dopa in the periphery, but the present observations still support a central hypotensive action.

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The potentiation of certain effects of amphetamine by inhibitors of prostaglandin synthesis

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Sever & Trelinski (1974) have shown that indomethacin, a prostaglandin synthesis inhibitor (PGSI), potentiates the hyperthermic effect of amphetamine in the rat.

We now report other studies in which we show that other PGSIs (mefenamic acid, flufenamic acid and antipyrine) also potentiate the amphetamine-induced hyperthermia in rats, and alter the pattern of behavioural stimulation in rats and mice.

Female Wistar rats (150-200 g body weight) were used, and the hyperthermic effect of amphetamine measured as described previously (Caldwell, Sever & Trelinski, 1974). Drug induced behavioural changes were measured both in rats (housed singly) and in female T.O. mice (20-25 g body weight) in groups of six (Sever, Caldwell & Williams, in preparation). The PGSIs were administered orally 1 h prior to the intraperitoneal injection of D-amphetamine (5 mg/kg). Control animals were treated with normal saline.

A dose related potentiation of amphetamine induced hyperthermia was caused by indomethacin (5-15 mg/kg) mefenamic acid (50-200 mg/kg), flufenamic acid (50-200 mg/kg) and antipyrine (50-150 mg/kg). However, paracetamol (50-300 mg/kg) had no effect on the intensity of the hyperthermia. All of the PGSIs altered the pattern of behavioural stimulation seen after amphetamine, but there was species variation in the nature of the changes. In the rat, the gross locomotor stimulation was decreased, but stereotyped behaviour was unchanged, while in the mouse, the converse occurred.

In further experiments, rats were given 6-hydroxydopamine (100 mg/kg i.v.) to destroy catecholamine-containing nerve terminals in the periphery. Forty-eight hours later, they were given PGSIs or saline, followed by amphetamine, as before. No hyperthermia was observed in either test or control group.

Indomethacin, mefenamic acid, flufenamic acid and antipyrine which are inhibitors of peripheral PG synthesis (Flower, 1974) all produced a potentiation of the amphetamine hyperthermia. However, this was not seen in animals pretreated with 6-hydroxydopamine. Paracetamol, which only inhibits brain PG synthesis (Flower, 1974), is without effect on the amphetamine hyperthermia, this hyperthermia depending on intact peripheral noradrenergic neurones (Caldwell *et al.*, 1974). It has been suggested that inhibition of PG synthesis abolishes the PG control over noradrenaline release (Smith, 1972), leading to a potentiation of the hyperthermic effect of amphetamine (Sever & Trelinski, 1974) and the results here are consistent with this view.

The pretreatment of animals with PGSIs followed by amphetamine also leads to changes in the pattern of behavioural stimulation due to amphetamine. Since the central stimulant action of amphetamine is apparently due to catecholamine release in the brain (Costa & Groppetti,

1970) it may be that inhibition of PG synthesis in the brain affects the actions of amphetamine in the same way as in the periphery.

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Dissociation of bacterial pyrexia from prostaglandin E activity

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Prostaglandins of the E series (PGE's) elevate body temperature in a number of species and have been implicated as hypothalamic mediators of fever (Milton & Wendlandt, 1971; Feldberg & Saxena, 1971). Whereas PGE_1 infused into the hypothalamus of adult fowls (Nisticò & Marley, 1973) or young chicks (Artunkal & Marley, 1974) elevated body temperature at a thermoneutral ambient temperature, it was found to be markedly hypothermic when infused into the hypothalamus of young chicks at an ambient temperature (Ta) below thermoneutrality, viz 16°C (Artunkal & Marley, 1974); 16°C is not a severe thermal load for chicks of this age (Marley & Stephenson, 1975). Both the hyperthermic and hypothermic effects of PGE_1 in young chicks were potentiated by indomethacin (Artunkal & Marley, 1974), a prostaglandin synthetase and dehydrogenase inhibitor (Ferreira, Moncada & Vane, 1971; Vane, 1971; Flower, 1974).

Present experiments exclude the possibility that this potentiation was solely due to inhibition of prostaglandin dehydrogenase, since similar potentiation was obtained after pretreatment with 5,8,11,14-eicosatetraynoic acid (TYA), 3.4 μmol/100 g, i.v., 30 min previously; TYA is an arachidonic acid analogue which selectively inhibits prostaglandin synthetase (Flower, 1974). The International Pyrogen reference preparation, *Shigella dysenteriae* (1 μg), infused into the hypothalamus of chicks consistently elevated body temperature by 0.5°-2.0°C after a delay of 1-2 h at ambient temperatures of 31° and 16°C, effects that were not potentiated by indomethacin (1.4 μmol/100 g., i.v., 30 min previously).

Comparison of the effects of PGE_1 with those of *Shigella dysenteriae* yielded two important differences: (1) PGE_1 was hypothermic at a TA of 16°C whereas *Shigella dysenteriae* elevated body temperature; (2) the effects of *Shigella dysenteriae* on body temperature, unlike those of PGE_1, were not potentiated by indomethacin. Nor could the hyperthermic effects of *Shigella dysenteriae* be attributed to PGE_2 since at a Ta of 16°C, PGE_2 (14.3 nmol) infused into the hypothalamus, lowered body temperature up to 4.75°C.

The results demonstrate that prostaglandins of the E series are not consistently hyperthermic in all species. Thus, apart from the results in young chicks, hypothermic effects of intraventricular injection of PGE_1 and PGE_2 (each 2 μg) have been demonstrated over a wide range of ambient temperatures in the *Echidna, Tachyglossus aculeatus* (Baird, Hales & Lang, 1974). Additionally, fever evoked in young chicks by bacterial pyrogen can be dissociated from the effects of PGE_1 or PGE_2 in at least two important ways.

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