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INTRACEREBROVENTRICULAR TAURINE IN RABBITS: EFFECTS ON NORMAL BODY TEMPERATURE, ENDOTOXIN FEVER AND HYPERTHERMIA PRODUCED BY PGE_1 AND AMPHETAMINE

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SUMMARY

1. Intracerebroventricular (I.C.V.) injections of taurine into rabbits resting at an ambient temperature (T_a) of 10° or 23° C caused hypothermia but at 30° C ambient temperature, rectal temperature was unchanged.

2. An I.C.V. bolus of 0·5 mg taurine immediately followed by a slow infusion of taurine (0·01–0·2 mg/min) into rabbits at 23° C ambient temperature caused sedation and peripheral vasodilation and blocked the febrile response to *Salmonella typhosa* endotoxin (1 μg/kg I.V.). Sustained fevers, characteristic of fevers caused by central administration of pyrogens, developed after taurine infusions were stopped. Control infusions of taurine at the same rates in the same rabbits when they were afebrile had little effect on rectal temperature.

3. An I.C.V. injection of 0·5 mg taurine reduced the hyperthermia caused by prostaglandin E_1 (PGE_1; 2 μg) given I.C.V. A dose of 5·0 mg not only blocked PGE_1 hyperthermia but also caused marked hypothermia.

4. Bilateral injections of taurine into the preoptic/anterior hypothalamic region, at sites where injections of *Salmonella typhosa* endotoxin caused long-lasting fevers, had no effect on rectal temperature. Similar injections into the reticular substance of the medulla oblongata, in the region believed to be concerned with a secondary temperature control function, were also without effect on body temperature.

5. Taurine (0·5 and 5·0 mg, I.C.V.) had no consistent effect on hyperthermia induced by amphetamine (2 mg/kg, I.V.).

6. We conclude that the hypothermic effect of taurine is not due to an action on the central neurone pool or pools concerned with the integrative control of thermoregulatory effectors. This amino acid appears to inhibit neuronal activity in efferent pathways which control peripheral

vasomotor tone and heat production and to depress the level of arousal. Taurine delays the onset and extends the duration of endotoxin-induced fever, perhaps by two separate actions: by inhibiting activity in central thermoregulatory pathways and by promoting accumulation of endogenous pyrogen in the brain.

INTRODUCTION

Taurine (2-aminoethanesulphonic acid), a sulphur-containing amino acid, is widely distributed in the body and highly concentrated in skeletal and heart muscle, retina and brain. The role of taurine in the brain is uncertain although it may act as a neurotransmitter (Haas & Hösli, 1973) or neuromodulator (Kaczmarek & Davison, 1972). Like γ-aminobutyric acid and glycine, taurine suppresses spontaneous neuronal firing (Curtis & Watkins, 1960) and evoked field potentials (Krnjević & Phillis, 1976). Taurine also suppresses induced seizures (van Gelder, 1972) and causes marked reductions of general activity (Sugihara, Nagasawa & Okabe, 1936).

One effect of centrally administered taurine is hypothermia (Hruska, Thut, Huxtable & Bressler, 1976; Sgaragli & Pavàn, 1972), but the mechanism by which this occurs has not been explained. Because taurine is taken up by the hypothalamus, Hruska *et al.* (1976) suggested that the hypothermia is caused by an increase in the extracellular level of taurine in this part of the brain. Sgaragli & Pavàn (1972) proposed that taurine and similar amino acids modify the function of neurones involved in thermoregulation, although they did not rule out the possibility that hypothermia was secondary to effects on respiration and blood circulation. Thus, taurine may act on central control mechanisms, or on pathways to thermoregulatory effectors.

The purpose of the present experiments was to obtain a better understanding of the possible mechanism or mechanisms by which centrally administered taurine influences body temperature. The effects of this amino acid on the elevated body temperatures caused by intravenous (I.V.) injections of an endotoxin and of amphetamine and by intracerebroventricular (I.C.V.) injections of prostaglandin E_1 (PGE_1), were determined. To learn whether taurine given I.C.V. acts in a general way on the central regulation of body temperature, the effects of taurine were measured at three ambient temperatures. To ascertain whether centrally administered taurine produces hypothermia by acting on hypothalamic and medullary regions specifically concerned with temperature control (Lipton, 1973), injections of taurine were made directly into the preoptic/anterior hypothalamic region and the medulla oblongata.

METHODS

Animals. Twenty-three male albino New Zealand rabbits weighing 2–4 kg were used. The animals were individually caged in a 21–23° C ambient temperature. Food and water were available *ad libitum*. Lights were on 12 hr and off 12 hr per day and all experiments were run during the light phase in an environmental chamber controlled at 23° C (± 0·5° C).

Surgical Procedures. The rabbits were anaesthetized with ketamine hydrochloride (Vetalar, Parke-Davis; 20 mg/kg, intramuscular) and pentobarbitone sodium (Nembutal, Abbott Laboratories; 20 mg/kg, I.V.) and placed in a Kopf rabbit head holder (David Kopf Instruments, Tujunga, California) modified according to procedures described elsewhere (Lipton & Romans, 1976). An injection cannula (no. 201, David Kopf Instruments) was implanted into a lateral ventricle using co-ordinates (1·0 mm anterior to bregma, 2–3 mm lateral, vertical until cerebrospinal fluid rose in the cannula) derived from the stereotaxic atlases of Sawyer, Everett & Green (1954) and Fifková & Maršala (1967). Dental acrylic was used to secure the cannula to stainless steel screws driven into the calvarium. In other animals bilateral guide cannulae constructed of 23 S.W.G. stainless steel tubing and fitted with obturators of corresponding length were implanted in the preoptic/anterior hypothalamic region (co-ordinates: 3·0 mm anterior, ± 1·0 mm lateral, 11·5 mm below brain surface) and the medulla oblongata (co-ordinates: 14·0 mm posterior ± 1·0 mm lateral, 16·0 mm below brain surface) using similar techniques. Benzathine penicillin G (Bicillin L-A, Wyeth Laboratories) was given post-operatively (100,000 u., intramuscularly). Locations of the injection sites in the preoptic/anterior hypothalamic region and in the medulla were determined in histological studies of brain tissue using techniques described earlier (Lipton, Dwyer & Fossler, 1974).

Materials and injection techniques. Taurine solutions were made up daily in non-pyrogenic isotonic saline (Abbott Laboratories). All single I.C.V. injections of taurine were made in a constant volume of 50 μl. followed by either a 20 μl. saline flush or a slow infusion of taurine. Fever was produced by injecting *Salmonella typhosa* endotoxin (1 μg/kg; Difco Laboratories) dissolved in 0·1 ml. saline into a marginal ear vein. Bilateral preoptic/anterior hypothalamic and medullary injections of taurine or endotoxin were made by inserting an injection cannula through each chronic guide cannula to a point 0·5 mm below the guide cannula tip. Injections (1 μl.) were made over 30 sec with a microlitre syringe and the injection cannula was left in place for an additional 30 sec. Ethanol in which PGE_1 was stored was evaporated by a stream of nitrogen and the remaining solid was re-dissolved in saline just before injection into the lateral ventricle. D-Amphetamine sulphate (Sigma Chemical Co.) dissolved in saline (40 mg/ml.) was stored at 4° C. Precautions taken to reduce the probability of contamination with extraneous pyrogens included baking glassware and utensils used in making up solutions for at least 4 hr at 200° C, sterilizing microlitre syringes, obturators and injection cannulae at 150° C immediately before use and using only commercial non-pyrogenic disposable syringes for I.C.V. and I.V. injections. Polyethylene injection tubing was stored in 70% ethanol and flushed with fresh alcohol, acetone and air immediately before using.

Procedures. Conscious rabbits were individually restrained in conventional rabbit holders and a thermistor probe was inserted about 10 cm into the rectum and taped to the tail. In some experiments the temperature of the ear was continuously recorded with a thermistor probe as an indication of peripheral vasomotor tone. Temperature recordings were made using either an automatic temperature recording system (Digitec, United Systems Corp.) or a polygraph (Grass Instruments). No

treatments were given until 30–60 min after the rectal probe was put in place. Although it appears that tolerance to repeated I.C.V. injections of taurine does not occur (Fig. 2), individual injection and infusion experiments were always separated by at least 3 days. Experiments in which bacterial endotoxin was given were separated by at least 14 days.

RESULTS

Effects of ambient temperature and repetition on the responses to I.C.V. injections of taurine

As in previous experiments with I.C.V. injections in the mouse (Hruska *et al.* 1976) and rat (Sgaragli & Pavàn, 1972), taurine caused hypothermia

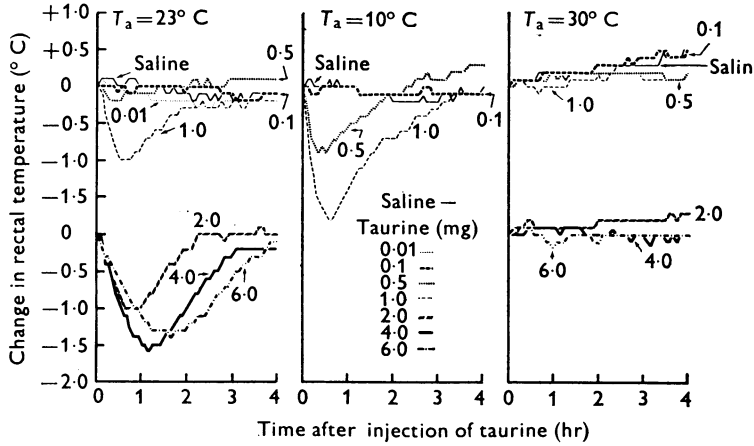

Fig. 1. Effect on rectal temperature of taurine injected into a lateral cerebral ventricle of rabbits exposed to neutral, cold and hot ambient temperatures (T_a). Each line represents the mean temperature response of six animals. Hypothermia developed after doses of 1·0 mg and greater in the 23° C environment and after 0·5 and 1·0 mg doses in the cold environment, but no changes were observed after taurine injections in the 30° C environment.

in a 23° C environment (Fig. 1). Doses (1–6 mg) produced rapidly developing dose-related decreases in body temperature while doses of 0·5 mg or less did not alter the rectal temperature (Tr_r). The falls in rectal temperature were generally associated with sedation and vasodilatation. In the cold environment, 0·5 mg taurine, a dose that did not alter rectal temperature in the 23° C environment, caused a 1·0° C decrease. A 1·0 mg dose caused rectal temperature to fall 1·8° C in the cold compared with 1·0 °C in the neutral environment. In the hot environment none of the doses had a large or consistent effect on rectal temperature.

Rectal temperature of three rabbits in a 23° C environment was

recorded after daily I.C.V. injections of a dose of taurine (2 mg) shown in the experiments above to reduce body temperature about 1·0° C. These injections consistently lowered rectal temperature 0·8–1·1° C in tests made over periods up to 5 days (Fig. 2), indicating that no marked tolerance to centrally administered taurine developed.

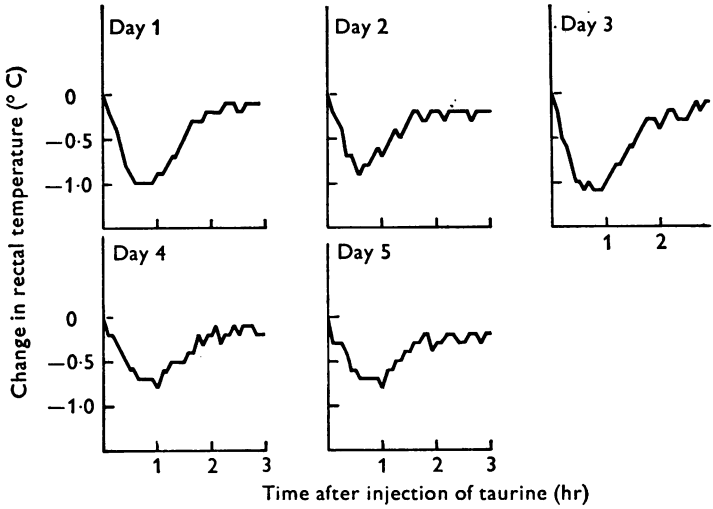

Fig. 2. Hypothermic responses produced in one rabbit by 2 mg taurine given I.C.V. each day for 5 days.

Effects of I.C.V. infusion of taurine on fever

In forty-six experiments on eleven rabbits there was: (i) an I.V. injection of bacterial endotoxin; (ii) an I.V. endotoxin injection followed by an I.C.V. infusion of taurine; or (iii) an I.C.V. infusion of taurine alone. Endotoxin (1 μg/kg) alone caused a biphasic fever with an average maximum increase of 1·4° C (range = 0·7–2·2° C) which occurred 2·8 hr (range = 1·1–4·0 hr) after injection. The average duration of fever measured from the time of injection until the rectal temperature had returned to the pre-injection level was 6·0 hr (range = 4·4–7·4 hr). By varying the rate of I.C.V. infusion of taurine after a 0·5 mg initial bolus, it was possible to arrest the febrile response, return the rectal temperature to its pre-pyrogen level and keep it there (Fig. 3). The arrest of the febrile response was preceded by sedation and vasodilatation in the ears (Fig. 4). Duration of taurine infusion was 0·25–5·2 hr, which was within the period of a normal febrile response. When infusion was stopped, rectal temperature rose rapidly an average 1·6° C (range = 0·8–2·7) and did not return to base line at the time after the endotoxin injection when

defervescence would normally occur. On the contrary, rectal temperature remained elevated 8·75–17·5 hr after infusions were discontinued in those experiments in which the temperature was measured continuously. In other experiments in which recordings were stopped after 4·75–12·2 hr, the final recorded rectal temperature was an average 1·1° C above base line. Administration of taurine using the same priming dose, infusion rates and times used to block fever in the same rabbits when they were afebrile caused no marked reductions in the rectal temperature and no fevers when infusions were stopped. Rectal temperature rose slightly (mean = 0·3; range = 0·2–0·7° C) over 4·5–9·0 hr after infusions were discontinued.

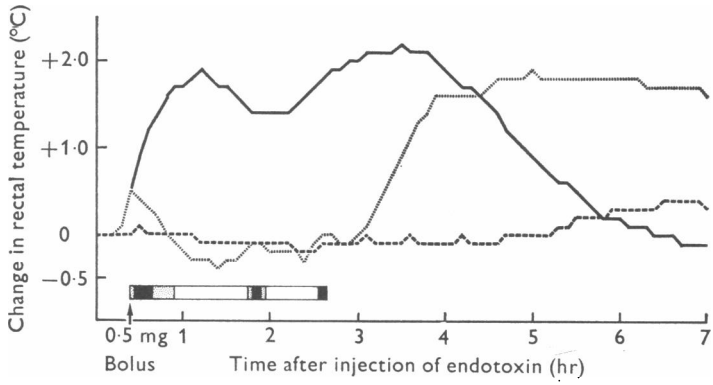

Fig. 3. Taurine infused into a lateral cerebral ventricle blocked the characteristic febrile response to peripheral endotoxin. Examples from a single rabbit showing: normal febrile response to I.V. *Salmonella typhosa* endotoxin (——), blockade of the febrile response by a bolus and controlled infusion of taurine in another experiment (. . . . . .) and the lack of effect of taurine control injections and infusions made in the same animal when it was afebrile (- - - - - -). Rate of infusion of taurine: 0, □; 0·01 mg min, ▦; 0·1 mg/min, ■.

Effects of taurine injected into the preoptic/anterior hypothalamus and medulla oblongata

Taurine (0·1–1·0 mg) injected bilaterally into the preoptic/anterior hypothalamic region at sites where injections of *Salmonella typhosa* endotoxin caused 1·5–2·0° C fevers with durations of up to 16 hr had no effects on rectal temperature (Fig. 5) in two rabbits. Similar injections of taurine into the region of the nucleus reticulo gigantocellularis at the level of the nucleus of cranial nerve VI and VII in the medulla oblongata were also ineffective in altering the rectal temperature in two animals.

Effect of taurine on hypothermia induced by PGE_1

Forty experiments were done on nine rabbits. An I.C.V. injection of PGE_1 (2 μg) caused increases in rectal temperature of 0·4–1·2° C when no taurine was administered (Fig. 6). A further I.C.V. injection of 0·5 mg taurine, given after PGE_1-induced rises in temperature had begun,

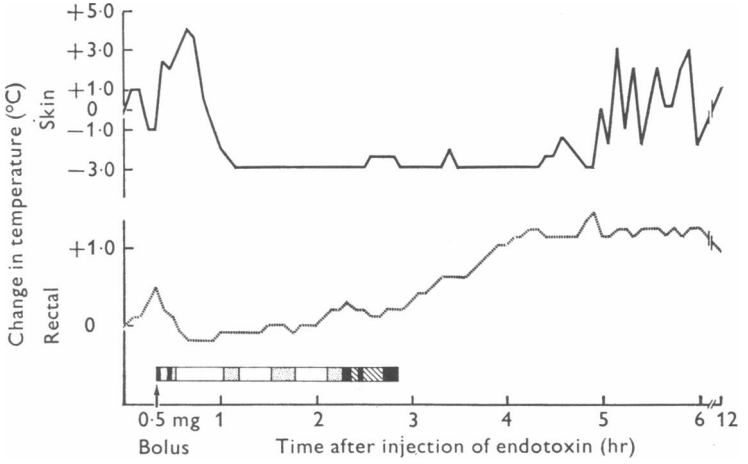

Fig. 4. Blockade of the febrile response to endotoxin by infusion of taurine into the cerebral ventricles was associated with marked peripheral vasodilatation indicated by increased temperature of the ears (skin, upper graph) and sedation. As in this and the previous example, long-lasting febrile response developed when taurine infusions used to block fever were stopped. Rate of infusion of taurine: 0, □; 0·01 mg/min, ▦; 0·1 mg/min, ■; and 0·2 mg/min, ▧.

reduced peak temperature an average of 0·4° C. An I.C.V. injection of 5·0 mg taurine not only prevented the hyperthermic response to prostaglandin but also lowered rectal temperature to 0·3–1·2° C below the base line. In five rabbits, the injection of 0·4 mg taurine and the subsequent slow infusion of taurine after I.C.V. injection of PGE_1 caused a reduction of hyperthermia that could be maintained by altering the rate of infusion of taurine. However, the complete suppression of the hyperthermic response to PGE_1 was possible only with infusion rates of taurine that caused marked hypothermia when given alone.

Effects of taurine on amphetamine-induced hyperthermia

Amphetamine given I.V. (2 mg/kg) to five rabbits caused hyperthermias with peaks of 0·6–2·1° C. Central administration of taurine during the rising phase of amphetamine-induced hyperthermia did not consistently

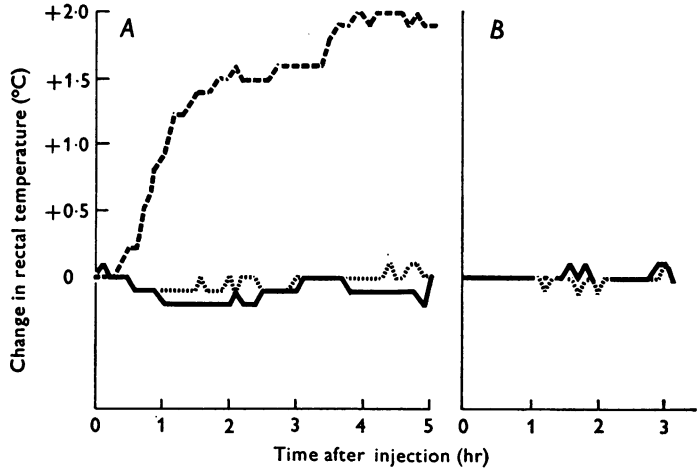

Fig. 5. Taurine did not affect rectal temperature when injected: *A*, into the preoptic/anterior hypothalamic; or *B*, medullary sites. *A*, example from a single rabbit of lack of effect of taurine (0·1 mg, ...) when injected bilaterally into sites where endotoxin injections (0·001 mg, - - - - - -) caused fever. Saline (——). *B*, typical rectal temperature record after intramedullary injection of taurine in another animal.

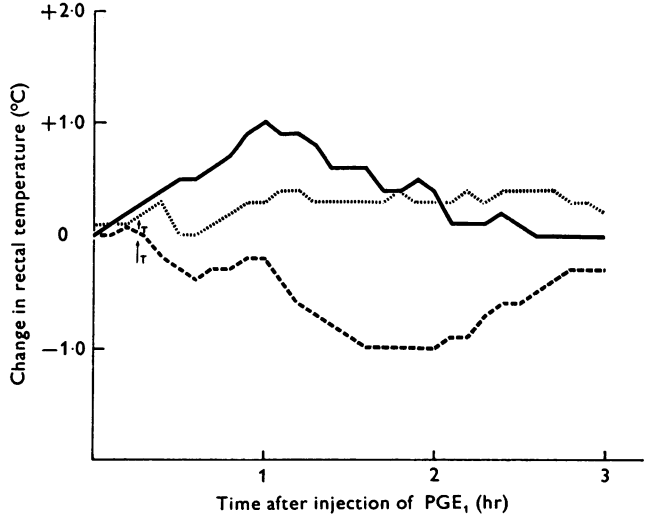

Fig. 6. Examples of hyperthermia produced by I.C.V. PGE_1 (0·002 mg, ——); reduction of hyperthermia by 0·5 mg taurine (- - - -) and total blockage of hyperthermia and development of hypothermia after 5·0 mg taurine (- - - -) in a single rabbit. PGE_1 given I.C.V. at time zero; arrows indicate I.C.V. injections of taurine.

attenuate the increase in rectal temperature (Fig. 7). With a 0·5 mg dose of taurine peak temperature was increased 0·5 and 0·7° C above those produced by amphetamine alone in two rabbits; it decreased 0·5° C in one animal and had no effect on the amphetamine-induced hyperthermia in two others. Taurine (5·0 mg) was given to three rabbits. This dose produced no change in response to amphetamine in one animal, a 0·5° C increase in another and a 0·3° C attenuation of the amphetamine-induced hyperthermia in the third animal. Injection of a high I.V. dose of amphetamine (5·0 mg) followed by a high I.C.V. dose of taurine (6·0 mg) caused increases in rectal temperature of up to 4·2° C, the rate of rise in rectal temperature accelerating immediately after the taurine injection.

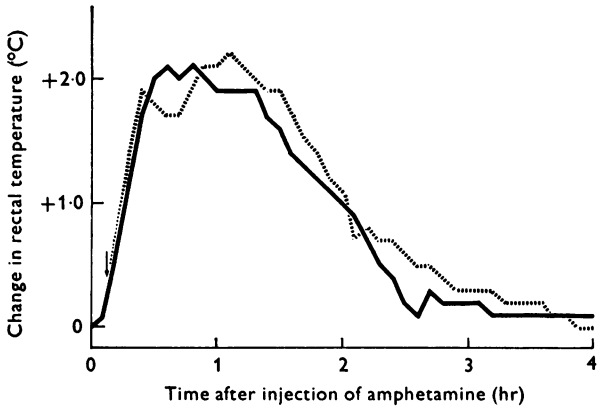

Fig. 7. Taurine did not block hyperthermia produced by I.V. amphetamine (2 mg/kg, ——). Single example: D-amphetamine given at time zero, 5·0 mg taurine (. . . . . .) given I.C.V. at arrow.

DISCUSSION

Taurine given I.C.V had three major effects on body temperature: (1) in effective doses it caused hypothermia in neutral and cold environments; (2) at infusion rates that did not alter afebrile rectal temperature it blocked endotoxin fever; (3) it reduced or blocked hyperthermia caused by PGE_1. Lowering of body temperature by taurine has been reported by Hruska *et al.* (1976) after acute intraventricular injections of taurine in unanaesthetized mice; Sgaragli & Pavàn (1972) found the same results after injections through chronically implanted ventricular cannulae in rats. What is the nature of the central action of taurine which causes marked decreases in core temperature? Because alterations in rectal temperature produced by taurine were dependent upon ambient temperature in the present and in previous experiments (Sgaragli & Pavàn,

1972), it is unlikely that this amino acid acts as if to change a 'set-point' of body temperature control. Decreases in rectal temperature after taurine at 23° C ambient temperature, greater decreases at 10° C and no change in rectal temperature at 30° C ambient temperature indicate that central taurine has an action unlike that of pyrogens (Palmes & Park, 1965), PGE_1 (Stitt, 1973) and tetrodotoxin (Clark & Coldwell, 1973), which cause changes in rectal temperature that are not dependent upon ambient temperature. Consistent with this interpretation taurine does not appear to act specifically on primary and secondary temperature controls in the preoptic/anterior hypothalamic region and medulla oblongata since direct injections of taurine into these brain regions had no effect on rectal temperature. Taurine inhibits neuronal activity (Curtis & Watkins, 1960) and stabilizes membrane potentials (Huxtable, 1976), so this amino acid may cause hypothermia by depressing the activity of neurones in pathways for control of vasomotor activity, heat production and the level of arousal. Inhibition of tonic discharge in vasoconstrictor fibres which largely derive from the floor of the fourth ventricle (Bard, 1960; Folkow, 1955) causes vasodilatation in the skin comparable to that which preceded hypothermia in the present experiments. Consistent with this interpretation, taurine was ineffective at the high ambient temperature when vasodilatation was, presumably, already maximal.

However, vasomotor changes alone cannot account for all the effects observed. If only vasoconstrictor tone was inhibited by the taurine, compensatory shivering should have occurred when core temperature fell, yet no shivering was observed. Possibly, therefore, taurine also blocks shivering pathways in the brain stem or reduces the general sensitivity of central temperature controls by altering arousal via depression of brain stem reticular substance, or it has both effects. The sedation noted in the present experiments is consistent with the latter explanation. Depression of habituated psychomotor activity (Baskin, Hinkamp, Marquis & Tilson, 1974), general activity (Sgaragli & Pavàn, 1972) and specific behaviours (Barbeau, Tsukada & Inoue, 1976) and the production of analgesia (Sugihara *et al.* 1936), have been observed previously after taurine administration and it appears that quieting, sedation or behavioural depression are characteristic effects of this amino acid. Our explanation of the hypothermic effects of taurine in terms of central inhibition of neurones in vasoconstrictor, arousal and heat production pathways generally concurs with the interpretations of Sgaragli & Pavàn (1972). We found no support, however, for the proposal of Hruska *et al.* (1976) that a direct influence of taurine on hypothalamic neurones is responsible for the hypothermic effect.

The finding that an I.C.V. injection of taurine followed by slow infusion

could block the rising phase of an endotoxin-induced fever and bring rectal temperature back to base line, at a dose level which had no effect on body temperature in the same animals when afebrile, is indicative of some other action of taurine. This antipyretic effect could be due to the depressive actions on heat conservation and production described above: perhaps taurine produces 'physiological antagonism' to the rise in rectal temperature by depressing vasomotor, arousal and heat production pathways even at the lower doses used in these fever experiments but the effects are detectable only when the animal is called upon to increase heat production and decrease heat loss, as in fever. In support of this idea, 0·5 mg taurine, which had no effect on rectal temperature in the 23° C ambient temperature, caused hypothermia in rabbits exposed to cold and thus compelled to increase heat production and reduce heat loss. The same dose reduced hyperthermia when given soon after injections of PGE_1. The depressive effects of taurine on heat conservation and heat production, however, do not account for the prolonged time course of the endotoxin-induced fever after the release of the central nervous system from the effects of the infused taurine.

This extended duration of fever after the delayed onset resembled the pyretic response to endotoxin injected into the preoptic/anterior hypothalamic region in the present and in previous research (Lipton & Fossler, 1974; Lipton & Trzcinka, 1976) and the prolonged fevers produced by I.C.V. leukocyte pyrogen (Clark & Cumby, 1975). Since control infusions of taurine without pre-treatment with peripheral endotoxin did not result in a subsequent fever there must be some relation between the treatments with taurine and endotoxin pyrogen. A current explanation of fever production is that exogenous pyrogens act on monocytes, granulocytes and Kupffer cells to cause production and release of an endogenous pyrogen (Atkins & Bodel, 1974). This endogenous pyrogen is believed to act on neurones which control the level around which body temperature is regulated. Since the extended duration of the endotoxin-induced fevers which occur after taurine infusion is discontinued resembles fever after I.C.V. leucocytic pyrogen (Clark & Cumby, 1975), it is possible that taurine causes the accumulation of leucocytic pyrogen in the brain which is suddenly released on to central sites when infusion is stopped. An observation that in some experiments the rate of taurine infusion had to be increased with time if rectal temperature was to be held at base line levels after endotoxin may support this interpretation.

Intracerebroventricular administration of an inert oil can apparently prevent the passage of leucocytic pyrogen out of preoptic/anterior hypothalamic tissue and into the ventricles (Cooper & Veale, 1972) and the resulting accumulation of leucocytic pyrogen enhances the magnitude

and duration of fever induced by peripheral leucocytic pyrogen administration. It is possible that I.C.V. taurine likewise reduces leutocytic pyrogen efflux into the ventricles while simultaneously depressing heat production and heat conservation pathways. If this is true, long-term fever might be expected to occur after inhibition of the effector pathways ceases. An alternative explanation is that the leucocytic pyrogen which escapes into the cerebrospinal fluid is bound by taurine causing a local increase in leucocytic pyrogen concentration. When taurine infusion is stopped the cerebrospinal fluid, relative to the surrounding tissue, becomes a source of leucocytic pyrogen rather than a sink, promoting long-term fever like that seen after acute I.C.V. injections of leucocytic pyrogen. Which, if either, of these alternatives is correct cannot be decided from the present evidence.

The third major effect of taurine, the inhibition of hyperthermia produced by I.C.V. PGE_1 is also believed to be due primarily to inhibitory actions of thermoeffector and arousal pathways. While there were no definitive data which would exclude the possibility of a specific relation between taurine and PGE_1, the marked hypothermia after 5·0 mg taurine, and the falls in rectal temperature observed when taurine infusion rates used to block PGE_1 hyperthermia were given to normal animals, suggest an action on thermo-effector pathways. In addition, as suggested above, even a low dose of taurine which is apparently without effect in other circumstances can be shown to have impaired heat production and heat conservation in an animal driven to increase body temperature. Taurine may therefore act at receptor sites nearer the effector outflow than those occupied by PGE_1. Taurine does not appear to interact with PGE_1 as it does with endogenous pyrogen in that no long-term fevers were observed after taurine was given to animals with PGE_1 hyperthermia.

Unlike the case of PGE_1, centrally administered taurine did not block hyperthermia induced by peripheral amphetamine in the present and previous (Hruska *et al.* 1976) experiments. Considerable controversy remains as to whether amphetamine hyperthermia is due to peripheral effects such as those arising from release of noradrenaline and a corresponding increase in plasma concentration of free fatty acids (Gessa, Clay & Brodie, 1969) or to central effects (Matsumoto & Shaw, 1971; Morpurgo & Theobald, 1967). Possibly both central and peripheral effects are responsible (Borbély, Bauman & Waser, 1974) since peripheral amphetamine readily crosses the blood–brain barrier. Taurine given I.C.V. either does not block central receptors and effector pathways or, more likely, does not reach the peripheral sites of action, responsible for production of amphetamine hyperthermia.

In summary, taurine appears to cause hypothermia by exerting an

inhibitory effect on thermoeffector and arousal pathways and to alter the febrile response through interaction with endogenous pyrogen. In common with certain putative neurotransmitters and alterations of central ionic ratios, this amino acid has marked influences on body temperature.

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