 0·001	15	6
T_a 25 °C	+0·18 ± 0·07	n.s.	−0·05 ± 0·01	n.s.	4	4

ΔT_b and ΔE.h.l. are the changes occurring in body temperature and evaporative heat loss between the pre-infusion period and the post-infusion period, ± S.E. of means. P is the value in the t test comparing pre-infusion measurements with post-infusion measurements. n_1 = number of experiments; n_2 = number of animals. Since the number of experiments on each animal was not always the same, the mean values for each animal were used in computation of the final mean.

TABLE 2. Effect of intravenous infusion of water in dehydrated and normally hydrated cats at high and low ambient temperatures (T_a)

	ΔT_b (°C)	P	Δe.h.l. (W/kg)	P	n_1	n_2
T_a 38 °C	Dehydrated					
	−0·45±0·07	< 0·001	+0·35±0·09	< 0·001	10	6
T_a 38 °C	Hydrated					
	−0·03±0·05	n.s.	+0·13±0·02	< 0·05	4	4
T_a 25 °C	Dehydrated					
	+0·01	n.s.	+0·01	n.s.	3	3

See Table 1 for explanations.

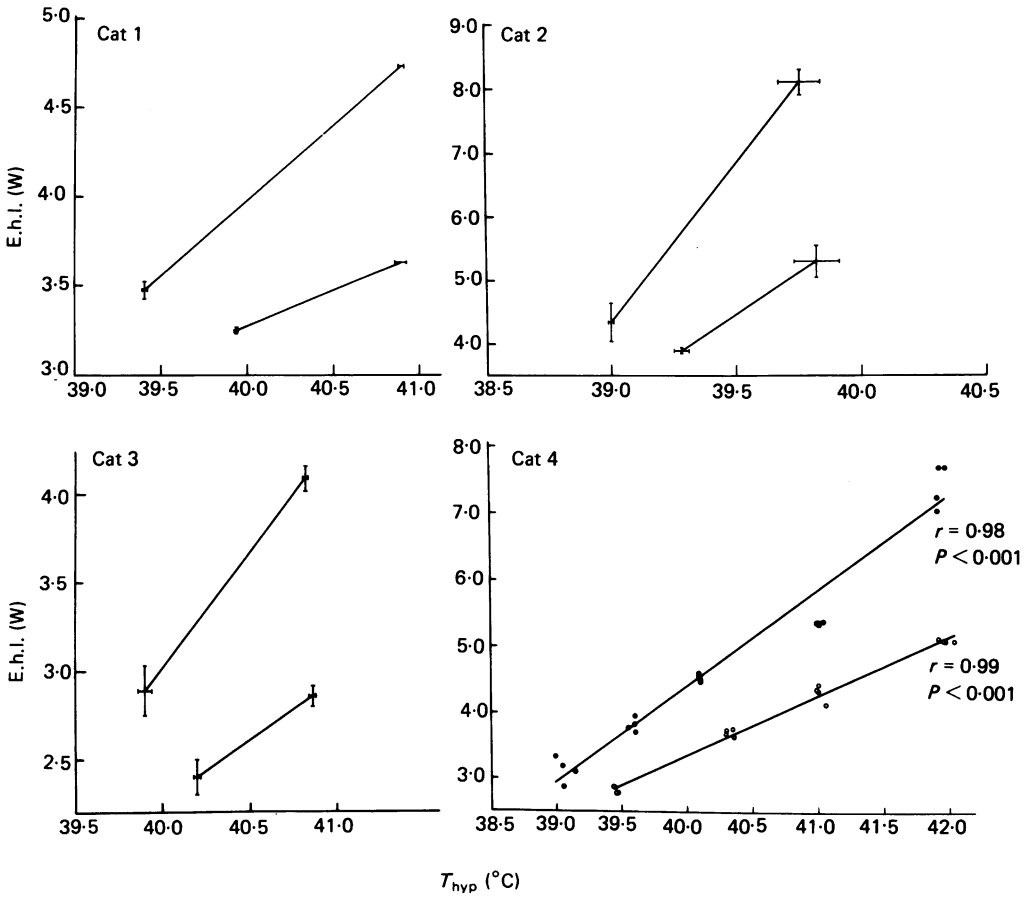

Fig. 1. Evaporative responses to hypothalamic heating before (upper line) and after (lower line) intravenous infusion of hypertonic saline in normally hydrated cats. In cats 1–3 each line is formed by joining mean values (±S.D.) for T_{hyp} and e.h.l. when no heat was applied to the hypothalamus with the values obtained for these variables during a single period of hypothalamic heating. In cat 4, several heating periods were conducted and each period is represented by the cluster of four points representing coincident values of T_{hyp} and e.h.l. occurring during each period. The lowest four points on each line represent values obtained without hypothalamic heating in cat 4. Body weights for cats 1–4 were 2·62, 4·32, 3·85 and 2·82 kg respectively.

Thermode experiments

Fig. 1 shows the relationship between T_{hyp} and e.h.l. in the four cats with hypothalamic heating thermodes before and after saline infusion when they were normally hydrated. Hypertonic infusion resulted in both elevated unheated T_{hyp} and lowered e.h.l. In each animal the sensitivity of the evaporative response as measured by the level of evaporation occurring in response to local hypothalamic heating was diminished subsequent to hypertonic infusion. Although there are only two points for each line for three of the animals, connecting the points shows a clear tendency toward a decrease in slope after infusion. Table 3 shows the slopes of the relationship between T_{hyp} and e.h.l. before and after infusions in all four cats. In cat 4, numerous periods of hypothalamic heating allowed us to evaluate the relationship statistically. This change in sensitivity is highly significant ($P < 0.001$, analysis of covariance) in cat 4.

TABLE 3. Sensitivity of evaporative response to hypothalamic heating

Normally hydrated animals, hypertonic saline infusion

	Sensitivity (W/°C)	
Cat no.	Before infusion	After infusion
1	0·85	0·41
2	5·00	2·73
3	1·33	0·70
4	1·46	0·90

Dehydrated animals, water infusion

	Sensitivity (W/°C)	
Cat no.	Before infusion	After infusion
1	0·35	0·56
2	2·71	4·70
3	0·14	0·78
4	0·64	1·03

The same approach was used to determine the effects of infusion of water into dehydrated animals. Fig. 2 shows the relationship between T_{hyp} and e.h.l. in dehydrated animals before and after water infusion. This relationship shows the opposite pattern of changes induced by hypertonic saline hyperosmolality. Water infusion displaced this relationship upwards and to the left in all animals. The sensitivity of the evaporative response to an increase in hypothalamic temperature is enhanced by water infusion (Table 3) and the unheated levels of T_{hyp} are lower and e.h.l. is higher than before infusion. The change in sensitivity of this relationship is highly significant ($P < 0.001$, analysis of covariance) in cat 4.

DISCUSSION

The results reported here provide evidence for an osmotic interaction, which may be independent of ionic ratios, with body temperature regulation in the resting, heat-stressed cat. This confirms the recently reported findings of Kozlowski *et al.*

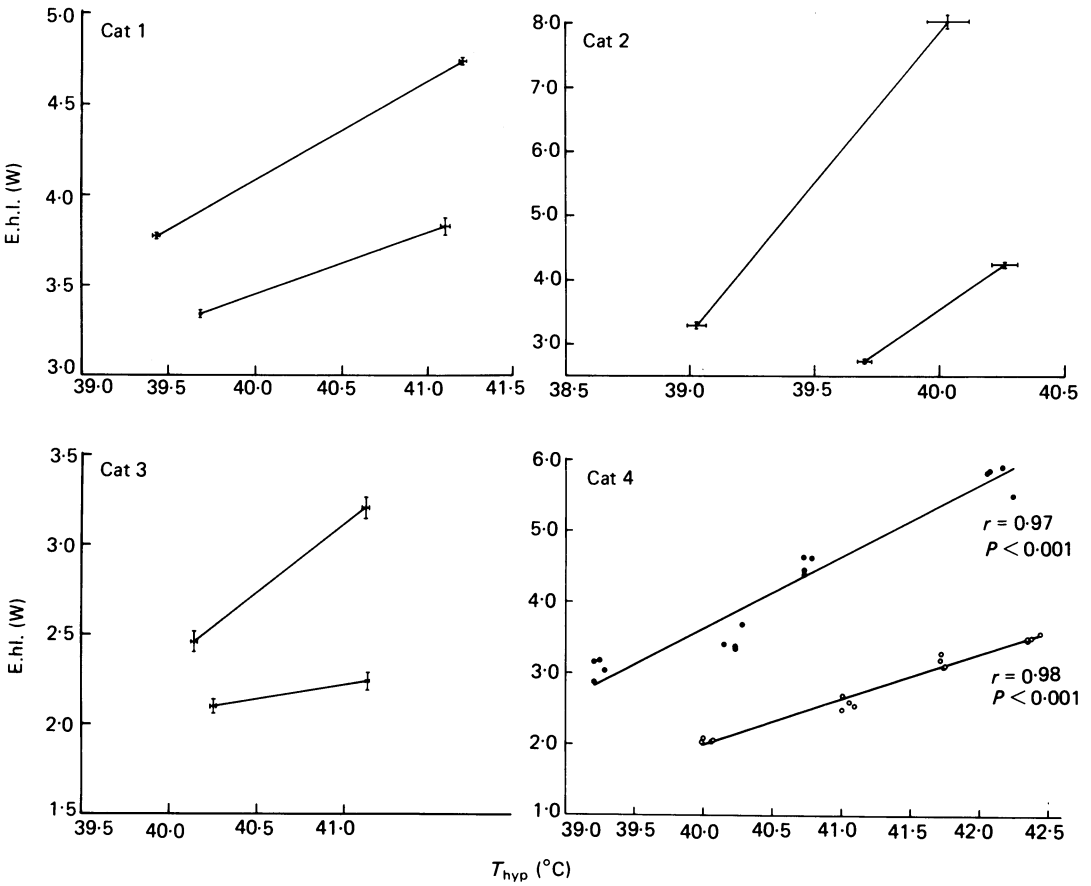

Fig. 2. Evaporative responses to hypothalamic heating before (lower line) and after (upper line) intravenous infusion of sterile water into dehydrated animals. Lines were formed as in Fig. 1.

(1980) that plasma hyperosmolality elevates equilibrium body temperatures in the exercising dog independent of changes in the levels of sodium and calcium ions. The hypothalamic heating studies included here indicate that the mode of action of this osmotic effect is to alter the responsiveness of neural systems controlling thermoregulatory evaporation (the evaporative pathway) to increasing body temperature.

In earlier studies in the rabbit, Turlejska-Stelmasiak (1974) found that intravenous infusion of 5% saline solutions during exposure to 20 °C ambient temperatures obliterated the panting response to hypothalamic heating in four out of five animals. At the higher ambient temperatures used in our study we found that infusion of hypertonic saline reduced but did not abolish the evaporative response to hypothalamic heating. Turlejska-Stelmasiak (1974) also reported no change in the respiratory frequency of dehydrated rabbits during hypothalamic heating. Our own previously reported experiments with the dehydrated cat (Baker & Doris, 1982) have shown a similar change in the evaporative response to hypothalamic heating in dehydrated as compared with hydrated cats, as is reported here before and after hypertonic saline infusion. In each case the hyperosmotic animals show higher levels of T_{hyp} and lower e.h.l. without hypothalamic heating. When heat is applied to the

hypothalamus of hyperosmotic animals a lowered sensitivity of the evaporative response to a given increase in T_{hyp} is observed.

The work of Myers and colleagues has generated evidence that alterations in body temperature produced by changing ionized sodium and calcium levels in the hypothalamus are defended in the face of applied thermal loads and hence represent true changes in the regulated level of body temperature or set point (Myers & Veale, 1971; Myers & Yaksh, 1971). Our results here indicate that intravenous hypertonic saline infusions are only capable of producing significant elevation of body temperature when ambient heat stress is also present, though the insignificant increases in body temperature occurring after hypertonic saline infusion in the absence of heat stress may be the result of a specific ionic effect. Failure of excess sodium ions to elevate body temperature significantly at the lower ambient temperature used in our experiments may reflect the slow rate of transfer of sodium ions into the central nervous system and the relatively high level of excess sodium ions required to achieve alteration of body temperature (Greenleaf, 1979). Infusion of water into dehydrated animals resulted in reduction in body temperature only during ambient heat stress. Since infusion of water alone adds no excess ions and is unlikely to alter the equilibrium between bound and unbound calcium ions significantly, this is further evidence that the changes in body temperature regulation observed in our experiments are not the result of an ambient temperature-independent alteration in set point produced by changing hypothalamic ionic ratios. The dependence of elevation of body temperature in hyperosmotic states upon either exercise or ambient heat loads has been reported uniformly in many studies (Turlejska-Stalmasiak, 1974; Maskrey & Nichol, 1975; Greenleaf *et al.* 1976; Baker, Kolb & Weitzman, 1978; Taylor, 1979; Kozlowski *et al.* 1980) and it must be concluded that such elevations can be independent of the influence of ionic ratios.

The findings reported here, in conjunction with our earlier findings in the dehydrated cat (Baker & Doris, 1982; Doris & Baker, 1981), permit speculation as to to the mechanism of the interaction of hyperosmolality and thermoregulatory control. Several models have been brought forth in an attempt to describe the mammalian thermoregulatory system. The model evolved by Hammel (1968) comprises a continuous proportional control system whose output is linked to the differential signal emerging from a comparison of body temperature with a reference signal representing the 'set point' temperature. The model of Mitchell, Snellen & Atkins (1970) differs from this principally in eliminating the need for a reference signal generator and ascribing the origin of the set temperature to the integrated output of central thermoreceptors responsive to rising and falling body temperature. Stitt (1976) has evolved a model incorporating aspects of both of these predecessors. In this model the set-point reference is retained and is considered to be altered during regulated alterations in body temperature such as occur during fever. Stitt's model also incorporates changing central thermosensitivity into an integrated mechanism of temperature control. However, in this model thermosensitivity is dependent on skin temperature and hence incorporates a link between the passive exchange of heat at the periphery and the central mechanism governing heat exchange.

The preoptic area of the anterior hypothalamus (p.o.a.) is considered to be a principal thermosensory source providing input in all three of the above models. Changes in the thermal responsiveness of p.o.a. neurones have been noted during fever

induced by pyrogen administration, and such changes have been incorporated into Mitchell's model as the basis for elevation of set point during fever. There does not, however, seem to be a clearly defined relationship between thermosensitivity of central thermoreceptors and the sensitivity of thermoeffector pathways to central thermal stimulation. Several studies have produced conflicting results in comparing thermoeffector sensitivity before and after induction of fever (Cooper, Cranston & Snell, 1964; Sharp & Hammel, 1972; Eisenman, 1974; Cranston, Duff, Hellon & Mitchell, 1976; Rosendorff & Cranston, 1968; Lipton & Kennedy, 1979). Changes in central thermoreceptor sensitivity are difficult to incorporate in a functional role in the concepts contained in Hammel's model. Stitt (1976), on the other hand, has generated substantial data from the rabbit indicating that the sensitivity of thermoeffector pathways is determined by peripheral temperature and is uninfluenced by prostaglandin fever (Stitt, Hardy & Stolwijk, 1974). In the light of these findings it is difficult to accept Turlejska-Stelmasiak's (1974) postulate that cellular dehydration acts to inhibit thermosensitive neurones in the p.o.a., thus providing the neural basis for increased body temperature during dehydration. Though largely compatible with the model of Mitchell *et al.* (1970), its full incorporation into this model would require that body temperature also be elevated at neutral ambient temperatures, which it clearly is not.

The changes in thermoregulatory control described here cannot be attributed to a change in set point such as this concept exists in the models of Hammel (1968) and Stitt (1976). Although hyperosmotic animals continue to defend T_{hyp} against further increase in temperature by increased e.h.l., the elevated equilibrium T_{hyp} maintained in these animals during thermal stress cannot be regarded as a set-point temperature in the context of these models. These regulated elevations are dependent on ambient temperature and, as pointed out before, are present only when the evaporative pathway would normally be operating. Although alterations in central thermosensitivity are a constituent part of Stitt's model, such variability in sensitivity is incorporated in this model as being consequent to altered peripheral temperature. Skin temperatures were not measured in the present study; however, osmotically induced changes in central thermosensitivity were all measured at an ambient temperature of 38 °C, thus making likely variations in skin temperature not only small, but largely due to altered deep body temperature. Changes in skin temperature which are secondary to alterations in deep body temperature cannot be viewed as responsible for the shift in central thermosensitivity occurring in our study. Rather, the altered central thermosensitivity generates the change in deep body temperature which then may bring about a small direct elevation of skin temperature.

The findings reported here and elsewhere can be interpreted as indicating that hyperosmotic states are associated with a reduced thermosensitivity of the evaporative heat-loss pathway which is produced by a specific inhibitory influence within this pathway. Since central thermoreceptor thermosensitivity is likely to be unaltered, increasing body temperatures will generate increasing central thermoreceptor drive for evaporation. However, inhibition of the pathway controlling evaporation, at some point beyond the central thermoreceptors, maintains lowered evaporative responses. That these modifications to thermoregulatory control take place within central control pathways is evidenced, at least in the case of the cat, by our previous finding that evaporative levels in dehydrated cats are sustained at or above levels occurring

in hydrated animals at an ambient temperature of 43 °C. These experiments clearly indicate that the reduction in e.h.l. which occurs in the dehydrated cat under less extreme heat loads is not the consequence of a diminished capacity for evaporation, but is a regulated reduction of evaporative water loss (Doris & Baker, 1981).

In conclusion, it appears that body fluid hyperosmolality, whether induced as in the experiments reported here by infusions of hypertonic solutions, or by dehydration achieved by removal of drinking water, interacts with body-temperature regulation in the heat-stressed cat. The phenomenon is ion-independent, although it may occur concurrently with ion-induced effects, and acts through modulation of central pathways which control, but do not generate the drive for, evaporative heat loss. Hyperosmolality inhibits the evaporative response to increasing body temperature, thus effectively reducing the gain of the coupling of body temperature to evaporation.

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