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Chapter I

Prostaglandins and Neural Functions: A Review

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Abstract

Prostaglandins are a group of 20-carbon fatty acids produced from arachidonic acid via the cyclooxygenase (COX) pathway in response to extrinsic stimuli. These fatty acids act through specific G-protein-coupled receptors to regulate biological functions such as hormone release, body temperature, cardiovascular activity, inflammation and development. In the nervous system, prostaglandins regulate behaviors such as reduced exploratory activity, decreased locomotion, sedation, convulsions, stupor and catatonia in many species. In goldfish, prostaglandins can synchronize sexual behavior in the opposite sex. Other neural functions such as analgesia, neurotransmitter release, neurogenesis, olfaction, sleep, synaptic plasticity and formation of dendritic spines are also associated with prostaglandins. Arachidonic acid or one of its metabolites can be synthesized selectively within a given cell type initially stimulated by a neurotransmitter and then released into the extracellular space. The compounds can then be metabolized in target cells by specific enzymes. In this mode, prostaglandins can play a diverse role in their attributed neural function. In addition, prostaglandins are involved in many pathological conditions such as autism, cerebral vasospasm and ischemia, migraine, malformations and neurodevelopmental defects. Therefore, understanding the effects and mechanisms of prostaglandins in neural pathogenesis could link to improvements in human health.

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Introduction

Prostaglandins are a group of 20-carbon fatty acids produced from arachidonic acid via the cyclooxygenase pathway in response to extrinsic stimuli (Smith 1989, 1992; Smith et al., 1991; Smith et al., 2011). Prostanoid biosynthesis (including classical prostaglandins PGD, PGE and PGF, as well as prostacyclins and thromboxanes) proceeds in three stages: (1) extrinsic stimuli-activated mobilization of esterified arachidonate from precursor lipids in the cell membrane through the action of lipases, (2) conversion of arachidonate to the prostaglandin endoperoxide (PGH_2) mediated by PGH synthases, and (3) cell-specific isomerization or reduction of PGH_2 by specific synthases (isomerases) or reductases to the major biologically active prostanoids PGD_2, PGE_2, $PGF_{2\alpha}$, prostacyclin (PGI_2), or thromboxane A_2 (TXA_2; Figure1, modified from Smith, 1992; Smith et al., 2011).

Prostaglandins are local hormones (i.e. autocoids; Smith 1989, 1992; Smith et al., 1991). Infused PGE and PGF derivatives fail to survive a single pass through the circulatory system. Their synthesis is not restricted to a central endocrine organ, but rather occurs in most organs, although not necessarily in all cell types. The plasma concentrations of these compounds, except in rare situations, are less than 10^{-9}M, a concentration normally unable to elicit responses.

The low plasma concentrations of prostaglandins are a consequence of active catabolism, which begins with oxidation of the 15-hydroxyl group to yield the 15-oxo-derivatives which have 10- to 100-fold less activity than the parent compounds. There are different 15-hydroxyprostaglandin dehydrogenases specific for different prostaglandins (Smith 1989, 1992; Smith et al., 1991). Prostaglandins are ubiquitously distributed in virtually all mammalian tissues and organs (Ito et al., 1992). Prostaglandin levels in snap-frozen samples are generally very low, in the range of ng/g (Wolfe et al., 1976). However, in different species, the predominant prostaglandins may vary (Wolff, 1988).

In the rodent brain, PGD_2 is the major cyclooxygenase metabolite, followed by lower concentrations of $PGF_{2\alpha}$, PGE_2 and PGI_2 (Abdel-Halim et al., 1977; Hayashi et al., 1987; Hertting and Serigi, 1989; Narumiya et al., 1982; Ogorochi et al., 1984; Sun et al., 1977).

In the human neocortex, only a minute amount of PGD_2 was found due to its rapid metabolism into 9α, 11β-PGF_2 (Wolfe, 1988; Wolfe et al., 1989). $PGF_{2\alpha}$ was first thought as the most abundant prostaglandin in human brain (Abdel-Halim et al., 1980a). Later, the presence of prostaglandins D_2, E_2 and $F_{2\alpha}$ was demonstrated *post-mortem* in various regions of the human brain, pineal body and pituitary. Prostaglandins D_2 and E_2 were abundant in pineal body, pituitary, olfactory bulb and hypothalamus. $PGF_{2\alpha}$ was more evenly distributed throughout the human brain (Ogorochi et al., 1984). Therefore, prostaglandins appear to have species-specific and tissue-specific compositions.

Prostaglandins exert powerful central effects on the regulation of behavior, body temperature, cardiovascular activity, and neurotransmitter functions (Chiu and Richardson, 1985). Different members of the prostaglandin family may serve different functions in the brain due to their differential distribution (Abdel-Halim et al., 1980a,b). Both PGD_2 and PGE_2 are implicated in physiological regulation of sleep (Hayaishi, 1988). PGD_2 also exerts neuromodulatory effects on hormone release, body temperature, olfactory function, and analgesia (Ito et al., 1989). Prostaglandins of the E and F series can mediate hyperthermia and fever (Eguchi et al., 1988; Feldberg and Milton, 1978; Lazarus, 2006), as well as

neurogenesis (Chung-Davidson et al., 2008b; Uchida et al., 2002). PGE_2 and $PGF_{2\alpha}$ have been implicated in various cerebral functions including the autoregulation of blood flow (Chemtob et al., 1990b). PGE_2 is also involved in inflammation (Hata and Breyer, 2004), development (Li et al., 1993), synaptic plasticity and formation of dendritic spines (Burks et al., 2007; Chen et al., 2002; Zhu et al., 2005).

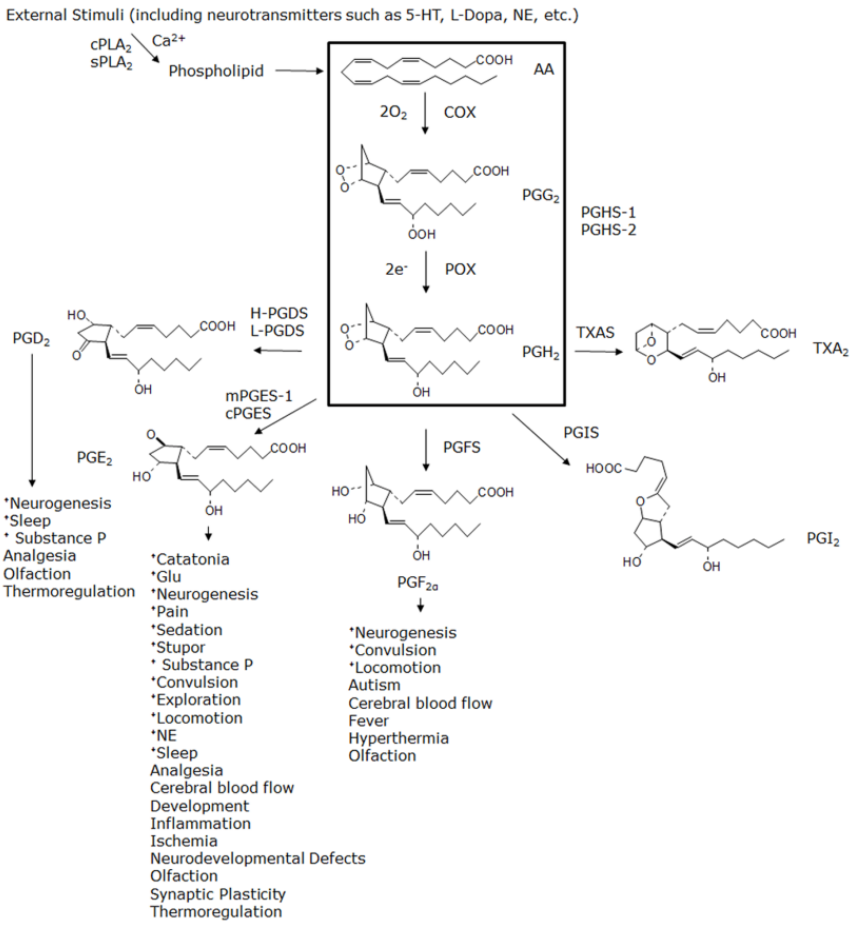

Figure 1. A schematic diagram of the biosynthesis and neural functions of prostaglandins. 5-HT, 5-hydroxytryptamine; AA, arachidonic acid; Glu, glutamate; $cPLA_2$, cytosolic phospholipase A_2; $sPLA_2$, nonpancreatic, secretory phospholipase A_2; PG, prostaglandin; PGHS, prostaglandin endoperoxide H synthase; COX, cyclooxygenase; POX, peroxidase; H-PGDS, hematopoietic PGD synthase; L-PGDS, lipocalin-type PGD synthase; cPGES, cytosolic PGE synthase; mPGES-1, microsomal PGE synthase-1; PGFS, PGF synthase; PGIS, PGI (prostacyclin) synthase; NE, norepinephrine; TXAS, thromboxane A synthase.

This chapter will briefly review the receptors and signal transduction pathways of prostaglandins and the roles of prostaglandins in neural functions such as neurotransmission, neurogenesis, behavior, pain, thermoregulation, and the possible risk of pathogenesis.

Prostaglandins Act through G-Protein Coupled-Receptors

Prostaglandins mediate important physiological functions in the nervous system via activation of G-protein-coupled receptors (Kennedy et al., 1982; Sasaki et al., 1985; Coleman, 1987; Santoian et al., 1989; Abran et al., 1994). Prostanoid receptors are classified into two groups. One group consists of the PGD_2 receptor, the PGE receptor in most tissues (EP_{2-4}), and the PGI_2 receptor, which are linked to cyclic adenosine monophosphate (cAMP) formation (Jumblatt and Paterson, 1991; Sugimoto et al., 1992). The other group comprises the $PGF_{2\alpha}$ receptor, the TXA_2 receptor, and EP_1 (a subtype of PGE receptor) which are linked to phosphoinositol metabolism and Ca^{2+} mobilization (Halushka et al., 1989; Ito et al., 1992; Suba and Roth, 1987).

Prostaglandins can exert diverse neural functions through the activation of different types of receptors and signal transduction pathways. The four G-protein coupled E-prostanoid receptors (EP_{1-4}) are well-characterized prostaglandin receptors. EP_1 is involved in regulation of intracellular calcium levels by the action of phospholipase C (PLC) and inositol 1,4,5-triphosphate (IP_3). EP_2 and EP_4 receptors mediate activation of protein kinase A (PKA) through the action of cAMP and calcium level via different mechanisms, depending on the type of associated G-proteins (Breyer et al., 2001).

Prostaglandins and Neurotransmitters

Several neurotransmitters can modulate prostaglandin release in the brain. 5-hydroxytryptamine (5-HT) enhances the release of prostaglandins (Wolfe et al., 1976; Schaefer et al., 1978). Micromolar concentrations of muscarinic agonists induce the release of PGE_2 and PGF_2 in cerebellar cortical slices (Reichman et al, 1987). However, acetylcholine, in the presence of physostigmine (Hillier et al., 1976), has no effect on prostaglandin release. Catecholamines and L-dopa have an effect on prostaglandin release from central nervous tissues under *in vitro* conditions (Chiu and Richardson, 1985).

Norepinephrine induces PGE_2 release in various rodent brain areas (Hillier et al., 1976, 1979; Schaefer et al., 1978; Schaad, 1989) through the activation of α1-adrenergic receptors (Burch et al., 1986a,b). Higher concentrations of norepinephrine are required to elicit $PGF_{2\alpha}$ release (Wolfe et al., 1976; Schaefer et al., 1978; Hillier et al., 1979; Seregi and Hertting, 1984).

However, the mechanism of $PGF_{2\alpha}$ release may not involve the catecholamine receptor since it is reduced by monoamine-oxidase inhibitors (Schaefer et al., 1978), which are known to inhibit PGI_2 synthesis (Gryglewski et al., 1976). Histamine has no effect on prostaglandin release (Wolfe et al., 1976).

Prostaglandins can also regulate neurotransmitter release. PGE_2 inhibits the release of norepinephrine in the peripheral nervous system and in cortical slices (Hedqvist, 1970; Bergstrom et al., 1973; Reimann et al., 1981; Templeton, 1988) via decrease in Ca^{2+} conductance (Mo et al., 1985). The release of substance P is increased by PGD_2 and PGE_2 in cultured sensory neurons (Vasko et al., 1989). Glutamate release was induced from astrocytes that are important for neuroblast survival and proliferation, and this signal may be accentuated following ischemia or-injury-induced PGE_2 release (Dave et al., 2010). It is conceivable that arachidonic acid or one of its metabolites such as PGH_2, is synthesized

selectively within a given cell type initially stimulated by a neurotransmitter and then released into the extracellular space.

The compounds can then be metabolized in target cells by specific enzymes. In this mode, prostaglandins can play a diverse role in their attributed neural functions (Schaad et al., 1991).

Prostaglandins and Behavior

In general, prostaglandins reduce locomotor behavior and induce sleep or stupor in animals. The most common behavioral effects of prostaglandin E series are sedation and the inhibition of locomotor and exploratory activities (Chiu and Richardson, 1985). Interestingly, prostanoids of the A and F series reduce locomotor activity but do not exert sedative effects (Horton and Main, 1965; Gilmore and Shaikh, 1972; Nistico and Marley, 1976). The differences in the pharmacological effects of A, E and F prostanoids may be quantitative (Chiu and Richardson, 1985). The three behavioral effects (reduced exploratory activity, decreased locomotor activity, and sedation) can be viewed as a continuum, such that the least potent agent can be expected to reduce the exploratory activity without affecting the other two parameters, whereas the most potent agent can produce all three behavioral effects. Thus ranked, the prostanoids of the E series are the most potent, while the F series are of intermediate strength, and the A series are the weakest in producing behavioral effects (Chiu and Richardson, 1985).

Prostaglandins of the E series, when injected into the lateral ventricles (i.v.t.) in the cat, produced stupor and catatonia (Horton, 1964). Similar effects were observed after i.v.t. injection of cholinergic agents such as physostigmine and acetylcholine in cats (Feldberg and Sherwood, 1954, 1955) and monkeys (Desijaru, 1973). Since catatonia does not result from either the i.v. or i.p. injection (Horton, 1964; Bloss and Singer, 1978), this effect is localized within the brain (Chiu and Richardon, 1985).

Prostaglandins of the E and F series reduce the debilitating effects of convulsions in animals (Chiu and Richardson, 1985). The level of prostaglandins, in particular of the F type, increases tremendously in the brain during convulsions in animals (Steinhauer et al., 1979) and humans (Egg et al., 1980). Such an increase in prostaglandin release may serve a protective role (Chiu and Richardson, 1985).

PGD_2 plays a role in sleep regulation (Giles and Leff, 1988; Hayaishi, 1989, 2002; Herlong and Scott, 2006; Huang et al., 2007). A single injection of PGD_2 increases the sleeping time in rats or monkeys by 400-600%. In contrast, PGE_2 suppresses slow wave- and REM-sleep while its antagonist reduced the awakening time (Matsumura et al., 1989).

In goldfish, $PGF_{2\alpha}$ plays a dual role as a hormone and a pheromone to synchronize male and female sexual behaviors (Stacey, 1987). At the time of ovulation, female oviducts synthesize and secret $PGF_{2\alpha}$ that induces reproductive behaviors (Stacey and Peter, 1979; Sorensen et al., 1988). $PGF_{2\alpha}$ and its metabolites (mainly 15-keto-$PGF_{2\alpha}$) are also released into water as postovulatory pheromones that induce male spawning behavior and increase male gonadotropin-II and sperm production (Sorensen et al., 1988, 1989; Sorensen and Goetz, 1993). Whether $PGF_{2\alpha}$ is involved in the sexual behavior of other animals has not been investigated.

Prostaglandins and Neurogenesis

Prostaglandins are involved in neurogenesis. The self-renewal and multipotency of neural progenitor cells are regulated by various humoral factors under physiological and pathological conditions such as ischemia (Nakatomi et al., 2002), seizure (Parent et al., 1997), and sleep (Guzmán-Marín et al., 2003). Since PGD_2 is the major cyclooxygenase metabolite in rodents (Abdel-Halim et al., 1977; Hayashi et al., 1987; Hertting and Serigi, 1989; Narumiya et al., 1982; Ogorochi et al., 1984; Sun et al., 1977), and plays a role in sleep regulation (Giles and Leff, 1988; Hayaishi, 1989, 2002; Herlong and Scott, 2006; Huang et al., 2007), it seems to be a good candidate for regulating neurogenesis. Indeed, PGD_2 has been shown to have biphasic effects on neural progenitor cell proliferation (Katura et al., 2010). 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2), a nonenzymatic metabolite of PGD_2, regulates progenitor cell proliferation (Katura et al., 2010). 15d-PGJ_2 is endogenously produced from PGD_2 through spontaneous nonenzymatic dehydration followed by isomerization and is an endogenous ligand for peroxisomal proliferator-activated receptor γ (PPARγ) (Forman et al., 1995), which plays a critical role in the regulation of cell differentiation and metabolism (Debril et al., 2001; Walczak and Tontonoz, 2002).

Although the exact mechanisms have yet to be identified, $PGF_{2\alpha}$ induces adult neurogenesis in the diencephalon of goldfish, which is known to be involved in reproduction (Chung-Davidson et al., 2008a,b). $PGF_{2\alpha}$ also induced neurogenesis in several brain regions including the telencephalon and brain stem motor nuclei in goldfish. This is the first evidence that prostaglandin $PGF_{2\alpha}$ can act as a pheromone through the olfactory system to induce neurogenesis in adult brains (Chung-Davidson et al., 2008b).

PGE_2 also regulates the activities of neural progenitor cells (Uchida et al., 2002). Neurogenesis persists in two regions of the adult brain in mammals: the subventricular zone (SVZ) along the lateral ventricles and the subgranular zone of the hippocampal dentate gyrus (Luskin, 1993; Lois and Alvarez-Buylla, 1994). Neurogenesis in the dentate gyrus of adult rodents is elicited by transient global ischemia (Liu et al., 1998; Uchida et al., 2002). COX-2, a rate-limiting enzyme for prostanoid synthesis, is also induced by ischemia (Uchida et al., 2002). Administration of a non-selective COX inhibitor to ischemic animals suppressed cell proliferation in the subgranular zone (SGZ) at the dentate gyrus of the hippocampus (Kumihashi et al., 2001; Uchida et al., 2002). Hippocampal injection of sulprostone, an analogue of PGE_2, increased the number of 5-bromo-2'-deoxyuridine (BrdU)-immunoreactive cells in the SGZ (Uchida et al., 2002). Therefore, PGE_2 may play an important role in cell proliferation in the SGZ (Uchida et al., 2002). PGE_2 exerts its neurogenic effects through four G-protein coupled E-prostanoid receptors (EP_{1-4}). EP_{1-4} receptor mRNA levels were elevated during neurogenesis in mouse (Tamiji and Crawford, 2010). PGE_2 may stimulate neurogenesis via EP_3 receptors in the dentate gyrus in rodents. However, the involvement of other prostaglandin receptors in neurogenesis remains to be elucidated (Uchida et al., 2002).

Prostaglandins and Pain

Chronic pain involves a mix of both inflammatory and neuropathic processes, and both processes involve numerous neurotransmitters, neuromodulators, and receptors of primary

afferent neurons relaying pain signals from the periphery to the central nervous system (Bridges et al., 2001; Kidd and Urban, 2001). Substance P (a well-known tachykinin peptide) encoded by the preprotachykinin-A (PPT-A) gene, an important neurotransmitter and/or a neuromodulator, is synthesized in the dorsal root ganglia (DRG) and released from primary afferent neurons to convey nociceptive information and transmit pain (Cao et al., 1998; Snijdelaar et al., 2000; Tang et al., 2007).

PGE_2 is a well-known pain and proinflammatory mediator abundantly produced in inflamed tissue. PGE_2-induced nociception is mediated through its four EP receptors expressed in nociceptive DRG neurons (nociceptors) and in the spinal dorsal horn neurons (Vanegas and Schaible 2001). It causes pain by directly exciting nociceptors (Vanegas and Schaible 2001) and indirectly stimulating the release of pain-related neuropeptides including substance P and calcitonin gene-related peptide (CGRP) from nociceptors (Vasko et al. 1994; Vasko 1995, White 1996).

Activation of neuronal and glial cells in the trigeminal ganglion by IL-β leads to an elevated expression of COX-2 in these cells. Newly synthesized PGE (by COX-2) in turn activates trigeminal neurons to release CGRP. There appears to be a glia-neuron interaction in the trigeminal ganglion, demonstrating a sequential link between COX-2 and CGRP, and this interaction could be the mechanism by which COX-2 inhibitors affect migraine (Neeb et al., 2012).

Neuropathic pain is an intractable chronic pain condition caused by direct physical damage or diseases of the nervous system responsible for pain generation and transmission. It is generally manifested as spontaneous pain, hyperalgesia (exaggerated response to painful stimulation) and allodynia (painful response to innocuous stimulation). Inflammatory mediators over-produced in injured nerves play a crucial role in the initiation and maintenance of neuropathic pain. Among numerous inflammatory mediators, COX-2 and its end product PGE_2 are persistently up-regulated in infiltrating macrophages and Schwann cells in injured nerves (Ma et al., 2012). Injured nerve-derived COX-2 and PGE_2 facilitate the up-regulation of pro-inflammatory cytokine interleukin-6 (IL-6) (Ma and Quirion, 2005) and pain-related peptides substance P and CGRP in invading macrophages following partial sciatic nerve ligation (Ma and Quirion, 2006; Ma et al., 2010b). EP_4 receptor, PKA, PKC, ERK/MAPK, CREB and NFκB signaling pathways are involved in PGE_2-induced IL-6 up-regulation in DRG neurons (St-Jacques and Ma, 2011).

Injured nerve-derived COX-2 and PGE_2 also up-regulate the production of transient receptor potential vanilloid-1 (TRPV1) and brain-derived neurotrophic factor (BDNF) in DRG neurons (Ma, 2010; Ma et al., 2010a; Duarte et al., 2012). EP_1 and EP_4 receptor subtypes, PKA, ERK/MAPK and CREB signaling pathways as well as nerve growth factor (NGF) are all involved in PGE_2-induced BDNF synthesis in DRG neurons related to neuropathic pain (Duarte et al., 2012).

Perineural or intraplantar injection of a non-selective or selective COX-2 inhibitor remarkably relieved neuropathic pain (Syriatowicz et al. 1999; Ma and Eisenach 2002, 2003; Ma et al. 2010). Blocking COX-2-PGE_2-EP_1 and EP_4 signalling in injured nerves might interrupt the amplification of nociceptive responses mediated by up-regulated pain mediators in DRG neurons (St-Jacques and Ma, 2011). In clinical studies, most COX-2 inhibitors are administered orally. The amount of COX-2 inhibitors reaching injured nerves is likely not sufficient to suppress the over-production of PGE_2 (Syriatowicz et al., 1999; Ma and Eisenach, 2002). This assumption is supported by the report that perineural injections of

nonselective or selective COX-2 inhibitors are able to relieve neuropathic pain in animal models. Thus, it is conceivable that COX inhibitors may be useful to treat some types of neuropathic pain via local injection, an attractive approach to secure high concentrations of COX inhibitors around injured nerves and to limit the serious cardiovascular side effects notoriously associated with systemic COX-2 inhibitors (Graham et al., 2005). With the emergence of more potent and selective COX-2 inhibitors, a new generation of nonsteroidal anti-inflammatory drugs may offer better benefits in treating certain types of neuropathic pain than the COX-2 inhibitors presently in use. This trend has been suggested by on-going phase II and III clinical trials of highly potent COX-2 inhibitors in treating neuropathic pain (Gilron and Coderre, 2007).

Prostaglandins and Thermoregulation

Prostaglandins of various kinds (E_1, E_2 and $F_{1\alpha}$) produced hyperthermia in many animal species and there seems to be no cross-species differences (Chiu and Richardson, 1985). Injections of prostaglandins E_1 or $F_{1\alpha}$ into the third ventricle of the cat caused a dose-dependent rise in body temperature (Milton and Wendlandt, 1970). PGE_2 appears to act on the anterior hypothalamus to induce fever (Coceani et al., 1989; Milton, 1989). IL-1, a potent endogenous pyrogen, acts via the synthesis of prostaglandins. In infectious diseases, IL-1 synthesis is activated and IL-1 can cross the blood-brain barrier and trigger PGE_2 synthesis.

The biosynthesis of PGE_2 can also be stimulated in cerebral microvessels by endotoxins of bacterial origin. However, injections of prostaglandins E_1, E_2 or $F_{2\alpha}$ into the hypothalamus can also elicit a hypothermic response (Artunkal et al., 1977; Artunkal and Marley, 1974). Thus, prostaglandins seem to be involved in thermoregulation.

Prostaglandins and Neural Pathogenesis

Prostaglandins are associated with several pathological conditions in the brain. The level of PGE_2 in the central nervous system is increased in various pathological conditions (Montine et al., 1999; Paoletti et al., 1998). For example, cerebral ischemia in rodents caused the up-regulation of COX-2 gene expressions and PGE_2 concentrations in the hippocampus (Ohtsuki et al., 1996; Nakayama et al., 1998). Individuals with autism spectrum disorders have elevated levels of lipid peroxidation and oxidative stress biomarkers such as 8-isoprostane-$PGF_{2\alpha}$ in the plasma (Al-Gadani et al., 2009; Mostafa et al., 2010).

The cerebrovascular actions of prostaglandins have been examined in detail (White, 1982; White and Hagen, 1982). PGE_2 and $PGF_{2\alpha}$ are the major prostaglandins in the brain and the cerebral vasculature (Gaudet et al., 1980; White and Hagen, 1982; Chemtob et al., 1990a,b). Concentrations of these prostaglandins in the blood and brain are much higher in the perinatal period than in adult life (Mitchell et al., 1978; Jones et al., 1993). Prostaglandins have been implicated in the pathogenesis of migraine (Parantainen and Vapaatalo, 1988). In addition, they seem to play a role in other pathological conditions such as cerebral vasospasm and ischemia (Watanabe et al., 1988). Furthermore, the vasodilation effect of VIP seems to be mediated by the effect of prostaglandins on dopamine release (Rotrosen and Wolkin, 1987).

Altered PGE_2 signalling due to abnormal lipid peroxidation and oxidative stress may underlie some pathologies of the nervous system. Prenatal exposure to misoprostol, a prostaglandin type E analogue, during the first and second trimester of pregnancy has been linked to a number of malformations and neurodevelopmental defects (Miller et al., 2005; Bandim et al., 2003). In summary, prostaglandins can act through specific G-protein-coupled receptors to elicit important neural functions. However, altered prostaglandin signaling due to abnormal lipid peroxidation and oxidative stress may underlie some pathologies of the nervous system. Understanding the effects and mechanisms of prostaglandin pathogenesis could link to improvements in human health.

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