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PROSTAGLANDINS AND BRAIN-GUT AXIS

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Prostaglandins (PGs) have well documented physiological and pharmacological actions on the gastrointestinal (GI) tract. This communication reviews the evidence for peripheral and central nervous system (CNS) physiological actions of PGs in order to determine their role in the brain-gut axis, if any. PGs are widely distributed in nearly all cells peripherally and centrally. Laboratory and clinical evidence indicate that there is a direct relationship between altered GI physiological functions and peripheral PGs biosynthesis. Either local or parenteral administration of natural E-series PGs alters GI physiological functions particularly those relating to mucosal defense. Furthermore, the cyclooxygenase enzymes (COX), which are responsible for the PGs biosynthesis, have been localized in the brain as well as peripherally. However, increased levels of PGs in the brain have been associated with pathological processes such as inflammation, pain, fever and addiction. Although PGs have been shown to modulate CNS effects of catecholaminergic, serotonergic and cholinergic neurons, there is no meaningful information concerning their direct central effect on GI function. The evidence for a clear physiological role of central PGs on the GI tract is not convincing. At this time, we conclude that PGs primarily manifest their activity on the GI tract by peripheral rather than by central mechanisms.

Key words: Addiction, CNS, COX, cyclooxygenase, cytoprotection, fever, inflammation, mucosal protection, pain, prostaglandins, PGE2, PGF2alpha, PGD2, thromboxane B2, TXB2, stress ulcers

INTRODUCTION

Prostaglandins constitute a family of unsaturated fatty acids with 20-carbon skeleton. Prostaglandins are found in almost every mammalian cell and are
considered locally acting hormones (autacoids). They are synthesized on demand and subsequently inactivated at or near the sites of their synthesis. Prostaglandins are metabolically unstable compounds and are not stored. Because of their omnipresence in nearly all cells, PGs possess wide variety of physiological and pharmacological action, which are occasionally troublesome in their clinical use as drugs (1). There is clear evidence that PGs have local and systemic action affecting GI physiology (2). However, the role of central PGs in the regulations of GI physiology and particularly mucosal defense is not clearly understood. The purpose of this communication is to review the evidence for a CNS role of PGs in GI physiology and pathophysiology in order to examine their role on the brain-gut axis, if any.

**Brain-Gut Axis Concept**

The concept supporting the existence of functionally important “brain-gut axis” was originally proposed to account for the fact that several peptides including bombesin, neurotensin and calcitonin-gene-related peptide occur both in brain and gut and seem to exert opposite actions on gut function when administered centrally and peripherally (3 - 5). Support for this concept is derived from clinical and laboratory studies showing that stress ulcer formation could be prevented by anxiolytic and antidepressant drugs. The reduction of anxiety, which is associated with the stressful stimuli, occurs by a direct effect on the CNS as shown by the inhibitory effects of a centrally administered imipramine on stress ulcer formation (6, 7). Furthermore, the phenothiazine tranquilizer thiopropazoate had been demonstrated to significantly potentiate the anti-ulcer action of cimetidine (a histamine-H$_2$-receptor antagonist) and propantheline (a peripheral anticholinergic drug) against stress ulcers (8). These laboratory studies indicate that the CNS mediated pharmacological actions of thiopropazoate potentiated the peripheral GI protective action of the anti-ulcer drugs cimetidine and propantheline, which provides further support for the concept of brain-gut axis (8).

Several lines of evidence indicate the involvement of dopamine in peripheral and central action of many drugs affecting the brain-gut axis (5, 9). As is shown in Table 1, there is laboratory and clinical evidence that peripheral and central dopamine deficiency is associated with duodenal ulcers (9, 10). Since prostaglandins and other eicosanoids are involved in the presynaptic release of the neurotransmitters dopamine and serotonin (11), it is possible that some of their physiological action on the gut may be mediated by these neurotransmitters. However, the effects of central administration of PGs on dopamine-mediated effects on the GI tract have not yet been adequately investigated.

Although PGs, growth factors and hormones possess direct cellular protective effects on the GI tract that is independent of a central influence, there is preliminary evidence which indicates that the CNS plays a contributory role towards this cytoprotection. In their cytoprotective study with gastric mucosal
cells, Bodis et al. (12) showed that intact peripheral innervations are needed for the maximum demonstration of the prostacyclin-induced gastric cytoprotection.

Table 1. Prostaglandins, Central Dopamine, Peptic Ulcer and Brain-Gut Axis

- Prostaglandins are involved in the presynaptic release of the neurotransmitters dopamine and serotonin.
- Central deficiency of dopamine, common in Parkinson Disease Patients, is positively associated with peptic ulcer (9).
- Cysteamine and propionitrile decrease tissue concentration of central and/or peripheral dopamine. These substances induce duodenal ulcers formation in animals (10).
- Psychiatric patients, who presumably have increased central dopamine concentration rarely develop peptic ulcer (9).

Szabo S, et al. (9, 10).

E-Prostaglandins and Gastrointestinal Physiology

Prostaglandins of the E-series are the principal autacoids localized in the GI tract and have several well-characterized physiological actions (1). E-series prostaglandins inhibit basal and stimulated acid secretion and protect the GI mucosa from injury induced by noxious agents. E- and F-series PGs have opposing dose-related effects on the lower esophageal sphincter and circular intestinal muscle causing relaxation and contractions, respectively (1, 13, 14). Other physiological effects of PGEs include an increase in hepatic blood flow, contraction of the gallbladder, relaxation of the sphincter of oddi, inhibition of pancreatic secretion and insulin release, and reduced absorption and induced secretion of electrolytes and water in the jejunum, ileum, but not the colon (Table 2).

A direct relationship exists between altered GI physiological function and prostaglandin synthesis (15, 16). For example, the nonsteroidal anti-inflammatory drugs (NSAIDs)-induced PGs depletion in the GI tract results in gastroduodenal ulceration and/or ulcer related GI complication (Table 3; 17). The administration of natural or synthetic PGEs, either by parenteral, oral or local routes, can overcome the GI toxicity associated with the mucosal depletion of PGE’s induced by NSAIDs (18 - 20). In addition, systemic or topical administration of natural and synthetic PGEs analogs can reproduce their well-characterized GI physiological actions on the inhibition of acid secretion and mucosal protection (2, 20). The fact that mucosal protection by PGs is demonstrated in-vitro on isolated gastric and duodenal cells clearly supports the idea that mucosal protection by PGs is a consequence of a direct action on PGs on the cells rather than manifestation of either a systemic or a CNS effects (21).
Table 2. Selected Peripheral Gastrointestinal Physiological Effects of Gut PGs. Data were adapted from Dajani (1).

<table>
<thead>
<tr>
<th>Physiological Effects</th>
<th>PGEs</th>
<th>PGFs</th>
<th>Prostacycline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric Acid Secretion</td>
<td>Inhibition</td>
<td>No inhibition</td>
<td>Inhibition</td>
</tr>
<tr>
<td>Gastric Blood Flow</td>
<td>Stimulation</td>
<td>Variable</td>
<td>Stimulation</td>
</tr>
<tr>
<td>Gastric Mucus Secretion</td>
<td>Stimulation</td>
<td>Stimulation</td>
<td>Stimulation</td>
</tr>
<tr>
<td>Intestinal Bicarbonate</td>
<td>Stimulation</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Gastric Mucosal Barrier</td>
<td>Active</td>
<td>Unknown</td>
<td>Active</td>
</tr>
<tr>
<td>Pancreatic Secretion</td>
<td>Inhibition</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Hepatic Blood Flow</td>
<td>Increase</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Small Intestinal Electrolytes &amp; Water Secretion</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Gall Bladder Muscle</td>
<td>Contraction</td>
<td>Contraction</td>
<td>Unknown</td>
</tr>
<tr>
<td>Sphincter of Oddi</td>
<td>Relaxation</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Lower Esophageal Sphincter</td>
<td>Relaxation</td>
<td>Contraction</td>
<td>Unknown</td>
</tr>
<tr>
<td>Gastric &amp; Intestinal Cytoprotection</td>
<td>Active*</td>
<td>Active</td>
<td>Active*</td>
</tr>
<tr>
<td>Experimental Ulcers</td>
<td>Active</td>
<td>Active</td>
<td>Active</td>
</tr>
</tbody>
</table>

*The dosages shown effective in animal cytoprotective studies are well below their gastric antisecretory doses.

Table 3. Prostaglandins and Gastrointestinal Physiology.

- A direct relationship exists between altered function and Prostaglandin biosynthesis (15, 16).
- Exogenously administered natural PGs alter physiological function.
- Prostaglandins depletion cause diseases (e.g., NSAID-induced GI ulcer) and exogenous administration of PGEs prevents and treat such ulcers (17, 18).

Prostaglandins and Central Nervous System

Prostaglandins and other eicosanoids have been identified in the CNS. The synthesis of PGE₂, PGD₂, PGF₂α, PGI₂, thromboxane A₂ (TXA₂), leukotriene C₄ (LTC₄), leukotriene B₄ (LTB₄), and other eicosanoids in the brain were well-demonstrated (Table 4; 22). Of interest is the observation that PGD₂ and PGF₂α are synthesized in large quantity in the brain (22). PGD₂ has recently been
proposed as a mediator responsible for sleep (23). Both stimulant and depressant effects of PGs on the CNS have been reported following their injection into the cerebral ventricle and the firing rates of individual brain cells may be increased or decreased after iontrophic applications of PGs (24). Intracerebroventricular administration of prostacyclin (PGI₂) produced sedation, stupor, catatonia as well as cataleptic behavior (25). PGs have been proposed to modulate catecholaminergic (26), serotoninergic (27) and cholinergic (28) neurons in the CNS. There is also accumulating data suggesting possible modulatory role of PGs on dopamine mediated behavior (29). However, the evidence for a modulating role of PGs on neuronal pathways is derived from limited in-vitro studies and no studies have investigated the central role of PGs on peripheral dopamine-mediated GI effects.

Table 4. Prostaglandins and Central Nervous System

- Many PGs have been identified in the CNS. PGD₂ and PGF₂ alpha are present in highest concentration in the brain.
- Both stimulant and depressive effects of PGs have been reported following their central administration.
- Many pharmacological effects have been observed following intracerebral administration of PGs, but no study has ever demonstrated a specific physiological effect on the GI tract.
- Convincing experimental data indicate that PGs function in the CNS in pathological processes such as pain, fever, drug dependence and possibly paralytic ileus.

Convincing experimental data indicate that PGs function in mostly pathological processes in the CNS, including drug dependence, nociception, fever induction, learning and memory, and excitotoxic brain injury such as stroke and epilepsy (30, 31). Elevated levels of PGE₂, PGF₂ alpha, thromboxane B₂ in cerebrospinal fluid have been found in patients with AIDs dementia. Abnormal central COX-2 expression had been found in patients with Parkinson’s disease and Down syndrome (32).

There is some emerging evidence indicating that central PGs may also be connected to an endogenous cannabinoids system as noted by the discovery that anadamide (arachidonyl ethanolamine), which is chemically an eicosanoid and is considered to possess cannabinoid agonist activity (33). However, it is beyond the scope of this paper to discuss all aspects of central PGs involvement in all pathological processes but rather focus on four principal actions of PGs as detailed below:

(a) Drug dependence: The central administration of PGE₂ facilitates acute dependence in morphine treated rats, while PGF₂ alpha (acting on dopaminergic
neurons) showed inconsistent attenuation of such dependence. Nielsen and Sparber (34) showed attenuation of morphine-induced withdrawal, while Nakagawa et al. (35) did not demonstrate any reduction of withdrawal symptoms following the intracerebral administration of PGF$_{2\alpha}$. Furthermore, Nakagawa et al. (35) showed that synthetic PGs acting on the prostaglandin EP$_{3}$ receptor attenuated withdrawal jumping in morphine dependent mice, however, the intracerebral administration of PGF$_{2\alpha}$ showed no such effect. Nechifor et al. (36) showed that two metabolically stable chemical analogs of PGF$_{2\alpha}$, when administered intraperitoneally, reduced several symptoms of the withdrawal syndrome in rats with morphine-induced dependence. These observations suggest a role of central PGs in the induction of drug dependence, either directly or indirectly via a modulating effect on catecholaminergic, serotonergic and cholinergic neurons in the CNS.

(b) Pain: Central PGs are clearly involved in pain perception and induction (31, 37). As reported by Turnbach et al. (38), the intrathecal administration of PGE$_{2}$ (1-100 nmol) or PGF$_{2\alpha}$ (1-100 nmol) produced profound and dose-dependent mechanical hyperalgesia, but only weak thermal hyperalgesia and touched-evoked allodynia in rats. Both PGs produced dose-dependent increases in response of nociceptive specific neurons to mechanical stimuli (38).

c) Inflammation: Prostaglandin E$_{2}$ is the major prostanoid produced centrally and in the periphery in animal models of acute and chronic inflammation, and its formation in both locations is blocked by COX-2 inhibitors (39). The PGE$_{2}$-induced inhibition by COX-2 inhibitors in the brain may occur secondarily to peripheral action mediated by inhibiting local PGs formation, which elicit increased firing of pain fibers and consequent activation in PGs synthesis in the CNS (39).

d) Fever: The systemic administration of PGEs induces fever in laboratory animals and man via a CNS mediated mechanism of action (30, 40, 41). Pyrogens such as interleukin-1 (IL-1) act via hypothalamic release of PGs (42).

**Prostaglandins and Brain-Gut Relationship**

As of now, there are no meaningful studies, which characterized the in-vivo effect of central PGs on GI physiology such as acid secretion, GI motility and cytoprotection. Miura et al. (43) examined the receptor subtypes mediating the effects of PGE$_{2}$ on parasympathetic preganglionic neurons that regulate the activity of pelvic visceral organs using neonatal rat spinal slices, in-vitro. These investigators showed that PGE$_{2}$ increased the firing frequency to depolarizing current pulses, induced after discharges and inhibited spike potential after hyperpolarization but did not affect phasic preganglionic neurons. These results indicate that PGE$_{2}$ acting via EP$_{1}$ and/or EP$_{3}$ receptors modulated the excitability and/or the excitatory synaptic input to tonic parasympathetic preganglionic
neurons. Clearly, these studies need to be repeated in order to confirm the neurophysiologic action of PGE\(_2\) in the gut.

From a pathophysiologic considerations, prostaglandins may be also be involved in etiology of postoperative ileus as evident by increased spinal expression of COX-2 suggesting a primary afferent activation. This activation of primary afferents may subsequently initiate inhibitory motor reflexes to the gut, contributing to postoperative ileus (44).

Given the limited available CNS information, the function of PGs in neuronal tissues rests on inferences from in-vitro studies and from the studies connected with COX inhibitors (32). The absence of specific PG receptor antagonists for E, D, F and I series has clearly hampered our understanding of the role of individual PG in the CNS as well as other tissues. We fully agree with the assessment of Morrow and Roberts (24) that there is no clear physiological role of PGs in the CNS. Furthermore, despite some indirect and preliminary evidence summarized in Table 5, there is no consistent data, which well demonstrate the involvement of PGs in the brain-gut axis.

In summary, PGs and COX enzymes are present in and out of the CNS. Elevated levels of PG are found in few pathological processes such as fever and pain. The function of PGs in neuronal tissues rest on inferences from in-vitro studies and from studies connected with COX inhibitors. We conclude that the GI physiological and mucosal protective effects of PGs are essentially mediated by direct effects on cells or organs rather than by a direct effect on the CNS. Clearly, additional studies are warranted to investigate the CNS role in the GI physiological actions of PGs to clarify the precise role of PGs in brain-gut axis.

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