Further evidence concerning the role of brain noradrenaline in mammalian thermoregulation

In 1964, Feldberg & Myers reported that intraventricular injections of noradrenaline and 5-hydroxytryptamine (5-HT) produced hypothermia and hyperthermia respectively in unanaesthetized cats. On the basis of these results they postulated that the control of body temperature depended on the balanced release of these amines from the hypothalamus. Subsequently, other workers demonstrated that substances other than these monoamines may also be involved in the chemical mediation of body temperature (Brezenoff & Lomax, 1970; Myers & Yaksh, 1969; Milton & Wendlandt, 1970; Myers & Veale, 1971; Metcalf, 1974). At present the relation, if any, between these various substances in unclear.

Whilst both intraventricular and intrahypothalamic injections of monoamines produce regular and characteristic changes in rectal temperature, the doses required are high in relation to the endogenous concentration of the amines in the hypothalamus. An alternative experimental strategy is to use drugs which selectively manipulate the release and metabolism of the endogenous amines. Previous results obtained with adrenergic blocking drugs (Feldberg & Saxena, 1971) and inhibitors of amine reuptake (Cranston, Hellon & others, 1972) have supported the original hypothesis of the role of noradrenaline in thermoregulation. The present preliminary report concerns the effects on body temperature of intraventricular injections of tyramine, a compound known to act indirectly via the release of noradrenaline from nerve endings (Smith, 1973).

Sterile solutions of tyramine were injected into five unanaesthetized cats in 0·2 ml artificial csf via a cannula implanted previously in the lateral ventricle. Rectal temperature was measured using a thermistor probe inserted 10 cm into the colon and recorded continuously on a potentiometric recorder. The data here presented were replotted directly from such records.

Doses of less than 100 μg tyramine had no effect on body temperature. Between 100 and 1600 μg tyramine produced a progressive hypothermia: doses of 100, 200, 400, 800, 1600 μg, i.cv., gave mean hypothermia values of respectively $-0{\cdot}16 \pm 0{\cdot}07$, $-0{\cdot}28 \pm 0{\cdot}05$, $-0{\cdot}41 \pm 0{\cdot}09$, $-0{\cdot}60 \pm 0{\cdot}09$, $-0{\cdot}81 \pm 0{\cdot}12$° centigrade $\pm$ s.e.m. ($n = 4$). Kennedy & Burks (1972) have also reported that 500 μg i.cv. of tyramine produces hypothermia. In contrast to the immediate hypothermia induced by noradrenaline, there was a latency of 5–7 min before temperature began to fall after

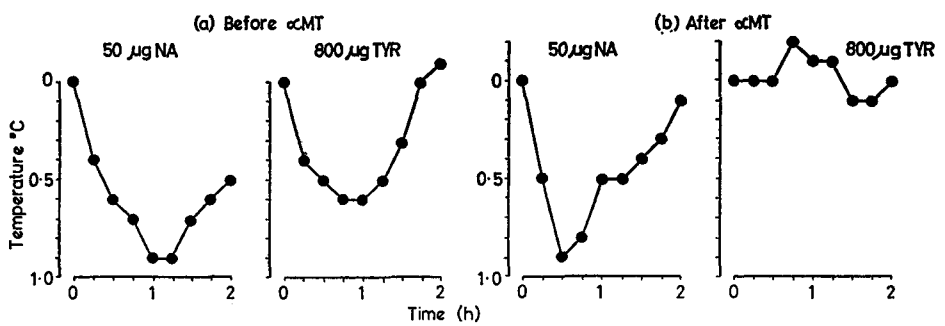

FIG. 1. The effect of α-methyltyrosine (αMT) on the hypothermia induced by either noradrenaline (NA) or tyramine (TYR) in the cat. Figure 1a depicts the control responses produced by intraventricular injections of 50 μg NA or 800 μg Tyr. Figure 1b depicts the responses obtained to the same doses after animals had been treated with αMT.

tyramine. Hypothermia was accompanied by vasodilatation and an increased respiratory rate. The maximum effect was produced in 15–45 min, and temperature returned to baseline levels 60–90 min after an injection. The animals were usually subdued after tyramine in a manner similar to the sedation observed after noradrenaline injections.

The ability of tyramine to release noradrenaline from post-ganglionic sympathetic nerves is now well established (Muscholl, 1966; Smith, 1973). To determine whether a similar mechanism could be used to explain the tyramine-induced hypothermia observed in these experiments, the fall in temperature produced by tyramine was compared with that produced by intraventricular injection of noradrenaline in a three part investigation. In the first part, hypothermia was induced in individual cats by either 800 μg tyramine or 50 μg noradrenaline (Fig. 1a). The animals were then treated with intraventricular α-methyltyrosine (total dose 110 mg administered in divided doses). This compound decreases endogenous noradrenaline by inhibiting the biosynthetic pathway (Levitt, Spector & others, 1965). Cranston & others (1972) have previously reported that central noradrenaline stores are depleted in the cat by a dosage regimen such as we used. Twelve hours after the last dose of α-methyltyrosine, the animals were again injected with either 50 μg noradrenaline or 800 μg tyramine (Fig. 1b). The hypothermic response to noradrenaline was essentially unchanged indicating that post-synaptic receptors were unimparied by the α-methyltyrosine treatment. Tyramine, however, produced no fall in temperature indicating a) that the compound did not interact directly with post synaptic receptors, b) that the compound was unable to provoke hypothermia in the absence of adequate amounts of endogenous noradrenaline.

Thus intraventricular injection of tyramine in cats produces a dose-related hypothermia indirectly by the release of endogenous noradrenaline. This supports the original suggestion made by Feldberg & Myers (1964) that release of noradrenaline from the hypothalamus is involved in the production of hypothermia in the cat.

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