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ORIGINAL PAPER

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# Non-thermal signals govern selective brain cooling in pigs

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**Abstract** We used implanted miniature data loggers and fine thermistors to measure arterial blood and brain temperatures in four female pigs, to a resolution of 0.04 °C, every 5 min, for 4 weeks. Within that period, pigs were exposed on different days, and in random order, to a cold (5 °C) or hot (38 °C) environment. In the thermoneutral environment of the pigs' home pens, brain temperature was usually lower than blood temperature. Such selective brain cooling was absent for 2 days after surgery, during handling and transport stress, and on waking. The magnitude of selective brain cooling was greatest when pigs were sleeping and body temperatures were low, and was smallest, or even absent, during hyperthermia and natural fever. Our results showed that selective brain cooling was present in pigs, but there was no clear relationship between blood temperature and the magnitude of selective brain cooling. Instead, the degree of selective brain cooling in pigs was governed by non-thermal factors, especially those associated with high sympathetic nervous system activity. Our results further support the concept that selective brain cooling does not serve to protect the brain from thermal damage during heat stress.

**Key words** Body temperature · Brain temperature · Fever · Sleep · Sympathetic activity

## Introduction

Free-ranging wildebeest (Jessen et al. 1994) and springbok (Mitchell et al. 1997) do not show selective brain cooling, and brain temperature reaches levels as high as 42 °C, when the animals are under greatest thermal stress during intense physical activity. Tame reindeer tend to exhibit selective brain cooling at high body temperatures, but the threshold temperature above which selective brain cooling is activated is elevated during exercise when thermal stress is greater than at rest (Kuhnen and Mercer 1993). A similar increase in this threshold, and a reduction in the magnitude of brain cooling, occurs in febrile goats (Kuhnen 1994). These results are difficult to reconcile with the hypothesis that selective brain cooling serves to protect the brain from thermal damage during hyperthermia (Brinnel et al. 1987).

Rather than being a mechanism which is implemented when animals are dangerously hyperthermic, selective brain cooling appears to be a component of routine thermoregulation. The onset of selective brain cooling occurs within the normothermic range of body temperature (Kuhnen and Jessen 1991; Jessen et al. 1994; Kuhnen 1997), and brain cooling is conspicuous during sleep, when heat stress is usually low (Hayward 1968; Hayward and Baker 1969; Fuller at al. 1998). If selective brain cooling was necessary to protect the brain from potentially lethal damage, one would expect it to be regulated entirely by body temperature and particularly by brain temperature. However, non-thermal factors provide important inputs in the control of selective brain cooling, often overriding strong thermal signals (Jessen et al. 1994; Mitchell et al. 1997; Jessen et al. 1998).

A current hypothesis for the role that selective brain cooling plays in thermoregulation, at least in artiodactyls, is that selective brain cooling reduces the drive on evaporative heat loss effectors, so saving water. Selective brain cooling inhibits respiratory water loss during heat stress (Kuhnen 1997) and is augmented in dehydrated goats (Jessen et al. 1998). If the role of selective brain cooling is to balance thermoregulatory and osmoregulatory functions in such a manner, then what is its status in pigs? Unlike other artiodactyls, pigs have a poor ability to dissipate heat by evaporation from either the

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skin or respiratory tract (Ingram 1974), so manipulating evaporative heat loss would be futile. Nevertheless, they have a well-developed intracranial carotid rete within a large cavernous sinus (Daniel et al. 1953; McGrath 1977) and presumably the capacity for selective brain cooling. No-one appears to have investigated whether pigs employ this rete for selective brain cooling. We therefore investigated whether selective brain cooling is present in pigs and, if so, whether its magnitude is influenced by the prevailing blood temperature and by non-thermal inputs, as it is in other artiodactyls.

## Materials and methods

Experiments were performed on four female Landrace pigs (*Sus scrofa*), which weighed between 15 kg and 20 kg at the start of the study. The pigs were housed communally in indoor pens with other pigs; ambient temperature varied between 21 °C and 25 °C, and the natural light-dark cycle was maintained. Water was provided ad libitum and commercial feed (1 kg/day; Pig Growth and Sow 150, Epol, Johannesburg) was provided once a day at ~1000 hours, after pens had been cleaned. The procedures were approved by the Animal Ethics Screening Committee of the University of the Witwatersrand (protocol no. 97/33/5).

Carotid artery and brain temperatures were measured with miniature data loggers, which were implanted surgically such that the loggers themselves and all their attachments were under the skin. Pigs were sedated with azaperone (40 mg IM; Stresnil, Janssen Pharmaceutica) and thiopentone sodium (150 mg IV; Intraval Sodium, RPR), intubated endotracheally, and maintained under anaesthesia using 1–2% halothane (Fluothane, Zeneca) in oxygen. Under sterile conditions, a thermistor in a blind-ended and thin-walled polytetraflouroethylene (PTFE) tube (outside diameter, OD, 0.9 mm; straight aortic flush 4F catheter, Cordis, The Netherlands) was advanced 80 mm into the left common carotid artery, and secured in position with a purse-string suture. Outside the artery, the PTFE tube was connected to silicone rubber cable (length ~100 mm, OD 3 mm) containing leads from the thermistor to the data logger. The data logger was covered with an inert wax (Elvax, Mini-Mitter, Sunriver, USA) and was positioned near the artery within a pocket made between the muscle layers. A second data logger connected to the brain thermistor was also positioned in the animal's neck, behind the left ear. The silicone rubber tube covering the leads was advanced over the occiput to the parietal skull, where it was connected to a head plate and guide tube. The guide tube, constructed from cellulose acetate butyrate tubing (OD 3.2 mm, inside diameter 1.6 mm; World Precision Instruments, Sarasota, USA) sealed at the tip by a steel cap, was 38 mm long and positioned ~5 mm rostral to the bregma, so that the probe tip would be positioned near the hypothalamus. The position of the tip was verified radiographically. The brain guide tube was attached to a small square headplate (20 mm × 20 mm × 5 mm), which was secured to the skull by two bone screws. Wounds were treated with 50 mg enrofloxacin (Baytril, Bayer) and a topical antiseptic (Acriflavin in Glycerin, Kyron Laboratories, Johannesburg). Animals received penicillin (2 ml IM; Duplocillin, Intervet, Johannesburg) twice at 3-day intervals and buprenorphine (0.5 ml IM; Temgesic, Centaur, Johannesburg) as required.

The miniature data loggers (StowAway XTI, Onset Computer, Pocasset, USA), covered in wax, had outside dimensions of ~50 mm × 45 mm × 20 mm, weighed ~40 g, and had a storage capacity of 32 KB. They were custom-modified for us, to have a measurement range from 34 °C to 46 °C, and a resolution of 0.04 °C. We set the scan interval at 5 min, allowing recording of body temperatures for 112 days. Temperature sensors were constructed from ruggedized glass-coated bead thermistors with insulated extension leads (bead diameter 0.3 mm; AB0E3-BR11KA103N, Thermometrics, Edison, USA). Each thermistor and logger was calibrated against a high-accuracy quartz thermometer (Quat 100, Heraeus, Hanau, Germany) in an insulated water bath, to an accuracy of one sampling step of the logger (0.04 °C).

After 2 weeks of data collection from the pigs in their home pens, we subjected the animals, in random order and at the same time of day, to cold and heat stress. Two pigs at a time, restricted to the space of a small trolley (0.6 $m^2$), were exposed, in a climatic chamber, to 5 °C (75% relative humidity) for 120 min, or 38 °C (40% relative humidity) for 90 min. The pigs were collected in the trolley and brought to a room outside the climatic chamber ~30 min before the start of a trial and were returned to their home pens immediately after the trial.

One pig developed an abscess at the site of the brain logger 6 days after surgery. The animal was treated with oral clindamycin (150 mg/day for 2 days; Antirobe capsules, Upjohn) administered in its food, and the wound was flushed with enrofloxacin (50 mg for 4 days; Baytril, Bayer). The abscess resolved after 5 days of treatment. At the end of the experiment, pigs were sedated with azaperone (80 mg IM) and killed with sodium pentobarbitone (3000 mg IV; Euthenaze, Centaur, Johannesburg). Data loggers were removed and downloaded. In two animals, the brain thermistor had broken before the end of data collection, and one pig removed its carotid data logger by attacking the wound site.

## Results

Figure 1 shows a typical pattern of brain and arterial blood temperatures in one pig, in its home pen over 24 h. There was no clear circadian rhythm in body temperature in any of the pigs, and brain temperature was much more variable than arterial blood temperature. Brain temperature was usually lower than blood temperature, particularly during the night (1800–0600 hours), when the temperature difference could be as much as 0.9 °C. However, as shown in Fig. 1, there were three distinct periods, as well as several sporadic episodes, when selective brain cooling was abolished, and brain temperature exceeded blood temperature by ~0.1 °C. A similar pattern was seen in all pigs. Although these elevations in brain temperature occurred irregularly, they were most likely to occur in the early morning

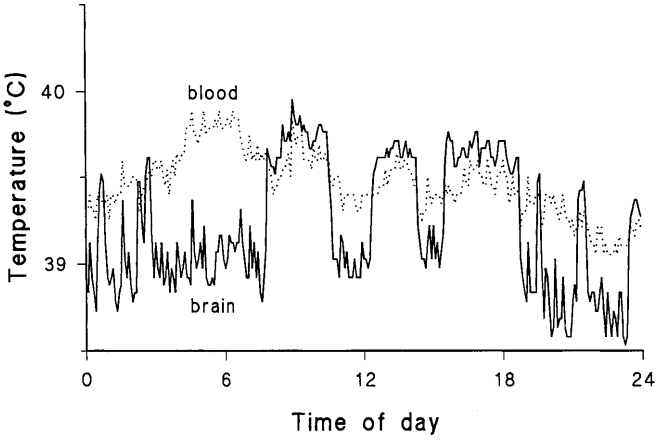


**Fig. 1** Original records of 5-min values of brain temperature (*solid line*) and blood temperature (*dotted line*) as a function of time of day in one pig

(~0745–1100 hours), at noon, and in the late afternoon (~1600–1900 hours). Elevations always had rapid onset and return. On some days, no elevations occurred.

The relationship between blood and brain temperature, in two of the pigs, is further analysed in Fig. 2. The data of this figure were obtained by sorting all 5-min measurements of arterial blood temperature into 0.1-°C classes and determining the mean, standard deviation, and maxima and minima of brain temperature at each class of blood temperature. Also shown in the figure, in lower panels, are the frequencies of each of the 0.1-°C classes of blood temperature. The range of blood temperature was small; 1.0 °C (39.2–40.2 °C) in one pig, and 1.6 °C (38.8–40.3 °C) in the other, and there were indistinct modes at 39.6 °C and 39.3 °C, respectively. The double modes may be artefacts arising from successive 0.1 °C blood temperature classes containing either two or three 0.04 °C steps.

The diagonal lines in the upper panels of Fig. 2 are the lines of identity between brain and arterial blood temperature. Mean brain temperature in both animals was lower than blood temperature over the entire distribution of blood temperature, except for one 0.1-°C class of blood temperature (38.8 °C) in one pig. Neither animal exhibited the clear relationship between blood temperature and the magnitude of selective brain cooling which is evident in other artiodactyls in the laboratory. Except for one data point from one pig, the brain temperature maxima were above the line of identity, so there was no blood temperature at which selective brain cooling was obligatory. Standard deviations in brain temperature were large (~0.3 °C), illustrating the variability in brain temperature at any given blood temperature.

The origin of the variability in brain temperature was the frequent and irregular, but large, transient deviations in brain temperature, which did not parallel changes in blood temperature (see Fig. 1). We analysed these short-term changes of internal body temperatures by calculating the changes in brain and blood temperature from one 5-min epoch (scan interval of the data logger) to the next, in one animal. The 7000 successive measurements of each temperature were sorted into 0.08-°C classes (twice the resolution of the logger). Figure 3 shows the relative frequencies of each class. In 77% of all cases, the change in brain temperature from one 5-min epoch to the next was less than ±0.16 °C, and in 21% of cases, changes were between ±0.16 °C/5 min and ±0.48 °C/5 min. In the remaining 2% of cases, changes were greater than or equal to ±0.48 °C/5 min. Changes in arterial blood temperature from one 5-min epoch to the next were usually smaller than those in brain temperature. Blood temperature changed by less than ±0.16 °C/5 min 97% of the time. In only 3% of cases were blood temperature changes between ±0.16 °C/5 min and ±0.48 °C/5 min, and there were no changes greater than ±0.40 °C/5 min. Increments and decrements in internal body temperatures occurred at approximately the same frequency.

Examination of individual records of temperature for each animal revealed that selective brain cooling was absent in pigs for at least 2 days after surgery. Figure 4, for example, shows 1-h means of arterial blood temperature and brain temperature in one pig during the 96 h following surgery. Brain temperature paralleled changes in blood temperature during the hyperthermia which prevailed in the first 24 h, increasing from ~38 °C immediately after surgery, to a peak of 40.6 °C 5 h later, before gradually dropping to ~39.5 °C. Over the course of the following 2 days, brain temperature gradually uncoupled from blood temperature, so that by the 4th day, brain temperature, on average, was lower than blood temperature throughout the day, by ~0.35 °C. Large, irregular variations in brain temperature, as illustrated in Fig. 1

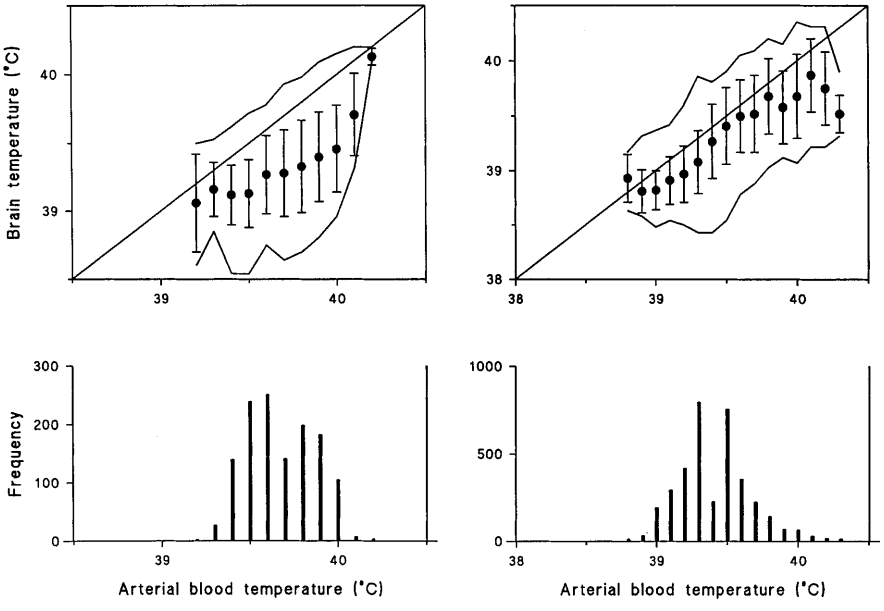


**Fig. 2** Brain temperature as a function of arterial blood temperature (*top panels*) and frequency distribution of blood temperature (*bottom panels*), in two pigs. The 5-min values of blood temperature were sorted into classes of 0.1 °C width. *Top panels* show means, SDs, minima and maxima of brain temperature for each 0.1-°C class of blood temperature. *Bottom panels* show absolute frequencies at which each 0.1-°C class of blood temperature occurred

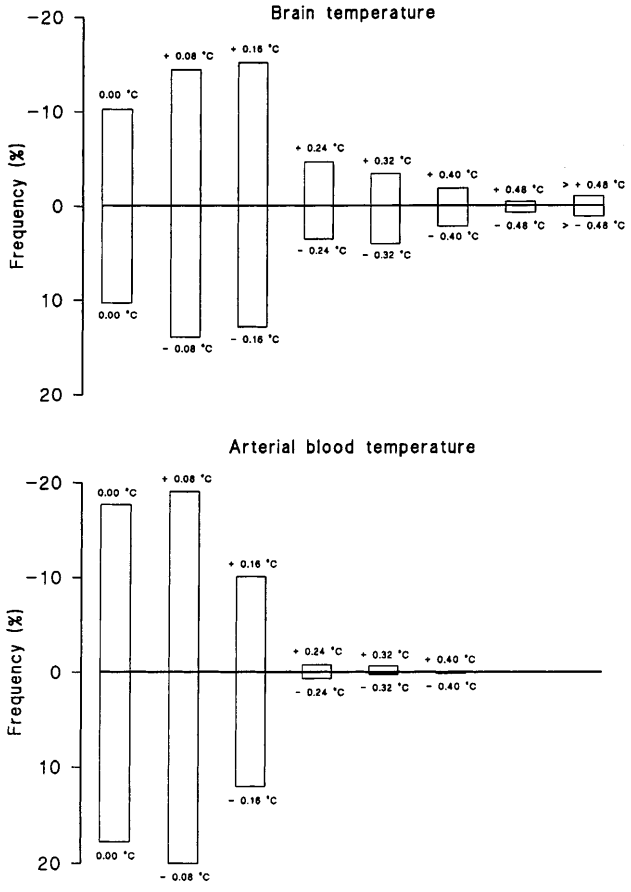


**Fig. 3** Relative frequencies of changes of brain temperature (*upper panel*) and arterial blood temperature (*lower panel*) from one 5-min epoch to the next. The furthermost *left bar* indicates no change (0.00 °C); *bars* to the right show frequencies in each 0.08-°C class (i.e., the *second bar* from the left shows 0.01 to 0.08 °C, and so on), and the *last bar* in the *upper panel* shows brain temperature changes greater than 0.48 °C. Data for 7000 consecutive measurements in one pig

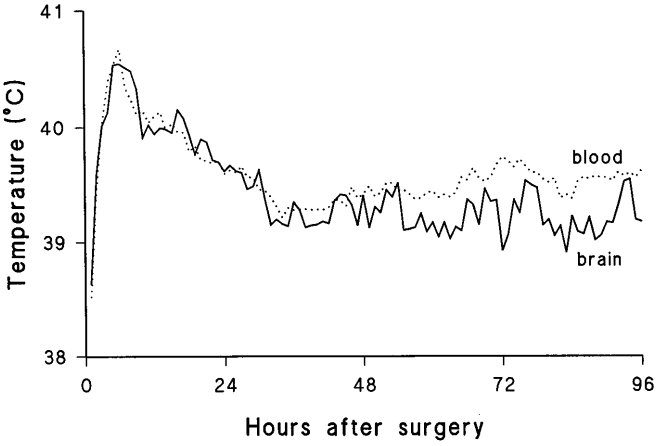


**Fig. 4** One-hour means of brain temperature (*solid line*) and blood temperature (*dotted line*) in one pig during the 96 h following surgery

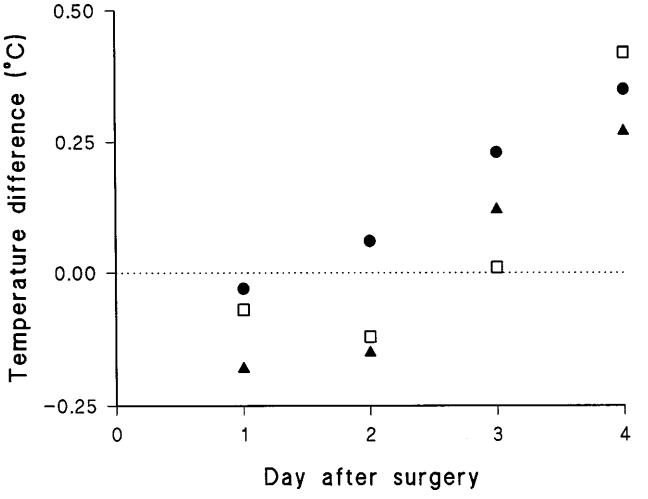


**Fig. 5** Mean 24-h difference between blood and brain temperature on the 4 days following surgery, in three pigs (each shown by a different symbol). Positive temperature differences (above the *dotted line*) indicate selective brain cooling, negative differences show brain temperature greater than blood temperature

and Fig. 3, once again were evident, particularly on days 3 and 4 after surgery, although they are partially masked by the averaging used to construct Fig. 4.

The relationship between brain and blood temperature after surgery is analysed further in Fig. 5, which shows the 24-h mean difference between blood and brain temperature on the 4 days following surgery, in three pigs. Data from the pig which developed the abscess shortly after surgery are excluded. Data obtained for each pig show a similar pattern; brain temperature exceeded blood temperature on the day following surgery, but this difference was gradually reduced, and then reversed, so that, by the 3rd day, on average over the 24 h, selective brain cooling was evident in all pigs. The difference between mean brain temperature and mean blood temperature achieved by day 4 was maintained thereafter.

In addition to measurements under thermoneutral conditions, we investigated the effect of cold and heat stress on the relationship between brain and blood temperature. At the time we conducted these trials, thermistors in some of the animals had broken, and we obtained data for only one pig during cold stress, and for two pigs in the heat. During cold stress, selective brain cooling was reduced from 0.9 °C to 0.3 °C, but was never completely abolished. Blood temperature in the animal did not change during the 2-h exposure. The pig started to shiver after 1 h and huddled next to the other pig in the trolley.

Figure 6 shows blood and brain temperatures during heat stress (38 °C, indicated by solid bar) in two pigs, carried out on different days. Arrows A and B show the time at which the pigs were put in the trolley and wheeled to and from the climatic chamber. A large, rapid increment in brain, but not blood temperature, occurred whenever an animal was transported. These increments were exaggerated at point A in Fig. 6, because the pig was sleeping when it was fetched from its home pen, and its brain temperature was falling. Both animals exhibited selective brain cooling at the end of

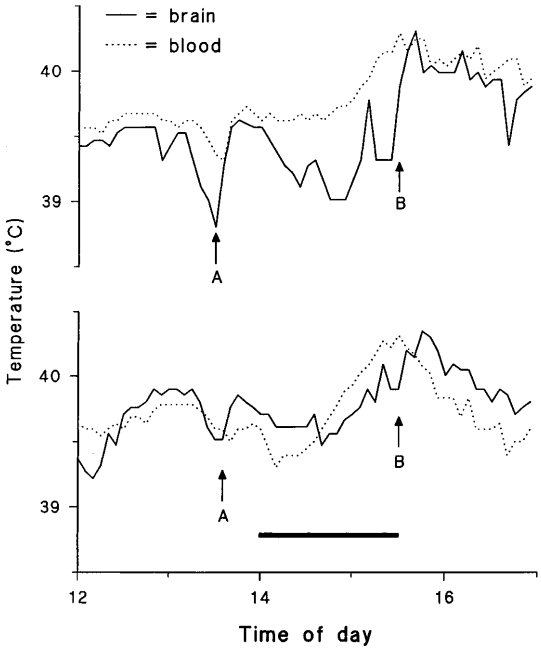


**Fig. 6** Brain temperature (*solid line*) and blood temperature (*dotted line*) in two pigs during heat stress (38 °C, shown by *solid bar*). *Arrows A* and *B* indicate the time at which pigs were transported to or from the climatic chamber

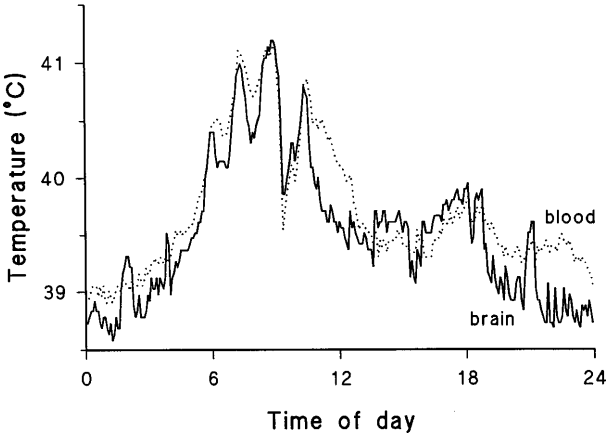


**Fig. 7** Brain temperature (*solid line*) and blood temperature (*dotted line*) in one pig, during a febrile episode

the period of heat stress, although in one pig (lower panel), where brain cooling was absent at the start of the trial, brain temperature dropped below blood temperature after only 40 min. The pigs lay down and slept in the trolley after ~30 min. The animals displayed signs of stress (vocalisations, defaecation and urination, chewing of rubber mat in trolley) after 60 min at 38 °C. During the last 30-min period in the chamber, brain temperature exhibited transient peaks which did not correspond to similar changes in blood temperature.

Additional data on responses during hyperthermia were serendipitously obtained when one animal developed an abscess, and fever ensued a few days later. This febrile episode is shown in Fig. 7. The pig's temperatures exceeded 41 °C, almost 1 °C greater than the normal maximum daily temperature. Nevertheless, during the peaks in blood temperature, selective brain cooling was abolished. Brain cooling was evident only during defervescence of the fever, when temperature rapidly dropped. At ~0900 hours, there was a large, rapid decrement in body temperature, which coincided with the pig being fed and becoming active. The fever, which lasted ~9 h, had resolved itself by the late afternoon. The pig experienced no similar febrile episodes on any other day of the study.

## Discussion

We measured brain and arterial blood temperatures to determine whether pigs, like other artiodactyls, exhibit selective brain cooling. Our results show that pigs do employ selective brain cooling and that they do so regardless of the prevailing blood temperature. Indeed, the magnitude of selective brain cooling was greatest when pigs were sleeping and body temperatures were low, and was smallest, or even absent, during hyperthermia and natural fever.

Pigs are intolerant of instrumentation and we were able to measure their brain and blood temperatures only after we had developed a novel method of implanting all equipment subcutaneously. Nevertheless, one pig still removed its blood temperature logger, and the brain thermistors in two other pigs were broken, presumably because pigs use their heads to butt. We kept our pigs in communal pens to simulate the rearing environment and to eliminate stress associated with being alone. A drawback of such communal living was that pigs could bite at each other's wounds. Infections which developed also could spread to other animals in the pen, and we had to exclude all data from two additional animals in which abscesses did not resolve themselves. Our data set therefore is limited to four animals and does not include results from experimental trials for all the pigs. Nevertheless, the data allow us to examine, for the first time in a member of the pig family, the relationship between brain and blood temperature.

Brain temperature in resting pigs, measured with miniature data loggers, was highly variable, and could change by more than 0.5 °C from one 5-min measurement to the next. Similar transient deviations were not seen in arterial blood temperature (Figs. 1, 3). Brain temperature was usually lower than blood temperature, but this selective brain cooling could be rapidly abolished at any time of the day. Large, rapid increments in brain temperature, but not blood temperature, coincided with the pigs being woken up, handled and transported. Selective brain cooling also was absent for 2 days after surgery, even though the animals experienced post-surgical hyperthermia. The common link between the events in which selective brain cooling was abolished is that they all are associated with increased sympathetic nervous system activity. Sympathetic discharge is

increased in response to novel stressors, and acute postoperative pain also results in sympathetic overactivity (Cousins 1994).

In species with a carotid rete, the cranial veins responsible for selective brain cooling are under sympathetic control (for review see Mitchell et al. 1987). Sympathetic stimulation of the veins reduces or abolishes selective brain cooling. Superior cervical sympathectomy therefore enhances selective brain cooling (Nijland et al. 1990), and the converse procedure, cervical sympathetic stimulation, reduces selective brain cooling (Bamford and Eccles 1983). Selective brain cooling is also abolished in free-ranging ungulates during capture procedures, even if the animals are severely hyperthermic (Jessen et al. 1994; Mitchell et al. 1997).

We propose that, in resting pigs in which sympathetic tone is low, cool venous blood leaving the nasal mucosa is diverted primarily to the cavernous sinus, where heat exchange occurs with the extensive carotid rete. Increased sympathetic activity vasoconstricts this conduit for blood flow, so that the cool blood bypasses the rete and brain temperature rises. Although this arrangement is well-described in reindeer (Johnsen et al. 1985; Johnsen and Folkow 1988) and sheep (Khamas and Ghoshal 1982; Nijland et al. 1990), it has still to be demonstrated in pigs and many other artiodactyls. Pigs, however, do appear to have the necessary anatomical apparatus. They have a particularly well-developed rete with extensive anastomoses across the midline, giving it the appearance of a single, large structure (McGrath 1977). Their nasal mucosa is highly vascularised and both arteries and veins receive a dense sympathetic innervation (Lacroix et al. 1988). However, the superficial venous drainage differs from that of other artiodactyls since pigs do not possess the angularis oculi vein (Popesko 1977). Blood, however, may still pass to the cavernous sinus by way of several other veins, including the frontal, sphenopalatine, major palatine or deep facial veins (Khamas and Ghosal 1982; Johnsen et al. 1985).

Further studies are needed to confirm that an increase in sympathetic vasoconstrictor outflow differentially affects blood flow to the cavernous sinus. Nevertheless, our results are consistent with a role for the sympathetic nervous system in the control of selective brain cooling. In particular, changes in sympathetic tone provide a plausible explanation for the patterns of selective brain cooling evident in pigs during the night, when body temperatures are lowest. Brain temperature drops independently of blood temperature during slow-wave sleep, but not during REM sleep (Hayward 1968; Hayward and Baker 1969). Slow-wave sleep is associated with a tonic reduction in sympathetic discharge, whereas REM sleep is characterised by phasic oscillations of parasympathetic and sympathetic discharges (Parmeggiani 1994). The majority of sleep in pigs comprises slow-wave sleep (Robert and Dallaire 1986), favouring selective brain cooling, but pigs are polyphasic sleepers, displaying approximately 24 sleep cycles during the night and 6 per day (Robert and Dallaire 1986), and waking up in between each cycle. When they awake, there are sudden, marked increases in heart rate (Launois et al. 1998), reflecting bursts of sympathetic activity, which may inhibit selective brain cooling and cause a rapid rise in brain temperature. Hayward (1968) reported that one "nervous" dog failed to show selective brain cooling during slow-wave sleep until such time as it was trained and adapted to the test situation, and that brain temperature rises rapidly with waking in dogs.

In addition to spontaneous arousals, our animals were awakened each morning at ~0800 hours by cleaning staff. Abolishment of selective brain cooling at this time, as seen at 0740 hours in Fig. 1, was clear in all our pigs. Pigs also slept during the day, although their sleep was disturbed by irregular, but frequent, human activity in the room, and each arousal was likely to inhibit selective brain cooling. Baldwin and Ingram (1968) also showed irregular fluctuations in brain temperature in pigs and remarked that large (up to 1 °C) increments in brain temperature coincided with the animals becoming alert or responding to disturbances (such as a door opening).

Non-thermal activation of the sympathetic nervous system certainly appears to influence selective brain cooling in other species (Jessen et al. 1994; Mitchell et al. 1997; Jessen et al. 1998), but thermal signals compete with the non-thermal factors. Particularly in the laboratory, the greater the brain temperature, the greater the extent of selective brain cooling. Thermal signals dominate over non-thermal signals, except under conditions of extreme stress, such as capture (Jessen et al. 1994). In pigs, however, thermal signals appear to have no effect on the relationship between blood and brain temperature. Indeed, pigs exhibited selective brain cooling at normothermic body temperatures; when blood temperature was highest, after surgery (Fig. 3) or in response to infection (Fig. 7), selective brain cooling was absent. These results, as well as those obtained in free-ranging ungulates (Jessen et al. 1994; Mitchell et al. 1997), provide strong evidence that selective brain cooling does not serve to protect the brain from thermal damage.

An alternative interpretation is that selective brain cooling prevents brain temperature sensors from detecting rises in blood temperature and, in so doing, reduces the drive on evaporative heat-loss mechanisms. Selective brain cooling therefore reduces water loss, a useful strategy in semi-arid environments (Jessen et al. 1994; Mitchell et al. 1997) or in dehydrated animals (Jessen et al. 1998). Pigs, however, do not sweat on exposure to heat and dissipate only a small percentage of their heat production by respiratory evaporation (Ingram 1974). The key to their survival in hot environments is through behavioural, rather than physiological adaptations. What then is the role of selective brain cooling in pigs? The answer simply may be that it serves no current physiological function. Carotid retes are present in cetaceans (McFarland et al. 1979; Vogl and Fisher 1981), which share common ancestry with

artiodactyls (Shimamura et al. 1997), so they probably did not originally evolve for the purposes of thermoregulation. Several authors have suggested haemodynamic functions: promoting venous return from the head (Barnett et al. 1958), dampening systemic pressure pulses (Edelman et al. 1972), or reducing blood flow during cerebral hypertension (Mitchell et al. 1980). Whether or not the rete's function was originally haemodynamic, the venous blood supply from the nasal mucosa may have developed sympathetic controls. Later in evolution, when the rete was co-opted for thermoregulation, thermal control mechanisms may have been superimposed. Since pigs had no function for selective brain cooling in thermoregulation and osmoregulation, those thermal controls did not develop. In pigs, therefore, but not in artiodactyls which employ evaporative cooling, selective brain cooling occurs independently of the prevailing blood temperature and is governed by non-thermal signals.

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