Prostaglandins, COX-2, and sensory perception

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Identification and understanding of the various processes which may underlie the pathogenesis of functional bowel diseases are complex. Apart from the possible contributions of misperception or error, there seem to be four major types of processes potentially involved, namely: (a) motor or secretomotor abnormalities; (b) enteric nervous dysfunction; (c) abnormal sensation; and (d) abnormal central responses to sensory input from peripheral sensations, leading to abnormal responses of efferent autonomic, endocrine, or behavioural activities. In this brief review I will focus on (c) and (d).

Unknown at the present time are: (i) the extent to which visceral pain emanates from hypersensitivity to mechanical, chemical, or other stimuli and (ii) the ways in which learning, conditioning, habituation, long term and short term memory, and explicit or implicit memory or neuronal potentiation, participate in these processes, including the possibility that plastic “memory” (for want of a better word) in peripheral cells and their components (dendrites, nuclei, or axons) or connections (synapses, ganglia, neural networks) is involved in ways in which early or repetitive traumatic life events might act to condition patients to have abnormal sensory responses to normal stimuli at a later stage. My particular inquiries have principally explored the answers to two questions: (1) Are prostaglandins (PGs) involved in these processes? (2) Is PG production from arachidonic acid, the action of cyclooxygenase 2 (COX-2), most relevant to functional bowel disease?

Various types of eicosanoids are made by a variety of cells of the nervous system including neurons (benign and neoplastic) in cell culture, nerve cells in brain, spinal cord, autonomic nerves, and peripheral ganglia, and also in juxta-neuronal cells (astroglia and capillary endothelia) in various products: products include those of both the cyclooxygenase and lipooxygenase pathways. While much is known about their localisation, regulation, and functional roles in central sites, less is known about these in spinal, autonomic, and enteric nervous systems but it is now emerging that many mechanisms elucidated centrally may also apply peripherally.

What is known is that there are high concentrations of PGs in all nervous tissue thus far explored. In brain, both COX-1 and COX-2 are expressed constitutively and are probably both inducible, although induction applies mainly to COX-2. In whole brain, concentrations of PGs in all nervous tissue seem to depend on neuronal activity rather than on regional blood flow.3 Basal levels are higher in awake animals and fall to low levels preceding or during sleep. Much of the activation is dependent on release of glutamate by presynaptic axons. In some synapses, release of an endogenous N-methyl-D-aspartate (NMDA) receptor agonist is produced by the action of 5-hydroxytryptamine or opioids on peripheral nerves; such stimuli seem to modify postsynaptic activity-dependent neuroplasticity. Expression of COX-2 is also stimulated by NGF increases the incorporation of arachidonic acid into PGs, the rise in PG synthesis always being accompanied by increases in c-fos, c-jun, or other immediate early genes (IEGs) and their products.

The processes of neuronal learning, conditioning, and both explicit and implicit memory must involve neural plasticity (in addition to other processes). The neural changes which contribute to plasticity include elimination of neurons by apoptosis, growth or proliferation of neurons, or of the synaptic connections on or between neurons, alteration in the configuration of neural networks, changes in dominant pathways, or modifications in the group of neurons affected by a particular signal. This fine tuning, based on use, goes on throughout life although it is much greater during development and within the “critical period”. Ultimately, the actual structure of neurons must change as their functions change. Exactly how this occurs has not been elucidated but it is clear that PGs are involved.

The sequence of events involves, in brain and spinal cord, release from glutaminergic nerves of neurotransmitter which then binds to NMDA receptors on postsynaptic dendrites, causing calcium to enter cells. This activates phospholipase A2 and releases arachidonic acid.

Abbreviations used in this paper: COX, cyclooxygenase; NGF, nerve growth factor; IEGs, immediate early genes; PGs, prostaglandins; NMDA, N-methyl-D-aspartate.
**Table 1** Prostaglandins and pain—sites of action

- Peripheral sensors? Lipoxgenase products?
- Peripheral nerves:
  - (i) PGs sensitize C fibres to analgesia
  - (ii) Monoclonal AB to PG given iv reduces hyperalgesic behaviour
- Spinal cord
  - (i) Peripheral inflammation induces NMDA, COX-2 mRNA, PGs and lipoxgenase products by spinal cord at relevant segment level.
  - (ii) Exposing cord to PGs induces hyperalgesia and allodynia: differential nerve effect.
- Intrathecal NSAIDs, at doses 1% of systemic, abolish inflammatory responses and pain in some models.
- Brain: Many stimuli upregulate COX-2 and COX-1, various loci.

**Table 2** COX-2: role in pain

1. Glutamate spinal cord hyperalgesia, probably via an increase in COX-2, which then degrades anandamide and PEA below normal tonic analgesic levels.
2. Blockade of spinal cannabinoid receptors by SR141716A, a CB1 antagonist, increases NMDA dependent hyperalgesia.
3. This effect is blocked dose dependently by D-AP-5 and MK-801, two NMDA antagonists.
4. Selective COX-2 inhibitors may relieve pain by preventing the degradation of endogenous cannabinoids.

COX, cyclooxygenase; NMDA, N-methyl-D-aspartate; anandamide, arachidonyl ethanolamide; PEA, palmitylethanolamide.
ethanolamide and palmitylethanolamide which respectively bind to CB-1 and CB-2 receptors, relieving pain. These appear to be metabolised to PGs by COX-2 but not by COX-1. Intrathecal injection of glutamate leads to hyperalgesia, probably in this way. Intrathecal injection of SR141716A, a CB-1 antagonist, increases NMDA receptor induced hyperalgesia, an effect blocked dose dependently by the NMDA receptor antagonists DAP5 and MK-801. These observations suggest that the analgesic effects of selective COX-2 inhibitor non-steroidal anti-inflammatory agents may be mediated by maintaining high tissue levels of endogenous cannabinoids involved in the normal damping down of painful stimuli. However, these cannabinoids are degraded in the presence of inflammation, or other inducers of COX-2, leading to pain (table 2). This may be prevented by drugs which inhibit COX-2, regardless of their selectivity. The study of PGs in the enteric nervous system seems to be a fruitful area for further research.