Receptors and Transmission in the Brain-Gut Axis: Potential for Novel Therapies
I. Receptors on visceral afferents

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Received 22 February 2001; accepted in final form 22 February 2001

Kirkup, Anthony J., Alan M. Brunsden, and David Grundy. Receptors and Transmission in the Brain-Gut Axis: Potential for Novel Therapies. I. Receptors on visceral afferents. Am J Physiol Gastrointest Liver Physiol 280: G787–G794, 2001.—Visceral afferents are the information superhighway from the gut to the central nervous system. These sensory nerves express a wide range of membrane receptors that can modulate their sensitivity. In this themes article, we concentrate on those receptors that enhance the excitability of visceral afferent neurons. Some receptors are part of a modality-specific transduction pathway involved in sensory signaling. Others, which are activated by substances derived from multiple cellular sources during ischemia, injury, or inflammation, act in a synergistic fashion to cause acute or chronic sensitization of the afferent nerves to mechanical and chemical stimuli. Such hypersensitivity is the hallmark of conditions such as irritable bowel syndrome. Accordingly, these receptors represent a rational target for drug treatments aimed at attenuating both the inappropriate visceral sensation and the aberrant reflex activity that are the foundation for alterations in bowel function.

spinal afferents; sensitization

THERE ARE TWO REASONS WHY receptors on the peripheral processes of afferent neurons are a rational target for treating conditions of visceral hyperalgesia like irritable bowel syndrome (IBS). First, these afferent nerve terminals initiate the sensory signals that are transmitted from the gut to the brain and ultimately bring about the perception of visceral events including nausea, satiety, and pain. Second, these same visceral afferents, through local and central reflexes, modulate gastrointestinal motor and secretory activity that ensures that the digestive needs of the individual are met and that, under certain circumstances, may be disturbed, leading to diarrhea or constipation. Therefore, the “Holy Grail” is a single therapeutic target with the potential to attenuate both visceral sensation and aberrant reflex activity and so restore motility and secretion to normal.

The properties of visceral afferents have been dealt with extensively in recent themes articles, and we do not propose to cover this ground. Instead, we focus on the excitatory receptors expressed on the afferent terminals in the gut wall and consider the role these receptors play in visceral sensation and how this may relate to the development of novel therapies. In this context, we exclusively consider the receptor mechanisms present in extrinsic afferent nerves of the gastrointestinal tract, which send processes to the central nervous system. The activation pathways of primary afferent neurons or intestinofugal fibers that are a component of the enteric nervous system are not covered because, although they may modulate conscious sensation indirectly through changing the environment around extrinsic afferent nerves, they do not themselves impinge on consciousness directly.

The mechanisms involved in visceral perception are generally less well understood than their corresponding sensations in the somatic realm, but there are a number of common features. Similar types of nerve, e.g., small-diameter unmyelinated (C) or thinly myelinated (Aδ) fibers convey both visceral and somatic painful sensations. However, visceral pain is poorly localized and is often referred to somatic sites because their inputs converge in the dorsal horn of the spinal cord. In addition, the thoracic and abdominal viscera project sensory information to the brain stem via vagal afferent pathways. From what we describe below, the available evidence indicates that these two classes of visceral extrinsic nerves (vagal and spinal) exhibit a number of contrasting properties, which in turn reflect their diverse roles in sensory signaling.

RECEPTORS ON SENSORY NEURONS

An enormous range of chemical mediators have been implicated in sensory signal transduction in the vis-
cera (Fig. 1). By and large, the evidence for a role of these substances in visceral sensation has come from studies on the cell bodies of visceral sensory neurons in the dorsal root or nodose ganglia. Electrophysiological, immunocytochemical, and molecular biological techniques revealed the functional expression of receptors to these mediators in these cells. To be firmly convincing for a role in sensory signal generation, such mediators should be effective when applied to the sensory nerve ending in the gut wall, and this has indeed been shown for several of the mediators we describe below. These substances are thought to produce their effects on visceral afferent nerves by three distinct processes: 1) direct activation, which generally involves the opening of ion channels present on the nerve terminals; 2) sensitization, which may occur in the absence of a direct stimulation but which usually results in afferent hyperexcitability to both chemical and mechanical modalities; and 3) alteration of the phenotype of the afferent nerve, for example through alterations in the expression of mediators, channels, and receptors or modulating the activity of these by changing the ligand-binding characteristics or coupling efficiency of other receptors. In addition to a role in the generation or modulation of sensory signals, the receptors and channels expressed may initiate or promote the release of preformed mediators in the afferent nerve endings such as substance P (SP) and calcitonin gene-regulated peptide (CGRP) either locally or from axon collaterals. These efferent functions form the basis of axon reflexes that appear to play an important role in “neurogenic inflammation,” and this may induce or exacerbate the sensitization and/or altered phenotype of afferent terminals in their vicinity. Any given mediator may recruit one or more of these pathways to produce its effect on visceral sensation, and interference with any of these mechanisms is likely to modulate the “gain” in visceral sensory pathways in the short and/or long term. By implication, manipulation of these processes therefore represents a valid therapeutic target to ex-

Fig. 1. Some of the potential receptor mechanisms underlying activation (depolarization) and sensitization at the terminal of a gastrointestinal sensory afferent. Separate mechanisms underlie activation and sensitization. Some mediators such as serotonin (5-HT) cause activation via 5-HT3 receptors, whereas others like PGE2 acting at EP2 receptors sensitize visceral afferent responses to other stimuli. Still others, for example, adenosine (Adeno), cause both stimulation and sensitization, possibly through distinct receptor mechanisms (4). Bradykinin (BK) has a self-sensitizing action, stimulating discharge through activation of phospholipase C (PLC) and enhancing excitability via prostaglandins (PGs) after activation of phospholipase A2 (PLA2). Inflammatory mediators can be released from different cell types (e.g., sympathetic varicosities, mast cells, and blood vessels) present in or around the afferent nerve terminal. 5-HT, ATP, and capsaicin (Cap) can directly activate nonselective cation channels (NSCCs), whereas adenosine, histamine, prostaglandins (not PGE2), and proteases such as mast cell tryptase (Tryp) and thrombin (Thro) act on G protein-coupled receptors, leading to a Ca2+−dependent modulation of ion channel activity. Sensitization, however, may be mediated by increased intracellular cAMP. Adenosine and PGE2 can generate cAMP directly through G protein-coupled stimulation of adenylate cyclase (AC). In contrast, histamine (Hist) may act indirectly through the generation of prostaglandins (4). The actions of cAMP downstream are currently unknown but may involve modulation of ion channels, interaction with other second messengers (e.g., Ca2+), or even changes in receptor expression. PARs, protease activated receptors; COX-1, COX-2, cyclooxygenase-1 and -2; AA, arachidonic acid; DAG, diacylglycerol; IP3, inositol 1,4,5-trisphosphate.
exploit in the management of unpleasant sensations and/or hypersensitive states of visceral origin. In the ensuing paragraphs, we discuss the mechanisms by which a number of diverse mediators elicit their effects on visceral afferent sensitivity.

Substances that produce a direct stimulation of visceral sensory nerve endings may function in one of two ways. The first function is as a component of a discrete sensory signaling pathway. In this case, the afferent neuron does not respond directly to a stimulus but responds after the release of a mediator from a primary sense cell. A classic example of this type of sensory signal transduction is found in the gustatory afferents innervating the taste buds. These gustatory cells release chemical mediators that act in paracrine fashion on sensory nerve endings within their close proximity. As discussed below, a similar “taste” mechanism exists in the gut mucosa to monitor luminal composition. The second function is as an “indiscriminate” modulator of visceral afferent sensitivity. Such substances are usually released under conditions of inflammation, injury, or ischemia from a plethora of cell types, e.g., platelets, leukocytes, lymphocytes, macrophages, mast cells, glia, fibroblasts, blood vessels, muscle cells, and neurons. Each of these specific cells (e.g., mast cells) may release several of these modulating agents, some of which may act directly on the sensory nerve terminal, whereas others may act indirectly after release of other agents from other cells in a series of cascades. This type of activation, which is analogous to an alarm system, is believed to initiate sweeping behavioral and reflex mechanisms that serve to protect the host. There are several examples of humoral agents that function in either or both of the described manners. We initially consider certain mediators that are primarily believed to function in dedicated sensory signaling roles before expanding on those agents that act on visceral afferent nerves in a more promiscuous fashion.

SENSORY SIGNAL TRANSDUCTION

Before activation of extrinsic afferent nerves, specific stimuli arising within the lumen of the gastrointestinal tract may activate specialized cells present in the mucosa. Examples of these cells, which effectively act as principal sensory transducers, are enterochromaffin (EC) cells, which release 5-hydroxytryptamine (5-HT). These epithelial cells are strategically positioned in the intestinal mucosa to “taste” luminal contents and release their mediators across the basolateral membrane to generate action potentials in the afferent nerve endings within the lamina propria. Stimulus intensity is encoded in the amount of mediator release and represents the balance between the mechanisms causing release and the uptake mechanisms that limit the site and duration of activation. In the case of 5-HT liberated from EC cells, this agent is thought to act directly on vagal extrinsic afferent nerves in the mucosa through activation of ionotropic 5-HT3 receptors expressed on the nerve terminal (17). The physiological stimuli for the release of 5-HT from EC cells may be, in certain instances, mechanical, suggesting a role for this process in mechanotransduction (13). However, a large body of data implicates this mechanism in the detection of bacterial enterotoxins, e.g., cholera toxin. These toxins trigger release of 5-HT from EC cells to bring about an orchestrated response to dilute and subsequently eliminate the pathogenic material from the body and preclude further consumption of the potentially harmful material. However, certain drugs used in cancer chemotherapy are thought to inappropriately trigger these mechanisms, thus provoking debilitating nausea and emesis in patients. These symptoms are responsive to selective 5-HT3 receptor antagonists, such as ondansetron and granisetron, which strongly supports the role for 5-HT in nausea and vomiting pathways from the gastrointestinal tract. However, other mechanisms may be involved, especially in the delayed emetic response to chemo- and radiotherapy (1). The mediator(s) responsible for emesis that is resistant to 5-HT3 receptor antagonists is not known, and this supports the view that there is the potential for plasticity in the emetic pathway. From a therapeutic perspective, elucidating the identity(ies) of the substance(s) that account for this delayed response may assist in the development of effective antiemetic agents for patients who are or become refractory to the presently available therapy.

Electrophysiological evidence suggests that 5-HT acts on a distinct population of vagal mucosal afferent nerves (16). As such, this represents an example of a high-fidelity, modality-specific signal transduction pathway. This mechanism more than likely functions in the detection of moment-to-moment changes in luminal composition and operates, in the main, below the level of consciousness. In contrast to such a specific signaling pathway, it is apparent that a battery of mediators, some of which are described below, may influence visceral sensation in a less ordered manner.

VICERAL HYPERSENSITIVITY

Vagal and spinal afferent fibers each respond to mechanical stimulation such as distension and contraction. Vagal afferents encode events within the physiological range. In contrast, spinal afferents respond over a wide dynamic range extending from physiological to pathophysiological levels of distension (12). These spinal endings can contribute to signaling visceral pain through some intensity code that recognizes extreme levels of distension or contraction. Other spinal afferents, however, respond only to noxious levels of distension, and an extreme example of these is the high-threshold mechanoreceptors that fail to respond under normal circumstances. These are the so-called “sleeping” or silent nociceptors that can be awakened under conditions of injury or inflammation (12). The latter illustrate the fact that mechanosensitivity is not fixed either in terms of threshold for activation or gain in the stimulus-response relationship, and as such the threshold can be reduced and the gain increased under certain situations. A number of proinflammatory me-
mediators have been implicated in this sensitization process (see Fig. 1), and examples of some of the key agents in this phenomenon are detailed below.

Bradykinin. Bradykinin (BK) is a nonapeptide that is generated from plasma during tissue damage and inflammation. This peptide mediates its effects via two G protein-coupled receptors, B₁ and B₂, with the latter being constitutive and the former induced by some cytokines and nerve growth factor (NGF) (see Ref. 5). In vitro studies in uninfamed preparations have shown that BK powerfully activates mesenteric spinal afferents with serosal terminals through an action on B₂ receptors and that BK-induced release of prostaglandins (see below) contributes to the overall magnitude of the response (4, 31). These findings corroborate whole animal studies showing that B₂ receptor antagonists attenuate visceral pain, at least in acute models in which inflammation is present (see Ref. 5). In contrast, it seems that in chronic inflammation models, the role of the inducible B₁ receptor in visceral nociception mechanisms becomes more dominant (5). The weight of evidence clearly indicates a role for BK in the generation of visceral pain in the acute and chronic phases of inflammation, and, therefore, antagonists of BK receptors could be useful therapeutically to treat visceral hypersensitivity in inflammatory conditions.

Prostaglandins and leukotrienes. Products of arachidonic acid oxygenation are a major contributor to hyperalgesia in the somatic realm, and recent evidence suggests that they may play a similar role in visceral sensory transmission. This group of mediators comprises the prostaglandins (PGs) and leukotrienes (LKS), which are synthesized from the precursor arachidonic acid by cyclooxygenase (COX) and lipoxygenase enzymes, respectively. PGE₂ acts through multiple EP receptors (see Ref. 14). In the gastrointestinal tract, EP₁ receptors appear to play a major role in direct activation of mucosal mesenteric afferents, but EP₂ receptors may also play a sensitizing role (14, 31). Critical to this latter function in visceral nerves may be the activation of adenylyl cyclase and elevation of intracellular cAMP, because the membrane-permeant cAMP analog dibutyryl cAMP mimics the sensitization process (Ref. 4; see Fig. 1). Such mechanisms may underlie the enhanced responsiveness of visceral afferent neurons to chemical and mechanical stimuli in inflammatory conditions and may be involved in wakening the so-called “silent nociceptors” after an inflammatory insult. Two isoforms of the COX enzyme have been characterized, and these are termed COX-1 and COX-2 (22). COX-1 is constitutive and may be involved in controlling baseline visceral afferent sensitivity because, in native tissue, naproxen significantly reduced the magnitude of the response to BK (31). However, during inflammatory conditions such as colitis, up-regulation of the inducible COX-2 occurs, leading to augmented PG synthesis, and this enzyme may therefore be important in the genesis of persistent pain in this syndrome (39). Interleukin (IL)-1β and tumor necrosis factor (TNF)-α may underlie this increased expression of COX-2 (41), which is consistent with the view that PGs contribute to the illness behavior and somatic and visceral hyperalgesia associated with elevated levels of these cytokines. PGs are derived from virtually every type of tissue, in particular sympathetic nerve terminals and immunocompetent cells, and these sources may be important in the maintenance of the inflammatory state. Very little is known about the role of lipoxygenase products such as LKB₄ in visceral nociception. However, lipoxygenase metabolites have recently been shown to activate vanilloid receptors, suggesting that they may contribute to visceral pain in inflammatory conditions (see below).

5-HT. 5-HT is discussed above in relation to EC cell mechanisms of luminal “tasting.” However, this humoral agent may also be released from a variety of other sources including platelets, mast cells (5), endothelial cells, and serotonergic neurons (13) in the gastrointestinal tract. mRNA for several 5-HT receptors is present in dorsal root ganglion cells (8), and this suggests that multiple potential signaling mechanisms are activated by this mediator. Although it remains to be unequivocally demonstrated in the gastrointestinal tract, the presence of 5-HT₃ receptors on visceral spinal afferent terminals (11) may explain the ability of some 5-HT₃ receptor antagonists to provide pain relief in certain IBS patients. However, the clearly defined functional role of these receptors in the peristaltic reflex (see Ref. 37) may explain the marked constipating side effects of such agents, which may ultimately limit their widespread clinical usefulness in the treatment of visceral hyperalgesia. Other 5-HT receptors such as the 5-HT₄ receptor have generated a recent upsurge in interest regarding a putative role of these receptors in modulating visceral sensation. 5-HT₄ receptors are generally coupled to adenylyl cyclase (15), which would be expected to promote an increase in neuronal excitability, but a partial 5-HT₄ agonist, counterintuitively, attenuates visceral spinal afferent transmission (38). Although the prokinetic effects of these agents, which would provide symptomatic relief in constipation-predominant IBS, are well documented (see Ref. 37), further studies are necessary to characterize the nature of this apparent inhibitory effect on visceral spinal afferent nerves.

ATP. There is good evidence that ATP, which is released from damaged tissues, participates in visceral afferent signaling. This molecule exerts its physiological effects through the interaction with two major classes of receptor (34). One group, which comprises ligand-gated cation channels, is termed P₂X receptors and is currently classified into seven subtypes. The other group, which consists of G protein-coupled receptors, is termed P₂Y receptors, and seven subtypes of these receptors have been functionally characterized in mammalian systems. To date, however, convincing evidence only exists for the presence of functional P₂X receptors in visceral neurons. Electrophysiological and immunocytochemical studies have demonstrated their expression in cells derived from nodose (30) and dorsal
root (7) ganglia, and recent evidence indicates the existence of functional P2X receptors on the peripheral endings of mesenteric afferent nerve bundles (23). These nerve trunks contain a mixed population of vagal, spinal, and intestinofugal afferent fibers, which terminate in different levels of the bowel wall (mucosa, muscle, and serosa), so whether ATP is involved in conveying luminal or noxious signals or mediating peripheral reflexes is not currently clear. The functional ATP-gated cation channels in native sensory neurons were initially thought to consist, on the one hand, of either homomeric P2X3 subunits in the case of spinal neurons (7) or, on the other, heteromultimers of P2X2 and P2X3 receptors in the case of vagal fibers (30). However, the situation is probably more complex, because functional channels with diverse properties can be formed from heterologous expression of individual types or combinations of different types of P2X receptors (34). Despite this potential complexity, studies with P2X3 receptor knockout mice have indicated possible roles of this subtype in sensory signal transduction in the visceral realm (9). Notably, these null mutants display hyporeflexia of the urinary bladder (9). Because ATP is released from the urothelium in response to stretch, it is possible that the loss of P2X3 receptors, which are normally present on fibers innervating the bladder, may impair the functioning of the micturition reflex (see Ref. 9). This raises the possibility that a similar process underlies a component of mechanotransduction in the gastrointestinal tract, because mechanical stress has been shown to stimulate the release of ATP from several types of cell that are present in the bowel wall (see Ref. 35). Indeed, ATP can be liberated from cells by stimuli as diverse as changes in cell volume, hypoxia, extracellular acidosis, inflammation, lipopolysaccharide exposure, and membrane receptor stimulation (see Ref. 35 for references). Clearly, there is a potential for this nucleotide to be involved in the transduction of nonnoxious and/or noxious stimuli arising in the viscera. It is tempting to speculate that the physiological and/or pathophysiological signaling roles of ATP may be determined not just by anatomic location of the afferent nerve endings in the gut wall but also by the differing expression at their peripheral terminals of homomeric and/or heteromeric P2X receptors. The studies with P2X3 receptor knockouts indicated certain modalities in which this subtype of receptor is involved in encoding. In view of the paucity of selective agents, investigations in knockouts of the other P2X receptors found in sensory ganglia (P2X2, P2X3, and P2X6) should permit the appreciation of the roles of these subtypes in sensory signal transduction in the gastrointestinal tract in both normal and dysfunctional states. This in turn should provide important information as to which of the P2X receptors should be specifically targeted to alleviate aberrant and/or noxious sensory signal transduction, without perturbing normal visceral sensation.

Adenosine. The enzymatic breakdown product of ATP, adenosine, may also function as a sensory signal-
ganglia (18), and the presence of mRNA for VR-1 has been confirmed in these neurons (32). Consistent with these observations, capsaicin sensitivity has been shown in vagal mucosal and muscle fibers (2) and spinal serosal afferent neurons (31) innervating the gastrointestinal tract. The identity of the natural ligand for this receptor is still not known, and this has hindered progress in understanding the physiological and/or pathophysiological roles of this receptor in visceral sensation. Nevertheless, protein kinase C and ligands such as BK, anandamide, and lipoxygenase products each increase VR-1 receptor channel activity (19, 33). Heat and protons also augment VR-1 receptor activity (6, 42). In the case of the latter, this mechanism may explain or at least contribute to its excitatory effects on visceral afferent nerve activity (42). In addition, protons augment the response of $P2X_3$ receptors to ATP (34). Because the extracellular fluid in inflamed tissues has a lower pH than normal, the effect of protons on these receptors may be relevant to visceral pain in inflammatory conditions of the gastrointestinal tract. In view of the fact that multiple signaling mechanisms affect the activity of VR-1, there may not be a single endogenous ligand for this channel. Instead, it may represent a general effector mechanism that is recruited by mediators under certain conditions to stimulate or enhance the activation of sensory neurons, which may not necessarily be involved in nociception in the bowel (12).

**Proteinase-activated receptors.** An emerging class of receptors that is provoking an explosion of interest is the proteinase-activated receptors (PARs) (10). The natural ligands of these receptors, which belong to the superfamily of G protein-coupled receptors, are serine proteases such as thrombin, mast cell tryptase, and trypsin (10). PARs exhibit a novel mechanism of receptor activation and are stimulated by a “tethered ligand” of six amino acid residues located on the NH$_2$-terminal domain, which is exposed after an end portion of the receptor is cleaved by the protease (10). Four types of PARs, denoted PAR1, PAR2, PAR3 (10), and PAR4 (21), have been identified, although PAR3 is probably a cofactor in the activation of PAR4. PAR1 and PAR4 are sensitive to thrombin, whereas mast cell tryptase activates PAR2 and trypsin stimulates both PAR2 and PAR4 (28). Transduction pathways to which the PARs are coupled include the stimulation of phospholipase C and mitogen-activated protein (MAP)-3 kinase mitogenetic cascades, the latter of which may have particular important functional significance with respect to long-term effects on visceral afferent signaling (10). PAR2 are expressed in dorsal root ganglion cells (40), and PAR1 has been recently described in this tissue (44). Preliminary evidence suggests that functional PAR2 is also present on the peripheral terminals of mesenteric afferent nerves (24). Because tryptase-containing mucosal mast cells reside in close proximity to afferent terminals in the lamina propria (43), these receptors, together with those for 5-HT and histamine, may participate in neuroimmune signaling from the gastrointestinal tract during allergic reactions. Furthermore, after a breach of the mucosal barrier, for example, by acid erosion, it is possible that trypsin may gain access to the submucosal space and activate the terminals of PAR2-expressing nerves in the vicinity, eventually leading to the orchestration of mucosal defense mechanisms. However, neither the level of the terminations nor the identity of the population of mesenteric afferent nerves functionally expressing PAR2 is known. Until such information is to hand, one can still only speculate on their function. In addition, whether PAR4 has a role to play in gastrointestinal afferent signaling awaits exploration.

**NGF.** NGF, acting through the trkA receptor located on spinal sensory neurons that also express SP and CGRP, is one mediator that has the potential to exert a long-term effect on the activity of visceral sensory neurons (see Ref. 5). NGF levels are rapidly increased during inflammatory responses, and sequestration of endogenous NGF leads to a decrease in hyperalgesia in experimental models (20). NGF, together with other trophic factors including neurotrophin-3 (NT3), brain-derived neurotrophic factor (BDNF, which acts through trkB receptors), and glia-derived neurotrophic factor (GDNF) evoke phenotypic changes in nociceptive neurons and may also be involved in the regeneration of sensory neurons after nerve injury (36). Intriguingly, nodose neurons express trkB but not trkA receptors (32), suggesting that different trophic influences may regulate the sensitivity of vagal and spinal visceral afferent nerves, but this still remains to be demonstrated.

**POTENTIAL FOR NOVEL THERAPIES**

Considerable recent progress has been made in our understanding of the receptor mechanisms that augment the excitability of visceral afferent nerves. This new information obviously has important implications for the development of novel treatments for conditions in which visceral hypersensitivity is a key feature, such as IBS. However, there are undoubtedly other potentially crucial mediators awaiting discovery, and this and other present deficiencies in our knowledge preclude a full appreciation of the complex interactions between mediators that occur at the level of the visceral afferent terminal. Despite this, it is not unreasonable to propose that an ideal therapeutic agent for the treatment of visceral hyperalgesia would be one that would not interfere with normal signal transduction but serve to prevent the release of, or reverse the sensitizing effect of, mediators released under pathophysiological conditions. In this respect, sensitizing agents act in a highly synergistic fashion and are generally excitatory, although there are other mediators such as somatostatin, $\kappa$-opioids, and GABA that do...
have an inhibitory influence. The concept of an inflammatory "soup" has been developed to incorporate the complex interactions that can occur between many different mediators and may help to explain the success of a variety of agents with some efficacy in IBS. Equally, there may be a degree of redundancy among the mediators such that the contribution of one is compensated for by plasticity in the mechanisms that control sensitivity. However, as mentioned above, unless the underlying cause of the visceral hypersensitivity in IBS is unraveled, any real possibility of developing an all-encompassing treatment is some way off.

The authors acknowledge the financial support of the BBSRC (UK), the DFG (Germany), and GlaxoWellcome Research and Development Ltd. (UK).

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