Normal Pain Transmission

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SUMMARY POINTS

- Acute (normal) pain transmission is part of a survival response to prevent tissue damage and attend to and protect damaged tissue.
- A cycle of afferent transmission, response to stimuli, followed by temporary hypersensitivity, then attenuation and resolution occurs.
- Primary afferent, spinal cord ascending and descending pathways are fixed; however the response elicited is highly dynamic and not a linear relationship with input intensity.
- Somatic inputs are topographically accurate, in contrast to diffuse visceral inputs.
- Primary afferents code differentially for stimuli (heat, acid, pressure etc) and intensity.
- The dorsal horn allows extensive modulation of initial inputs, either excitation or inhibition.
- Higher CNS areas allow extensive modulation of inputs, account for the conscious recognition of pain: the intensity, location, emotional and memory aspects.
- Descending pathways arising from midbrain regions can be inhibitory or excitatory.

Introduction

Normal or acute pain is the process of nociceptive transmission, with the initial reflex withdrawal and then the location and attention to offending stimuli. Inhibition of the afferent inputs and resolution of the excitation state back to the normal resting state occurs, coupled with a learnt response to avoid the stimuli again. This is the basis of evolutionary survival, to protect and avoid tissue damage. To this end the nociceptive pathways are relatively complex, requiring a dynamic ability to code the type and intensity of stimuli. They code for noxious (as opposed to non-noxious) stimuli which result in potential or actual damage. The inputs can be intensified (i.e. windup, see dorsal horn section) to ensure attention to damage, or inhibited (attenuated) to allow attention to other activities whilst tissue healing occurs. The reflex withdrawal circuit ensures rapid motor withdrawal action to noxious stimuli even prior to conscious recognition of damage. Complex supra-spinal networks provide accurate location, differentiation of intensity and attention to injury but also ensure that sensations are learnt and stimuli avoided through a series of sensations of unpleasantness and fear (Fig.1).

In addition to the neural network stimulation, often a corresponding activation of a mobile immune network is stimulated. Close positive and negative feedback loops exist between primary afferents and immune cells, which allow peripheral excitation and attenuation as well as recruitment of defence and repair to sites coding for tissue damage.

Peripheral Interactions

Transduction

Alterations in the neuronal milieu are detected by specialised receptors on primary afferents. These code for pressure (compression), inflammatory mediators (prostaglandins, nerve growth factors, cytokines, interleukins), ATP (adenosine triphosphate), protons and temperature amongst others (Fig. 2). Individual receptors may be bound or pressure detected, but for a peripheral depolarisation to be transmitted to the dorsal horn the depolarisation has to exceed the threshold for action potential generation. Predominately three classes of neurones code for the peripheral stimuli, A β (non-noxious), A δ and C fibres (see Table). A β fibres are thickly myelinated, providing rapid transmission for a wide range of non-noxious stimuli. A δ fibres are thinly myelinated, thus slower than A β transmission, but once fired are involved in the afferent part of the spinal reflex loop. A δ fibres require a higher noxious threshold to be reached before depolarising and can alter the rate of firing depending on the intensity of stimuli. C fibres are non-myelinated and slowest conducting. There is a wide range of activation thresholds and firing response within C fibres. For example, some C fibres have a range of threshold activation or are activated by a wide range of noxious stimuli, others are more specific to a stimuli type (such as heat or pressure), or a specific threshold (such as silent nociceptors).

Figure 1

The diagram simplistically summarises normal acute noxious input from the periphery, through the dorsal horn to the brain. From the left, noxious stimuli, such as heat, chemical or mechanical injury are transduced via specific receptors namely temperature coding receptors, acid sensing ion channels (ASIC), tyrosine kinase (TrkA) (inflammation) or pressure receptors. Transduction allows a flow of positive ions into the cell, which causes depolarisation and action potentials.

This is transmitted along the neurone via sodium (NaCh) and voltage gated calcium (VDCC) channels, to the dorsal root ganglion (DRG) and the dorsal horn. The sympathetic nervous system (SNS) lies close to the DRGs but is unaffected in acute noxious transmission.

In the dorsal horn extensive modulation of the input can occur. Neurotransmitters such as substance P (SP) or Glutamate (Glu) amongst others are released from the primary afferent and diffuse across the synapse. An array of receptors can be triggered, including N-methyl D-aspartate (NMDA), α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), neurokinin 1 (NK1), adenosine (A1/A2). Other neurotransmitters are also released either locally such as enkephalins (μ opioid receptor), gamma-aminobutyric acid (GABA) which are inhibitory or via descending pathways such as noradrenalin (α Ad receptor), serotonin (5HT1 or 3 receptors).

The overall modulated signal (either increased or decreased) is transmitted to the brain via ascending pathways to the CNS. This is presented simplistically as 2 ascending pathways, the spinothalamic from lamina V leading to the cortex, and the parabrachial from lamina I leading to the hypothalamic areas. Descending pathways arise from the brain and pass through the peri-aqueductal grey (PAG) and rostro-ventral medulla (RVM) areas before terminating in the dorsal horn.

Transmission

Neurons are held at a negative potential (around -70mV) and transmit action potentials via consecutive depolarisation. In myelinated fibres depolarisation is concentrated at the Nodes of Ranvier, hence the fast transmission. The transduction at the distal receptors allows the initial influx of sodium or calcium ions, although some receptors are non-ionic and responsible for longer term alterations in receptor distribution and internal calcium store activation. The initial influx

allows local depolarisation which, if the threshold is reached, converts into a transmitted action potential, via non-synaptic sodium, calcium and potassium channels. The action potential is propagated along the neurone to the dorsal root ganglion, and then onto the dorsal horn synaptic terminus. The rate and frequency of action potentials is dictated by the intensity of the stimuli and the opening characteristics of the array of sodium and voltage gated calcium (VDCC) and potassium channels. The characteristics of individual channels vary within the vast families of each channel type. For example, sodium channels can be divided into two main family types, Tetrodotoxin (TTX) sensitive and resistant, the latter particularly important in nociceptive neurones. In each there are multiple family members with different expression, thus Nav1.8 is upregulated in neuropathy, Nav 1.3 is a fast opening channel expressed in the foetus (activation dependent neuronal survival) and also in neuropathy.

The dorsal root ganglion comprises the cell bodies of the primary afferents entering the spinal cord at a given level (Fig. 3). The cell body is an active component in maintaining cell function, regulating the tonic level of activity and receptor expression. Receptors are transported in both a retro- and ante-grade manner, with the expression and transportation altering in response to depolarisations and retrograde bound receptor transport. This allows longer lasting alteration in the neuronal characterisation, and is in part responsible for peripheral sensitisation or attenuation. There is a dynamic communication between primary afferents and the surrounding milieu. For example, activation of a C fibre may result in release of neurokinins (such as substance P (SP)) producing a positive feedback loop for neuronal activation (via neuronal neurokinin-(NK)1 receptors), and recruitment of inflammatory infiltrate. This infiltrate in turn will release enkephalins and cannabinoids, which alter the

Figure 2

Schematic representation of peripheral transduction of noxious stimuli via acid sensing ion channels (ASIC), temperature, vallioid (VR1) and nerve growth factor (NGF) and the neural release of neurokinins, cytokines and bradykinins. Transmission to dorsal root ganglion (cell body) and dorsal horn is via sodium and calcium channels.

Table. Summary of the main characteristics of the three principal primary afferent fibres (From Hunt SP and Mantyh PW, (2001), *Nature Neurosci Rev* 2: 83-91)

Afferent Fibres	A β	A δ	C
Diameter	Large, 6-20 μ m	Small, 1-5 μ m	Small, 0.2-0.5 μ m
Myelin	++	+	-
Conductance	80-120m/s	35-75m/s	0.5-2m/s
Activation stimuli	Non-noxious	Non-noxious /noxious	Polymodal noxious
Dorsal Horn termination	lamina III	lamina I, IV	70% - peptidergic, Trk A +, lamina I/II _o 30% - non-peptidergic, IB4+, lamina II/III

phasic and tonic activation of the primary afferent, via activation of peripheral opioid and cannabinoid receptors.

Dorsal Horn

The primary afferents have a distinct termination pattern within the dorsal horn of the spinal cord. Under the light microscope the spinal cord has been classically divided into lamina, which by luck corresponds to specific afferent termination (or motor efferent, in the ventral horn). Thus the A β fibres (non-noxious) terminate in lamina III, synapsing with interneurons. A δ fibres terminate superficially in lamina I or deeper in lamina IV / V. The superficial terminations synapse with interneurons, 70% of which are NK1 receptor positive, and then with projection neurones of the spino-parabrachial pathway. C fibres also terminate superficially in lamina II and can be further characterised by the neurotransmitters released (see Table).

The majority of primary afferents synapse to interneurons, which allow significant modulation to occur before finally synapsing to projection neurones of the spinothalamic, spino-parabrachial or to a lesser extent the dorsal column tracts. Synapses allow modulation, as they are a point where neurotransmitters (amino acids, peptides or gases such as NO, CO, free radicals) can stimulate a range of neuronal and non-neuronal cells (Fig. 3). For example, an excitation synaptic exchange may involve the primary afferent release of SP, which binds to the post-synaptic metabotropic NK1 receptor, allowing some depolarisation. The primary afferent release of glutamate may bind to a range of the glutamate family receptors which include AMPA (amino-3-hydroxy-5-methyl-4-isoxazole), an ion channel receptor, NMDA (N-methyl D-aspartate) or one of the metabotropic glutamate receptors. The binding of NK1 and AMPA receptors allows sufficient depolarisation for the NMDA receptor (if simultaneously binding glutamate and glycine) to open. This triggers a massive influx of

calcium, (some sodium) and an excessive excitation (windup) of the neurone (Fig. 4).

Calcium, whether released from intracellular stores or by cellular influx, is a potent trigger for numerous intracellular events, i.e. signalling secondary messenger cascades (such as mitogen-activated protein (MAP) kinase pathway), which in turn alters activation or deactivation of other receptors, and the production of excitatory gases NO, CO. In addition, activation of G protein linked receptors (i.e. metabotropic glutamate receptors) have actions via different secondary

Figure 3

A high power schematic view of dorsal horn modulation. The primary afferent release of glutamate and substance P, binding to excitatory or inhibitory interneurons, and the subsequent output action potentials (in this figure modulation has been excitatory).

Figure 4

A summary of the effect of opening the NMDA receptor allowing influx of calcium. Magnesium (Mg^{2+}) binds to the pore of the channel, effecting a block at normal resting potentials. However this block will be released if the resting potential is less negative (around $-50mV$), glutamate binds and glycine is already bound. The opening of the NMDA receptor allows a massive influx of calcium (some sodium) into the cell, with the consequent depolarisation.

The effect on dorsal horn neurones is demonstrated in the graph. NK1 and AMPA activation give small linear depolarisations (allowing the resting potential to be less negative), then with continuing stimuli, the NMDA receptor opening allows massive increase in action potentials to be generated for the same given stimuli (wind-up). As the stimuli ceases the neurone gradually winds down to normal.

signalling pathways, which alter receptor activation thresholds, and gene expression.

Inhibition, like excitation, is a complex inter-connecting series of networks. Principal inhibitory neurotransmitters such as glycine, GABA (γ -aminobutyric acid), endocannabinoids and enkephalins provide tonic inhibition to the dorsal horn. In addition, acute attenuation of excitatory pathway can occur via release of glycine and GABA from inhibitory inter-neurons, which have been activated via glutamate AMPA/NMDA receptors on GABA-ergic neurones. GABA can bind to GABA-A or C ionic receptors which causes rapid re-polarisation or via G-protein linked GABA-B receptors. The intrinsic inhibitory opioids system is evident throughout the CNS and especially within the dorsal horn. Enkephalins are released via activated interneurons (and descending pathways) that bind to μ receptors. 70% of μ receptors are expressed on primary afferents allowing direct attenuation of input signal. The remaining are on various post-synaptic neurones, providing a means of tonic and phasic inhibition. Other members of the opioid family such as δ (dynorphin) or κ (kappa) receptors can have inhibitory actions although that is more dependent on the site and activation of the neurone. Exogenous additions of opioids are the mainstay of analgesic therapy; however the role for current cannabinoid-(CB)1 receptor agonists is yet to be fully elucidated.

Glia cells (microglia and astrocytes) which have similar receptors to neurones are also activated. Glia are now known to be intrinsically involved in initiation and maintenance of neuronal activation, in part by regulating the synaptic glutamate (via glutamate transporter family), the production of cyclo-oxygenase (COX) receptors in response to cytokine release and feed forward loop to neurones via chemokines. Inhibition of glia has been shown to attenuate hyperalgesia.

A huge number of receptors and neurotransmitters are involved in a complex dynamic communication within the dorsal horn neuronal synapses. At this point there is extensive modulation of the primary afferent input, such that the output via spino-CNS tracts (such as spinothalamic, spino-brachial) is a summation of all events. The original 'gate theory' hypothesis by Melzack and Wall first indicated the possible attenuation of C fibre inputs at the dorsal horn level. The principle of 'gate theory' remains although the complexity and dynamic nature of the modulation means it is somewhat more complex and subtle than originally proposed.

Supra spinal connections

Until recently the supraspinal connections and functions were little understood, and many pain experiences / expressions were labelled as 'functional', 'supratentorial' or 'all in the mind'. With the uniting of complex retrograde neuronal pathway activation, midbrain *in vivo* and *in vitro* neuronal electrophysiology and functional magnetic resonance (fMRI) / positron electron tomography (PET), and EEG, a gradual unlocking of the complexity of the supra spinal networks is emerging (Fig. 5).

Figure 5

A summary of the supraspinal connections and interconnections to and from the spinal cord. The affective and sensory components of pain are separately relayed to parabrachial and spinothalamic pathways respectively. Simple interconnections are shown in blue and the descending system (inhibitory and excitatory) are shown in red.

Whilst the dorsal horns' modulation might look daunting enough it is nothing compared to the complexity of the dynamic and plastic central neural networks. At its simplest the parabrachial projection neurones from lamina I carry information to the hypothalamic / limbic / amygdala areas (relay to hippocampal areas), which are responsible for the aversive, affective and memory recall, and tonic emotional state components of nociception. Some neurones in this pathway have relatively few synaptic connections, allowing a rapid aversive response, even before a fully conscious awareness of location is triggered.

The spinothalamic (and dorsal column) pathways traverse and synapse in the huge relay station of the thalamus and on to the sensory cortex. This allows for topographical mapping of the stimuli, and evoking a conscious motor response. The insular and cingulate cortices are complex with different regions particularly involved in coding for aspects of the stimuli. Thus the anterior cingulate cortex appears to be involved in attending to stimuli, pain being a primary cause of attention; this can be modulated by distraction experiments, which diminish intensity experience. Alternatively depression can increase activity in this area leading to greater attention to 'pain'. In addition parts of the insular cortex code the character of the pain (burning, ache etc) and part of the emotional response to the painful stimuli. The midinsular region preferentially codes for visceral / autonomic stimuli, and links viscerovisceral loops and autonomic responses.

Descending pathways can arise from any level and are fed through the peri-aqueductal grey (PAG) and rostro-ventral medulla (RVM) in the midbrain. Here a complex series of on-off neutral cells allow descending inhibitory or excitatory pathway activation. Descending pathways are predominately noradrenergic (NorAd) and serotonergic (5HT). The NorAd binds to post-synaptic receptors inhibiting neuronal depolarisation. 5HT actions depend on the receptors, thus it is excitatory when binding to 5HT₃ primary afferent receptors and inhibitory when binding to post-synaptic 5HT₁ receptors.

Summary

Normal pain transmission is a complex, dynamic process. It allows a wide variety of noxious stimuli to be transduced into electrical transmission via specialist primary afferents. These afferents in themselves allow for modulation of the action potentials, for example

inhibition via activation of peripheral opioid receptors or excitation via neurokinins. The primary afferents terminate in the dorsal horn of the spinal cord, where the signal can be extensively modulated by intrinsic spinal interneurons, glia and descending pathways. The response to a given peripheral noxious stimulus may be increased by excitation of the dorsal horn (for example via activation of windup via NMDA receptor) or attenuated via release of GABA, enkephalins and other inhibitory neurotransmitters. Ascending pathways activate higher CNS centres which allow conscious awareness of pain, attention or facilitation of pain. Normal pain transmission allows rapid attending to a noxious stimuli, removal of stimuli (where possible), learning and memory of noxious stimuli / action, and ultimately inhibition of pain whilst healing and repair occurs, and a return to the baseline non-active state.

FURTHER READING:

- Carpenter KJ, Dickenson AH (2002) *Pharmacogenomics J*, **2**, 87-95.
- Cervero F, Laird JM (2004) *J Neurobiol*, **61**, 45-54.
- Suzuki R, Dickenson A.H. (2000) *Neuroreport*, **11**, R17-21.
- Suzuki R, Rygh LJ, Dickenson AH (2004) *Trends Pharmacol Sci*, **25**, 613-7.
- Tracey I (2005) *Pain*, **116**, 173-4.
- Tsuda M, Inoue K, Salter MW (2005) *Trends Neurosci*, **28**, 101-7.
- Woolf CJ, Mannion RJ (1999) *Lancet*, **353**, 1959-64.

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