“Role of pre-emptive analgesia in modulating the post-operative pain between practice and facts”

Essay

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By

Marianne Magdy Youssef

(M.B.B.CH.)

Supervised By

Prof. Dr .Randa Ismail Badawi

Professor of Anesthesiology and Intensive Care
Faculty of Medicine
Cairo University

Prof. Dr. Maged Sallah Abdullah

Assist. Professor of Anesthesiology and Intensive Care

Faculty of Medicine
Cairo University

Dr. Pierre Zarif Tawadros

Lecturer of Anesthesiology and Intensive Care
Faculty of Medicine
Cairo University

Faculty of Medicine
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Abstract

Postoperative symptoms and complications can be prevented by a suitable choice of anaesthetic and analgesic technique for specific procedures. The aim of analgesic protocols is not only to reduce pain intensity but also to decrease the incidence of side-effects from analgesic agents and to improve patient comfort. Moreover, adequate pain control is a for the use of rehabilitation programs to accelerate recovery from surgery. Thus, combining opioid and/or non-opioid analgesics with regional analgesic techniques not only improves analgesic efficacy but also reduces opioid demand and side-effects such as nausea and vomiting, sedation, and prolongation of postoperative ileus.

Good pain control after surgery is important to prevent negative outcomes such as tachycardia, hypertension, myocardial ischemia, decrease in alveolar ventilation, and poor wound healing. Preemptive analgesia, an evolving clinical concept, involves the introduction of an analgesic regimen before the onset of noxious stimuli, with the goal of preventing both peripheral and central sensitization of the nervous system to subsequent stimuli that could amplify pain. Owing to this 'protective' effect on the nociceptive system, pre-emptive analgesia has the potential to be more effective than a similar analgesic treatment initiated after surgery.

Key word:

Physiology Of Pain

Modalities

Controversies

Preemptive Analgesia

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Abbreviations

CNS	Central nervous system
PNS	peripheral nervous system
ASIC	Acid sensitizing ion channel
TPRC	Transient potential receptor channel
DRG	Dorsal root ganglion
RVM	Rostral ventromedial medulla
5-HT	serotonin (5-hydroxytryptamine)
PET	Positron emission tomography
MRI	Magnetic resonance imaging
IASP	The International Association for the Study of Pain
NMDA	N-Methyl D-Aspartate
LTP	long-term potentiation
EAA receptors	Excitatory amino acid receptors
IM	Intra muscular
IV	Intravenous
IA	Intraarticular
VAS	Visual analogue score
PCA	Patient controlled analgesia
GI	Gastro-intestinal
PG	Prostaglandins
PO	By mouth(per os)
ASA	American society of anaesthesiologists

Chapter one

Physiology of pain

NEUROPHYSIOLOGY OF NOCICEPTION

The cardinal function of the pain system is to protect the body from impending or actual damage. When functioning normally, the major components of the system primary afferent fibers (primary sensory neurons), spinal cord, and brain integrate key information about noxious stimuli, allowing for perception of its quality, intensity, and location and permitting an appropriate behavioral response that includes withdrawal from the stimulus, activation of the autonomic nervous system, an emotional response, and a deeply unpleasant sensation that called pain. Sir Charles Sherrington a century ago defined nociception as the sensory detection of a noxious event or a potentially harmful environmental stimulus. Now it recognize that most clinical pain is not actually nociception the detection of noxious stimuli but rather production of pain either in the absence of any peripheral stimulus (spontaneous pain) or in response to a stimulus that normally would be experienced as innocuous (allodynia) and therefore is not noxious.

Pain system has four basic anatomical components. *Nociceptors* are specialized high-threshold sensory afferent or primary sensory neurons that are located in the peripheral nervous system (PNS) whose peripheral terminals are capable of detecting or reacting normally only to intense noxious stimuli and transmit this information along their axons, which run in peripheral nerves to the spinal cord. *Ascending nociceptive tracts,* including the **spinothalamic, spinobulbar,** and **spinohypothalamic tracts**, convey nociceptive information from the dorsal horn of the spinal cord to *higher centers in the central nervous system* that are responsible for cognitive, affective, and complex motor responses to noxious

stimuli as well as production of conscious awareness or perception of the stimulus and interaction with learned behaviors.

Finally, *descending systems* in the CNS are involved in the processing or control of transfer of nociceptive information at multiple levels of the nervous system (Fig. 1–1). [1, 2]

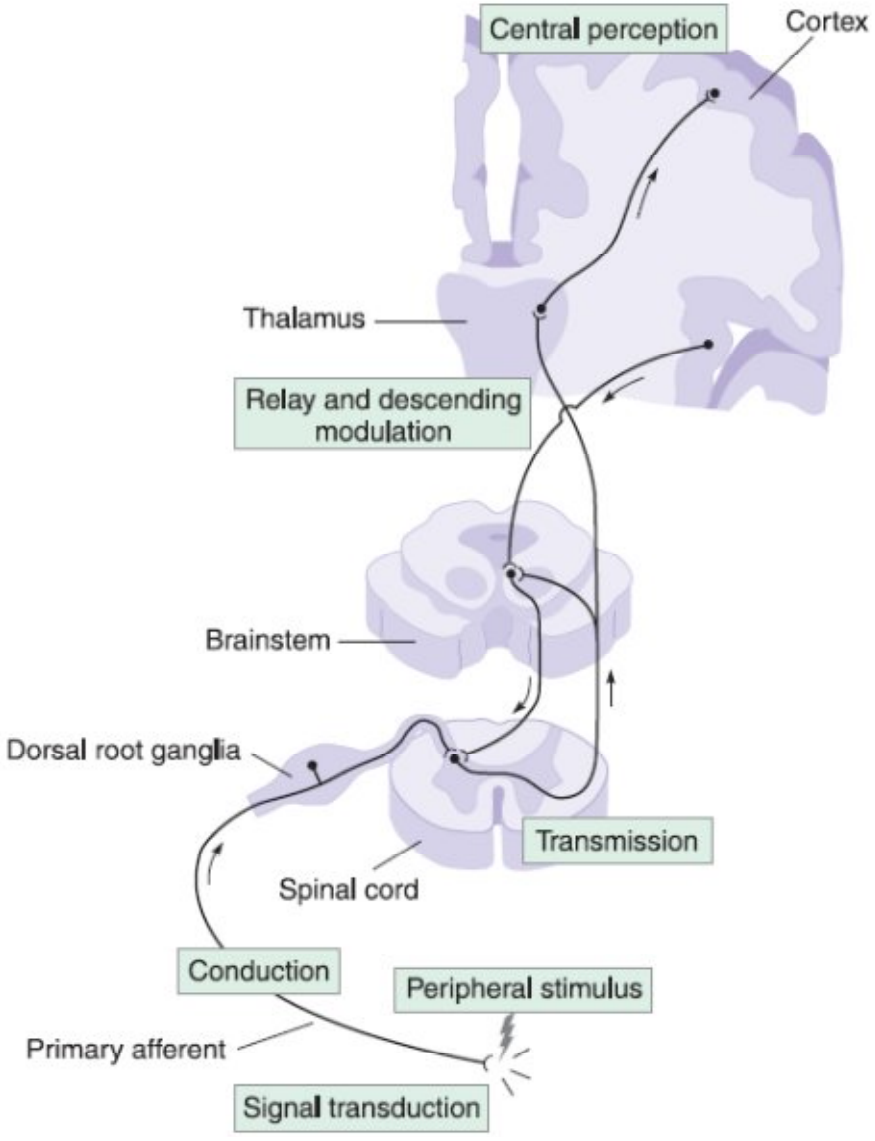

FIGURE 1-1: Overview of a basic nociceptive circuit. [1]

NOCICEPTIVE PATHWAYS:

Primary Afferents:

Transduction and Conduction to the Spinal Cord:

The high-threshold primary afferent neurons responsible for detection of high intensity noxious stimuli are termed nociceptors. Nociceptors include both thin myelinated A-delta and unmyelinated C-fibers. They represent one of several functional groups of sensory fibers in peripheral nerves (Table 1-1), including proprioceptors, low-threshold mechanoreceptors, and detectors of innocuous thermal stimuli.

TABLE 1-1: classification of fibers found in peripheral nerves [3]

Classification of Fibers Found in Peripheral Nerves

Fiber Type	Innervation	Mean Diameter (μm)	Mean Conduction Velocity (m/s)
Sensory			
A-β	Cutaneous touch and pressure afferent fibers	8	50
A-δ	Mechanoreceptors, nociceptors, thermoreceptors	2–3	15
C	Mechanoreceptors, nociceptors, thermoreceptors, sympathetic preganglionic	1	1
Motor			
A-α	Primary muscle spindle, motor to skeletal muscle	15	100
A-γ	Motor to muscle spindle	6	20
Sympathetic			
B	Sympathetic postganglionic	3	7

Nociceptors are classified based on the presence or absence of myelination and the type(s) of stimuli to which the sensory neuron responds. Nociceptors transduce mechanical, chemical, thermal, single or, more commonly, combinations of stimuli

(polymodal). Table (1–2) summarizes the characterization of nociceptors based on their response characteristics.

TABLE 1-2: Functional classification of primary afferent nociceptors [3]

Functional Classification of Primary Afferent Nociceptors

Type of Fiber	Nociceptor Type	Noxious Stimuli Detected
A-δ (2–30 m/s)	AM	Mechanical
	AMC	Mechanical and cold
	AH	Heat
	AMH type I	Mechanical, heat >53°C
	AMH type II	Mechanical, heat <51°C
	A-Chem	Chemical
C fiber (0.5–2 m/s)	CM	Mechanical
	CH	Heat
	CMH[a]	Mechanical, heat
	CMC	Mechanical, cold
	C-Chem	Chemical (algesic & pruritic)
	CMi[b]	None in resting state, mechanical (after activation)

The membrane of peripheral terminals of nociceptors contains a set of highly specialized receptors/ion channels that transduce mechanical, chemical, and thermal noxious stimuli into inward currents that excite the terminal (Fig. 1–2 and Table 1-3).

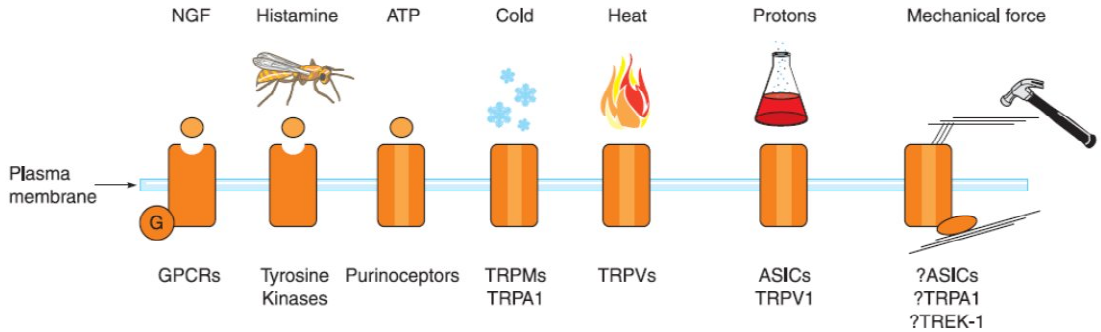

FIGURE 1–2. Different type of noxious stimuli

Transduction of nociceptive stimuli. The first step in the sensation of physiologic or "nociceptive" pain is the transduction of high-intensity stimuli by primary sensory afferents. [4]

TABLE 1-3: Ion channels & metabotropic receptors (found on primary afferent peripheral terminals) involved in noxious stimulus transduction. [4]

Ion Channel and Metabotropic Receptors (Found on Primary Afferent Peripheral Terminals) Involved in Noxious Stimulus Transduction

Ion Channel Receptors	Permeable to	Activated by
Transient Receptor Potential (TRP) channels		
TRPV1	Cations, especially Ca^{2+}	Heat (>109°F [>43°C]), low pH, capsaicin
TRPV2	Cations, especially Ca^{2+}	Heat (>126°F [>52°C])
TRPV3	Cations, especially Ca^{2+}	Warm (88–102°F [31–39°C])
TRPV4	Cations, especially Ca^{2+}	Warm (>81°F [27°C])
TRPM8	Cations, especially Ca^{2+}	Cold (~ 46–79°F [~8–26°C]), menthol
TRPA1	Cations, especially Ca^{2+}	Cold (<63°F [17°C]), mustard oil
Acid-Sensing Ion Channels		
$ASIC_1$, $ASIC_2$, $ASIC_3$	Na^+	Low pH, ? mechanical
Purine receptor, P_2X_3	Ca^{2+}	ATP
Metabotropic Receptors	**Second Messenger**	**Activated by**
Purine receptor, P_2XY	G-protein–coupled receptor	ATP
Bradykinin receptor, B1& B2	G_q protein-coupled receptor	Bradykinin

ATP, Adenosine triphosphate.

Upon stimulation transduction receptor/ion channels undergo conformational changes that alter their conductance, allowing an influx of cations. This cation influx leads to depolarization of the terminal membrane known as the *generator potential* that, if of adequate amplitude, reaches the threshold to generate an action potential. The generator potential is graded in amplitude and duration and reflects stimulus intensity and timing. In contrast, action potentials are all-or-none events.

Primary afferent nociceptors transfer information from the periphery to the CNS by frequency, and duration of firing of action potentials arising in the peripheral terminal that accurately encode the onset, intensity, location, and duration of nociceptive stimuli. One particular class of C-fiber afferents, termed silent nociceptors, is inactive in the resting state, becoming responsive to noxious stimuli only after inflammation or injury.

Thermal sensitivity is conferred upon nociceptors by the presence of thermosensitive nonselective cation channels called transient receptor potential (TRP) channels. The thermoresponsive TRPs are a family of channels, each sensitive to a different thermal stimulus range. $TRPV_1$ (the capsaicin receptor) is activated by a variety of stimuli, including noxious heat (>42°C), vanilloid ligands including capsaicin (the pungent component of chili peppers), low extracellular pH, lipids such as anandamide (an endogenous cannabinoid agonist), and polyamines. [5-6]

Nociceptors respond to a variety of chemical stimuli, some of which directly activate the terminal, producing generator potentials (chemical activators) and thereby an action potential output and pain. Other agents alter the threshold of the nociceptor (sensitizing agents) without directly exciting them. Nociceptor activators typically are associated with injury, such as low pH (i.e., protons), and kinins or irritants such as capsaicin and mustard oil. $TRPV_1$ is sensitive to protons, as are a family of channels known as acid sensitive ion channels (ASICs). Injury and ischemia are associated with low extracellular pH . Nociceptors have specific receptors for bradykinin, the G-protein–coupled B1 and B2 receptors. Bradykinin is produced by cleavage of the precursor kininogen by kallikrein.