Effect of bacterial pyrogen and antipyretics on prostaglandin activity in cerebrospinal fluid of unanaesthetized cats

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It has been found (Feldberg & Gupta, 1972) that c.s.f. collected in unanaesthetized cats from a cannula implanted into the third ventricle with its tip near the anterior hypothalamus, contracted the rat's stomach fundus strip rendered insensitive to 5-hydroxytryptamine by bromolysergide. This prostaglandin-like activity was low in samples of c.s.f. collected when the animals' temperature was normal and rose in samples collected during fever produced by 75 ng of the bacterial pyrogen derived from *Shigella dysenteriae* injected into the third ventricle. The activity was again low when the fever was brought down by an intraperitoneal injection of paracetamol.

In the present experiments on unanaesthetized cats, similar results were obtained with c.s.f. collected from the cisterna magna, through a cannula chronically fixed to the back of the skull with the tip resting above the atlanto-occipital membrane. To collect c.s.f. and to inject intracisternally, the membrane was pierced by a hollow needle attached to polythene tubing (Feldberg, Myers & Veale, 1970). Fever was produced by injecting the bacterial pyrogen of *Shigella dysenteriae* either into the third ventricle, the cisterna magna, or intravenously. The fever was brought down by an intraperitoneal injection of either paracetamol (50 mg/kg) or indomethacin (2 mg/kg). The c.s.f. was assayed for prostaglandin-like activity on the rat's stomach fundus strip treated with methysergide (200 ng/ml) and indomethacin (1 μg/ml). The activity of the c.s.f. was expressed in terms of ng/ml PGE_1.

The PGE_1 activity of c.s.f. collected before the injection of *Shigella dysenteriae* was low and corresponded to between 0 and 2·5 ng/ml. It rose during fever by whatever route the bacterial pyrogen was injected. On injection of 75 ng into the third ventricle it rose to between 2·5 and 50 ng/ml (mean 14 ng/ml, 8 experiments), on injection of 150 ng into the cisterna magna to between 9 and 63 ng/ml (mean 25 ng/ml, 6 experiments), and on intravenous injection of 250 μg to between 11 and 33 ng/ml (mean 19 ng/ml, 4 experiments). Both paracetamol and indomethacin brought down the fever produced not only by intraventricular and intracisternal, but also by intravenous injection of the bacterial pyrogen, and the PGE_1 activity of the c.s.f. collected during the fall in temperature became again low, corresponding to 1 ng/ml or less.

The finding that the prostaglandin-like activity of c.s.f. increased many times during fever produced by *Shigella dysenteriae* not only when the bacterial pyrogen was injected into the liquor space, but also when it was injected intravenously, and further, that the prostaglandin-like activity of the c.s.f. again became low when the fever was brought down by antipyretics, provides direct experimental evidence for the theory put forward during the last two years to explain pyrogen fever (Milton & Wendlandt, 1970, 1971 ; Feldberg & Saxena, 1971a, 1971b ; Vane, 1971 ; Feldberg & Gupta, 1972). According to this theory prostaglandins are the

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mediators of the fever response to pyrogen. The action of pyrogens would be to increase synthesis and release of prostaglandins, and that of the antipyretics to inhibit the increased synthesis.

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Effect of prostaglandins A_1, A_2, B_1, E_2 and $F_{2\alpha}$ on the forearm arterial bed of man

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The effect of prostaglandins (PGs) on the forearm arterial bed of man was studied by measuring the changes in forearm blood flow produced by brachial artery infusions of PGs A_1, A_2, B_1, E_2 and $F_{2\alpha}$. Flow was measured plethysmographically by means of mercury-in-rubber strain gauges; the upper arm congesting cuff pressure was 40 mmHg and wrist cuff occluding pressure 200 mmHg. Saline, or PGs in saline, were infused through a 26 SWG unmounted needle introduced under local anaesthesia. Each dose of PG was infused for 5 min to obtain cumulative dose-response curves, and flows were measured for 10 s in every 15 s; the mean of the last five measurements at each dose rate was taken as the response. In most experiments PGs were infused at three dose levels.

All the PGs studied caused an increase in forearm blood flow, although in the case of $PGF_{2\alpha}$ subdilator doses produced a transient reduction in flow. Dose dependent increases in flow were seen in response to PGs A_1 and A_2 when infused over the dose range 0·1–10 μg/min (5 experiments), to PGB_1 in doses of 2 and 10 μg/min (3 experiments) and PGE_2 over the dose range 0·5–12·8 ng/min (3 experiments). Although the increases in flow were similar in studies with each PG, the pattern of the responses differed: within about 30 s of starting the infusion of PGs A_1 and A_2 there was an abrupt increase in flow which rose to a peak and then fell within 30–60 s to a level intermediate between the peak and the control. This pattern was repeated with each increase in dose. In contrast, the dilator response to PGs B_1 and E_2 developed slowly. The dilator response to $PGF_{2\alpha}$ was seen at infusion rates of 2–10 μg/min (5 experiments) and the constrictor response was seen at rates of 0·4–2 μg/min (7 experiments). The duration of