Purinergic receptors as future targets for treatment of functional GI disorders

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The concept of purinergic signalling arose from experiments designed to find the identity of the non-adrenergic, non-cholinergic (NANC) inhibitory neurotransmitter in the gut. However, it has taken many years for the more general importance of the various roles of ATP as a physiological messenger in the gut to be recognised. Later, after the concept of co-transmission was established, ATP, nitric oxide and vasoactive intestinal polypeptide were recognised as co-transmitters in NANC nerves, although the proportions vary in different gut regions. Following cloning experiments in the early 1990s, four subtypes of P1 (adenosine) receptors, seven subtypes of P2X ion channel receptors and eight subtypes of P2Y G-protein-coupled receptors have been recognised. Many of these purinoceptor subtypes have been identified on the myenteric, submucosal motor, sensory and interneurons involved in synaptic neurotransmission and neuromodulation, and reflex activity of several kinds, including ascending excitatory and descending inhibitory reflex pathways (see fig 1). Nucleotide receptors have also been shown to be expressed on enteric glial cells and interstitial cells of Cajal. Purinergic mechanosensory transduction, involving release of ATP from mucosal epithelial cells during distension to stimulate subepithelial nerve endings of intrinsic and extrinsic sensory nerves to modulate peristalsis and initiate nociception, respectively, is attracting current attention. While most studies of purinergic signalling in the gut have been carried out in animal models, purinergic synaptic transmission has also been described in the human enteric nervous system.

Xu and colleagues have carried out an original and interesting study in a growth area of considerable current interest (see page 1230). While purinergic nociceptive signalling in a rat model of colitis has been studied where 30% trinitrobenzenesulfonic acid was administered by intrarectal enema, this is the first time that the role of P2X receptor signalling has been studied with a rat model of irritable bowel syndrome (IBS)-like visceral hyperalgesia, using acetic acid (AA) infusion into the colon. The authors have shown that visceral hypersensitivity in their model is reversed by 2′,3′-O-[(2,4,6-trinitrophenyl)]-ATP, a

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Figure 1 Schematic showing the localisation of receptors of purines and pyrimidines on neurons and non-neuronal effector cells in the gut, although some of the interacting pathways are not yet known. Extrinsic vagal and sacral parasympathetic nerves connect with non-adrenergic, non-cholinergic (NANC) inhibitory neurons in the myenteric plexus expressing P2X2, P2X3, P2Y1, P2Y6 and A1B receptors, as well as with cholinergic motor neurons; these neurons are also activated by descending interneurons. Extrinsic sympathetic nerves modulate motility via excitatory motor neurons and constrict blood vessels in the gut via P2X1 receptors. Extrinsic sensory nerves arising from cell bodies in dorsal root ganglia and with subepithelial terminals mediate nociception. Intrinsic sensory neurons in both myenteric and submucosal plexuses express P2X3 and P2X7 receptors, while a subpopulation also express P2Y12 receptors; they connect with motor pathways involved in peristalsis. Extrinsic motor neurons express P2X2, P2X3, P2X4/2, P2X5 and P2Y2 receptors and connect with both interneurons and secretomotor neurons. Interneurons express P2X3 and P2X4 receptors. Enteric glial cells express P2Y1 and P2X3 receptors, while interstitial cells of Cajal express P2X2, P2X4 and P2Y4 receptors. P2X7 and P1 receptors appear to act as prejunctional modulators of both motor and interneurons. AH, after-hyperpolarising; NA, noradrenaline; S, synaptic.
The involvement of purinergic signalling in other gut disorders is also being explored, including: oesophageal reflux and swallowing, diabetes, postoperative ileus, ischaemia, Hirschsprung’s disease and Chaga’s disease. A recent report has shown that intraduodenal administration of ATP concomitantly with ingestion of non-steroidal anti-inflammatory drugs attenuates the indomethacin-induced increase in small intestinal permeability in healthy humans and may indicate that ATP will be of benefit in the treatment of intestinal disorders in which intestinal permeability changes are involved.

Although it has taken a long time, it is now clear that purines and pyrimidines play pivotal roles in a variety of physiological activities in the gastrointestinal tract of mammals, including man. The most recent work has focused on the pathophysiological roles of purinergic signalling in the gut, and I believe that the time is ripe for serious exploration of the therapeutic potential of purinergic compounds for a variety of gut disorders. While there are some studies of perinatal development of purinergic signalling in the mammalian gut, I believe that further studies should be encouraged, particularly concerning purinergic signalling in enteric stem cells involved in development and regeneration, with implications in paediatric and geriatric medicine.

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REFERENCES