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CHANGES IN BODY TEMPERATURE OF THE UNANAESTHETIZED MONKEY PRODUCED BY SODIUM AND CALCIUM IONS PERFUSED THROUGH THE CEREBRAL VENTRICLES

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SUMMARY

1. In the unanaesthetized Rhesus monkey, solutions containing sodium, calcium, potassium or magnesium in excess of the normal concentration of extracellular fluid were perfused from a lateral to the fourth ventricle through chronically implanted cannulae.

2. Sodium (11·0–88·0 mM in excess of the physiological concentration) perfused through the ventricles, caused an immediate rise in body temperature which was accompanied by vasoconstriction, piloerection and shivering. The latency of the hyperthermia was related directly to the rate of perfusion and the concentration of sodium, whereas the magnitude of the response depended upon the concentration only. When the perfusion was terminated, shivering ceased and the temperature of the monkey returned to the base line level.

3. When calcium ions were perfused in concentrations 2·5–47·9 mM in excess of that of extracellular fluid, a fall in the temperature of the animal occurred. The magnitude of the decreases depended upon the concentration of calcium in the perfusion fluid. Vasodilatation, sedation and a reduction in withdrawal reflexes accompanied the calcium-induced hypothermia. After the perfusion ended, the temperature continued to fall until the monkey began to shiver and vasoconstriction was observed in many skin areas.

4. The perfusion through the cerebral ventricles with modified Krebs solution alone or with the Krebs solution which contained potassium or magnesium ions in concentrations five to ten times normal had virtually no effect on the temperature of the monkey.

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5. Since the temperature of the monkey was unchanged as long as the physiological ratio of sodium to calcium in the perfusion fluid remained constant, we conclude that the balance between these two essential cations within the brain stem could determine the neural mechanism whereby the set-point for body temperature of the primate is established.

INTRODUCTION

A solution containing sodium ions but no calcium ions causes a rise in temperature when it is perfused from the lateral ventricle to the cisterna magna of the unanaesthetized cat (Feldberg, Myers & Veale, 1970). From this observation, it was suggested that the level of calcium or the permeability of the neuronal membranes in the hypothalamus as it is influenced by calcium may be involved in the set-point for body temperature.

Recently, it was proposed that the ratio between sodium and calcium ions may be the mechanism whereby the set-point is established, and that this mechanism is localized in the posterior area of the hypothalamus (Myers & Veale, 1970). This concept was based on experiments in which a physiological solution containing an excess of either sodium or calcium was perfused at isolated sites within the brain stem of the unanaesthetized cat. The selective elevation in the concentration of sodium only within the posterior hypothalamus resulted in shivering and a rise in temperature, whilst at the same site an increase in the calcium concentration produced an immediate vasodilatation and a fall in the cat's body temperature (Myers & Veale, 1971).

The present experiments were carried out to determine whether, in a primate, a relationship exists between the concentration of certain cations in the brain stem and body temperature. In the unanaesthetized Rhesus monkey, the ratio of the cations was altered by perfusing sodium or calcium ions, in excess of their normal physiological concentrations, from a lateral to the fourth cerebral ventricle. The results suggest that the relative concentration of ions within the brain of this species, as in the cat, may also play an important role in establishing the temperature set-point.

METHODS

Seven male Rhesus monkeys (*Macaca mulatta*) weighing from 5·4 to 6·8 kg were acclimated to special primate restraining chairs for 1 week before surgery. The animals were kept at a room temperature of 23–25° C, and monkey biscuits and water were always freely available.

Surgical procedures

Each monkey was anaesthetized with pentobarbitone sodium (35 mg/kg) injected into the saphenous vein. Two lateral and one fourth ventricle guide cannulae were

implanted aseptically following surgical techniques described previously (Myers, 1967). Each guide was cut from a length of 17 gauge stainless-steel tubing and attached to a modified hub of a Collison cannula (Myers, Yaksh, Hall & Veale, 1971). The lengths of the lateral and fourth ventricle guide tubes were cut so that the tips would be placed at depths of 10 and 35 mm below the dura and immediately above the ventricular spaces, respectively. After two craniotomy holes 2·6 mm in diam. had been drilled bilaterally, 7 mm off mid line and 11 mm anterior to the interaural line, they were tapped and the cannulae were screwed into the skull. The fourth ventricle guide cannula was implanted stereotaxically through a craniotomy hole drilled on mid line at a point 7 mm posterior to the interaural line. A thermistor bead was also implanted caudal to the fourth ventricle cannula, and positioned against the posterior portion of the falx cerebri at 5–8 mm below the dura. Two anchor screws were inserted into the skull just anterior and posterior to the lateral guide cannulae and a thin layer of cranioplast cement was then packed around the cannula array and thermistor connector. During the post-operative recovery period of 10 days, penicillin was administered daily.

Procedure for perfusion

Before an experiment was begun, a thermistor probe (401, Yellow Springs Instrument Co., Yellow Springs, Ohio) was inserted into the colon to a depth of 6–8 cm and affixed by adhesive tape to the base of the tail. Both brain and colonic temperatures were monitored continuously. In many experiments, the ear temperature of each monkey was also measured using a disk probe (427, Yellow Springs Instrument Co.) attached to the pinna with a small amount of liquid latex cement.

To establish contact with the ventricles, inflow and outflow cannulae cut from stainless-steel tubing were lowered through each guide tube to a level just beyond the tip, until outflow of the c.s.f. was observed.

In the experiments, solutions were perfused at rates varying from 50 to 200 μl./min for periods of 30–40 min. A minimum of 24 hr was allowed to elapse between experiments. The experimental sequence in which the different ions were tested was random. During a perfusion, the rate of outflow was monitored constantly. A reduction in the outflow, the appearance of discoloration or any other signs of occlusion was sufficient cause to terminate the experiment immediately.

The fluid used for perfusion was either 0·9% (w/v) NaCl solution or a modified Krebs solution containing Na^+ 143·0 mM; K^+ 5·9 mM; Ca^{2+} 2·5 mM; Mg^{2+} 1·2 mM; Cl^- 127·7 mM; $H_2PO_4^-$ 1·2 mM; SO_4^- 1·2 mM; HCO_3^- 25·0 mM; and glucose 5·6 mM. The latter solution is similar in composition to the extracellular fluid of the primate (Woodbury, 1965; Davson, 1967; Turbyfill, Cramer, Dewes & Huguley, 1970). To examine the effect of increasing the concentration of various ions selectively, Na^+, Ca^{2+}, Mg^{2+} or K^+ was added in the form of a chloride salt to the perfusion fluid in a sufficient quantity to bring the total amount to two, five, ten or twenty times that contained in the modified Krebs solution. An 0·9% or 1·3% NaCl solution was considered, therefore, to be 11·0 and 88·0, respectively, in excess of the normal sodium value in modified Krebs solution. In addition, the *p*-toluene-sulphonate salt of sodium ($C_7H_7SO_3Na.H_2O$) was used to elevate the concentration of sodium without altering the chloride concentration, according to the procedure described by Bülbring & Kuriyama (1963).

The perfusion solution was prepared immediately before an experiment in glass-distilled ion-exchange water and then passed through a sterile 0·45 μ Millipore filter (Millipore Filter Corp., Bedford, Mass.). Glassware and infusion syringes were rendered pyrogen-free by heating at 140° C for 45 min. Polyethylene tubing and

cannulae were stored in 70% ethanol and were repeatedly flushed with pyrogen-free saline immediately before the perfusion.

When a series of experiments was completed, the areas within the ventricular system reached by the perfusate were verified by one of two methods described previously (Myers *et al.* 1971). First, Angio-Conray (Malinckrodt, St Louis, Missouri), a radio-opaque dye, was perfused at the rate of 100 μl./min and X-radiographs were taken sequentially in the sagittal plane. Secondly, 0·1% bromophenol blue dye was perfused at a rate of 50–100 μl./min for approximately 5 min. Then, the animal was killed by an overdose of pentobarbitone sodium; the brain was perfused with a 10% formol-saline solution, and, after the calvarium was removed, the ventricles were carefully opened in order to see the tissue that was stained by the dye.

RESULTS

An alteration in the ratio of sodium to calcium in the fluid perfused through the cerebral ventricles caused a change in the body temperature of the unanaesthetized monkey. Sodium produced hyperthermia, whereas calcium evoked hypothermia, when either of these ions was perfused through the ventricular system in excess of that amount found in the modified Krebs solution. Both of the temperature responses were related to the relative concentration of one ion to the other.

The latency of onset and the rate of the temperature rise depended upon the rate of perfusion as well as the concentration of the sodium, whether elevated in the perfusate in the form of sodium chloride or sodium *p*-toluene-sulphonate. The magnitude of the temperature increase was determined generally by the concentration of sodium during the interval of perfusion. Fig. 1 illustrates the hyperthermic response to sodium, in four concentrations, ranging from 11·0 to 88·0 mM in excess of that in the modified Krebs solution. In one monkey, 34·0 and 68·0 mM excess sodium was perfused at 50 μl./min (*top*) and 100 μl./min (*middle*). Each tracing was obtained at an interval of 48–96 hr. In another monkey, solutions of sodium chloride, perfused at a rate of 100 μl./min, which were 11·0 or 88·0 mM in excess of that in the modified Krebs solution, produced a marked hyperthermia. Fig. 1 (*bottom*) illustrates the temperature increase of 0·7° C with the lower concentration and 1·5° C with the higher.

Within 3–6 min after the perfusion with the excess sodium began, piloerection, vigorous shivering in the pectoral, trapezius, and other muscle groups occurred and vasoconstriction usually preceded the rise in temperature. The intensity of these responses again depended upon the concentration of sodium in the perfusate as well as the rate of its perfusion. As soon as the perfusion was terminated, shivering diminished markedly, and within 30 min all signs of muscle fasciculations were abolished. In one experiment, the monkey ceased shivering and became vasodilatated toward the end of the sodium perfusion (Fig. 1, *middle*, continuous line)

and its temperature declined. During the perfusions with excess sodium, the monkey usually remained undisturbed although the animal often drew its limbs tightly against its body and appeared to be huddling.

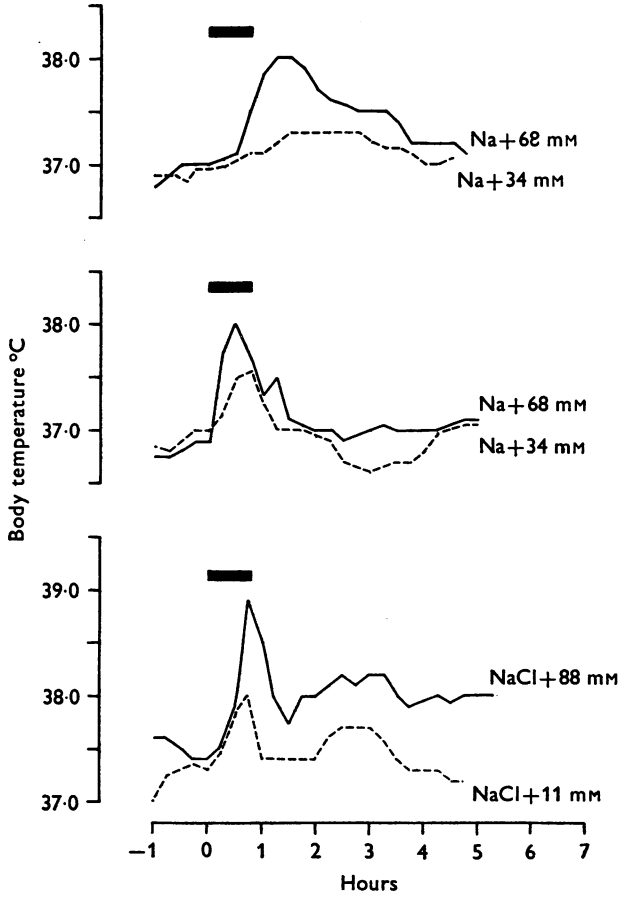

Fig. 1. Changes in body temperature in response to the 40 min perfusion (▬) beginning at zero hour from the lateral to the fourth ventricle of a Krebs solution containing 34·0 or 68·0 mM excess sodium perfused at 50 μl./min (*top*); 34·0 or 68·0 mM excess sodium at 100 μl./min (*middle*), and 11·0 or 88·0 mM excess sodium perfused at 100 μl./min (*bottom*). The *top* and *middle* records were obtained from one monkey, the *bottom* record from another monkey.

Calcium in excess of that contained in the modified Krebs solution had an effect opposite to that of sodium ions when perfused through the cerebral ventricles. Within 2–6 min after the perfusion started, the monkey's temperature fell sharply at a rate and to a level which was

related directly to the concentration of calcium ions in the perfusion fluid. Fig. 2 (*top*) illustrates the effect of calcium ions perfused at 100 μl./min in three concentrations, at 48 hr intervals in the same monkey. Hypothermia was elicited when calcium was 10·1 or 22·7 mM in excess of that amount in the modified Krebs solution, and even a slight fall was evident

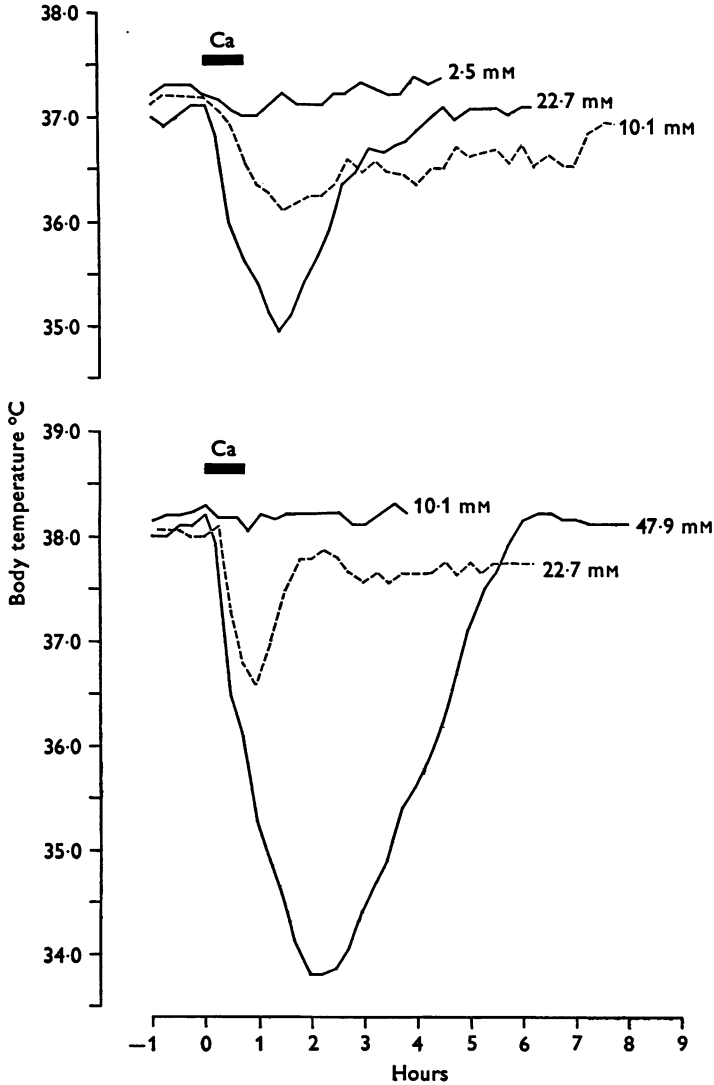

Fig. 2. Temperature records of two unanaesthetized monkeys in response to the 40 min perfusion (▬) from the lateral to the fourth ventricle at 100 μl./min of a Krebs solution containing 2·5, 10·1 or 22·7 mM excess calcium (*top*); and 10·1, 22·7 or 47·9 mM calcium (*bottom*).

during perfusion with calcium 2·5 mM in excess. However, in three experiments with a second monkey, 10·1 mM excess calcium was without effect, whereas 22·7 and 47·9 mM excess calcium produced a long-lasting hypothermic response which depended upon the concentration of calcium. This is illustrated in Fig. 2 (*bottom*).

The intensity of the hypothermia varied between monkeys even though the same concentration of calcium was used. When the perfusate contained 22·7 mM excess calcium, the temperature of one monkey fell 2·2° C (Fig. 2, *top*), but declined 1·4° C in the second monkey (Fig. 2, *bottom*). Unlike the perfusion-dependent nature of the hyperthermic response to sodium, the temperature often continued to decline even after the perfusion with calcium had been terminated. As shown in Fig. 2 (*bottom*), excess calcium in a concentration of 47·9 mM caused a fall in temperature of 2·0° C during the interval of perfusion and an additional decline of 2·0° C during the following 45 min. In this case, the temperature of the animal did not return to the base line level until over 4 hr had elapsed.

Within 3–5 min after the start of the perfusion of calcium, the ear vessels became dilatated, the animal became flushed and the surfaces of the skin including the footpads and palms became warm to the touch. In several monkeys, the respiratory rate also increased, but this was not a consistent response to excess calcium ions. When calcium in a low concentration was perfused, the monkey remained alert, but at the higher concentrations calcium produced a general diminution of responses which was characterized by the suppression of the withdrawal reflex to nociceptive stimuli as well as an impairment of the orienting responses to auditory and visual stimuli. Within an hour after the perfusion had ended, vasoconstriction occurred, and shortly thereafter the animal began to shiver vigorously. It is interesting that in these experiments, calcium did not ordinarily cause an 'over-shoot' in body temperature, which is often observed following the hypothermia induced by an anaesthetic (Feldberg & Myers, 1965). As the temperature of the animal approached the base line, shivering decreased and abated altogether when the temperature was within 0·3–0·4° C of the preperfusion level.

The perfusion of the cerebral ventricles with control solutions or with solutions containing an excess of two other essential cations had virtually no effect on the body temperature of the monkey. A 40-min perfusion with modified Krebs solution, or with magnesium or potassium five to ten times their normal concentration in the modified Krebs solution, failed to alter the temperature of the animal (Fig. 3). The only observable effect following the perfusion of 10·6 mM excess magnesium and 52·8 mM excess potassium ions was a slight suppression of activity produced by magnesium in one monkey. From these results, it is clear that the perfusion did not affect

body temperature in a non-specific manner, nor was a pyrogenic factor present in the perfusion fluid.

By alternate perfusions of sodium and calcium, it was possible to alter the animal's temperature above and below the set-point level within a short interval. Fig. 4 illustrates such an experiment in which sodium per-

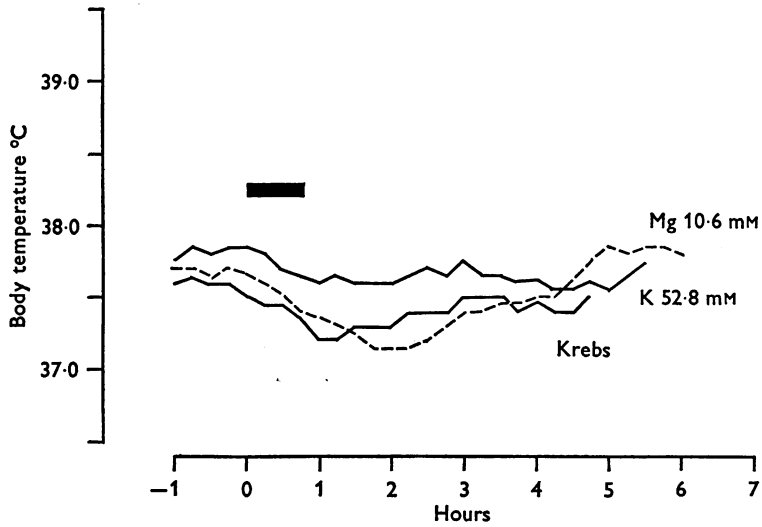

Fig. 3. Temperature records from an unanaesthetized monkey in response to the 40 min perfusion (▬) from the lateral to the fourth ventricle at 100 μl./min of either a normal Krebs solution containing 10·6 mM excess magnesium or 52·8 mM excess potassium.

fused through the cerebral ventricles in a concentration of 34·0 mM in excess of the Krebs solution caused a rise of nearly 1·0° C in colonic temperature and 0·7° C in brain temperature. Four hours later, the perfusion of a solution containing 10·1 mM excess calcium evoked a fall in both colonic and brain temperature of approximately 1·5° C. Although the temperature as measured from the colon was approximately 1·0° C higher than that of the brain, as Fig. 4 shows, the two records almost parallel one another. On the other hand, the pinna temperature was independent of both colonic and brain temperature. During the perfusion with 34·0 mM excess sodium, the temperature of the ear, which had started to rise, fell again and remained low. As soon as calcium, in a concentration of 10·4 mM excess was perfused, the temperature of the pinna rose abruptly, and returned to the base line level after the calcium perfusion had ended. These changes in the surface temperature of the pinna reflected the vasodilatation or vasoconstriction of the ears in response to the perfusion with solutions containing an excess in sodium or calcium.

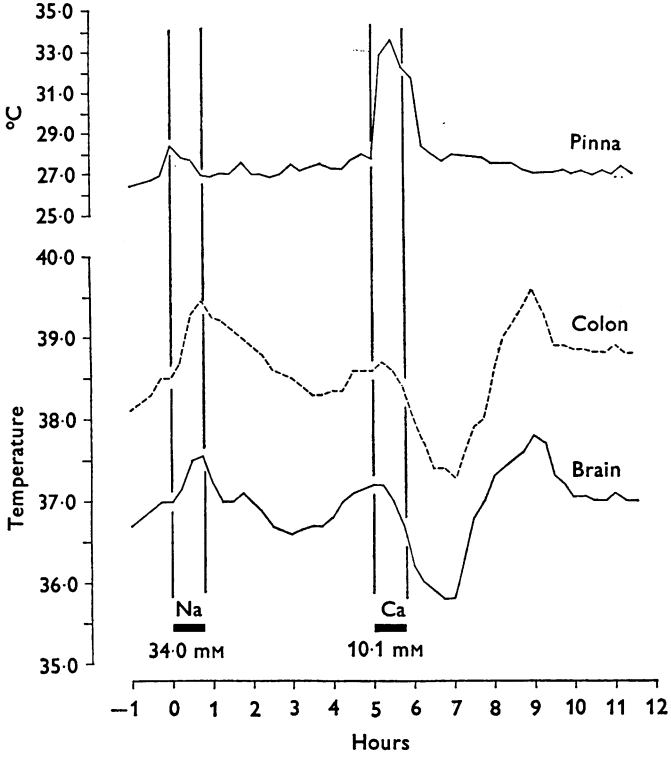

Fig. 4. Temperature records obtained from the pinna (*top*), colon (*middle*) and brain (*bottom*) of an unanaesthetized monkey in response to the perfusion (▬) from the lateral to the fourth ventricle at 100 μl/min of a Krebs solution containing 34·0 mM excess sodium followed 4 hr later by the perfusion (▬) at the same rate of a Krebs solution containing 10·1 mM excess calcium.

DISCUSSION

Recently, it was postulated that the constancy in the ratio between sodium and calcium ions in the caudal region of the hypothalamus may be the mechanism whereby the set-point for body temperature is established (Myers & Veale, 1970). This hypothesis was based on experiments with the unanaesthetized cat in which the balance in these essential cations was shifted selectively within the posterior hypothalamus and other isolated areas of the brain-stem.

In the present experiments, an alteration in the ratio of sodium to calcium ions within the cerebral ventricles of the primate also evoked a profound change in temperature. In this case, sodium caused hyperthermia whereas calcium produced hypothermia. These results are in agreement

with those obtained when the ventricular spaces of the unanaesthetized cat or rabbit were perfused with a solution in which the normal physiological concentrations of these cations had been changed (Feldberg *et al.* 1970; Feldberg & Saxena, 1970).

An important aspect of these results was the fact that the magnitude of hyper- or hypothermia produced by sodium and calcium respectively was dependent upon their concentration in the perfusion fluid. Although the reasons for this are not clear, there are several explanations which may account for this finding. First, as the concentration of a given ion in the perfusate was increased, a larger population of neurones could have been affected as the concentration gradient extended from the ependymal wall into diencephalic structures. Secondly, the firing pattern of the individual cell could have been affected selectively by the increase in the relative concentration of the calcium or sodium. The differences in the time required for the animal's temperature to return to base line after the intraventricular perfusion of calcium and sodium could reflect a difference in the rate at which the two ions were inactivated locally by binding, diffusion or by another process.

At present, the mechanism by which the two cations act to affect the thermoregulatory system is not understood. It is known, however, that an increase in the extracellular calcium results in a reduction in excitability of the nerve (Brink, Bronk & Larrabee, 1946). Moreover, excess calcium also has been shown to lower the permeability of the cell membrane to an ion such as sodium or potassium (Shanes, 1958). Similarly, the magnitude of the depolarization of the cell membrane is related to a change in the extracellular concentration of sodium, as predicted by the Nernst equation (Hodgkin, 1964). From recent investigations it is apparent that certain cells in the brain are particularly sensitive to a change in the extracellular concentration of sodium (Andersson & Westbye, 1970; Mouw & Vander, 1970). It is possible that one of the cations could liberate a neurohumoral transmitter which would activate the heat loss pathway, whereas the other could release a second transmitter which subserves the heat maintenance pathway. In this connexion, it has been shown that an elevation of extracellular calcium within the hypothalamus and other diencephalic areas of the cat causes an increase in the rate of 5-hydroxytryptamine (5-HT) release to a level several times that of the resting level (Myers, Veale & Beleslin, 1970). Further, the presence of calcium ions may play an important role in the metabolic system involving the mobilization of extracellular cyclic AMP (Duncan, 1967).

It is particularly important that neither potassium nor magnesium had any observable effect on either the body temperature of the monkey or its general level of activity, when these ions were perfused through the cerebral

ventricles. Although magnesium and calcium are both divalent cations, only calcium in the concentrations used caused a hypothermia. This finding, together with the lack of effect of potassium, would tend not to support the view that sodium and calcium are acting in a non-specific way to affect the discharge properties of those neurones mediating divergent temperature responses.

It is interesting that the differential effects on body temperature of these ions is the same in the cat, rabbit and monkey. This continuity across species is not in accord with the results obtained when monoamines are injected either into the cerebral ventricles or directly into the anterior hypothalamus. That is, 5-HT and noradrenaline given by these routes in the cat and monkey produce hyper- and hypothermia, respectively, but these amines evoke responses opposite to those in the rabbit (Cooper, Cranston & Honour, 1965; Feldberg & Myers, 1964, 1965; Myers & Yaksh, 1969). From an evolutionary standpoint, therefore, one would expect that the maintenance of a constant ionic ratio is vital to the function of those structures concerned with the set-point for body temperature. For this reason, additional experiments are essential in which the regional effects of sodium and calcium on body temperature are localized in the primate in the same way as has been done in the cat (Myers & Veale, 1971). If a generalization can be made between species that is based on the experiments with the amines, then one would expect that the posterior hypothalamus of the monkey would be the area sensitive to a disequilibrium in the ratio of calcium to sodium ions.

In order to demonstrate that the set-point for temperature is a function of the balance between sodium and calcium levels in the hypothalamus, a transient alteration in the actual concentration of ions in the hypothalamus must be verified at the cellular level. Thus, when the set-point changes, as is proposed to occur with fever, the ionic concentration should also shift accordingly. Finally, if the set-point is indeed altered by a change in local ionic constituents, then it should be possible to demonstrate that the monkey would thermoregulate around the new set-point.

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