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CHANGES IN PLASMA NORADRENALINE AND ADRENALINE ASSOCIATED WITH CENTRAL AND PERIPHERAL THERMAL STIMULI IN THE PIG

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SUMMARY

1. The role of catecholamines in thermogenesis has been investigated in trained young pigs in various situations which increase heat production. Plasma noradrenaline and adrenaline concentrations were estimated by radioenzymic assay of samples taken from an indwelling jugular catheter to prevent disturbance and stress.

2. During 3 hr at ambient temperatures of between 25 and −5 °C, there was a curvilinear increase in noradrenaline concentrations as temperature decreased, but adrenaline did not change. After 1–3 days at 5 or 1 °C, the concentrations of both amines were similar to those found at thermal neutrality.

3. Cooling the cervical region of the spinal cord resulted in a large increase in plasma noradrenaline whereas local cooling of the hypothalamus was associated with a small increase in the hormone. When cooling either region of the central nervous system, plasma adrenaline concentrations did not change.

4. During exposure to 45 °C, rectal temperature increased to 43 °C. Concentrations of catecholamines remained low or declined until the rectal temperature was above 41·5 °C when the concentrations increased in most animals.

5. Induced physical activity lasting 40 min was associated with an increase in both noradrenaline and adrenaline concentrations.

6. Blood samples from the inferior vena cava, just cephalad to the outlet of the adrenal veins, had much higher concentrations of noradrenaline during cold exposure than those taken simultaneously from the jugular vein. Therefore, at least part of the increase in noradrenaline concentrations reported above may have been due to release of the hormone from the adrenal medulla.

7. It is concluded that during short-term exposure to cold, and in exercise, there is a rapid catecholamine response, producing concentrations in the blood which could be high enough to stimulate thermogenesis. During longer-term cold exposure, catecholamine output is low and other factors must be of greater importance in maintaining thermogenic processes. Further, catecholamine output may result from thermal stimuli not only from outside the external surface of the animal but also from within the central nervous system.

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INTRODUCTION

The increased thermogenesis and heat conservation which occur during exposure to cold environments are probably assisted by the action of peripheral catecholamines. Part of their action is in mobilizing fuels for increased metabolism (Young & Landsberg, 1977) and in adjusting blood flow to some tissues (Gale, 1973). Catecholamines can also exert their effects on thermogenesis directly by stimulating heat-generating processes not involved with shivering i.e. non-shivering thermogenesis, particularly in brown adipose tissue (Smith, 1964) but possibly in other tissues as well (Jansky, 1973).

In large mammals in which there is relatively little brown adipose tissue, cold-induced thermogenesis is mediated mainly by shivering (Tanche, 1976). Catecholamines also play a direct role in this mechanism by an action on β-adrenotropic receptors (Marsden & Meadows, 1970; Bülbring, 1976). The control of catecholamine output in response to a decrease in temperature depends on thermally sensitive elements both at the periphery and in the hypothalamus (Andersson, Brook, Gale & Hökfelt, 1964). Such an interaction has been demonstrated in the young pig, which responds to cooling of the hypothalamus in a cold environment with an increase in urinary noradrenaline (Baldwin, Ingram & LeBlanc, 1969). In many other studies the extent to which catecholamines are involved in the control of thermogenesis has been determined from the measurement of the concentrations of catecholamines and their breakdown products in urine (see Gale, 1973). Using such methods it is not possible to detect short-term changes or to identify sites of release, and the possibility that concentrations of blood catecholamines have been modified by changes in handling by the kidney cannot be excluded.

The recent development of more sensitive assay methods has made it possible to measure catecholamines in very small samples of plasma (Callingham & Barrand, 1976; Bühler, Da Prada, Haefely & Picotti, 1978; Callingham & Barrand, 1979). Therefore the role of catecholamines in the control of thermogenesis can now be examined more directly.

In the present study the changes in the plasma concentrations of catecholamines in blood from the jugular vein, and from the inferior vena cava close to the adrenal vein have been studied in the pig (i) during short-term and long-term exposure to cold and (ii) during local cooling of the preoptic region of the hypothalamus and the spinal cord. In order to provide a basis with which to compare these changes, catecholamines were also measured during exercise, when increased thermogenesis also occurs. Part of this work has been the subject of a preliminary communication (Ingram, Dauncey, Barrand & Callingham, 1980).

METHODS

Animals

Twenty-three pigs of the Large White breed including both males and females were studied. They had been living in the Institute farm and were aged 6–10 weeks and weighed 12–20 kg. They were housed individually in pens and unless otherwise stated the room temperature was 25–26 °C, which was within the thermally neutral zone for these animals. A commercial feed was given once a day at the level of 40 g feed/kg body weight. Water was available *ad lib.*

Catheters and thermodes

A catheter (outside diameter 2 mm) was placed into the jugular vein using general anaesthesia and sterile conditions. Approximately 0·5 m of the catheter was led out to the back and secured in place with surgical adhesive tape. This was done to enable blood samples to be taken later while the animal was resting or standing quietly and unaware of the sampling procedure. In five animals a catheter was placed in the inferior vena cava which was exposed by a retroperitoneal approach. The tip of the catheter was inserted so as to lie just cephalad to the entrance of the veins from the adrenal glands. Several attempts were made to introduce two catheters into the inferior vena cava, one cephalad and the other caudad to the junction with the adrenal vein, but except for one instance this led to the obstruction of blood flow.

Thermodes were placed into either the hypothalamus or spinal cord using general anaesthesia and aseptic conditions. In three animals the hypothalamic thermode was positioned by X-radiography, within 2 mm of the mid line. The hypothalamic thermode consisted of a disc-shaped copper chamber (outside diameter 5 mm and depth 2 mm) mounted at the end of stainless-steel tubes. A bead thermistor was fixed to the outside of the chamber and the whole apparatus was coated with resin to reduce toxicity to the brain tissue. When cool liquid was drawn through the thermode so that its surface temperature was 10 °C the hypothalamic temperature 5 mm distant was reduced from 39 to 37 °C. Details of the thermode and its use have been published previously (Baldwin & Ingram, 1967). In three other pigs a thermode was placed over the cervical region of the spinal cord. This thermode consisted of a length of catheter (outside diameter 2 mm) which was bent to form a 'U'. It was inserted between two thoracic vertebrae and pushed along over the cord as far as the skull, leaving the two open ends outside the skin. The position of the thermode was checked by filling it with radio-opaque liquid and taking a radiograph. A blind-ended catheter (2 mm outside diameter) was then also inserted between two vertebrae so that its end was half-way along the thermode. During experiments a thermojunction was threaded down this catheter to record temperature changes induced by passing cold liquid through the thermode (Ingram & Legge, 1971). The temperature gradients created in the spinal cord when the thermode was cooled were also large. When the thermode was cooled to 20 °C at a body temperature of 37 °C then the tissue directly in contact with the thermode was also at 20 °C. At a distance of 5 mm into the cord the tissue temperature was 36 °C, and on the opposite side of the cord it was 37 °C. Since the exact position and distribution of the thermally sensitive neurones are not known the relevant tissue temperature can not be estimated. Moreover serial radiographs over a period of days indicated that the position of the thermode over the cord changed slightly.

All the animals were walking about and eating within 0·5–1 hr of inserting the catheter or thermode. No further work was carried out with the animals for the next 5–10 days.

Blood samples

Samples of 5 ml. blood were withdrawn, placed into heparinized tubes and kept on ice until centrifugation at 1500 *g* for 15 min at 4 °C. Reduced glutathione at 60 mg/ml. was added to the plasma (20 μl./ml.) and the plasma was then stored at -20 °C until assayed for catecholamines.

Exercise

The animals were exercised by walking them at approximately 4 km/hr round the indoor animal holding area which measured 2·5 × 6·5 m. At 10 min intervals the pig was placed in a cage for 1–1·5 min while a blood sample was taken.

Assay of catecholamines

Noradrenaline and adrenaline were estimated simultaneously in 250 μl. portions of plasma by a radioenzymic assay described previously (Callingham & Barrand, 1979).

Experimental

The animals were used to being handled and were familiar with the people who took the blood samples. This training procedure was essential for ensuring that changes in catecholamine levels were not due to any outward signs of disturbance or stress except where stated otherwise. During any work with the animals they were therefore usually lying, sitting or standing quietly, except when they were exercising or at a very high ambient temperature when they tended to become vocal.

RESULTS

Catecholamine concentrations in jugular blood

The fluctuations in plasma catecholamine concentrations in the jugular vein during steady-state conditions were examined in one pig which had not been fed since the previous day. Blood samples were taken at 5 min intervals over a 1 hr period and the variation in noradrenaline was found to be 0·08–0·18 ng/ml. plasma and that for adrenaline was 0·01–0·03 ng/ml. plasma indicating the range of concentrations that occur over this period in the absence of experimental stimuli.

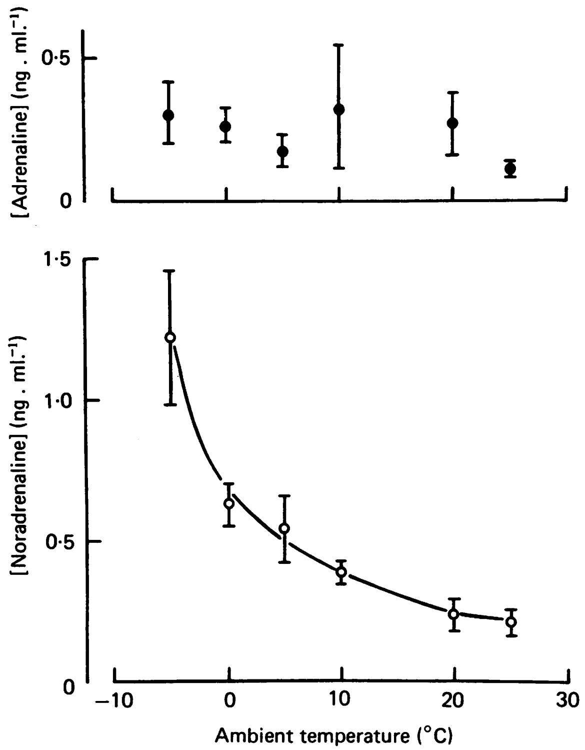

Fig. 1. Effect of exposure to six different ambient temperatures at and below the critical temperature of 25 °C for between 2 and 3 hr on plasma adrenaline (●) and noradrenaline (○) concentrations in eight animals of 12–20 kg body weight. Vertical bars indicate S.E. of mean.

Short-term exposure to cold

The results obtained from eight pigs exposed to a series of ambient temperatures at and below the critical temperature of 25 °C are given in Fig. 1. The pigs, which had been fed 3–4 hr previously, were left in the selected temperature for 2 hr and two to four blood samples were then taken over the next hour. The average values for each animal were found, and from these the mean ± S.E. of mean for all pigs was calculated. It was found that the concentration of noradrenaline increased in a curvilinear fashion as the ambient temperature declined. By contrast, the values for adrenaline displayed no consistent variation in relation to temperature.

In one pig the time course of the change in hormone levels was followed as the ambient temperature declined from 25 to 5 °C (Fig. 2). During the periods of blood sampling the animal was sitting quietly at 25 °C, and from 20 down to 5 °C it was standing quietly, with occasional movement. From this experiment it appeared that the concentration of noradrenaline did not begin to rise until the ambient temperature had been declining for over 1 hr and the temperature had fallen below 10 °C. A conspicuous feature was the high peak at 3·5 hr which had fallen by the time of the next reading. This raised at least the possibility that the noradrenaline may have been produced from the adrenal in spurts rather than at a steady rate. The assay for this high value was repeated and confirmed. Adrenaline concentrations did not change.

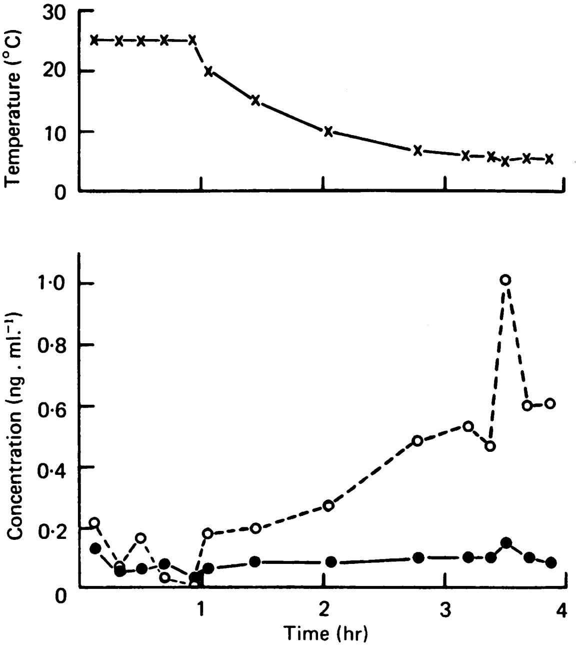

Fig. 2. Changes in plasma adrenaline (●) and noradrenaline (○) concentrations in one animal during a decline in ambient temperature (×) from 25 down to 5 °C over a 4 hr period.

Long-term exposure to cold

In order to study the effects of more prolonged exposure to cold conditions five animals were kept at temperatures of 5 or 1 °C for periods of 3 days. Four samples were taken each day beginning 24 hr after the initial exposure to cold and 3–4 hr after the pigs had been fed. The changes in noradrenaline were small by comparison with those seen after only 2 hr exposure to cold, for animals at both 5 and 1 °C, and there was very little change in the concentration of adrenaline (Table 1).

TABLE 1. Catecholamine concentrations (ng/ml. plasma) during long-term exposure to cold (3–5 days at 5 or 1 °C) in five young pigs of 12–20 kg body weight. Values are means ± S.E. of means

	Time of exposure (hr)		
	30–34	54–58	78–82
Noradrenaline	0·18 ± 0·052	0·18 ± 0·031	0·35 ± 0·015
Adrenaline	0·05 ± 0·012	0·07 ± 0·034	0·11 ± 0·055

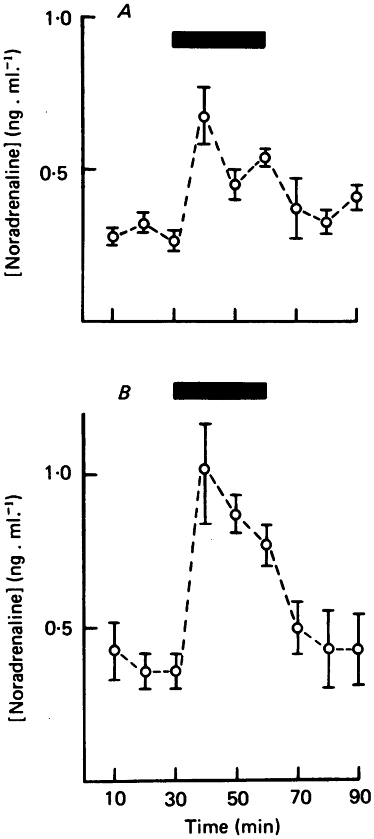

Fig. 3. Plasma noradrenaline concentrations (○) before, during (horizontal bar) and after *A*, cooling the hypothalamus in three animals, and *B*, cooling the spinal cord, also in three animals. Vertical bars indicate S.E. of the mean.

Cooling the central nervous system

In three pigs the thermode in the hypothalamus was cooled to a surface temperature of 10 °C, corresponding to a fall in hypothalamic temperature 5 mm from the thermode of 2 °C, while the ambient temperature was 10 °C. There was a small rise in noradrenaline, but adrenaline concentrations did not alter. In three other animals a thermode over the spinal cord was cooled to a temperature of 20 °C, as indicated by the thermojunction over the cord at an ambient temperature of 10 °C. In each instance there was a rise in the level of noradrenaline but not in adrenaline, with the increase in noradrenaline being greater when the spinal cord was cooled. As seen in Fig. 3 the rise in noradrenaline was greatest immediately after the cooling started and tended to decline thereafter. As soon as the cooling of the thermode was stopped noradrenaline levels returned towards the control value.

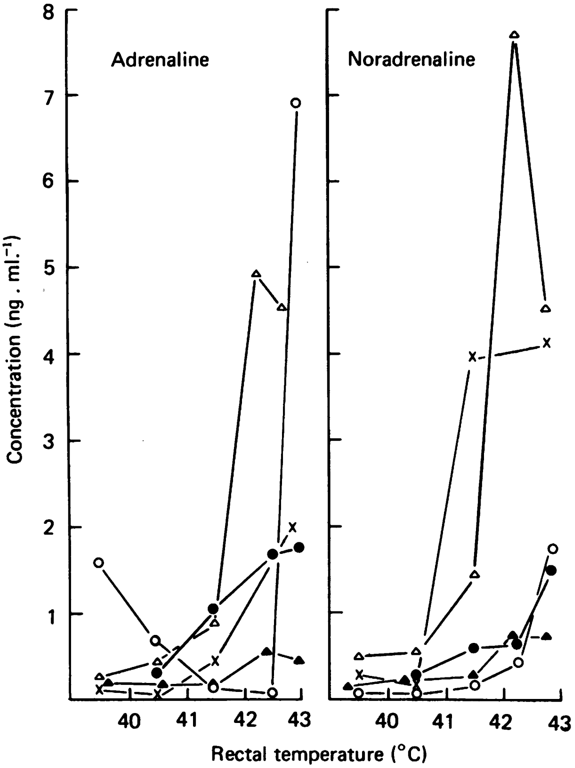

Fig. 4. Changes in plasma adrenaline (graph on left) and noradrenaline (graph on right) in five animals during 2–2·5 hr at an environmental temperature of 45 °C, with an increase in rectal temperature of from 39·5 to 43 °C. Each symbol (●, ○, ▲, △, ×) represents a different animal.

The effects of hyperthermia

Pigs were exposed to an environmental temperature of 45 °C and the rectal temperature allowed to rise to 43 °C over a period of 2–2·5 hr. During this time respiratory frequency increased from a resting level close to 20 breaths/min to over 300 breaths/min. Blood samples were taken at given rectal temperatures and the values for levels of noradrenaline and adrenaline in the five animals are presented in Fig. 4. During the onset of hyperthermia the concentrations of catecholamines remained low and in the one pig in which they had been high at the start the concentrations declined as rectal temperature increased from 39·5 to 41·5 °C. A pronounced increase in both adrenaline and noradrenaline did not occur until the body temperature was above 41·5 °C; in some pigs the increase was considerable, but in others the change in noradrenaline concentration was similar to that found in response to 2 hr at −5 °C. In one animal the levels of both hormones remained low even when the rectal temperature was 43 °C and the animal was quite noisy and active. As soon as the rectal temperature reached 43 °C, the environmental temperature was reduced and body temperature then returned to normal over the next 2 hr.

Exercise

The effects of exercise were examined in five pigs in experiments carried out in the animal-holding area at an ambient temperature of approximately 20 °C. The results are given in Table 2. The values for each pig before the beginning of the exercise were derived from the average concentration of plasma catecholamines in blood samples taken during a 40 min period at 10 min intervals while the animals were in the handling trolley in the exercise area. During the 40 min exercise the values for each pig were similarly obtained from blood samples taken at 10 min intervals. After the exercise had finished another four samples were taken over the next 40 min. Towards the end of the period of exercise the respiratory frequency increased to 50–60 breaths/min from the resting rate of 20–25 breaths/min. At the end of the exercise period the pigs usually lay down in the trolley while the sample was being taken, but although the animals seemed tired in no instance were they judged to be exhausted. The levels of both catecholamines increased during exercise, although the extent of the increase did not seem to be progressive.

TABLE 2. Catecholamine concentrations (ng/ml. plasma) during 40 min periods before, during and after exercise in five young pigs of 12–20 kg body weight. Values are means ± S.E. of means. ($n = 5$)

	Exercise		
	Before	During	After
Noradrenaline	0·26 ± 0·06	0·99 ± 0·11	0·39 ± 0·09
Adrenaline	0·10 ± 0·02	0·23 ± 0·02	0·14 ± 0·04

Origin of the increased levels of catecholamines

The extent to which the secretions of the adrenal gland contributed to the changes in noradrenaline in plasma from the jugular vein was examined during short-term exposure to cold and to exercise. In only one pig was it possible to obtain simultaneous blood samples from sites in the vena cava just caudad and just cephalad to the adrenal veins. Measurements were made in this animal when it was transferred from a thermally neutral ambient temperature at 25 °C to a cold room at 0 °C and the results are shown in Fig. 5. The very large spurt of noradrenaline to 40 ng/ml., which was accompanied by a rise in adrenaline to 10 ng/ml., must have been derived from the adrenal gland.

In five other animals simultaneous samples were taken from the jugular vein and from the inferior vena cava just cephalad to the entrance of the adrenal veins. During exposure to cold the concentration of noradrenaline tended to be higher in blood taken from near the adrenal, although the differences were mostly in the order of only

0·2 ng/ml. However, on one occasion the blood near the adrenal had a concentration of 12 ng/ml. whereas that in the jugular was only 0·2 ng/ml. and on another occasion the values were 5·1 and 2·7 ng/ml. A possible explanation for these larger differences is that the adrenal gland secreted a burst of hormone similar to that illustrated in Fig. 5. During exercise the blood taken from near the adrenal usually had a greater concentration of noradrenaline than that in the jugular, but no very large differences were found. The changes in adrenaline did not follow the same pattern as that of the noradrenaline (Fig. 6).

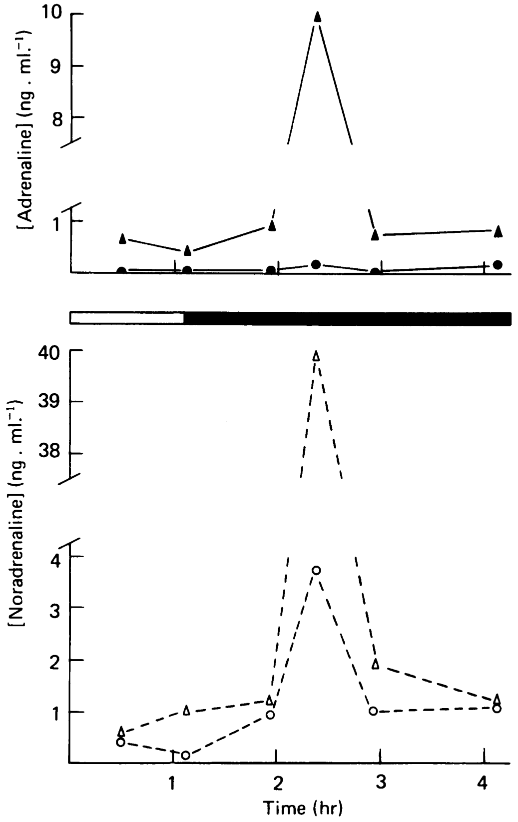

Fig. 5. Effect of a change in ambient temperature from thermal neutrality at 25 °C (open bar) to 0 °C (filled bar), in one animal, on adrenaline (filled symbols) and noradrenaline (open symbols) concentrations in plasma from the inferior vena cava; blood samples taken just caudad (●, ○) and just cephalad (▲, △) to the entrance of the adrenal veins into the inferior vena cava.

DISCUSSION

During short-term cold exposure the present study demonstrated an increased output of noradrenaline but not adrenaline into the circulation. This finding agrees with earlier studies which showed raised urinary noradrenaline levels in the pig and other species (Baldwin *et al.* 1969; Webster, Heitman, Hays & Olynyk, 1969; Gale, 1973). Work with rats kept at 4 °C also showed an increase in the turnover of noradrenaline in the heart (Landsberg & Young, 1978). Plasma catecholamines were found to increase in the dog during immersion in cold water; but whereas the rise in noradrenaline still occurred after cold adaptation by repeated immersions, the rise in adrenaline became less pronounced (Therminarias, Chirpaz, Lucas & Tanche, 1979).

It has been inferred from the lack of adrenaline output in some people during short-term exposure to cold that sympathetic vasoconstriction makes a greater contribution to the increase in circulating catecholamines than does the adrenal medulla (Wennmalm, 1973), although in other work on the rat a rise in urinary adrenaline has been demonstrated (Leduc, 1961). In the present investigation sampling from the inferior vena cava cephalad and caudad to the adrenal vein revealed a very large spurt of noradrenaline accompanied by a lesser amount of adrenaline, and in other experiments high values of noradrenaline were recorded near the adrenal vein during cold exposure. These limited observations must be interpreted with caution. First the results illustrated in Fig. 5 provide some evidence for the view that the adrenal makes a contribution to the rise in catecholamine concentrations during

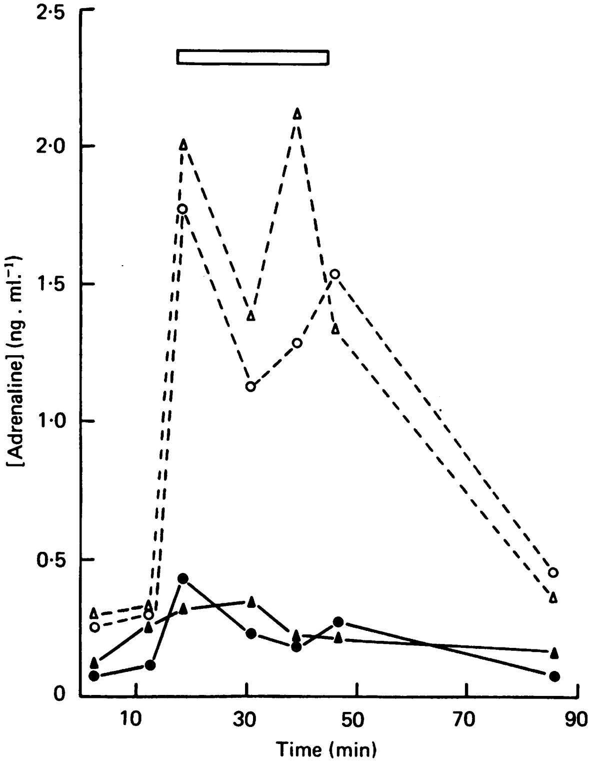

Fig. 6. Effect of exercise on the plasma concentrations of adrenaline (filled symbols) and noradrenaline (open symbols) in samples taken from the jugular vein (●, ○) and the inferior vena cava cephalad to the entrance of the adrenal veins (▲, △). Bar indicates period of exercise.

cold exposure, although the possibility that this release of hormone was related to some emotional disturbance not associated with the effect of cold can not be discounted. Secondly in those studies in which blood was taken from only one site in the inferior vena cava some of the catecholamine may have been derived from sites other than the adrenal gland.

The increase in noradrenaline concentration which is detectable in blood from the jugular vein represents the sum of residual amounts of amine which have escaped re-uptake after release not only from the adrenal medulla but also from nerve endings in several sites in the circulation. Attempts to identify which of these sites are more important during cold exposure are complicated by the association of sympathetic discharge with both cardiovascular and metabolic adjustments. Quantitative determination has demonstrated clearly that redistribution of blood occurs in sheep on exposure to cold (Hales, Bennett & Fawcett, 1976). The redistribution of blood involves both a decrease in peripheral blood flow, with a consequent increase in thermal insulation, and also an increase in blood flow to the sites of heat production. In the pig, direct measurements of blood flow in the tail have shown vasoconstriction to be maximal at ambient temperatures below 20 °C (Ingram & Legge, 1971). Thus in the present study although the possibility that the inreasing concentrations of noradrenaline seen at lower ambient temperatures were associated with peripheral vasoconstriction cannot be excluded, it seems more probable that the catecholamines were involved with an increase in thermogenesis associated with the mobilization of fuels (Young & Landsberg, 1977) and also with modifying the contractions of skeletal muscle to cause shivering and an increase in muscle tone (Bülbring, 1976; Robertshaw, 1977). The extent to which brown adipose tissue is involved in the thermogenic response to short-term cold exposure in large mammals is unclear. Although the quantity of this tissue is relatively small in large animals, its contribution may be of greater importance than was previously realized (Rothwell & Stock, 1979; Dauncey, Wooding & Ingram, 1981). Other tissues such as muscle may also make a contribution to non-shivering thermogenesis (Jansky, 1973).

During longer-term exposure to moderate cold the concentrations of catecholamines were not significantly greater than those found at thermal neutrality. A decrease in plasma catecholamines during continuous cold exposure has also been found in rats (Benedict, Fillenz & Stanford, 1977) and in dogs (Therminarias *et al.* 1979); this agrees with earlier findings for urinary catecholamines in some species (Gale, 1973). In the present study the animals continued to shiver throughout the period of cold exposure, indicating that there may have been an increase in tissue sensitivity to catecholamines and also a change in the turnover rates of catecholamines. Indeed, in dogs which had been exposed to periods of low temperature on each of 5 consecutive days, the capacity to increase oxygen consumption in response to noradrenaline was enhanced (Therminarias *et al.* 1979). Heldmaier (1974) also found that the pig responded to repeated short periods of cold exposure by decreasing the deep body temperature, in spite of the increased ability to respond to noradrenaline by increasing oxygen consumption. In man a diminution in the sympathetic response, as indicated from blood pressure and heart rate, has also been observed after repeated short exposures to severe cold (LeBlanc, Dulac, Côté & Girand, 1975).

The increase in plasma noradrenaline observed during cooling of the hypothalamus agrees with earlier work in which there was an increase in urinary noradrenaline in the pig (Baldwin *et al.* 1969), goat (Andersson, Gale, Hökfelt & Ohaga, 1963) and baboon (Gale, Jobin, Proppe, Notter & Fox, 1970). However, a more pronounced increase in plasma noradrenaline was observed when the spinal cord was cooled. This greater response to spinal cooling is paralleled by the greater increase in metabolic rate during spinal cooling than during cooling of the hypothalamus (Carlisle & Ingram, 1973). The precise significance of these differences cannot be assessed since the exact temperature of the temperature-sensitive neurones was not known, but it seems unlikely that the neurones in the cord were cooler at a thermode temperature of 20 °C than those in the hypothalamus were at a thermode temperature of 10 °C. In the present study blood was not sampled from near the adrenal vein during cooling of the spinal cord or hypothalamus. Therefore, because of the extensive uptake of catecholamines which occurs in some tissues when blood passes through the vascular beds (Sharman, 1975), the changes found in jugular blood may not have reflected precisely the responses of the adrenal medulla. A definitive statement on the relative effects of cooling the hypothalamus and spinal cord on catecholamines must therefore await studies in which adrenal venous blood is sampled.

The present finding that during exposure to a high ambient temperature plasma catecholamines did not rise until the rectal temperature was above 41 °C agrees with studies in the dog (Symbas, Jellineck, Cooper & Hanlou, 1964) and ox (Robertshaw & Whittow, 1966). The large proportion of adrenaline relative to noradrenaline suggested that the adrenal medulla probably played a major part in this response. It is unlikely that the catecholamines were released in order to play a physiologically protective role; although the injection of catecholamines causes discharge of the cutaneous glands in the pig, this species does not sweat on exposure to heat (Ingram, 1967). A more probable explanation for the rise in plasma concentrations is that they were related to the emotional disturbances involved in pronounced hyperthermia. Any thermoregulatory role for the catecholamines would in any event have been expected to operate before the deep body temperature had reached 41 °C and to have involved all the animals equally.

Measurements of catecholamine levels during moderate exercise were made to provide an assessment of the range of values observed in the pig in response to peripheral and central thermal stimuli. In man the effect of exercise in increasing the level of plasma catecholamines is well documented (Frankenhauser, 1975; Callingham & Barrand, 1979) and the changes found in the pig were of the same order of magnitude. Moderate exercise increased the noradrenaline level in the jugular vein to a similar extent as did cooling the spinal cord, or exposure to -5 °C for 2 hr, but the increase was much less than that which sometimes occurred during hyperthermia. The extent to which the rise in catecholamines during exercise was associated with cardiovascular changes as compared with an increase in metabolic rate is not known, but it was established that the adrenal medulla contributed to the increase in plasma concentrations of both hormones.

Thus during exercise and after a central or a peripheral cold stimulus when metabolism is increased, there was an increase in the circulating levels of noradrenaline, part of which was derived from the adrenal gland. These levels were probably great enough to stimulate thermogenic processes both directly and indirectly. Whether this increased output of noradrenaline was directly related to any particular thermogenic processes has still to be determined.

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