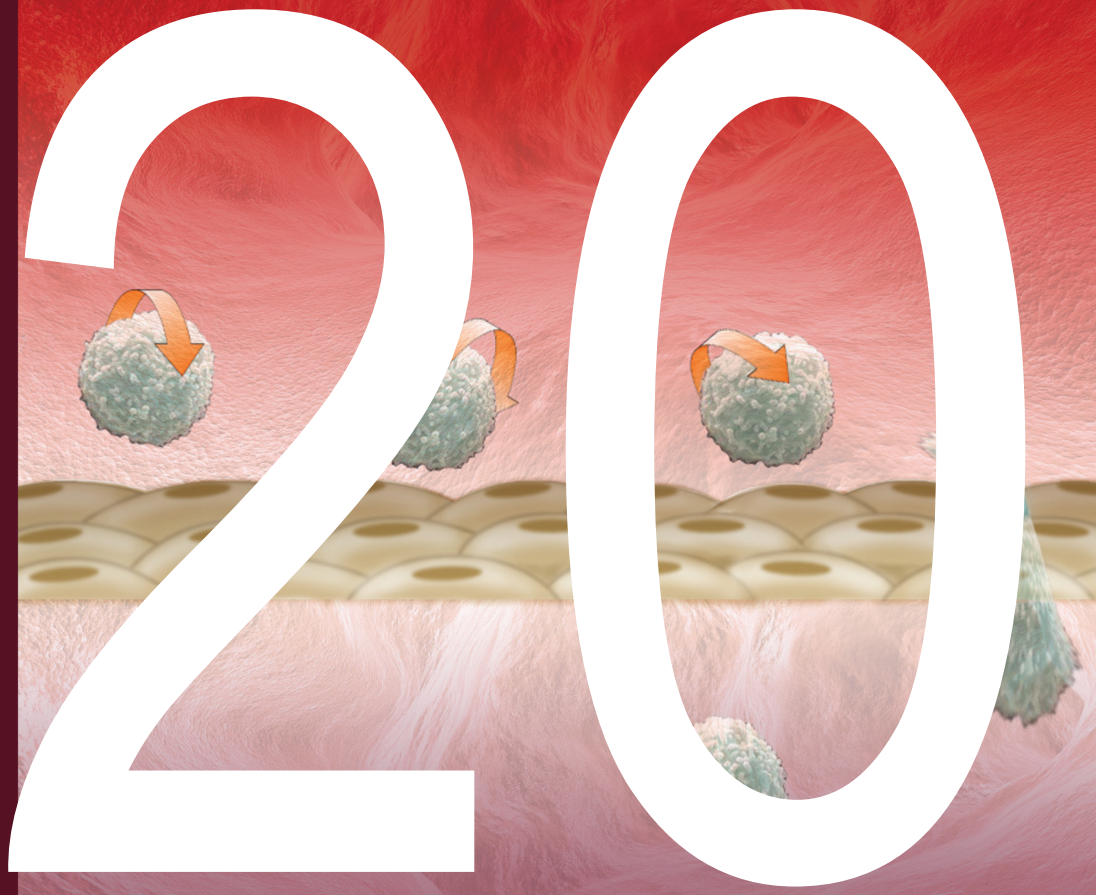
Mechanisms of Vascular Disease:

A Reference Book for Vascular Specialists



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Mechanisms of Vascular Disease

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A Reference Book for Vascular Specialists

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Abbreviation List

a1-PI	a1-protease inhibitor
5-HT	5-Hydroxytryptamine/Serotonin
AAA	Abdominal aortic aneurysm
AAS	Acute aortic syndrome
AAV	Adeno-associated viruses
ACE	Angiotensin converting enzyme
ACS	Acute coronary syndrome
ACS	Abdominal compartment syndrome
ACTH	Adrenocorticotropic hormone
ADAMTS	A disintegrin and metalloproteinase with thrombospondin motifs
ADP	Adenosine diphosphate
AIDS	Acquired immune deficiency syndrome
ALI	Acute lung injury
AMP	Adenosine monophosphate
AMPA	α-amino-3 hydroxy-5-methylisoxazole
ANA	Anti-nuclear antibody
ANCA	Anti-neutrophil cytoplasmic antibody
AOD	Aortic occlusive disease
AP1	Activated protein 1
APC	Activated protein C
APC	Antigen presenting cell
APLAS	Antiphospholipid antibody syndrome
ApoAI	Apolipoprotein AI
ApoE	Apolipoprotein E
APS	Antiphospholipid antibody syndrome
APTT	Activated partial thromboplastin time

ARDS	Acute respiratory distress syndrome
AT	Antithrombin
ATP	Adenosine triphosphate
AVP	Ambulatory venous thrombosis
β2-GPI	β2-glycoprotein Ib
bFGF	Basic fibroblast growth factor
BKCa	Large conductance calcium activated potassium channel
BMPs	Bone morphogenetic proteins
BMS	Bare metal stent
CAD	Coronary artery disease
CaM	Calmodulin
CAM	Cell adhesion molecule
cAMP	Cyclic adenosine monophosphate
CCK	Cholecystokinin
cGMP	Cyclic guanine monophosphate
CD	Cluster of differentiation
CD40L	Cluster of differentiation 40 ligand
CEA	Carotid endarterectomy
CETP	Cholesteryl ester transfer protein
CFD	Computational fluid dynamics
CG	Cationized gelatin
CGRP	Calcitonic gene regulated peptide
CHD	Coronary heart disease
CI	Confidence interval
CIMT	Carotid intimal-media thickness
c-JNK	c-Jun N-terminal kinase
CK-MB	Creatinine kinase (Myocardial specific)
CNCP	Chronic noncancer pain
cNOS	Constitutive nitric oxygen synthase enzyme
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
CROW	Charcot restraint orthotic walker
CRRT	Continuous renal replacement therapy

CRP	C-reactive protein
CRPS	Complex regional pain syndromes
CT	Computational tomography
CTA	Computed tomographic angiography
CTD	Connective tissue disorders
CTGF	Connective tissue growth factor
CYP	Cytochrome P450
CVD	Cardiovascular disease
CVI	Chronic venous insufficiency
DAG	Diacylglycerol
DES	Drug-eluting stent
DRG	Dorsal root ganglion
DNA	Deoxyribonucleic acid
DSA	Digital subtraction arteriography
DTS	Dense tubular system
DVT	Deep vein thrombosis
EC	Endothelial cell
ECM	Extracellular matrix
EDCF	Endothelium-derived contracting factor
EDH	Endothelium-dependent hyperpolarisation
EDS	Ehlers-Danlos syndrome
EET	Epoxyeicosatrienoic acids
ELAM-1	Endothelial-leukocyte adhesion molecule-1
ELG	Endoluminal grafts
ELISA	Enzyme linked immunosorbent assay
E_K	Equilibrium potential
E_M	Membrane potential
eNOS	Endothelial nitric oxide synthase enzyme
EPC	Endothelial progenitor cells
EPCR	Endothelial protein C receptor
ePTFE	Expanded polytetrafluoroethylene
ERK	Extracellular signal-regulated kinase
ESR	Erythrocyte sedimentation rate

ET	Essential thrombocytosis
ET-1	Endothelin 1
EVAR	Endovascular aortic aneurysm repair
EVLA	Endovenous LASER ablation
FDA	Food and drug administration
FDPs	Fibrin degradation products (soluble)
FGF	Fibroblast growth factor
FGF-2	Fibroblast growth factor 2
FMN	Flavin mononucleotide
FVL	Factor V Leiden
GABA	Gamma-aminobutyric acid
GABA B	Gamma-aminobutyric acid subtype B
G-CSF	Granulocyte colony stimulating factor
GMCSF	Granulocyte-macrophage colony stimulating factor
GP	Glycoprotein
GPCR	G-protein coupled receptor
GSV	Great saphenous vein
HDL	High density lipoprotein
HDL-C	High density lipoprotein cholesterol
HIF	Hypoxia inducible factor
HIT	Heparin induced thrombocytopenia
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HMG Co-A	Hydroxymethylglutaryl coenzyme-A
HMW	High molecular weight
HPETE	Hydroperoxyeicosatetraenoic acid
HETE	Hydroxyeicosatetraenoic acids
HR	Hazard ratio
hsCRP	High-sensitive C-reactive protein
HSP	Heat shock protein
HUV	Human umbilical vein
IAH	Intra-abdominal hypertension

IAP	Intra-abdominal pressure
IAPP	Intra-abdominal perfusion pressure
ICAM-1	Inter-cellular adhesion molecule-1
ICAM-2	Inter-cellular adhesion molecule-2
ICP	Intra-compartmental pressure
ICU	Intensive care unit
IFN	Interferon
IGF-1	Insulin-like growth factor-1
IHD	Ischemic heart disease
IL	Interleukin
IL-1	Interleukin-1
IL-1α	Interleukin-1 alpha
IL1-β	Interleukin-1 beta
IL-6	Interleukin-6
IL-8	Interleukin-8
ILT	Intraluminal thrombus
IKCa	Intermediate conductance calcium-activated potassium channels
IMH	Intramural haematoma
IMP	Inosine monophosphate
iNOS	Inducible nitric oxide synthase enzyme
IP(3)	1,4,5-inositol triphosphate
IRI	Ischemia reperfusion injury
IVIG	Intravenous pooled immunoglobulin
IVUS	Intravascular ultrasound
KGF	Keratinocyte growth factor
KGF-2	Keratinocyte growth factor-2
LAP	Latency associated peptide
LCS	Limb compartment syndrome
LDL	Low density lipoprotein
LDS	Loeys-Dietz syndrome
LLC	Large latent complex
LEC	Lymphatic endothelial cells

LFA-1	Lymphocyte function-associated antigen-1
LO	Lipoxygenase
LOX	Lysyl oxidase
LOPS	Loss of protective sensation
LPA	Lysophosphatidic acid
LPS	Lipopolysaccharide
LTA	Lipoteichoic acid
LTGFBP	Latent TGF binding protein
MAC-1	Macrophage-1 antigen
MAPK	Mitogen activated protein kinase
MCP-1	Monocyte chemoattractant protein-1
M-CSF	Macrophage-colony stimulating factor
MFS	Marfan syndrome
MHC	Major histocompatibility
MI	Myocardial infarction
MIP-1	Macrophage inflammatory protein-1
MLC_{20}	Myosin light $chain_{20}$
MLCK	Myosin light chain kinase
MLCP	Myosin light chain phosphatase
MMP	Matrix metalloproteinase
MODS	Multiple organ dysfunction syndrome
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MRSA	Methicillin resistant *Staphylococcus aureus*
MRSE	Methicillin resistant *Staphylococcus epidermidis*
MRTA	Magnetic resonance tomographic angiography
MTHFR	Methylenetetrahydrofolate reductase
MT-MMP	Membrane-type MMP
MVPS	Mitral valve prolapse syndrome
NADPH	Nicotinamide adenine dinucleotide phosphate
NGF	Nerve growth factor

NFκB	Nuclear factor kappa B
NiTi	Nitinol
NJP	Non-junctional perforators
NMDA	N-methyl-D-aspartate
NNH	Number needed to harm
NNT	Number needed to treat
NO	Nitric oxide
NOS	Nitric oxide synthase enzyme
NSAID	Non-steroidal anti-inflammatory drug
NV	Neovascularisation
OCP	Oestrogen/progesterone contraceptive pill
OPN	Osteopontin
OPG	Osteoprotegerin
OR	Odds ratio
OxLDL	Oxidised low density lipoprotein
PAD	Peripheral arterial disease
PAF	Platelet activating factor
PAI	Plasminogen activator inhibitor
PAI-1	Plasminogen activator inhibitor-1
PAR	Protease activated receptor
PAR-1	Protease activated receptor-1
PAR-4	Protease activated receptor-4
PAU	Penetrating aortic ulcer
PC	Protein C
PCA	Poly (carbonate-urea) urethane
PCI	Percutaneous coronary intervention (angioplasty)
PCWP	Pulmonary capillary wedge pressure
PDGF	Platelet-derived growth factor
PDGFβ	Platelet-derived growth factor-β
PDS	Polydioxanone
PECAM-1	Platelet-endothelial cell adhesion molecule-1
PEDF	Pigment epithelium-derived factor
PES	Paclitaxel-eluting stent

PET	Positron emission tomography
PF4	Platelet factor 4
PGI_2	Prostacyclin
PGG_2	Prostaglandin G_2
PGH_2	Prostaglandin H_2
$PGEI_2/PGI_2$	Prostaglandin I_2
PGN	Peptidoglycan
PHN	Postherpetic neuropathy
PHZ	Para-anastomotic hyper-compliant zone
PI3K	Phosphatidylinositol 3-kinase
PIP2	Phosphatidylinositol 4,5-bisphosphate
PLC	Phospholipase C
PLOD	Procollagen lysyl hydroxylase
PMCA	Plasma membrane Ca^{2+} APTases
PMN	Polymorphonuclear leukocyte
POSS	Polyhedral oligomeric silsesquioxanes
PPAR	Peroxisomal proliferation activating receptor
PPI	Proton pump inhibitor
PRV	Polycythaemia rubra vera
PS	Protein S
PSGL-1	P-selectin glycoprotein ligand-1
PT	Prothombin time
PTCA	Percutaneous coronary angioplasty
PTFE	Polytetrafluoroethylene
PTS	Post-thrombotic syndrome
PUFA	Polyunsaturated fatty acid
PVI	Primary valvular incompetence
rAAA	Ruptured AAA
Rac	Ras activated cell adhesion molecule
RANTES	Regulated upon activation, normal T cell expressed and secreted
RAS	Renin angiotensin system
RCT	Randomised controlled trial

RF	Rheumatoid factor
RFA	Radiofrequency ablation
rhAPC	Recombinant human activated protein C
RNA	Ribonucleic acid
ROS	Reactive oxygen species
RR	Relative risk
RSD	Reflex sympathetic dystrophy
S1P	Sphingosine-1-phosphate
SAPK	Stress-activated protein kinase
SCF	Stem cell factor
SCS	Spinal cord stimulation
ScvO2	Superior vena cava venous oxygen saturation
SDF-1	Stromal-cell-derived factor-1
SERCA	Sarco/endoplasmic reticulum CaATPases
SEP	Serum elastin peptides
SES	Sirolimus-eluting stent
SEPS	Subfascial endoscopic perforator surgery
SFA	Superficial femoral artery
SFJ	Sapheno-femoral junction
SIRS	Systemic inflammatory response syndrome
SKCa	Small conductance calcium-activated potassium channels
SLE	Systemic lupus erythematosus
SMA	Smooth muscle alpha actin
SMC	Smooth muscle cell
SMP	Sympathetically maintained pain
SNARE	Soluble N-ethylmaleimide-sensitive factor activating protein receptors
SNP	Single nucleotide polymorphisms
SNRI	Serotonin/Noradrenaline reuptake inhibitors
SPJ	Sapheno-popliteal junction
SPP	Skin perfusion pressure
SR	Sarcoplasmic reticulum
SSRIs	Selective serotonin re-uptake inhibitors
SSV	Small saphenous vein

SVT	Superficial thrombophlebitis
STIM1	Stromal interacting molecule 1
TαCE	TNFα converting enzyme
TAAD	Thoracic aortic aneurysm disease
TAD	Thoracic aortic dissection
TAFI	Thrombin-activatable fibrinolysis inhibitor
Tc-99 MDP	Technetium-99 methylene diphosphonate
TCA	Tricyclic antidepressant
TCC	Total contact cast
TCR	T-cell receptor
TENS	Transcutaneous electrical nerve stimulation
TF	Tissue factor
TFPI	Tissue factor pathway inhibitor
TGF	Transforming growth factor
TGF-α	Transforming growth factor-alpha
TGF-β	Transforming growth factor-beta
TGL	Triglycerides
Th	T helper
TIA	Transient ischemic attack
TIMP	Tissue inhibitors of metalloproteinase
TLR	Toll-like receptors
TNF	Tumour necrosis factor
TNF-α	Tumour necrosis factor-alpha
tPA	Tissue-type plasminogen activator
TRP	Transient receptor potential
TRPC	Transmembrane receptor potential canonical
TRPV1	Transmembrane receptor potential Vanilloid-type
TXA2	Thromboxane A2
uPA	Urokinase
UT	University of Texas
VCAM	Vascular cell adhesion molecule
VCAM-1	Vascular cell adhesion molecule-1
VEGF	Vascular endothelial growth factor

VEGF-R	Vascular endothelial growth factor receptor
VIP	Vasoactive intestinal peptide
VLA-1	Very late activating antigen-1
VOCC	Voltage operated calcium channels
VPT	Vibratory perception threshold
VSMC	Vascular smooth muscle cells
VTE	Venous thromboembolism
VV	Varicose veins
vWF	von Willebrand factor
XO	Xanthine oxidase

20 • Pathophysiology of Pain

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INTRODUCTION

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage.[1]

The mechanism by which a damaging stimulus in the body is perceived as painful by the brain is a complex one which is not yet fully understood. The complexity of the process results from the nervous system not being a 'hard wired' system, but exhibiting plasticity that enables it to modify its function under different conditions.

As shown by the definition, pain serves the purpose to prevent tissue damage and protect the body while it is healing. Under certain conditions, pain can become maladaptive and persist as chronic pain. This pain serves no protective function and is described as pathological pain as opposed to physiological pain;[2] it is then no longer a symptom of another disease, but a disease in its own right.[3] Another term for pathological pain has been suggested recently: dysfunctional pain.[4]

In order to adequately treat physiological, but even more pathological pain, an understanding of pain mechanisms is required.

PERIPHERAL MECHANISMS

Nociception/Transduction

Painful stimuli are detected by nociceptors, which are free nerve endings located in tissues and organs. They have high thresholds and, under normal circumstances, only respond to noxious stimuli.

There are two distinct types of nociceptors

- High threshold mechanoreceptors which stimulate small myelinated Aδ-fibres and transmit a well-localised sharp or pricking sensation that lasts as long as the stimulus.
- Polymodal nociceptors that stimulate small unmyelinated slowly conducting C fibres. As well as responding to mechanical stimuli they are activated by thermal and chemical stimuli e.g. hydrogen ions, potassium ions, bradykinin, serotonin, adenosine triphosphate and prostaglandins.

The ion channels for noxious stimuli have been partially identified; the transient receptor potential (TRP) family of these ion channels and in particular the vanilloid-type

TRP 1 (TRPV1) have been studied in most detail.[5] This receptor is sensitive to higher temperatures, acidity and capsaicin, an exogenous ligand (extract of chilli pepper) and receptors like this one are currently investigated as therapeutic targets for pain therapy.

Nerve growth factor (NGF) is also involved in the transduction process, as it binds to its receptor TrKa and thereby triggers increased transduction in pain states, in particular inflammatory pain. A monoclonal antibody against NGF, tanezumab, has shown very promising effects in early stage trials in osteoarthritis and chronic low back pain.[6]

Conduction

Voltage-gated sodium channels mediate conduction along primary sensory afferents. As for all other impulses throughout the body, action potential propagation is dependent on these channels. There are two types of sodium channels, differentiated by their sensitivity to tetrodotoxin. Both types are present in nociceptive neurons, with the tetrodotoxin-resistant type only present in nociceptors, which makes it a potential target for novel analgesics. Further research has identified two such sodium channels, labelled NaV1.7 and NaV1.8, which seem to have a specific role in pain modulation.[7] Mutations of these channels are linked to congenital insensitivity to pain and erythromyalgia and attempts are made to identify blockers of these channels, which might be therapeutic in chronic or neuropathic pain.

Nociceptors also have voltage-gated calcium channels, which are found on the presynaptic membrane and are involved in neurotransmitter release at the dorsal horn. These are modulated by alpha-2-delta compounds such as gabapentin and pregabalin, new first-line treatments of neuropathic pain and central sensitisation.[8]

Pain is transmitted by primary afferents, which have their cell bodies in the dorsal root ganglion (DRG). They terminate in the dorsal horn of the spinal cord. The dorsal horn cells are divided into specific regions or laminae called Rexed's laminae with lamina I being the most superficial.[9]

- Aδ-fibres are fast conducting and transmit the first sharp pain on initial stimulation. They terminate mainly in lamina I, but also send some fibres to lamina V of the dorsal horn where they synapse with second order neurones. They contain the neurotransmitter L-glutamate.
- C fibres are unmyelinated slow conducting fibres which transmit a less well localised persistent aching pain that lasts after the initial stimulus has gone. They terminate in lamina II of the dorsal horn. As well as glutamate they contain several other neurotransmitters including neuropeptides, such as substance P, and calcitonin gene-related peptide (CGRP), cholecystokinin, brain-derived neurotrophic factor and glial-derived neurotrophic factor. C fibres express several presynaptic receptors that modulate transmitter release. These include cholecystokinin (CCK), opioid and gamma-aminobutyric acid subtype B (GABA B) receptors. Apart from the CCK receptor, they inhibit the release of transmitter.
- Aβ-fibres conduct low intensity mechanical stimuli which convey touch and not pain, however in chronic pain states they are involved in the transmission of pain. They terminate deeper in the dorsal horn in laminae III-VI.

SPINAL CORD MECHANISMS

Primary sensory afferents terminate in the spinal cord where they synapse with cells

of the dorsal horn. Nococeptive specific neurons are located mainly in laminae I and II but also lamina V and respond only to noxious inputs under normal conditions

There are a number of different cells involved in the relay of painful stimuli including nociceptive specific cells and wide dynamic range neurons. Wide dynamic range neurons are located mainly in lamina V, but also in III and IV to a lesser extent, where they respond to stimuli from Aβ-, Aδ- and C-fibres.[9]

The cells of the dorsal horn involved in nociception express a number of receptors.

- AMPA (a-amino-3 hydroxy-5-methylisoxazole) receptors which bind glutamate.
- NMDA (N-methyl-D aspartate) receptors which also bind glutamate, neurokinin receptors NK-1 which bind substance P.
- GABA-A receptors which are ligand-gated calcium channels that hyperpolarize the cell and reduce responsiveness to stimulation.
- Voltage-gated calcium channels.
- Glycine receptors that provide an inhibitory function

The ability to detect a potentially damaging noxious stimulus is mediated by glutamate acting on the AMPA receptor following stimulation of Aδ-fibres. The other receptors and neurotransmitters are involved in the modulation of the response.

When a high intensity noxious stimulus arrives at the dorsal horn via C-fibres, initially glutamate is released which acts via the AMPA receptor. As stimulus intensity increases, then other neurotransmitters are released such as Substance P. Slow post-synaptic currents are set up which are mediated by a number of receptors including the NMDA receptor. These are also involved in the modulation of the pain response.[10]

Ascending systems

Noxious information is conveyed from the dorsal horn to the brain via several ascending tracts in the spinal cord. The majority of the wide dynamic range neurons and nociceptive specific neurons are conveyed anterolaterally in three pathways:[11]

- The spinothalamic tract: Its fibres cross over to the contralateral side and pass through the brainstem to nuclei in the thalamus, finally terminating in the somatosensory cortex where pain is perceived and localised.
- The spinoreticular tract: It terminates in the reticular formation and has projections, which terminate in the pons, medulla and periaqueductal grey matter. It is involved in descending inhibition of pain.
- The spinomesencephalic tract: It is also involved in the modulation of descending control.

Descending control

The dorsal horn receives inputs from higher centres that modulate the response to nociceptor input.[12]

The descending control of output from the dorsal horn comes mainly from areas in the brainstem, namely the periaqueductal grey matter, the raphe nuclei and the locus coeruleus.[13] Inhibitory tracts descend in the dorsolateral fasciculus and synapse in the dorsal horn. The key neurotransmitters involved are noradrenaline and serotonin. Noradrenaline acts via post synaptic α-2 receptors, the action of serotonin is less specific. Endogenous opioids are also involved in descending inhibition at a spinal and supraspinal level.[13] These endorphins and enkephalins acting via the descending system are thought to be responsible for the analgesia induced by stress.

As well as descending control from the brainstem, nociceptive impulses are also attenuated by input via Aβ-fibres (transmitting information on touch), which is the basis for the use of Transcutaneous Electrical Nerve Stimulation (TENS) for analgesia, but also for simply rubbing a hurting body part. This observation formed the basis for the initial gate-control theory of pain.[14]

PAIN MODULATION

The above description of pain explains the initial sensation of pain immediately following injury, however it does not explain the more complex phenomena associated with pathological pain due to neuroplastic changes.

These phenomena have a number of different causal mechanisms, which occur initially in the periphery, but later mainly in the dorsal horn as the main site modulation of painful stimuli.

Peripheral sensitisation

Tissue injury results in the release of inflammatory mediators, such as bradykinin, histamine, K+, H+, 5-Hydroxytryptamine (5-HT), ATP and nitric oxide from damaged cells.[15] Breakdown of arachidonic acid by cyclo-oxygenase produces leukotrienes and prostaglandins. Immune cell activation results in the release of further mediators including cytokine and growth factors. These mediators provide an 'inflammatory soup' which produces a painful area of primary hyperalgesia. These inflammatory mediators spread into the tissues surrounding the initial area of injury to produce an area of secondary hyperalgesia.

They act either by stimulating nociceptors themselves or by acting via inflammatory cells to stimulate release of additional pain inducing agents. They also modify the response of primary afferents to subsequent stimuli either by changing the sensitivity of the receptors or by modulating the voltage-gated ion channels. For example, after tissue and nerve injury, N-type calcium channels become more active resulting in greater release of glutamate in the spinal cord.[16] The magnitude of the current generated by sensory-neuron specific sodium channels is also increased.

Chronic inflammation and also nerve injury has an effect on the presence and distribution of voltage-gated sodium channels, which can become concentrated in areas of injury and produce ectopic discharges. Sensory-neurone-specific sodium channels have a significant role in chronic pain states. Studies have shown them to become concentrated in neurones proximal to a site of nerve injury and play a role in the hyperalgesia and allodynia of chronic pain states.[9] In addition, NGF binding to TrKa receptors increases peripheral sensitivity as discussed before.[6]

Not all sensory neurons are active all the time and this peripheral sensitisation will recruit 'dormant' nociceptors, thus increasing the receptive fields of dorsal horn neurons and increasing the intensity and the area of pain.[17]

Central sensitisation in the dorsal horn

Central sensitisation is an increase in the excitability of the dorsal horn so that the dorsal horn cells have a lower threshold and respond to low intensity stimuli that are not usually painful. It also results in a greater response to supra threshold stimuli thus producing the symptoms of allodynia and hyperalgesia.

There are several mechanisms, which occur at the dorsal horn and contribute to

chronic pathological pain states by central sensitisation. These will be discussed in the context of neuropathic pain, as they are most relevant there.

NEUROPATHIC PAIN

Neuropathic pain arises following disease or injury to nerves from a number of aetiologies eg, ischaemic, traumatic, infection. Characteristics of neuropathic pain include spontaneous stimulus-independent pain and pain that is stimulus dependent and exhibits the features of allodynia and hyperalgesia. There are a variety of different mechanisms responsible for the generation of symptoms, which may be quite different from patient to patient.[18]

Mechanisms of neuropathic pain

The pathophysiology of neuropathic pain involves central and peripheral mechanisms and is in principle a 'maldaptive response of the nervous system to damage'.[4] Usually more than one mechanism may be involved and producing a unifying hypothesis for all neuropathic pain states is inappropriate.[19]

Peripheral mechanisms

Electrophysiological evidence over the last 25 years shows that activity in sensory neurones after injury is necessary for the development of neuropathic symptoms. Some proposed mechanisms are:

Spontaneous ectopic discharge

Normal primary afferent neurones require the input of a stimulus in order to reach firing potential. It has been shown that after a nerve injury spontaneous firing in the afferent neurone occurs. A and C fibres have been shown to demonstrate oscillatory activity resulting in ectopic firing. Cross excitation of other neurones increases this effect. These phenomena may be particularly relevant to the development of hyperalgesia, allodynia and chronic pain after nerve injuries.

Reorganisation of expression of ion channels in the peripheral nerves is responsible for the ectopic discharge. Both sodium and calcium channels have been shown to be involved with their altered expression increasing the excitability of neurones. The afferent barrage provided by spontaneous discharge from neurones provides a constant input to the central nervous system that may induce central sensitisation.[20]

Altered gene expression

Damaged peripheral sensory neurones undergo Wallerian degeneration and lose contact with peripheral targets and the supply of neurotrophic factors. The sensory neurones undergo altered gene expression, the result of which is a change in the type and level of neurotransmitters released in the spinal cord.[21] For example, some A-β fibres appear to release transmitters normally associated with nociceptors such as substance P. This seems to contribute to central sensitisation.[22] A change in gene expression also results in either up or down regulation of ion channels, in particular different types of sodium channel involved in ectopic spontaneous activity.

Spared sensory neurons

Changes have also been found in uninjured sensory fibres that are along side those with a lesion. They frequently show the opposite gene expression changes from their damaged neighbours; possibly due to increased bioavailability of neurotrophic factors. This can result in increased activity in the spared afferents, although the exact mechanism is not understood.[21]

Involvement of the sympathetic nervous system

Some patients exhibit neuropathic pain that is dependent on activity in the sympathetic nervous system.[23] After a peripheral nerve injury, a coupling develops between the sympathetic nervous system and the sensory nervous system. Axons involved develop increased α-adrenoceptors and therefore have an exaggerated response to circulating catecholamines. Morphological changes to the nerve follow with sympathetic axons sprouting into the dorsal root ganglion forming baskets around the cell bodies of sensory neurones. These changes lead to sympathetically maintained pain. Evidence for a sympathetic component to a patient's pain include sympathetically maintained, often unilateral limb pain, oedema, vasomotor and sudomotor asymmetries.

Collateral sprouting

Sprouting of fibres from sensory axons in the skin has been shown to occur in denervated areas, for example after crush injuries. However this does not occur in proportion to the degree of neuropathic pain experienced and is likely to be a small if at all significant factor in its pathophysiology.

Effects of bradykinin

This main plasma kinin, a vasodilator peptide, is involved in hyperalgesia associated with inflammatory pain, with a change in expression of its binding sites within the dorsal root ganglion after nerve injury.

Central mechanisms

The central mechanisms potentially involved in the generation of neuropathic pain are thought to result in neuroplastic changes in the CNS. A phenomenon termed central sensitisation occurs after peripheral nerve injury. Central sensitisation changes the way the neurones respond to subsequent inputs.[4] This may result in spontaneous ongoing pain and abnormally evoked pain (allodynia and hyperalgesia).[17] The mechanisms that are thought to be responsible occur primarily in the dorsal horn.

Wind-up

The term wind up describes the altered response of the dorsal horn neurones to repeated input from C-fibres.[10,17] Following brief, repetitive C-fibre stimulation, the dorsal horn cells respond in a linear fashion. However if the stimulus continues, further C-fibre activation produces an amplified response in the dorsal horn to the same intensity of stimulus.

This phenomenon is mediated by the NMDA receptor. Activation by sustained C fibre input leads to opening of the channel, an increased intracellular calcium concentration and an increased response to glutamate. Glutamate is the main excitatory neurotransmitter released from primary afferent neurones that acts at postsynaptic receptors. The NMDA receptor in its resting state is blocked by magnesium which is released when the cell is depolarised thus opening the channel in the receptor and allowing an influx of sodium and calcium and further depolarisation. When a painful stimulus arrives at the dorsal horn, the cells are initially depolarised by glutamate acting at the AMPA receptor thus allowing removal of the magnesium block. Once the stimulus is removed, the dorsal horn cells continue to fire for several seconds.

There is potential for this to be modified pharmacologically and a number of studies suggest that NMDA antagonists may prevent these phenomena and prevent hyperalgesia.[10]

Wind up is relatively short lived (seconds to minutes), whereas central sensitisation persists so the exact relationship remains unclear.

Central sensitization

Central sensitisation is also mediated by the NMDA receptor. Under conditions of prolonged C-fibre activation, depolarisation of the dorsal horn cells causes the NMDA receptor to lose its magnesium block.[10] Substance P acting via its receptor, the neurokinin-1 receptor, prolongs this depolarisation and allows further influx of calcium. The increase of calcium in the dorsal horn activates calcium dependent kinases such as protein kinases A and C, which are then able to phosphorylate amino acids within the NMDA receptor to produce a conformational change in the structure. This permanently removes the magnesium block in the receptor and allows it to be activated by glutamate. The process of central sensitisation differs from windup in that the changes remain long after the C-fibre input has ceased. Furthermore, the magnesium is removed by posttranslational changes in the NMDA receptor and is not just depolarisation induced.[17,22,24]

Central disinhibition

Central disinhibition results from loss of modulatory control mechanisms, which may lead to abnormal excitation of central neurones.[25] The main inhibitory neurotransmitter is γ-aminobutyric acid (GABA). It has been shown that suppression of this pathway results in allodynia. Within two weeks after a peripheral nerve injury, GABA receptor levels are reduced. So it seems that down regulation of GABA mediated pathways may be in part responsible for central sensitisation.

Expansion in receptive field size (recruitment)

Receptive fields of dorsal horn neurones contain subliminal areas; these represent a reservoir of activity.[26] With ongoing activation after injury there is an expansion of receptive field size leading to increased perception of pain, resulting in secondary hyperalgesia. This expansion of receptive fields does not reflect peripheral nerve or nerve root distribution, but spinal cord architecture. It might therefore be confusing from a diagnostic point of view, as it transgresses the boundaries imposed by a hard-wired model of the CNS.[27]

Immediate early gene expression

Immediate changes in gene expression in dorsal horn cells occur in response to Aδ- and C-fibre stimulation. These changes persist for a variable length of time and may contribute to central neuroplasticity. Noxious stimulation mediated by Aδ- and C-fibres produces an immediate change in the expression of certain genes within the dorsal horn cells.[28] These changes are detected within minutes of stimulation and may last for months or even years. The gene c-*fos* encodes for a protein, *fos*, which forms part of a transcription factor which may control the expression of other genes which produce long term changes in the dorsal horn. *C-fos* activation occurs as a result of increases in intracellular calcium following release of neurotransmitters like substance P and glutamate involved in relay of nociceptive information.[29] This is followed rapidly by the appearance of *fos* protein which can be detected in laminae I, II and V of the dorsal horn. The presence of *fos* protein can be used as a marker of noxious stimulation and thus also to determine the effect of agents to reduce noxious stimulation.

Anantomical re-organisation of the spinal cord

Primary afferent neurones synapse in the laminae of the dorsal horn with second order ascending neurones. Under normal conditions, Aδ- and C-fibres terminate in laminae I and II, whereas Aβ-fibres terminate in laminae III and IV.

Following C-fibre injury, the large unmyelinated Aβ-fibres sprout terminals into lamina II. Aβ-fibres, which are activated by low intensity non-painful stimuli can thus stimulate the dorsal horn neurons present in lamina II, usually associated with noxious sensation.[30] This observation could explain allodynia, as Aβ-fibres form synapses with second order neurones and their low-threshold non-noxious inputs will be signalled as nociceptive in origin.

However, doubt surrounds this theory as a main mechanism of allodynia as sprouting is not fully established until 2 weeks after the injury. Furthermore it has been suggested that this sprouting only occurs in a small subgroup of Aβ neurones.[21]

As well as sprouting fibres into lamina II, Aβ-fibres also undergo phenotypic switching and produce the neurotransmitter substance P and calcitonin gene related peptide. These neurotransmitters are usually produced only by C-fibres, but after nerve injury their expression by C-fibres is down-regulated. Aβ-fibres begin to release these at the dorsal horn following low intensity stimulation. This release of substance P can maintain the central sensitisation changes in the dorsal horn at the NMDA receptor that is usually only maintained by continued C-fibre input.

Contribution of glial cells to pain conditions

There is now increasing recognition that neuropathic pain is not only the result of changes in neuronal cells and pathways, but also that glial cells, thought to be not relevant to neuronal function, play a major role here.[31] Schwann cells, spinal microglia and astrocytes, more regarded as components of the immune system, seem to have relevant contributions to the development of chronic pain states and make it plausible that these have features of a neuroimmune disorder and may offer new approaches to treatment.

Symptoms of neuropathic pain

Patients with neuropathic pain usually experience persistent and/or paroxysmal pain.[18] The pain often has an abnormal quality, for example burning, electric-shock like, shooting, lancinating or numbing. Neuropathic pain can occur in an area of neurological deficit, but might also arise from areas still innervated normally.[32] Neuropathic pain exhibits often one or more of the following characteristic features:

- *Dysaesthesia*, an unpleasant abnormal sensation, whether spontaneous or evoked.
- *Hyperalgesia*, an increased response to a painful stimulus.
- *Allodynia*, pain elicited by a normally non noxious stimulus
- *Hyperpathia,* a painful syndrome characterised by increased reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold.
- *Hypoalgesia,* diminished pain in response to a normally painful stimulus.

Clinical features of neuropathic pain are often summarised as stimulus-dependent, stimulus-independent and sympathetically-maintained pain:[32]

Stimulus-dependent pain

Following nerve injury, increased C-fibre activity causes central sensitisation within the dorsal horn via activation of the NMDA receptor as described earlier.

Central sensitisation produces three main effects:

1) enlargement of the sensory field of a dorsal horn neuron (secondary hyperalgesia)
2) increase of the response to a suprathreshold stimulus (hyperalgesia)
3) generation of a response to a subthreshold stimulus (allodynia)

These phenomena represent stimulus-dependent pain, although the relationship between stimulus and response might be widely varying.

Stimulus independent pain

As mentioned earlier, there are two types of sodium channels present on sensory neurons. The tetrodotoxin resistant channels are implicated in the generation of the spontaneous pain of pathological pain states.

Following injury there is reorganisation of the expression and location of the various types of sodium channel within the neuron. The tetrodotoxin resistant channels relocate to the neuroma, where it produces areas of hyperexcitability and ectopic discharges. After nerve injury, both injured nerves and uninjured nerves close to the site of injury display spontaneous discharges. The alterations in expression of sodium channels are thought to be due to alterations in the supply of neurotrophins such as nerve growth factor and glial-derived neurotrophic factor.[33]

Sympathetically maintained pain (SMP)

In a small but significant proportion of chronic pain sufferers the pain has a definite sympathetic system element to it and is said to be sympathetically maintained.

Following partial nerve injury in these patients, both injured and uninjured primary afferents express alpha-2 adrenoceptors on their membranes so they become sensitive to circulating catecholamines and noradrenaline release from sympathetic nerve terminals.[17]

Direct coupling also occurs between the sympathetic and peripheral nervous systems with sympathetic nerves sprouting axons into the dorsal root ganglion to form baskets around the cell bodies of nociceptor neurons, where they form functional synapses. This sprouting is thought to occur under the influence of nerve growth factor. Other more central mechanisms of somatosensory-sympathetic coupling are also investigated.[23]

Neuropathic pain syndromes

There are many causes of neuropathic pain including a number of disease states.

Peripheral neuropathies

Metabolic/Endocrine: Diabetics can develop different types of neuropathies, these include polyneuropathies, autonomic neuropathy, compression neuropathy and focal neuropathies. There are more than 15 million diabetics in the USA and more than half of them over 60 years have neuropathic pain.

Many diabetics, especially those with poor blood glucose control develop a distal, symmetrical, proximally spreading and painful neuropathy.[34] Severe pain is often a feature and may be described as burning, aching or have lightning components to it. It seems that the main cause is demyelination and to a lesser extent axonal degeneration. The first stage in prevention and treatment of early neuropathies is good glycaemic control. Additionally, hyperglycaemia may have a direct effect on neuropathic pain by altering pain thresholds, tolerance and affecting opioid receptors.

Mononeuropathies, usually involve the motor supply to extraocular muscles and also nerve supply to the limbs. The third cranial nerve is most frequently affected. Pain is often a symptom. Additionally, an asymmetrical proximal predominantly motor neuropathy can occur, especially in older patients with poor glycaemic control.

Untreated hypothyroidism may result in neuropathic pain.

Toxic: Well-known neuropathies here include those caused by alcohol, chemotherapy (where the neuropathy maybe the dose

limiting factor) and, more recently anti-AIDS drugs e.g. isoniazid.

Postinfectious: The most common problem here is Post Herpetic Neuropathy (PHN), which increases in incidence, intensity and persistence with age.[35] The pain persists in the distribution of a peripheral nerve after herpes zoster infection (shingles). It is thought that chronic inflammatory changes result in damage to sensory nerves resulting in deafferentation of nociceptive fibres. The pain is persistent and can become intolerable with associated allodynia. Treatment is very difficult, particularly in later stages.

Hereditary: Fabry's disease, a rare lipid storage disorder, often presents with a painful neuropathy.

Malignant: Neuropathies can occur as a non-metastatic complication of malignant disease, usually a sensory neuropathy that can sometimes be painful. Neuropathic pain can also be caused as the result of direct tumour invasion involving nearby nerves.

Idiopathic: Trigeminal neuralgia (tic douloureux) is defined by the IASP as a 'sudden, usually unilateral, severe, brief, stabbing, recurrent pains in the distribution of one or more branches of the fifth cranial nerve'.[1] It can occasionally be secondary to an underlying condition e.g. tumour, multiple sclerosis. The diagnosis is made on clinical grounds as the patients describe a characteristic pain. It occurs most frequently in the maxillary division and least in the ophthalmic division of the trigeminal nerve. The pain is triggered by light touch, eating, talking and the cold. Examination in the absence of other neurological symptoms reveals very little. There is no definitive diagnostic test. Magnetic resonance imaging (MRI) can reveal an underlying cause or nerve compression, but is otherwise not highly sensitive or specific. Magnetic resonance tomographic angiography (MRTA) has been used in delineating the pathophysiological process and may provide a helpful diagnostic image but there is insufficient evidence at present.

The pathophysiology is not completely understood. The most evidence supports vascular compression of the nerve, resulting in hyperexcitability and abnormal neuronal activity, causing pain. This theory is supported by the fact that patients often experience immediate pain relief from microvascular decompression and has been confirmed radiologically in a study utilising MRTA.[36]

Spontaneous remission may occur so surgery is reserved for those refractory to medical treatment. Complications of surgical microvascular decompression include facial nerve damage, haematoma, cerebrospinal fluid leak and infection. However, despite its risks microvascular decompression is currently the best option from a variety of surgical procedures. The other surgical techniques include gasserian ganglion surgery, radiofrequency thermocoagulation, percutaneous retro Gasserian glycerol injection or microcompression, posterior fossa surgery and gamma knife irradiation.

Patients should be made aware of the risks associated with the chosen surgical technique and warned that the pain relief may not be permanent and balance these against the benefit from potential long term analgesia in cases refractory to medical management.[37]

Vascular: Vascular pain is a complex issue. Pain can be arterial, microvascular or venous in origin. Neuropathy can in particular follow venous insufficiency.[38] In every vascular disease, sympathetic changes may develop which contribute a neuropathic element to the ischaemic pain. The patient may develop skin hyperalgesia, dystrophic skin with a shiny appearance, muscle atrophy and vasomotor

phenomena. Sympathetic blocks may be beneficial.[39]

Posttraumatic: Posttraumatic neuropathies are common and can develop after any nerve injury. Even minor demyelination injuries without neurological sequelae can result in neuropathies. Examples are sciatica, neuroma or nerve entrapment after surgery or trauma, phantom limb pain, complex regional pain syndromes (CRPS) type I (without neurological deficit, previously called Reflex Sympathetic Dystrophy RSD) and Type II (with neurological deficit, previously called causalgia) and post-thoracotomy pain.

Central neuropathies

Central pain is due to a lesion or dysfunction of the CNS.[40] These lesions may have associated symptoms that affect the patient and their pain eg ataxia, motor weakness and hearing/visual loss. Epilepsy and depression are also common with cerebral lesions. These aspects need to be addressed along with treatment of the pain.

Central pain is associated with spinothalamocortical dysfunction and may develop over a length of time and varies widely between individuals regardless of aetiology.

Vascular lesions in the brain and spinal cord: The aetiology here includes infarction, haemorrhage, and vascular malformation. Stroke is the most common cause of central pain due to its high incidence.[41] Around 8% of patients with acute stroke have been shown to suffer from central pain in the following 12 months.

Multiple sclerosis: This demyelination process can result in neuropathic pain by a variety of mechanisms. Cranial nerve neuropathies, but also widespread central pain syndromes are common consequences and often difficult to treat.[42]

Trauma, tumours and infections: Brain injury, but by far more commonly spinal cord injury, can result in a variety of central pain syndromes.[43] Syringomyelia and syringobulbia as a consequence of such injuries can cause further central pain. Tumours of the brain and spine as well as infections and abscesses can cause similar symptoms.[40]

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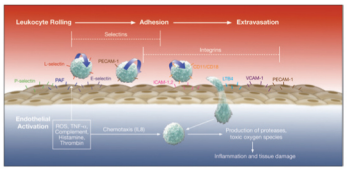

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