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# THE ROLE OF PROSTAGLANDINS IN THE CENTRAL NERVOUS SYSTEM

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## INTRODUCTION

The prostaglandin system is implicated in physiological and pathological responses of most tissues of the body. The background and breadth of this subject are documented in many reviews and recent symposia (15, 25, 27, 28, 51, 108, 112, 114, 135). This review on the CNS covers advances in the past three years and concerns specifically the possible involvement of the prostaglandin system in the regulation of physiological and pathophysiological processes.

A wide range of stimuli (hormones, enzymes, trauma, inflammation, pyrogens, immune and allergic reactions, etc) activate a plasma membrane enzyme sequence in mammalian cells that leads to the rapid de novo synthesis of several prostaglandin types and in certain tissues thromboxanes as well. The biologically active compounds do not accumulate intracellularly and, therefore, under physiological conditions they occur only in trace amounts in tissues and most body fluids. Following formation, action and release, the compounds are rapidly converted by several enzymatic sequences to less active or inactive metabolites, which appear in blood and urine. Arachidonic acid, the predominant precursor unsaturated fatty acid in mammalian cells, becomes oxygenated to the prostaglandin endoperox-



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ides and their products. Arachidonic acid must be released from a complex lipid precursor by deacylases before it can be transformed. The biosynthesis of prostaglandins and thromboxanes by central nervous tissue and factors that affect it have been reviewed recently (42, 135, 136). A new finding is that $PGD_2$ is formed in excess of $PGF_{2\alpha}$ by cerebral tissues of the rat (1).

## CEREBROSPINAL FLUID

The existence of prostaglandin-like material in cerebrospinal fluid (CSF) of experimental animals has been recognized for some time (25, 135). Recent studies show CSF levels of $PGF_{2\alpha}$ in human subjects without neurological disease usually to be below 100 pg $ml^{-1}$ (range 30–140 pg $ml^{-1}$) in cell-free fluid (55, 73, 137). Either $PGE_2$ is not detectable or it is present at the same low levels as $PGF_{2\alpha}$. Thromboxane $B_2$ is also a normal constituent (range 80–300 pg $ml^{-1}$), at least in the cat (F. Coceani, unpublished results). In contrast to most other tissues (89, 135), the brain has very low capacity either to take up or metabolize $PGF_{2\alpha}$ and $PGE_2$ to the 15-keto and 15-keto-13,14-dihydro metabolites. Consequently, prostaglandins normally produced endogenously are primarily cleared into the general circulation through choroidal and extra-choroidal transport mechanisms (16, 55).

Marked increases in CSF $PGF_{2\alpha}$ levels are found in patients with epilepsy, meningoencephalitis, hydrocephalus, and after surgical trauma; but levels are variable even in the same patient. Likewise, patients with vascular lesions, subarachnoid hemorrhage, and stroke also show significant albeit variable (200–3000 pg $ml^{-1}$) increases in $PGF_{2\alpha}$ and $PGE_2$ levels (22, 55, 74, 137). Prostaglandins in the CSF may affect brain function directly or through local changes in the circulation.

## CEREBRAL CIRCULATION

It is now well accepted that prostaglandins and thromboxanes contribute to vascular homeostasis through a direct action on smooth muscle in the vessel wall and, possibly, a modulation of muscle responses to neural and hormonal stimuli (27, 78, 125). The evidence supporting this concept is as follows: (*a*) Vessels are endowed with an enzyme system for the synthesis of primary prostaglandins and $PGI_2$, the latter being the predominant prostaglandin. With one exception (umbilical artery), all vessels lack the thromboxane $A_2$ synthetic enzyme. (*b*) Prostaglandins and thromboxane $A_2$ exert potent and varied actions on vessels. While the action of the primary prostaglandins changes depending on the species and the vascular bed, $PGI_2$ and thromboxane $A_2$ are relaxant and constrictor agents, respectively, at all sites. Prostaglandin endoperoxides are also vasoactive, and

their action may be direct or mediated by the intramural formation of primary prostaglandins and $PGI_2$. (*c*) Indomethacin and other nonsteroidal anti-inflammatory drugs constrict or dilate vessels in vitro and in vivo.

Although these findings implicate intramural prostaglandins in the control of vascular tone, extramural prostaglandins may also be important, particularly under pathological conditions. Thromboxane $A_2$, which is released in great amounts from aggregating platelets, may gain access to muscle cells in the vessel wall and cause constriction. Furthermore, prostaglandins and thromboxane $A_2$ formed within the parenchyma of organs may act upon small resistance vessels.

The above scheme may also apply to the cerebral circulation. All primary prostaglandins and $PGI_2$ are formed in cerebral vessels (56, 133). Moreover, indomethacin reduces cerebral blood flow (99, 101), which implies that vessels are normally maintained in a relaxed state by a prostaglandin. The identity of the active compound is not known. However, evidence obtained in other vascular beds and the demonstration that $PGE_2$ and $PGF_{2\alpha}$ are both constrictors on cerebral vessels (100, 139) suggest that this compound is $PGI_2$. Thromboxane $A_2$, though not formed in cerebral vessels (56), is a potent constrictor (39). In fact, thromboxane $A_2$ is the most potent vasoconstrictor among agents acting on the cerebral circulation.

According to current ideas, prostaglandins and allied compounds, besides being involved in the normal control of cerebral blood flow, are also responsible for the hemodynamic changes occurring under certain pathological conditions—in particular, cerebral vasospasm (132). For example, thromboxane $A_2$, formed in damaged brain tissue or in aggregating platelets, is considered a prime determinant of the vasospasm-complicating thromboembolism and subarachnoid hemorrhage (39, 131). Thromboxane $A_2$ action may be complemented by that of the prostaglandins and other vasoactive agents (5-hydroxytryptamine) (2). Indeed, thrombin stimulates $PGF_{2\alpha}$ and $PGE_2$ synthesis when injected intrathecally (54). Brain ischemia following head injury is possibly another prostaglandin-mediated process. Prostaglandins, specifically $PGE_2$, have also been implicated in the pathogenesis of migraine (58, 131). $PGE_2$, a constrictor of intracranial vessels, dilates extracranial vessels (100); therefore, it may be involved both in the prodromal phase and in the headache phase of the migraine attack.

## HYPOTHALAMIC FUNCTION

Prostaglandins have been implicated in several hypothalamic mechanisms. Only temperature regulation, water balance, and food intake are considered here. Involvement of prostaglandins in hypothalamo-adenohypophyseal function has been discussed in recent reviews (53, 68, 70, 110).

## *Temperature Regulation*

The subject of hypothalamic transmitters involved in thermal homeostasis has been well covered recently (29, 42, 62, 77, 99, 107, 128, 140) and does not require further elaboration here. It is sufficient to say that three compounds, 5-hydroxytryptamine (5-HT), norepinephrine (NE), and acetylcholine (ACh) are generally assigned a key role in temperature regulation. According to most authors, body temperature is controlled through the opposing actions of 5-HT and NE on neurons in the anterior hypothalamic/preoptic region (AH/POA). These amines have species-specific signs of action while maintaining reciprocal effects. ACh is considered a transmitter in the temperature-raising pathway in all species. The extracellular concentration of ions within the posterior hypothalamus, and specifically the balance between sodium and calcium, may be an additional controlling factor. This ionic mechanism is thought to work in concert with the neurohumoral mechanism to determine the "set-point" around which body temperature is regulated.

The prostaglandins are a relatively recent addition to the field of thermoregulation. Interest in these compounds dates back to the early 1970s when it was found that $PGE_1$ was a potent pyretic agent (84) and that antipyretics blocked prostaglandin synthesis in various organs including brain (48, 112). These two findings implicated a prostaglandin in the genesis of fever. Research in this area developed actively and led to the demonstration that: (*a*) $PGE_2$, a normal constituent of hypothalamic tissue (70), is as potent as $PGE_1$ in producing fever (45–47, 57, 65, 76, 86, 93, 94, 102, 106, 121); moreover, both compounds are like pyrogens in that their action is not influenced by ambient temperature (57, 65, 121, 126); (*b*) $PGE_2$ acts upon neurons in the AH/POA that are also the main target for pyrogens (121, 126); (*c*) thermo-sensitive neurons in AH/POA respond in the same manner to $PGE_2$ and pyrogens (117); (*d*) $PGE_2$ fever, unlike pyrogen fever, does not abate following administration of antipyretics (24, 79, 84, 85); and (*e*) pyrogen fever is associated with elevated levels in the CSF of a prostaglandin with the biological and immunological properties of $PGE_2$ (34, 37, 43, 44, 83, 95). Collectively, these findings indicate that $PGE_2$ is well suited for being the "central messenger" of fever and specifically of pyrogen fever (cf 62, 80, 128). According to current knowledge, pyrogens from outside the body (*exogenous pyrogen*), and foremost among them bacterial endotoxin, as well as pathological conditions causing tissue inflammation and damage (e.g. infarction, malignancy) elicit the formation of a pyrogenic substance (*endogenous pyrogen*) in neutrophils and in cells of the reticuloendothelial system. The endogenous pyrogen, which is therefore a key intermediate in the sequence of events leading to fever, is then carried to the rostral region

of the hypothalamus by the circulation. Because the blood-brain barrier is seemingly impermeable to endogenous pyrogen (cf 80), and because prostaglandins are rapidly removed from the circulation (cf 124), one must assume that the vessel wall is the main site where pyrogen action is translated into increased prostaglandin synthesis. Consistent with this hypothesis is the notion that vessels, including cerebral vessels, are endowed with an active prostaglandin-generating system and that hypothalamic blood flow is increased during pyrogen fever (109). The latter finding implies activation of prostaglandin synthesis in the vessel wall. Alternatively, $PGE_2$ could be released from phagocytosing leucocytes sequestered in the capillary bed of AH/POA (128). Any pyrogen crossing the blood-brain barrier may stimulate prostaglandin synthesis in neural tissue (140). $PGE_2$, whether formed in the tissue of the AH/POA or from the vessels, acts at appropriate sites in the thermoregulatory pathways to elevate the "set-point" for temperature regulation, thus causing fever. Once its action is completed, $PGE_2$ is either inactivated enzymatically in situ or enters the extracellular fluid and CSF whence it is transported into the circulation. Interference with the latter mechanism results in enhancement of pyrogen effects (30).

Although the experimental evidence implicating $PGE_2$ in the pathogenesis of fever seems quite convincing, there have been reports contradicting the above scheme. In the monotreme, *Tachyglossus aculeatus* (Echidna), $PGE_1$ and $PGE_2$ are hypothermic agents, whereas endotoxin causes fever (12). Dissociation between pyrogen and PGE effects also occurs in the newborn lamb which, after appropriate sensitization, may develop fever in response to pyrogens but not in response to prostaglandins (103, 105). A similar phenomenon has been described in the adult animal following destruction of AH/POA (126). Potentially germane to these findings is the demonstration that prostaglandin antagonists block $PGE_2$ but not pyrogen fever (31).

Because pyrogen fever is susceptible to antipyretic treatment in the above experiments, a possible explanation for the inconsistencies could be that an arachidonic acid metabolite other than $PGE_2$ contributes to, or is the main determinant of pyrogen effects. Consistent with this is the finding that fever following administration of arachidonic acid, while abolished by antipyretics, is only partially blocked by prostaglandin antagonists (71). Theoretically, several compounds could have this role; however, available data limit the choice to two compounds, $PGI_2$ and thromboxane $A_2$, because prostaglandin endoperoxides and $PGD_2$ are inactive (41, 59), and $PGF_{2\alpha}$ is a pyretic agent but only in high doses (41, 47, 86). While no information is available on the central action of $PGI_2$, recent work showing that levels of thromboxane $B_2$ in the cerebrospinal fluid rise during pyrogen fever (F. Coceani, unpublished results) suggests that thromboxane $A_2$ might be the

hypothetical mediator. If so, it would not be a coincidence that intracranial bleeding, a condition in which AH/POA may be exposed to massive amounts of thromboxane $A_2$ formed in aggregating platelets, is commonly associated with fever (113).

Some findings suggest that fever may develop independently of the prostaglandin system. In the rabbit, salicylate at certain doses has little or no effect on the febrile response to pyrogen while it completely reverses the elevation in prostaglandin levels in the CSF (34). The question remains whether the dose of salicylate used was sufficient to block the synthesis of $PGE_2$ or any other pyrogenic derivative of arachidonic acid in the AH/-POA. However, more cogent evidence against the involvement of the prostaglandin system in fever is afforded by recent work in the chick (4, 5) in which it was shown that PGEs are hyper- or hypothermic agents depending on the ambient temperature and that pyrogen fever is only marginally affected by indomethacin at a dose exceeding the therapeutic range (cf 48). Etiocholanolone fever in man, which is mediated by endogenous pyrogen (19), is also resistant to antipyretic treatment.

Summing up, a large body of evidence supports the existence of a "$PGE_2$ link" in the central action of endogenous pyrogen; but this prostaglandin may work in concert with another product, or more than one product, of arachidonic acid metabolism. Some forms of pyrogen fever, however, do not involve the prostaglandin system, and their central mechanism remains obscure.

Prostaglandins probably do not contribute to normal temperature regulation. Antipyretics, whether given systemically (24, 66, 79) or injected into the anterior hypothalamus (6, 35), produce little or no hypothermia in the afebrile animal, nor do they reverse the hyperthermia following cold stress (32, 104). Furthermore, prostaglandin levels in the CSF remain unchanged during thermoregulatory adjustments to cold or hot environments (21, 33). When present, hypothermic effects of antipyretics (cf 115) are ascribed to activation of the heat loss mechanism rather than to blockade of prostaglandin synthesis (79). Indeed, iontophoretically applied salicylate may stimulate warm-sensitive neurons in the AH/POA of the afebrile animal (13).

The intimate mechanism of prostaglandin action in producing fever remains a subject of speculation. It has been debated for some time (cf 28, 62) whether the prostaglandin and monoaminergic mechanisms are functionally interdependent, and this issue is far from being settled. In essence, two schemes have been proposed for linking the prostaglandins, specifically $PGE_1$ and $PGE_2$, to the monoamines. According to one (7), monoamine actions leading to elevation in body temperature are mediated in part by a prostaglandin. In support of this concept is the finding that 5-HT stimulates the release of PGEs from brain (64) and that epinephrine as well as 5-HT-

induced hyperthermia are suppressed by antipyretics (7, 69, 82, 85). However, the validity of results with the antipyretics has been questioned (36, 82), moreover, this hypothesis is not easily reconciled with the notion that monoamine effects (17, 62), unlike prostaglandin effects (57, 65, 121, 126), are affected by ambient temperature. Alternatively, it has been suggested on the basis of work with specific monoamine depletors and antagonists that monoamines are intermediates in the action of prostaglandins on temperature-raising mechanisms. Again, no firm conclusion can be drawn from these studies (cf 28) because positive results in one species [rabbit (20, 66, 72)] contrast with inconsistent results in another [cat (82, 126)]. Furthermore, an explanation for the constancy of prostaglandin effects at different ambient temperatures must be provided before accepting this hypothesis. Equally controversial is the question of the role of cyclic nucleotides in PGE fever. While findings in the rabbit suggest that cyclic AMP is a central mediator of PGE fever (138), findings in the cat argue against this idea (81).

## *Control of Body Water*

The homeostatic regulation of body water content is dependent on the concerted action of two brain mechanisms, namely, the function of a "thirst sensor" possibly located in the subfornical organ (40) and other circumventricular organs (97), and the secretion of antidiuretic hormone (ADH). Both mechanisms are under the direct control of angiotensin II (40, 118) and may also be influenced by the prostaglandins. Angiotensin, whether formed in situ or blood-borne, stimulates thirst and the formation of ADH. The latter action is exerted on the synthesis [supraoptic and paraventricular neurons (87)] and release [neurohypophysis (50, 63)] of the hormone. When injected into the common carotid artery or the cerebral ventricles, $PGE_1$ and $PGE_2$ mimic angiotensin in stimulating ADH release (75, 129). Moreover, these prostaglandins share with angiotensin a dual site of action (50, 75, 129). Prostaglandin action on thirst mechanisms is a subject of controversy. While it has been reported that $PGE_1$ and $PGE_2$ (but not $PGF_{2\alpha}$) antagonize the dipsogenic effect of angiotensin in the rat (40, 91), the same compounds have opposite effects in the goat (3, 75). This discrepancy is unlikely due to the dose of prostaglandin used (40, 75), because the sign of responses in the rat remained the same over a wide range of doses. Differences may reflect a genuine species variation, the significance of which is not known.

Because low doses of $PGE_1$ and $PGE_2$ given by the ventricular route affect water balance without altering thermoregulatory neurons, responses are possibly indicative of a physiological process. This applies specifically to $PGE_2$, which is present in brain. Future experiments employing blockers

of prostaglandin synthesis may confirm this point. Regardless of whether responses are physiological or pharmacological, the mechanism of prostaglandin action remains to be elucidated. Prostaglandins and angiotensin, which are both vasoactive agents, may act, or interact, on blood vessels supplying target neurons in the subfornical organ and the hypothalamus. Alternatively, their action may be exerted directly on neurons. Indeed, subfornical and supraoptic neurons respond to iontophoretically applied angiotensin (92, 96). It is still a question whether the same holds true with the prostaglandins.

### *Regulation of Food Intake*

It is generally assumed that food intake is primarily controlled through the opposing action of two neuronal systems located in the hypothalamus: a lateral system signalling the urge for food ("feeding center"), and a ventromedial system suppressing food intake ("satiety center") (60). Several neurohumoral agents, including the prostaglandins, have been implicated in the function of these neurons (cf 8). When given systemically, various prostaglandin types, including $PGE_1$, $PGE_2$, and $PGF_{2\alpha}$, inhibit food intake without overtly affecting behavior, body temperature, and water intake (116). $PGE_1$ is also effective when injected into the hypothalamus; however, its site of action varies with the species. While in the rat responsive sites are located in the anterior commissure region and the lateral hypothalamus (11), in the ewe they are located in the anterior and medial hypothalamus (10). Furthermore, in the ewe $PGE_1$ may also stimulate feeding (10). Prostaglandin effects occur in both food-deprived and satiated animals (38), which implies a central action for these compounds.

Although these findings implicate the prostaglandins in the hypothalamic control of energy balance, some facts are inconsistent with this possibility. $PGE_2$, even though it suppresses feeding by the systemic route, has no effect on sites in the hypothalamus that are sensitive to $PGE_1$ (10). Moreover, effective doses of $PGE_1$ by the intrahypothalamic route are in the microgram range (10, 11, 127, 134), indicating a pharmacological rather than a physiological action. Another difficulty in accepting this idea arises from the fact that distribution of prostaglandin-sensitive sites in the hypothalamus is species-specific in spite of a seemingly constant organization of the neuronal systems controlling feeding behavior (9).

## INTERACTION WITH CYCLIC NUCLEOTIDES AND NEUROTRANSMITTERS

A large body of evidence suggests that cyclic nucleotides, and particularly adenosine 3',5'-monophosphate (cyclic AMP), play a role in peripheral and

central synapses (52, 67, 90). In the CNS, cyclic AMP has been implicated in the mediation of postsynaptic effects of several neurotransmitters (52, 67, 90); however, evidence of such a role is strongest in the case of dopaminergic synapses on caudate neurons (120) and β-adrenergic synapses between fibers originating in the locus coeruleus (LC) and cells in the cerebellum (Purkinje cells) and the hippocampus (pyramidal cells) (18). Some data also suggest that guanosine 3',5'-monophosphate (cyclic GMP) is involved in the muscarinic actions of ACh (52, 88, 90, 118). In fact, it has been proposed that cyclic AMP and cyclic GMP have a reciprocal function in the regulation of neuronal activity (123).

Prostaglandins may also interact with the cyclic nucleotides. Findings in cerebellar Purkinje cells afford a model of some of their possible functions in synaptic events. In brief, it is proposed (cf 28; 18, 90) that NE released from LC fibers impinging upon Purkinje cells triggers the postsynaptic formation of cyclic AMP, which in turn causes an appropriate change in membrane potential (i.e. hyperpolarization) through the phosphorylation of specific membrane proteins. The same model assumes that $PGE_2$, formed in response to NE or cyclic AMP action, modulates the synaptic process by inhibiting the synthesis of cyclic AMP. A similar sequence of events is thought to occur in other noradrenergic synapses (90), whereas prostaglandins are assigned a stimulatory action on the cyclic AMP–generating system in dopaminergic synapses (120).

Although supported by findings in peripheral synapses (52), the above scheme has been challenged on various grounds. The idea that cyclic AMP is an essential intermediate in the postsynaptic action of NE has been questioned, and the points of contention are discussed in several reviews (28, 90, 98). Furthermore, different investigators (cf 23, 28, 122) have been unable to confirm at several sites in the CNS (cerebral cortex, hypothalamus and brain stem in mammals, and spinal cord in the frog) that E-type prostaglandins modify neuronal responses to the monoamines. Negative results with spinal neurons (23) are particularly significant because the amphibian CNS, unlike the mammalian CNS, is endowed with an active enzyme system for prostaglandin inactivation (26; F. Coceani, unpublished results) and would, therefore, seem to be a well-suited site for prostaglandin involvement in synaptic events. It is conceivable, however, that prostaglandins may influence postsynaptic actions of the monoamines only in certain neuronal systems. Future work must take into consideration effects of the endoperoxides and thromboxanes, which may turn out to be more important endogenous modulators of adenylate cyclase than the primary prostaglandins.

A separate line of investigation suggests that $PGE_2$ may modulate noradrenergic and dopaminergic transmission through inhibition of transmitter

release. However, this concept is based on work in peripheral synapses (61), whereas findings in the CNS are negative (130) or inconsistent (14, 111, 119).

## CONCLUSIONS

### *Facts*

Central nervous tissue has a complete system for the biosynthesis of prostaglandins and thromboxanes. The prostaglandin system is either directly or indirectly connected with neuronal activity, and its possible function is best documented in the case of hypothalamic homeostatic mechanisms. Cerebral blood vessels synthesize prostaglandins, which likely contribute to normal hemodynamics. There is compelling evidence that prostaglandins are formed at multiple sites in the CNS, both neural and non-neural, and interact in a varied manner in physiological and pathological situations.

### *Outstanding Issues*

The activity and control of synthetic enzymes in neural and non-neural constituents of CNS; the identity of compounds active at various sites; the role of $PGF_{2\alpha}$ and $PGD_2$, which are relatively inactive in spite of being formed in excess of $PGE_2$; the likelihood of prostaglandin-degrading enzymes being confined to certain neuronal types and the importance of such enzymes in the termination of prostaglandin effects; and the specific involvement of prostaglandins in synaptic events are the outstanding issues.

### *Prospectives*

Most of the outstanding issues will be hard to resolve because of limitations in assay methodology, the multitude of compounds to be assayed, the potential for new compounds or pathways in the metabolism of arachidonic acid, and difficulties in following the time-sequence of biosynthetic events in vivo. In spite of these problems, refinements in assay methods and the development of new and more selective blockers of arachidonic acid metabolism should afford a better knowledge of the functional organization of the prostaglandin system in the CNS. Advances in this field should also have an impact in the clinic—particularly in the management of neurological diseases in which the neural deficit follows a vascular insult.

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