A Study into a Possible Mechanism of the Analgesic Effect of Ibuprofen in a Model of Post-surgical Pain beyond the Conventional COX Inhibition Theory

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List of Abbreviations

5-HT	Serotonin
AMPA	a-amino-3-hydroxy 5-methyl-4- soxazeloproprionic acid
ASA	Acetyl salicylic acid
BL	Baseline
cGMP	cyclic guanosine monophosphate
CGRP	Calcitonin gene-related protein
CCK	Cholecytokinin
COX	Cyclooxygenase
DRG	Dorsal root ganglia
GABA	Gamma-Aminobutyric acid
h	hours
i.c.v	Intracerebroventricularly
i.p	Intraperitoneally
i.t	Intrathecally
IASP	International Association for the Study of Pain
NA	Noradrenaline
NE	Norepinephrine
NMDA	N-methyl-D-aspartate
NO	Nitric oxide
NOARG	L-NG-nitro arginine
NOS	Nitric oxide synthase
NSAID	Non-steroidal anti-inflammatory drug
p.o	per os
PG	Prostaglandin
RVM	Rostral ventromedial medulla
SG	Substantia gelatinosa
VFWT	Paw-withdrawal threshold to von Frey filaments

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ABSTRACT

Abstract

Background: Postoperative pain control is still far from satisfactory. NSAIDs represent an attractive class of analgesics because of their relatively low toxicity. Accumulating evidence demonstrated the analgesic effect of NSAIDs could be explained beyond the COX inhibition theory. Nitric oxide (NO) and α adrenoreceptors may play a role in ibuprofen's postoperative analgesic effect. Ibuprofen's pre-emptive analgesic effect needs further assessment as well.

Materials & Methods: The antiallodynic effect of graded doses of ibuprofen (30,100 & 300 mg/kg) administered 30 minutes pre-incisional, or (100 mg/kg) 30 minutes post-incisional was assessed using von Frey's filaments in a plantar incisional model of pain in Swiss albino mice. The α_1 and α_2-selective antagonists; prazosin and yohimbine respectively, as well as a NO precursor; L-Arginine and a competitive inhibitor of nitric oxide synthase; L-NAME, were also used. Spinal NO level was measured 2 hours post-incision.

Results: Plantar incision significantly decreased the withdrawal threshold to von Frey filaments (VFWT) and increased spinal NO levels. Pre-incisional ibuprofen increased the VFWT and decreased spinal NO levels in a dose dependent manner. Pre-incisional ibuprofen was more effective than post-incisional in increasing the VFWT and decreasing spinal NO levels. L-NAME resulted in an increase in the VFWT and decreased spinal NO levels. Preceding ibuprofen by either L-Arginine or yohimbine resulted in decreasing its VFWT, while prazosin had no effect. Yohimbine also abolished its lowering effect on NO.

Conclusions: Pre-incisional ibuprofen produced pre-emptive analgesia that was superior to post-incisional ibuprofen. α_2 and not α_1 adrenoceptors and inhibition of NO synthesis contribute to the analgesic activity of ibuprofen in postsurgical pain. NO may also be involved in the α_2 adrenoceptors mechanism of ibuprofen's analgesic effect.

Keywords: Ibuprofen, incisional pain, pre-emptive analgesia, nitric oxide, alpha adrenoreceptors, mechanical allodynia.

REVIEW OF LITERATURE

Review of literature

"The Relief of Pain Should be a Human Right" is a motto adopted by the International Association for the Study of Pain (IASP). Pain sensation is protective against tissue injury. However, pain may persist and turn into a continually annoying symptom ***(Hamza & Dionne, 2009).*** Pain has been defined by the (IASP) as "an unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage" ***(Omoigui, 2007).***

There is increasing acceptance of pain as the fifth vital sign, on a par in significance with blood pressure, pulse, temperature and respiratory rate ***(Lanser & Gesell, 2001).***

Analgesics may provide complete pain relief in only one out of five patients ***(Kulmatycki & Jamali, 2007).*** Despite the advances in the study of pain, it continues to be a major health problem. In fact, in five European countries, from January 2010 to January 2011, approximately 49 million people reported to have pain and 11.2 million reported severe pain with a subsequent impairment of quality of life, increased healthcare resources utilization, and decreased labor force participation. For all these reasons, further understanding this complex phenomenon continues to be a growing need ***(Allegri et al., 2012).***

Pain: A Historical Perspective

The origin of the theory that the transmission of pain is through a single channel from the skin to the brain can be traced to René Descartes in 1664. Descartes' reflex theory directed both the study and treatment of pain for more than 330 years. This theory proposes that a specific pain pathway carries the messages from a pain receptor in the skin to a pain center in the brain, implying

that the simple cutting of this pathway should alleviate all pain **(fig1)**. The results of many clinical cases can confirm that this type of manipulation does not routinely relieve pain. In fact, damage to nerves can often result in exacerbation of painful symptoms, leading to central unremitting pain ***(DeLeo, 2006).***

Fig (1): Line diagram shows the principle of pain transmission as described by René Descartes (1596-1650) which was first published in 1664, quoted from ***DeLeo, (2006).***

At the beginning of the twentieth century, Sherrington (1910) introduced the term nociception from the Latin *nocere,* "to harm" ***(Le Bars et al., 2001).***
Ronald Melzack and Patrick Wall intensely disputed Descartes' theory with their gate control theory, proposed in 1965, which rejuvenated the field of pain study. The classic picture of a single pain mechanism was being swept away in favor of a dynamic interlocking series of biological reactive mechanisms ***(Bishop, 1980).***

Melzack and Wall suggested that in each dorsal horn of the spinal cord there is a gate-like mechanism which inhibits or facilitates the flow of afferent impulses into the spinal cord before it evokes pain perception and response ***(Melzack &Wall, 1965).***

Laminae of the dorsal horn of the spinal cord receive pain stimuli from Aδ (for cold and well-localized pain sensations) and C (for poorly localized pain or pain caused by heat or mechanical stimuli) fibers. Laminae also receive input from nonnociceptive fibers that convey tactile information. These nonnociceptive Aβ fibers indirectly inhibit the effects of the pain fibers, 'closing a gate' to the transmission of their stimuli ***(Melzack, 1999).***

The Aβ and C fibers also form synapses with an inhibitory interneuron that also synapses on the projection neuron (neurons whose axons project to more distant regions of the brain or spinal cord). The C fiber's synapse would inhibit the inhibitory interneuron, indirectly increasing the projection neuron's chance of firing. On the other hand, the Aβ fiber forms an excitatory connection with the inhibitory interneuron, thus decreasing the projection neuron's chance of firing. Thus, depending on the relative rates of firing of C and Aβ fibers, the firing of the nonnociceptive fiber may inhibit the firing of the projection neuron and the transmission of pain stimuli ***(Nathan & Rudge 1974; Raja et al., 1988;*** **fig2*).*** Descending pathways (to be discussed later) from the brain close the gate by inhibiting the projector neurons and diminishing pain perception ***(Mazars, 1975).***

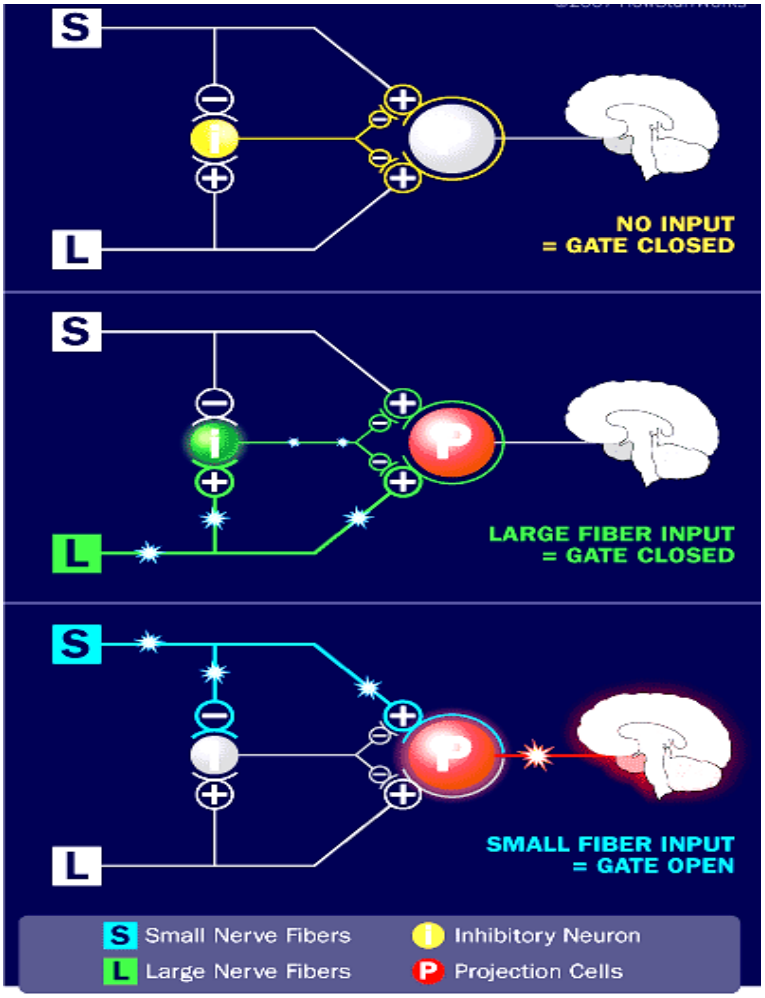

Fig (2): ***Ronald Melzack and Patrick Wall's Gate Control theory of pain.*** 1) When no input comes in, the inhibitory neuron prevents the projection neuron from sending signals to the brain (gate is closed). 2) When there is more large-fiber stimulation. Both the inhibitory and the projection neuron are stimulated, but the inhibitory neuron prevents the projection neuron from sending signals to the brain (gate is closed). 3) Nociception happens when there is more small-fiber stimulation. This inactivates the inhibitory neuron, and the projection neuron sends signals to the brain informing it of pain (gate is open), quoted from http://drpinna.com/pain-medicine-2-3154/gate-theory-pain.