Sensitisation of gastrointestinal tract afferents

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Sensory innervation of the viscera serves a number of important functions, including regulation of visceral motility and secretory activity, and transmission of visceral sensations, including pain. There are many ways in which the sensitivity of visceral sensory neurones might be modulated, and these are discussed. Altered sensory neurone responsiveness may contribute to pathophysiological states such as irritable bowel syndrome, and the mechanisms leading to sensory neurone sensitisation offer novel targets for the treatment of such disorders.

SUMMARY

Sensory innervation of the viscera in general and the gastrointestinal tract in particular serves a number of important functions, including regulation of visceral motility and secretory activity, and transmission of visceral sensations, including pain. However, the transduction properties of visceral afferents are not stable and can be altered by a large number of factors. The word plasticity is often used to describe these altered properties, although it is worth noting that this term has no formal definition and is taken to mean different things by different authors. In the context of visceral sensory neurones, functionally relevant forms of plasticity are those that affect the encoding and transmission of sensory information. Increased excitability of sensory neurones can have dramatic functional consequences, and may contribute to chronic pain states and conditions of hyper- or dysreflexia.

There are two broad types of sensory neurone plasticity that need to be distinguished. Firstly, rapid onset peripheral sensitisation (or desensitisation) of sensory terminals, arising without altered gene expression, and secondly, a slower onset phenotypic change in sensory neurone properties as a consequence of altered gene expression. This latter form of plasticity can affect sensory transmission in a variety of ways, and both forms of plasticity are discussed in more detail below.

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PERIPHERAL SENSITISATION

Tissue injury and inflammation and a great many algesic chemicals produce changes in the stimulus-response functions of the primary sensory neurone terminals in peripheral tissues. If the stimulus-response function shows a leftward shift, the neurone is sensitised and a greater afferent barrage is generated for a given stimulus. Less studied, but potentially important, is the fact that neurones can be desensitised and show rightward shifts in stimulus-response functions.

As illustrated in fig 1A, stimuli that trigger sensitisation may activate G protein coupled receptors in the nociceptor terminal (for instance, prostanoids acting at EP receptors,[1] adenosine triphosphate (ATP) acting at P2Y receptors,[2] bradykinin at B2 receptors,[3] and some agents acting at chemokine receptors).[4] Alternatively, there may be stimuli that activate ligand gated receptors (such as capsaicin or heat acting on VR1,[5] or ATP acting at P2X receptors).[6] Finally, several trophic factors and cytokines acting at tyrosine kinase receptors may cause sensitisation (most notably, nerve growth factor (NGF) acting at tyrosine kinase A (trkA) receptors).[7 8]

As shown in fig 1B, these different stimuli recruit a variety of intracellular signalling cascades, including protein kinase A (PKA) and protein kinase C (PKC),[9–11] or the map kinase extracellular regulated kinase (ERK)1/2.[12 13] The final effector mechanism underlying sensitisation of nociceptors is also quite variable and, as illustrated in fig 1C, can involve modulation (often by phosphylation) of Na^+, K^+, or Ca^{++} channels.[14 15] Modulation of these channels can affect the ease with which the membrane can be brought to threshold. Clearly this would affect the responsiveness of the neurone to all forms of stimulation. Another more specific means of affecting responsiveness is by modulation via phosphylation of some receptors such as VR1[16] and P2X.[17] Modulation of VR1 has been particularly well studied and it is clear that its sensitisation can be so large as to lead to activation of the receptor at body temperatures.[2 18] It is also clear that a great many stimuli are coupled to VR1 sensitisation. It is worth noting that to date we have no strong data about the molecular nature of the mechanical transducer, although it is clear that sensitisation to mechanical stimulation can readily occur in visceral sensory neurones.[19] The absence of information is unfortunate as it is this form of sensitisation of visceral sensory neurones that is likely to have the most important functional consequences.

Peripheral sensitisation of neurones typically arises within seconds of application of an adequate stimulus and persists, to a transient

Abbreviations: ATP, adenosine triphosphate; NGF, nerve growth factor; ERK, extracellular regulated kinase; trkA, tyrosine kinase A; PKA, protein kinase A; PKC, protein kinase C

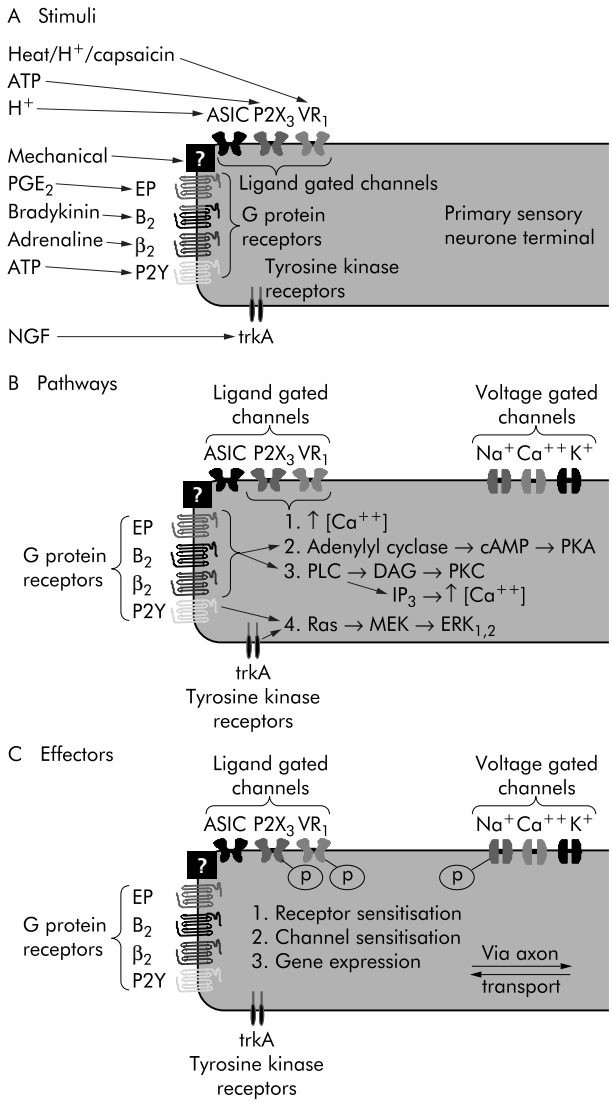

Figure 1 Modulation of primary sensory neurone sensitivity. (A) A list (on the left) of many of the stimuli which can lead to sensory neurone sensitisation. (B) Illustration of the second messenger cascades by which sensitising stimuli induce their local effects. (C) Illustration of the main effector mechanisms by which altered sensory neurone responsiveness is achieved.

stimulus, for a matter of minutes. However, in the presence of ongoing tissue injury or inflammation, sensitisation may also be prolonged. The sensitising effects of NGF on heat responsiveness of sensory neurones has been particularly well studied. On isolated DRG cells in culture and on sensory neurone terminals studied using a skin-nerve preparation, NGF acutely sensitises many nociceptive neurones,[20] although the mechanism of sensitisation has variously been ascribed to PKA, PKC, phosphatidylinositol-4,5-biphosphate, and ERK dependent mechanisms. Small diameter sensory neurones chronically exposed to elevated NGF levels (in a NGF over expressing mouse) showed marked heat sensitisation.[21] While the exact mechanism of sensitisation is not known in this latter case, the data none the less demonstrate that persistent peripheral sensitisation is possible.

ALTERED GENE EXPRESSION IN NOCICEPTORS

A second form of sensory neurone plasticity involves regulation of gene expression in those neurones. There is now a very large body of experimental data suggesting that such regulation readily occurs as a consequence of tissue injury, most notably persistent injuries associated with peripheral tissue inflammation. The plasticity of gene expression affects many aspects of sensory neurone function, including: genes coding for neurotransmitters released with activity from the central terminals of nociceptors; genes coding for receptors which are transported to both the peripheral and central terminals of sensory neurones; and genes coding for ion channels expressed throughout the neurone and potentially affecting its sensitivity. Genes regulating structural proteins in nociceptors are also affected and this may affect some anatomical features of these neurones.

There are several potentially important signals for this plasticity of gene expression. The most important (and certainly the best studied) is NGF. This molecule is upregulated in many experimental models of inflammation (including those induced by carrageenan and Freund's adjuvant) and in some clinical inflammatory disorders.[22–28] NGF is known to be internalised following its binding to trkA. In addition to its peripherally sensitising effects discussed above, it is known to be transported retrogradely from peripheral terminals to cell bodies. Evidence from several sources suggests that NGF itself cannot initiate signalling in the cell soma, but that the NGF/trkA complex maintains autophosphorylation and activates transcription factors such as cyclic AMP response element binding protein and Oct-2 (a member of the POU family of transcription factors) that control gene expression.[29 30] The importance of NGF is supported firstly, by its ability (when administered exogenously) to induce changes in gene expression and secondly, from the many studies which have shown that nociceptor plasticity to inflammation is greatly reduced with strategies that block NGF actions.[31] While the data for NGF are particularly extensive, it is also clear that other neurotrophic factors such as glial cell line derived neurotrophic factor can regulate gene expression in some primary sensory neurones.[32]

CONCLUSIONS

In summary, there are many ways in which the sensitivity of visceral sensory neurones might be modulated. Some of these are rapid and are triggered by many of the stimuli that normally impinge on the sensory neurones. Other forms of modulation have a slower onset and are more persistent. These frequently involve altered gene expression in the sensory neurones, triggered by altered availability of neurotrophic factors. Altered sensory neurone responsiveness may contribute to pathophysiological states such as irritable bowel syndrome, and the mechanisms leading to sensory neurone sensitisation offer novel targets for the treatment of such disorders.

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