Faculty of Medicine

Chronic Pain as an Outcome of Surgery

Essay

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Mohammed Reda AbdelFattah Mohammed Ashour

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List of Abbreviations

Abb.	Full term

ACC ..... *Anterior Cingulate Cortex*
AMPA ..... *α-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptor**s***
APS..... *American Pain Society*
ASA..... *American Society of Anesthesiologists*
ASIC ..... *Acid-sensitive ion channels*
ATP..... *Adenosine triphosphate*
BDNF ..... *Brain derived neurotrophic factor*
BPI..... *Brief Pain Inventory*
CGRP ..... *Calcitonin-gene related peptide*
CNS ..... *Central nervous system*
COMT..... *Catechol -O-methyltransferase*
COX-2..... *Cyclo-oxygenase-2*
COXIBs, ... *COX-2-selective inhibitors*
CPM..... *Conditioned pain modulation*
CX_3CR1 ..... *The Cytokine fractalkine receptor*
DAMPs ..... *Danger -associated molecular patterns*
DNIC ..... *Diffuse noxious inhibitory control*
GM ..... *Gray matter*
GPCR ..... *G protein coupled receptors*
HPA..... *Hypothalamo-pituitary axis*
IASP ..... *The international association for the study of pain*
ICD ..... *International Classification of Diseases*
IL-1â..... *interleukin 1â*
IL-1β ..... *Interleukin 1β*
IV ..... *Intravenous*
K2P..... *Two -pore potassium channels*
KCC2 ..... *Potassium chloride co-transporter-2*
LTD ..... *Long-term Depression*
LTP..... *Long Term Potentiation*
MAPK..... *Mitogen -activated protein kinase*
NAc..... *Nucleus Accumbens*

List of Abbreviations (Cont...)

Abb.	Full term

NaV ..... *Voltage gated sodium channels*
NE ..... *Norepinephrine*
NGF ..... *Nerve growth factor*
NMDA ..... *N-methyl D-aminotransferase*
NPRS ..... *Numerical Pain Rating Scale*
NRM ..... *Nucleus raphe magnus*
NS ..... *Nociceptive specific neurons*
NSAIDs ..... *Non-steroidal anti-inflammatory drugs*
NSC ..... *Nonselective cation*
OPRM1 ..... *Opioid receptor gene - one*
PAG ..... *Periaqueductal grey*
PCA ..... *Patient controlled analgesia*
PKA ..... *Protein kinase A*
PKC ..... *Protein kinase C*
PPSP ..... *Persistent Post-Surgical Pain*
PTSD ..... *Post-traumatic stress disorder*
RTK ..... *Receptor tyrosine kinases*
RVM ..... *Rostral ventral medulla*
SCD ..... *Sickle -cell disease*
SNPs ..... *Single nucleotide polymorphisms*
TENS ..... *Transcutaneous electrical nerve stimulation*
TLR4 ..... *Toll-Like Receptor-4*
TLRs ..... *Toll-Like Receptors*
TNF-á ..... *Tumor necrosis factor á*
TRPV1 ..... *Transient receptor potential VI*
VAS ..... *Visual Analogue Scale*
VRS ..... *Verbal Rating Scale*
WDR ..... *Wide dynamic range*

Introduction

Nearly every surgery can elicit a rather therapy-resistant chronic postoperative pain. Spinal mechanisms of pain amplification are regarded as fundamental to pain chronification. Indeed, not every surgical patient develops chronic postoperative pain. Progress in our neurobiological understanding of postoperative pain includes scientific discoveries of 'vulnerability factors' including opioid use, medical history and co-morbidities. Clinical and experimental approaches reduce spinal pain amplification mechanisms **(Basbaum et al, 2009).**

Primary afferent fibres Aδ and C fibres transmit information to nociceptive specific neurons in Rexed lamina I and II. Complex interactions occur in the dorsal horn between afferent neurons, interneurons and descending modulatory pathways. There are two main pathways that carry nociceptive signals to higher centres in the brain: the spino-thalamic tract and the spino-reticular tract. Imaging techniques such as functional magnetic resonance imaging (fMRI) have demonstrated that a large brain network is activated during the acute pain experience. This is often called the 'pain matrix' (**Serpell, 2006).**

Postoperative pain is not purely nociceptive in nature, and may consist of inflammatory, neurogenic, and visceral components. Therefore, multimodal analgesic techniques utilizing a number of drugs acting on different analgesic mechanisms are becoming increasingly popular **(Popping et al, 2014).**

Nerve injury is often related to surgery (e.g. the intercostal nerve in thoracotomies and the intercostobrachial nerve in axillary clearance in breast cancer surgery). There is also a strong association between sensory abnormalities and persistent pain indicating a significant role for neuropathic mechanisms in persistent post-surgery pain (**Haroutiunian et al, 2013).**

Most studies have shown a clear association between the intensity of acute pain and chronic post-surgery pain. The simplest explanation would be that the extent of tissue or nerve injury causes more acute pain and is more likely to lead into long-lasting pain. Prospective studies can assess several factors that can increase pain sensitivity. Several studies have indicated that a high body mass index is related to a higher risk for persistent post-surgery pain. Obesity represents a pro-inflammatory state that can sensitize to pain. Moreover, epidemiological studies suggest a strong connection between impaired glucose tolerance and chronic pain **(Gottschalk and Ochroch, 2008).**

Many have studied the optimal timing of regional anesthesia, a concept called pre-emptive analgesia. Current evidence suggests that surgical technique has an important role in minimizing persistent pain after surgery, but that specific modifications, such as use of minimally invasive and muscle or nerve-sparing techniques are needed. Conduction blockade (paravertebral and epidural) is helpful for reducing persistent pain in the case of breast surgery and thoracotomy to the extent that chronic pain after surgery, devastating and difficult to treat, could be prevented in one patient out of every four to five patients treated. Postoperative adjuvant analgesia should be considered for patients in high-risk surgical groups (**Andreae and Andreae, 2012).**

The Pain Pathway

Definition

Pain is derived from the Latin word "Poena" meaning fine, penalty, or punishment. It can be defined as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". This definition avoids tying pain to the stimulus. Activity induced in the nociceptive pathways by a noxious stimulus is not pain, which is always a psychological state **(Loeser et al, 2012).**

Types of pain

Based on pain physiology, it includes nociceptive, neuropathic and inflammatory pain. Nociceptive pain represents the normal response to noxious insult whether somatic or visceral stimuli. Neuropathic pain initiated or caused by a primary lesion or disease in the somatosensory nervous system, presented with a range from deficits perceived as numbness, hypersensitivity or paresthesias. Inflammatory pain a result of activation and sensitization of the nociceptive pain pathway by a variety of mediators released upon tissue inflammation **(Kennedy, 2007).**

Pain Theories

Several theoretical frameworks have been proposed to explain the physiological basis of pain, **(Figure 1).** The *Specificity Theory of Pain*; each modality (touch and pain) is encoded by specialized sense organs in separate pathways to distinct centers in the brain. The *Intensity Theory of Pain*; there are no distinct pathways for low- and high-threshold stimuli. Rather, the number of impulses in neurons determines the intensity of a stimulus. There must be some form of summation that occurs for the subthreshold stimuli to become unbearably painful **(Perl, 2007).**

The *Pattern Theory of Pain* posits that different somatic sense organs have different levels of responsivity to stimuli. A population code or the pattern of activity of different neurons encodes the modality and location of the stimulus **(Kennedy, 2007).**

The *Gate Control Theory* is the cornerstone while discussing the anatomy of the pain pathway. The *Central Biasing Theory;* various networks have been implicated in the experience of pain. Furthermore, it has been demonstrated that in chronic pain conditions, brain structure and function undergo plasticity and that network dynamics are altered**.** Cognitive effects can alter sensory discrimination. The cognitive modulation of pain is reflected in the effects of placebo, cognitive behavioral therapy and other treatments for chronic pain. Neuroimaging suggests that brain function may not be modular but rather, likely involves networks **(Seifert and Maihofner, 2011).**

Anatomy of the pain pathway

Primary afferent nociceptors are pseudounipolar; a single process emanates from the cell body in the dorsal root ganglion or trigeminal ganglion and bifurcates, sending a peripheral axon to innervate the skin and a central axon to synapse on second-order neurons in the dorsal horn of the spinal cord or the trigeminal nucleus, **(Figure 2)**. They transmit to the somatosensory cortex via the thalamus, informing about the location and intensity of the painful stimulus **(Latremoliere and Woolf, 2009)**.

Other projection neurons engage the cingulate and insular cortices via connections in the brainstem (parabrachial nucleus) and amygdale. This ascending information also accesses neurons of the rostral ventral medulla and midbrain periaqueductal gray to engage descending feedback systems that regulate the output from the spinal cord **(Basbaum et al, 2009).**

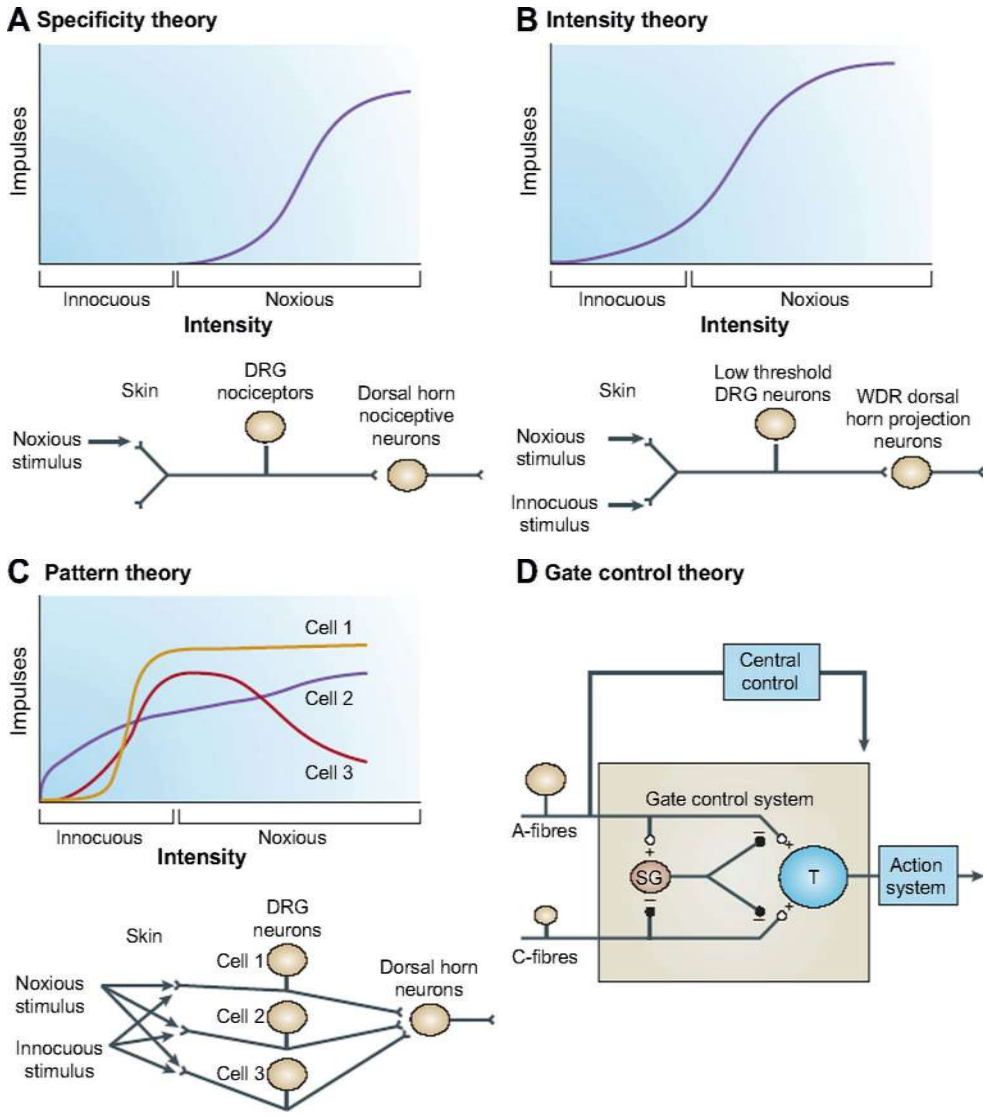

Figure (1): Schematic diagrams of pain theories (Perl, 2007).

Based on the *Gate control theory*, pain depends on the relative amount of traffic in two different sensory pathways which carry information from the sense organs to the brain. There is a very precise laminar organization of the dorsal horn of the spinal cord; subsets of primary afferent fibers target spinal neurons within discrete laminae. The slow unmyelinated, peptidergic C and myelinated Aδ nociceptors end most superficially synapsing upon large projection neurons located in lamina I. The unmyelinated, non-peptidergic nociceptors target small interneurons in the inner part of lamina II **(Seifert and Maihofner, 2011).**

By contrast, innocuous input carried by the fast myelinated Aβ fibers terminates on PKCγ expressing interneurons in the ventral half of the inner lamina II, **(Figure 3)**. A second set of projection neurons within lamina V receive convergent input from Aδ and Aβ fibers **(Perl, 2007).**

Nociceptor diversity

There are a variety of nociceptor subtypes that express unique repertoires of transduction molecules and detect one or more stimulus modalities. These fibers rapidly activate, adapt during prolonged heat stimulation, fatigue between heat stimuli, and are sensitive to capsaicin, a selective agonist of the mammalian heat-activated nonselective cation (NSC) channel transient receptor potential VI (TRPV1) **(Basbaum et al, 2009).**

These fibers also express a host of sodium channels and potassium channels that modulate nociceptor excitability and/or contribute to action potential propagation. Three major C-fiber nociceptor subsets are shown here (heat-sensitive afferents express TRPV1, cold-sensitive afferents and mechanosensitive afferents), but the extent of functional and molecular diversity is undoubtedly more complex and considered a matter of ongoing study **(Olausson et al, 2008).**

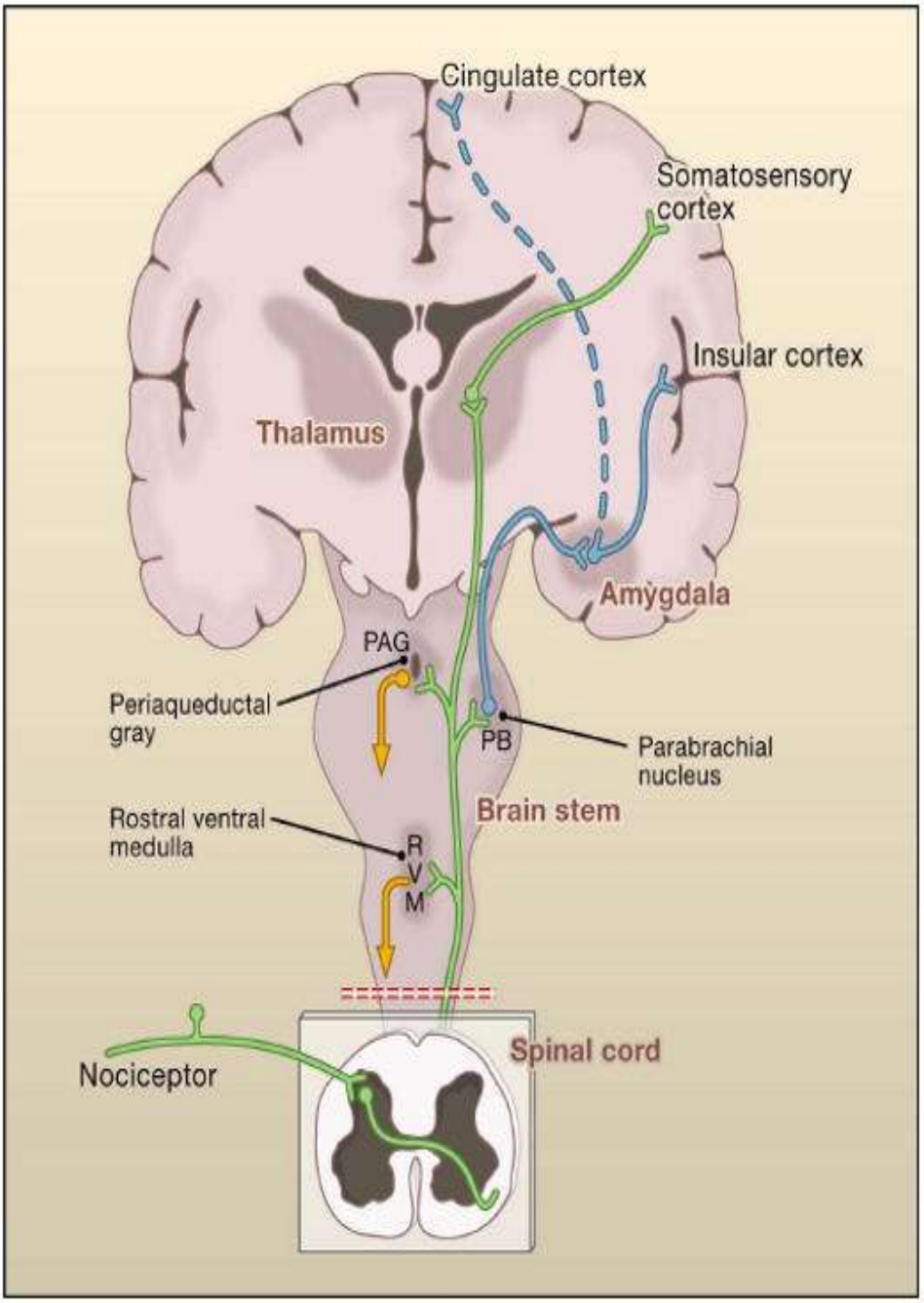

Figure (2): Anatomy of the pain pathway (Basbaum et al, 2009).

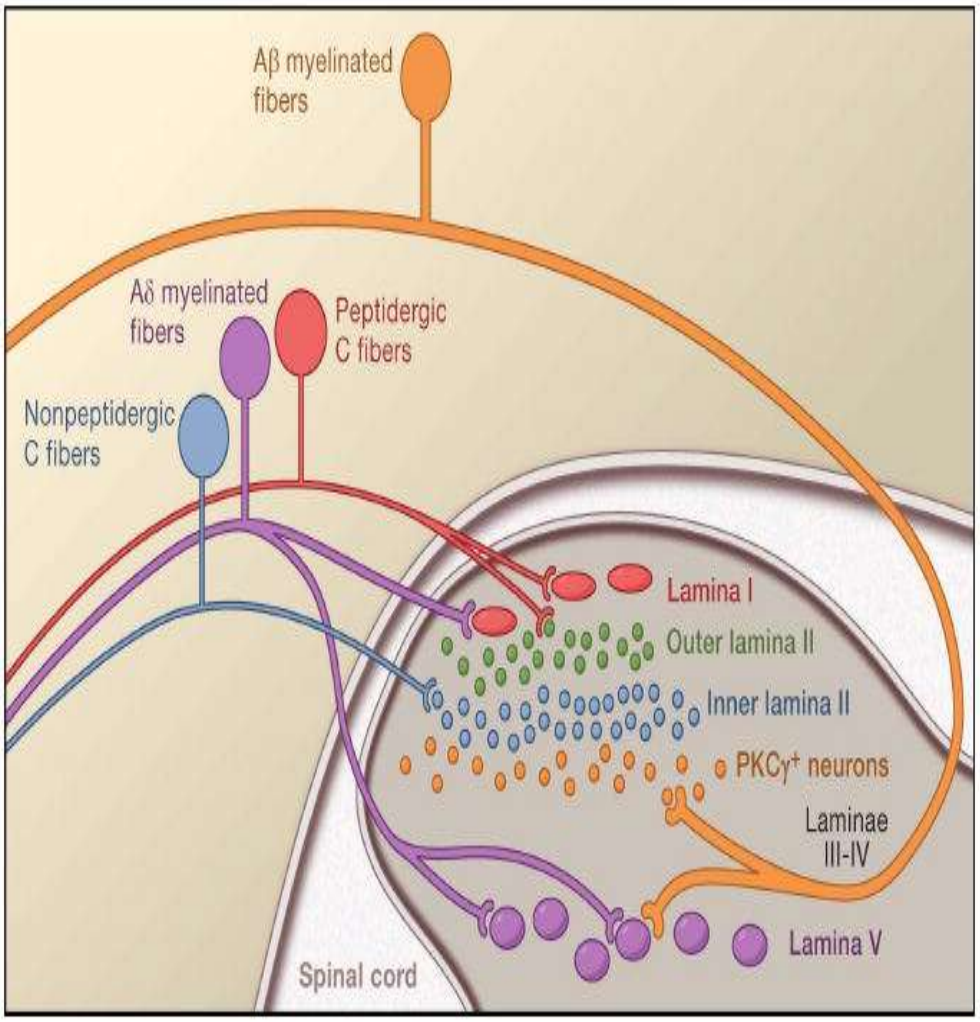

Figure (3): Connections between primary afferent fibers and the spinal cord (Basbaum et al, 2009).

The activity of voltage gated sodium channels (NaV) underpins electrogenesis in excitable cells. The 9 genes encoding the a-subunits exhibit tissue specific expression and describe proteins with varying biophysical characteristics. Of those expressed in peripheral neurons, 3 channels (NaV1.7, NaV1.8, and NaV1.9) are strongly associated with pain behaviours in both rodents and

humans. It is thought that NaV1.9 acting through G protein–coupled pathways, may play an important role in the activation of sensory nerves by inflammatory mediators. This hypothesis is supported for somatic pain by behavioural studies demonstrating reduced hypersensitivity to inflammatory stimuli in rodents where NaV1.9 has been deleted or knocked down. However, evidence for its role in visceral pain processing is controversial **(Hockley et al, 2014).**

There is growing evidence that some pain states do not involve classical nociceptor activation, consistent with the proposal of the intensity theory that suggests neurons responding to innocuous stimuli may activate central pain pathways in some circumstances. Further evidence for the complexity of peripheral nociceptive mechanisms comes from sodium channel gene ablation studies. Global deletion of Nav1.3, Nav1.8, or Nav1.9 has quite different effects on cold and mechanical allodynia produced by different neuropathic pain models. These findings provide support for the existence of multiple mechanisms involving different subpopulations of sensory neurons that can produce apparently identical pain phenotypes **(Minett et al, 2014).**

Conduction

The speed of transmission is directly correlated to the diameter of axons of sensory neurons and whether or not they are myelinated. Most nociceptors have slow small diameter unmyelinated axons (C-fibers) bundled in fascicles surrounded by Schwann cells and support conduction velocities of 0.4–1.4 m/s. Initial fast-onset pain is mediated by A-fiber nociceptors whose axons are myelinated and support conduction velocities of approximately 5–30 m/s (most in the slower Aδ range) **(Perl, 2007).**