Prostaglandin effects in the neuro-endocrine mammalian brain

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Summary

Various prostaglandins (PGs) have been found in several areas of the brain. PGs of the E series have been found in the pituitary and pineal glands and the median eminence, and they have been shown to influence hypothalamic endocrine-release characteristics and release of melatonin from the pineal gland. It has been suggested that they may act, along with membrane phospholipids, as a link between neuronal depolarization, calcium uptake and neurotransmitter release. They may also influence postsynaptic effects of neurotransmitters. These latter effects may be due to interaction with membrane phospholipid- and cyclic nucleotide-induced changes of specific protein kinases. The PGs may act as intracellular mediators of neuro-endocrine control.

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The control of the hypothalamic-pituitary adrenal (HPA) axis occurs at various levels, traditionally through hormonal feedback loops.[1] Nevertheless the hypothalamic release of releasing factors from neurosecretory cells is also under neuronal control, and this neuro-endocrine activity involves the biogenic amines (adrenaline, dopamine, serotonin), acetylcholine, γ-aminobutyric acid and histamine, and possibly other neurotransmitters.[1] The individual neurons involved in each neurotransmitter release may interact with each other, and it is this interneuron interaction which finally determines hypothalamic neuronal output and secretion.[1] In addition, circulating hormones or their degradation products (e.g. oestrogens[2]/catechol oestrogens,[3] glucocorticoids[4]) are known to affect neurotransmission through presynaptic (neurotransmitter turnover and release) and postsynaptic (neurotransmitter receptor) influence, and these compounds may modify HPA function by direct hypothalamic-neuronal interaction.[2] Through this neuronal interaction the steroids can therefore indirectly affect the cyclic nucleotides. The neurons involved originate in various areas of the brain, and of particular importance with regard to HPA function (Fig. 1) are the median eminence, which is where many of the afferent neurons originating in other brain areas converge and from which the hormone-releasing factors are predominantly derived, and the pineal gland, which is thought to control circadian rhythm and is the site of melatonin biosynthesis.[1] These areas exist, as does the pituitary gland, outside the blood-brain barrier,[1] and are therefore more readily accessible to mediation by compounds in the circulation, although steroids can cross this barrier freely. Blood flow through the median eminence is extremely rapid (± 10 μl/min/mg tissue in rats[1]).

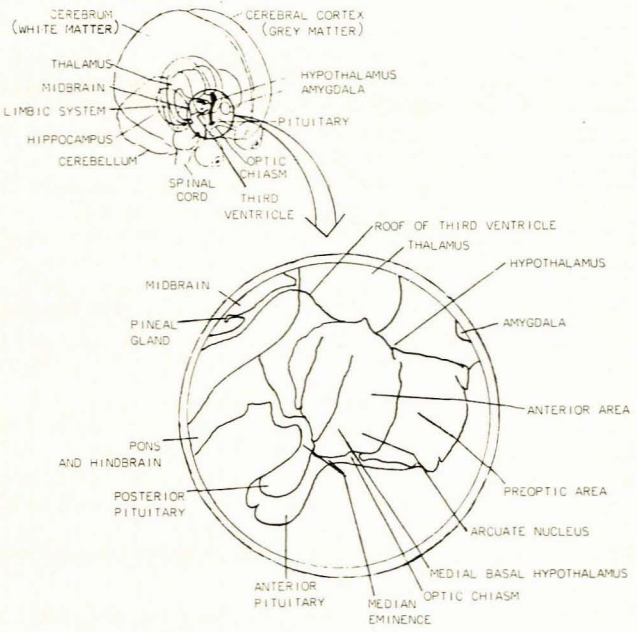

Fig. 1. Relevant areas of the mammalian brain.

The neuronal events which lead to nerve cell discharge, calcium uptake and neurotransmission are not completely understood, but at the molecular level phospholipids and prostaglandins (PGs) are now thought to play important roles in these processes[5] and therefore to be of importance in the neuro-endocrine control of intermediary metabolism.

Synthesis of PGs and distribution in the rat brain

PGs have recently been discussed in this journal,[6-8] and only a brief outline of the PG synthesis cascade is shown in Fig. 2. The PGs are generally regarded as local hormones, but when they are synthesized by circulating cells, e.g. platelets, mast cells and polymorphonuclear neutrophils, they may be regarded as 'circulating hormones'. Most of these 'circulating PGs' have vasoconstrictor and chemotactic properties, e.g. thromboxane and leukotriene LTB_4, and are involved in body defence mechanisms, i.e. inflammation or response to trauma through chemotactic, chemokinetic and vaso-active reactions.[9] Different PGs have also been found in several discrete areas of the rat brain. Originally the predominant PG was thought to be PGD,[10] but more recent work[11] suggests the presence of equivalent amounts of $PGF_{2\alpha}$ and prostacyclin and approximately half that amount of thromboxane and PGE_2. To our knowledge no work has yet demonstrated the presence of leukotrienes in the brain (see Wolfe[12]), although *in vitro* work

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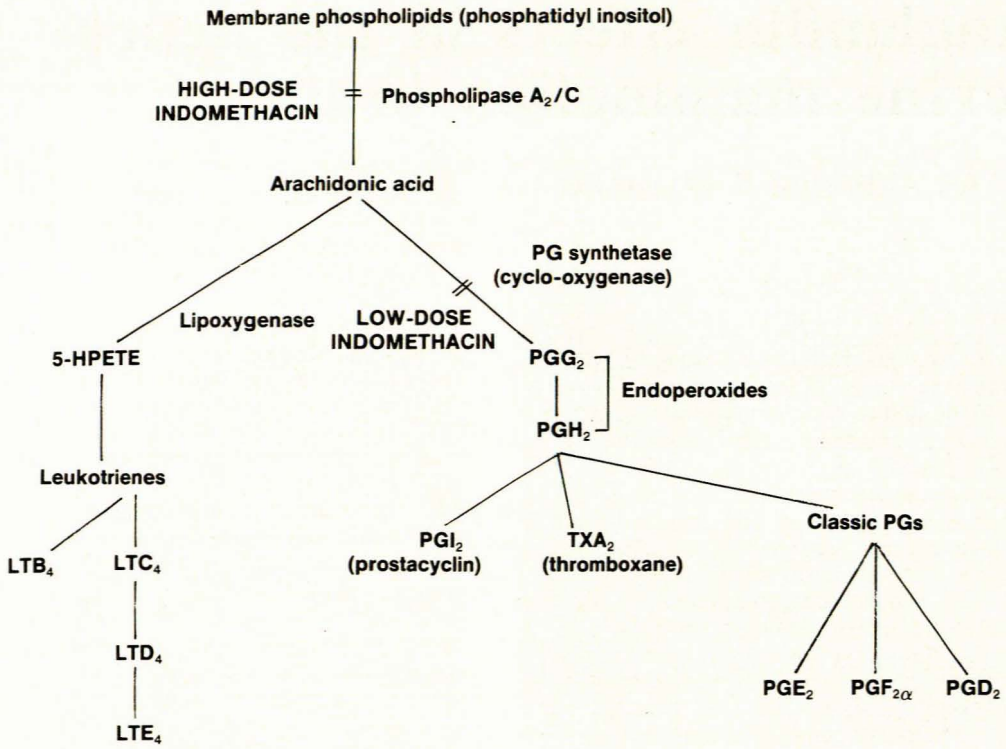

Fig. 2. Brief outline of the PG (two-series) synthesis cascade (5-HPETE = 5-hydroxyeicosa-6,8,11,14-tetra-enoic acid).

with liposomes has shown that LTB_4 may act as a calcium ionophore.[13] The prostanoids are found mainly in the pituitary and pineal glands and are most abundant in the median eminence area of the hypothalamus.[11] Specific high-affinity PGE_2 receptors have been localized to the synaptosomal fraction of the hypothalamus, amygdala and posterior lobe of the pituitary gland.[14] Prostacylin (PGI_2) is formed in cerebral blood vessels and capillaries.[12]

Neuro-endocrine effects of PGs

In 1969 Zor *et al.*[15] demonstrated that PGE-induced cyclic adenosine monophosphate (cAMP) accumulation in the anterior lobe of the pituitary gland *in vitro* did not affect luteinizing hormone (LH) release, and in the same year de Wied *et al.*[16] suggested that PGE stimulated adrenocorticotrophic hormone (ACTH) release *in vivo*. This early work suggested that PGE could affect pituitary hormone secretion at the hypothalamic and pituitary level, and a wealth of evidence has now accumulated which demonstrates that PGs (generally PGE_2) can affect secretion of ACTH, thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), LH, growth hormone (GH) and prolactin (PRL), at a pituitary and/or neuronal level[17] (Table I). At this time (1981) it was uncertain whether these events were pre- or postsynaptic in nature, but in some cases they could be attributed to PG mediation of neurotransmitter-induced effects, i.e. increased noradrenaline (NA) binding increases PGE, which stimulates cAMP formation. It has been suggested that PGE may act as a physiological intermediary in NA action,[18] and may regulate autonomic noradrenergic neurotransmission.[19,20]

At the sympathetic neuronal level NA has now been shown to increase PGE through an α-adrenoceptor mechanism, and

TABLE I. SUMMARY OF THE EFFECTS OF PGs ON PITUITARY HORMONE SECRETION*

Hormone	Prostaglandin	Site of action	Comment
TSH	**PGE, PGF**	**P**	**No effect on TRF**
ACTH	**PGE, PGF**	**P/ME**	**CRF?**
GH	**PGE**	**P/ME, AN**	**GRF ↑. Calcium-dependent effect on somatotrophs**
PRL	**PGE > PGF, PGI_2**	**ME**	**PIF ↓ PRF ↑ Needs steroids Affects DA neurotransmission**
FSH, LH	**$PGE_2 > PGE_1 > PGF_{2\alpha}$**	**MBH, ME, POA, AHA**	**LHRF ↑ Influenced by oestrogens NA effect > DA effect**

*Summarized from the review by Ojeda *et al.*[17]
P = pituitary; ME = median eminence; AN = arcuate nucleus; MBH = medial basal hypothalamus; POA = pre-optic area; AHA = anterior hypothalamic area; TRF = thyrotrophin-releasing factor; CRF = corticotrophin-releasing factor; GRF = GH-releasing factor; PIF = PRL-inhibiting factor; PRF = PRL-releasing factor; LHRF = LH-releasing factor; DA = dopamine.

PGE has been shown to reduce NA release from presynaptic nerve endings *in vitro* and to reduce stimulated NA neurotransmission through restriction of calcium availability.[21] Other PGs have less significant effects on NA neurotransmission, although PGG_2, PGH_2 and PGD_2 do show similar effects to PGE_2, while $PGF_{2\alpha}$ may have opposite effects.[21] These *in vitro* results conflict with results obtained *in vivo*. Most of the *in vivo* results, however, have been based on experiments involving indomethacin blockade of PG synthesis; however, since this compound is known to inhibit phosphodiesterase and cAMP-dependent protein kinase activity too,[22] the *in vivo* results may not be due to effects on PG synthesis. These differences may also be due to dose-related effects and differential presynaptic (decreased NA release) and postsynaptic (increased synthesis of cAMP) effects of PGE, to increased leukotriene synthesis on cyclo-oxygenase (low-dose) blockade,[9,21] or to a baroreceptor feedback mechanism operating *in vivo*.[21]

PGs have also been shown to affect pineal gland function. Secretion of melatonin from the pineal gland is mainly under noradrenergic neuronal control,[23] although many extrinsic factors affect pineal function, e.g. steroids, thyroid hormones, PRL and PGE_2.[24] The level of cytoplasmic oestrogen binding sites and their translocation to the nucleus are in turn under noradrenergic ß-receptor-mediated control.[25] These endocrine-neural and neural-endocrine interactions may be modulated by PGs.[26]

In 1976 Szabo and Friedhoff[27] demonstrated that indomethacin affected pineal gland enzyme activity. It has since been shown that PGE_2 increases the efflux of melatonin from the pineal gland 13 - 20-fold,[27] and that these effects can be reduced by treatment with indomethacin and re-established by the addition of PGE_2.[28] PGE_2 at a concentration of ± 10 nM has been shown to increase cAMP levels.[29] The PGE_2 effects are thought to be postsynaptic and they exhibit a dose-dependence on α-adrenergic binding site activation,[30] although this increase also takes place on addition of PGE_2 to pineal explants *in vitro* in the absence of adrenergic input.[31] PGE_2 up to a level of 100 nM has no effect on potassium-induced NA release in the pineal gland[28] (presynaptic), and specific binding sites for PGE_2 have been found in the bovine pineal gland.[32] The emerging picture is similar to that demonstrated in hypothalamic and sympathetic neurons, i.e. increased NA binding leads to increased PGE_2 which stimulates cAMP formation (postsynaptic), while higher concentrations of PGE acting on PGE receptors reduce NA release (presynaptic). PGE may act — through overflow into the synaptic cleft — as a feedback control and modulator of adrenergic neurotransmission,[31] although this possibility is still controversial.[12] In addition, some of the effects of melatonin closely resemble effects of indomethacin,[31] and melatonin and the pineal gland may exert management of neuro-endocrine function through PG interaction.

Importance of phospholipids (PLs) in PG effects

For many years PLs have been thought to play an active role in exocrine and endocrine gland metabolism.[33] Membrane structural PLs are not only substrates for PG synthesis (Fig. 1) but they are also thought to play a role in calcium uptake and neurotransmitter release and in the activation of certain protein kinases. Therefore the effects of isolated PG treatment *in vitro* may not necessarily reflect *in vivo* PG-PL-mediated processes. Phosphatidate (PA) has been shown to increase calcium uptake at time intervals up to 3 seconds (i.e. fast calcium current)[34] and to increase dopamine release in synaptosomes from rat brain,[35] and phosphatidyl serine has been shown to promote catecholamine metabolism in mouse brain[36] and the release of acetylcholine from rat brain cortex[36] and to influence synaptosomal Na^+, K^+-ATPase.[37] In smooth muscle the increase in PA is mediated through α-receptors and was blocked by phenoxybenzamine.[38] Diacylglycerol induces protein phosphorylation at tyrosine residues,[39] possibly through activation of a specific calcium-dependent (10^{-7}M), calmodulin-independent protein kinase,[40] and together with PA is thought to supply arachidonate for PG synthesis from receptor-stimulated breakdown of phosphatidyl inositol (PI) (Fig. 3).[41] It has therefore been suggested that PI may be involved in PL and PG biosynthesis[42] and protein kinase C activation,[40] and that these processes may interact with cAMP- and cyclic guanosine monophosphate-activated protein kinases to control cellular function[40] (Fig. 4). In platelets PI breakdown and subsequent protein phosphorylation is inhibited by cAMP and PGE,[40] and in rat brain the PI-PA effect has been localized in synaptic vesicles[43] and a large quantity of protein kinase C has been found in the synaptosomal fraction.[40] The PL-PG- (or PI-PA-) receptor-stimulated effects represent a link between cell-membrane receptors, changes in membrane structure and activation of protein kinases, and they may act as a molecular link between polarization/depolarization, calcium uptake and neurotransmission.[35,42] It is possibly at this second messenger level that the integration of hypothalamic neuronal input occurs.[5,42,44]

The unravelling of the function of PGs in the central nervous system is important as regards molecular biology, and may explain basic and important neuro-endocrine control mechanisms and clinically relevant processes such as the role of lithium[45,46] and cationic drugs[42] in the treatment of depression. The presence of a similar participation of PGs in peripheral neurotransmission may explain the ubiquitous presence

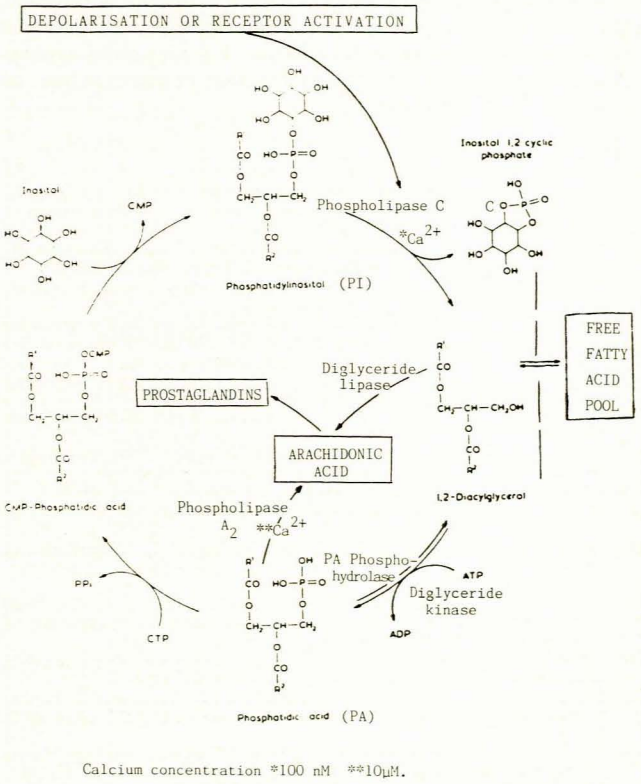

Fig. 3. Generation of PLs and PGs from cell membranes — possible pathways (adapted from Pearce;[54] based mainly on the work of Michell,[42] Michell and Kirk,[55] Billah *et al.*,[41] Pickard and Hawthorne,[43] and Hokin and Hokin[33,56]): (*i*) the R^1 and R^2 fatty acids may exchange with the free fatty acids present in the cell; (*ii*) the initial event may be breakdown of PI mono- or diphosphate,[42] and (*iii*) an alternative pathway for PG synthesis is possible from phosphatidylcholine, involving methylation of PLs and possible ß-receptor involvement.[12] R^1 = stearic acid; R^2 = arachidonic acid in mouse brain.[56]

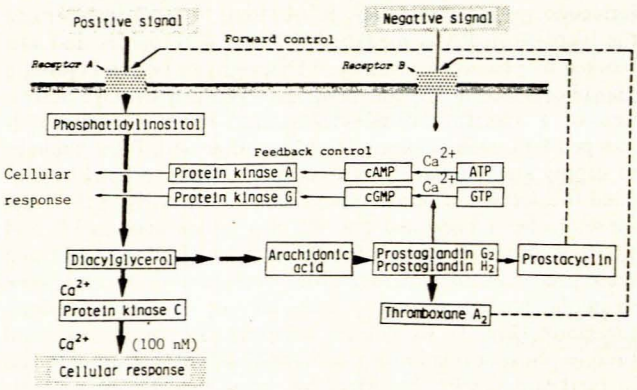

Fig. 4. A possible role of PGs in transmembrane control of neuronal function (from Nishizuka[40]). The above scheme was constructed using platelets as a model system. It may occur in neuronal junctions where E-series PGs may act in a manner similar to PGI_2. At the moment PGI_2 and thromboxane would appear to play a minor role in neurotransmission. In the context of this article *receptor A* = α-adrenergic receptor. The details with regard to pre-/postsynaptic localization of receptors are at this time uncertain. Acetylcholine also activates the PI-PA cycle through action on muscarinic receptors,[42] and serotonin through serotonin receptors ($5\text{-}HT_1$).[5] The reduced formation of PA may limit calcium uptake and exert negative feedback on activation of protein kinases A and G.

of PGs in various tissues,[21] or endogenous PGs may act as part of the second messenger system in these tissues.[42] PGs and PLs may influence such events as insulin release from the pancreas[47] and the cellular proliferation induced by tumour promoters such as phorbol esters.[40,48–52] Certainly PLs can no longer be regarded as merely structural membrane components, and *in vitro* work with liposomes has already suggested that conformational changes in membrane PLs induced by calcium and protein may explain the functioning of some of the ion channels in cell membranes.[53]

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