Prostaglandins and the central nervous system

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Prostaglandins (PGs) are natural constituents of the brain and spinal cord. They are released from the central nervous system (CNS) spontaneously, in response to electrical and chemical stimulation and during fever. In addition to their action on brain-stem neurones when applied iontophoretically (Avanzino, Bradley and Wolstencroft, 1966), they have potent CNS effects which are now considered.

Body temperature

Probably the current most investigated aspect of PGs is their effect on body temperature ($T_b$). Thus PGEs infused into the brain of many species at various ambient temperatures ($T_a$), elevated $T_b$ (Feldberg, 1975), the site of action (preoptic and anterior hypothalamic areas) being ostensibly indistinguishable from that for fever evoked by endogenous pyrogens. Exceptions to such a general finding are of interest in that some overlooked pharmacological feature of PGs may emerge. The adult spiny anteater is one such exception, since intraventricular PGE$_1$ and PGE$_2$ lowered $T_b$ over a wide range of $T_a$ although intravenous bacterial pyrogen (Eberthella typhi) induced fever (Baird, Hales and Lang, 1974). In the young chick, another non-placental animal, PGEs infused into the hypothalamus at thermoneutrality elevated $T_b$, whereas below thermoneutrality such infusion lowered $T_b$, partly by physical and partly by chemical thermoregulatory mechanisms (Artunkal and Marley, 1974).

During fever produced by endotoxin or endogenous pyrogen, increased PG-like activity occurs in the cerebrospinal fluid (CSF) (Feldberg, 1975). The current hypothesis is that these agents enhance synthesis of PGs in brain, particularly within the preoptic/anterior hypothalamic area, through stimulation of the rate-controlling step releasing the precursor fatty acids; the PGs formed act locally on neurones to produce fever. PGs synthesized at other sites may act there to affect behaviour, or may do so at sites reached after transfer into the CSF.

The aspirin-like drugs reduce fever and prevent release of PGEs into the CSF. Their therapeutic action is ascribed to inhibition of prostaglandin synthetase (Vane, 1971), brain synthetase being more sensitive to aspirin-like drugs than that of other tissues (Flower and Vane, 1972). If PG synthesis is an essential link in the action of pyrogen then it should not be possible to dissociate fever and brain synthesis of PGs. This has proved not to be the case for rabbits in which sustained fever was induced by intravenous infusion of endogenous pyrogen, yet the prior infusion of sodium salicylate sufficient to inhibit PG synthesis by at least 50% did not significantly diminish fever although preventing an increase in PGs in the CSF (Cranston, Hellon and Mitchell, 1975). Another problem is that fever induced by intraventricular pyrogen was unaffected by the simultaneous administration of PG antagonists in doses which abolished PG-induced fever (Cranston et al., 1976). To complicate matters further, extensive lesions of the preoptic/anterior hypothalamic area rendered rabbits insensitive to the hyperthermic effects of intraventricular or intrahypothalamic infused PGEs but not to intraventricular or intravenous leucocyte pyrogen (Veale and Cooper, 1975). Various explanations for these discrepant findings were canvassed, although the possibility that the present account of the involvement of PGs in fever has been too simplified must now be considered seriously.

The most clear-cut dissociation between fever induced by bacterial pyrogen and the actions of PGEs was observed in the spiny anteater (see above); and in young chicks tests below thermoneutrality, PGEs infused intrahypothalamically antagonized or reversed endotoxin fever (Artunkal, Marley and Stephenson, 1975, 1977a). Moreover, fever was obtained, in chicks, with Shigella when PG synthesis had been arrested (Ali and Stephenson, unpublished data). Thus while there is much evidence to link bacterial fever with PGs, the association is not absolute.
Behaviour

Intense behavioural and electrocortical sleep are induced in a number of species when PGEs but not PGFs are infused intraventricularly or into the hypothalamus. Catatonia has also been described in cats (Horton and Main, 1965). Probably as a consequence of their soporific action, PGEs potentiate barbiturate sleep, protect against chemically- and electrically-induced convulsions (Holt and Horton, 1968; Poddibiuk, 1976) and reverse arousal evoked by dexamphetamine (Artunkal, Marley and Stephenson, 1977b). Conditioned avoidance and escape responses are depressed (Potts and East, 1971). Additionally, PGEs (and PGFs in some of the tests) impair motor coordination, reduce spontaneous activity, locomotor activity and exploratory activity (Holt and Horton, 1968; Poddibiuk, 1976).

The mechanism of the soporific effect is unknown although, apart from a direct effect of PGEs, reduced transmitter release could be responsible (Bergrström, Farnebo and Fuxe, 1973). Alterations of blood supply through arteriolar vasoconstriction may be contributory.

Analgesia

Intraventricular PGs (E1, E2, F1α, F2α) produced analgesia in rats, measured by the hot-plate method (Poddibiuk, 1976).

Food intake

This is reduced following PGE1 infused into the medial and lateral hypothalamus of rats (Baile et al., 1973) but increased with infusions into similar sites in sheep (Martin and Baile, 1973).

Endocrine effects

PGEs and PGFs given by various routes, including infusion into the median eminence and into the third cerebral ventricle, led to the release into the circulation of various hormones from the adenohypophysis (ACTH, LH, FSH, GH, prolactin) and from the neurohypophysis (ADH, oxytocin) (Wolfe, 1975). Application directly to the anterior parietal lobe and basal hypothalamic regions was without effect.

Spinal cord reflexes

The effect of PGEs given intravenously and intra-arterially to chicks and cats depended on whether they were intact and chloralosed, or made spinal. Thus, in spinal preparations, a mono- and a polysynaptic spinal reflex were enhanced whereas in intact animals these were diminished. These different effects could be attributed to a supraspinal and therefore indirect action of PGE2 in intact animals but a direct action on the spinal cord in the spinal preparations (Holt and Horton, 1968; Duda, Horton and McPherson, 1968). PGFs enhanced a spinal cord reflex in spinal and in intact chicks but the effects in cats were variable. The conclusion is that the main effect of the PGEs and the PGFs is excitation of spinal cord α-motor-neurones. Studies with PGs on the frog isolated superfused spinal cord accord with this view (Phillis and Tebécis, 1968; Cocceani and Viti, 1973).

References


