Pain
A Medical and Anthropological Challenge

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With 111 Figures

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Preface

The First Convention of the Academia Eurasiana Neurochirurgica was devoted to one of the main problems not only of medicine in general and especially of neurosurgery but also of theology and anthropology. Many of these aspects have been discussed. Experts in the fields of biological and neurosciences, representatives of different religions and philosophers have contributed to a better understanding of the somatic aspects of pain and its medical treatment and of its religious, cultural, and philosophical interpretations and interactions.

It really was a unique event to bring together scientists and physicians, priests, theologians and philosophers, make them give reviews of their fields and have them discussing the many facets of pain and suffering. To achieve such a difficult goal was mainly the achievement of the late Hans Werner Pia, the first President of the Academia Eurasiana Neurochirurgica and organizer of this Convention.

Because the Convention is inseparably related to the Inauguration of the Academia Eurasiana Neurochirurgica the speeches and lectures given on this occasion and dealing with the aim of the Academia, the founding of Academies in history and with the anthropological challenge of pain are also published in this Supplement Volume of Acta Neurochirurgica.

The Convention and the Inauguration of the Academia Eurasiana Neurochirurgica are a fitting memorial to the personality of Hans Werner Pia. Its proceedings are dedicated to him.

F. Loew J. Brihayè
## Contents

### I. Somatic Aspects of Pain

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pia, H. W.</td>
<td>Introduction</td>
<td>3</td>
</tr>
<tr>
<td>Basbaum, A. I.</td>
<td>Cytochemical Studies of the Neural Circuitry Underlying Pain and Pain Control</td>
<td>5</td>
</tr>
<tr>
<td>Jänig, W.</td>
<td>Neuronal Mechanisms of Pain with Special Emphasis on Visceral and Deep Somatic Pain</td>
<td>16</td>
</tr>
<tr>
<td>Saria, A.</td>
<td>The Role of Substance P and Other Neuropeptides in Transmission of Pain</td>
<td>33</td>
</tr>
<tr>
<td>Herz, A.</td>
<td>Opiates, Opioids and Their Receptors in the Modulation of Pain</td>
<td>36</td>
</tr>
<tr>
<td>Brune, K., Lanz, R.</td>
<td>Nonopioid Analgesics</td>
<td>40</td>
</tr>
<tr>
<td>Hoffmeister, H., Central Analgesics</td>
<td></td>
<td>41</td>
</tr>
<tr>
<td>Hoffmeister, F., Stille, G.</td>
<td>Drug Abuse: Control Through National and International Regulatory Practice</td>
<td>44</td>
</tr>
<tr>
<td>Hoffmeister, F.</td>
<td>Evaluation of Antinociceptive, Reinforcing and Aversive Properties of Psychotrophic Agents and Analgesics in Animals: Models for Prediction of Their Analgesic Activity and Dependence Liability</td>
<td>50</td>
</tr>
<tr>
<td>Gybels, J., Kupers, R.</td>
<td>Central and Peripheral Electrical Stimulation of the Nervous System in the Treatment of Chronic Pain</td>
<td>64</td>
</tr>
<tr>
<td>Franetzki, M., Kollert, D.</td>
<td>Externally Portable and Implantable Devices for Continuous Delivery of Analgetics</td>
<td>76</td>
</tr>
<tr>
<td>Chrubasik, J.</td>
<td>Spinal Infusion of Opiates and Somatostatin</td>
<td>80</td>
</tr>
<tr>
<td>Fan, Shao-Guang</td>
<td>Acupuncture Analgesia</td>
<td>82</td>
</tr>
<tr>
<td>Sano, K.</td>
<td>Neurosurgical Treatments of Pain—a General Survey</td>
<td>86</td>
</tr>
</tbody>
</table>

### II. Psychological, Theological and Anthropological Aspects of Pain

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pia, H. W.</td>
<td>Introduction</td>
<td>99</td>
</tr>
<tr>
<td>Violon, A.</td>
<td>Psychological Determinants in Chronic Pain</td>
<td>101</td>
</tr>
<tr>
<td>Bastiaans, J.</td>
<td>Sociopsychosomatic Aspects of Individual, Familial and National Suffering and Pain</td>
<td>105</td>
</tr>
<tr>
<td>Violon, A.</td>
<td>Psychological Therapy of Pain</td>
<td>111</td>
</tr>
<tr>
<td>Bastiaans, J.</td>
<td>Difficulties in Psychotherapy of Victims of Man-Made Disasters</td>
<td>114</td>
</tr>
<tr>
<td>Reich, W. T.</td>
<td>Models of Pain and Suffering: Foundations for an Ethic of Compassion</td>
<td>117</td>
</tr>
<tr>
<td>Autiero, A.</td>
<td>The Interpretation of Pain: the Point of View of Catholic Theology</td>
<td>123</td>
</tr>
<tr>
<td>Rössler, D.</td>
<td>About Anthropology of Pain: View of Protestant Theology</td>
<td>127</td>
</tr>
<tr>
<td>Levinson, N. P.</td>
<td>Pain and Suffering: Views of Jewish Theology</td>
<td>129</td>
</tr>
<tr>
<td>Al-Jeilan, M.</td>
<td>Pain: Points of View of Islamic Theology</td>
<td>132</td>
</tr>
<tr>
<td>Pandya, S. K.</td>
<td>Hindu Philosophy on Pain: an Outline</td>
<td>136</td>
</tr>
<tr>
<td>Tu, Wei-Ming</td>
<td>A Chinese Perspective on Pain</td>
<td>147</td>
</tr>
<tr>
<td>Sano, K.</td>
<td>Pain and Japanese Zen</td>
<td>152</td>
</tr>
<tr>
<td>Schoffeniels, E.</td>
<td>Pain Understanding and Suffering Considered by an Agnostic</td>
<td>154</td>
</tr>
<tr>
<td>Bieri, P.</td>
<td>Pain: a Case Study for the Mind-Body Problem</td>
<td>157</td>
</tr>
<tr>
<td>Kern, E.</td>
<td>Cultural-Historical Aspects of Pain</td>
<td>165</td>
</tr>
<tr>
<td>Bagchi, A. K.</td>
<td>Pain and Language</td>
<td>182</td>
</tr>
<tr>
<td>Luyendijk, W.</td>
<td>Pain Understanding and Treatment—an Interdisciplinary Challenge. Summary of a Round Table and General Discussion</td>
<td>185</td>
</tr>
</tbody>
</table>

### III. Inauguration of the Academia Eurasiana Neurochirurgica

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pia, H. W.</td>
<td>The Aims of the Academy</td>
<td>191</td>
</tr>
<tr>
<td>Böckle, F.</td>
<td>The Anthropological Challenge of Pain</td>
<td>194</td>
</tr>
<tr>
<td>Luyendijk-Elshout, A.M.</td>
<td>Non solum gloria. The Foundings of Academies in History</td>
<td>196</td>
</tr>
</tbody>
</table>
I. Somatic Aspects of Pain
Introduction

Hans Werner Pia*

The first part of the Convention is devoted to the contemporary “state of the art” and research concerning somatic pain. Several experts will report about the origin, transmission, perception and processing of pain, including basic knowledge, chemical neuroanatomy, clinical and experimental physiological findings recorded in the peripheral, sympathetic and central nervous system and the problem of “pain measurement” in the nociceptive system. Further topics are the important discovery of endogenous opiates and other substances connected with membrane receptors. Clinical contributions to the session will deal with pathogenesis and diagnosis of chronic pain seen in the light of new clinical and experimental research work.

Modern concepts of pharmacotherapy will focus upon the site of action of peripheral and central analgesic substances and relations between the effects of analgesics, neuroleptics, and psychotropic drugs.

Important social problems of drug abuse, tolerance, dependency and addiction and about the national and international efforts to get it under control, will be discussed.

Finally, new developments and the present state of analgesia including techniques of local and infiltration analgesia, neurosurgical stimulation and ablative procedures upon the peripheral and central pain pathways and nuclei will be dealt with. It is obvious that acupuncture will be discussed in the context of exact physiological measurements.

All referents are experts who have contributed enormously to the research of pain. We are grateful to them for agreeing to present here a review of their studies. Without knowledge about the origins, transmission, perception and processing of pain the considerations about the psychology and anthropology of pain which are dealt with later would be lacking an important foundation.

I declare open the 1st Convention of the Academia Eurasiana Neurochirurgica devoted to “Pain—a medical and anthropological challenge”. I do hope that we can face this challenge and that we will obtain a better insight into the problem of pain and suffering in man.

* Prof. Dr. med. Dr. med. h.c. Hans Werner Pia, Late Head of the Department of Neurosurgery of the University of Giessen and President of the Academia Eurasiana Neurochirurgica. He died on July 9, 1986.
Cytochemical Studies of the Neural Circuitry Underlying Pain and Pain Control

Allan I. Basbaum*

Introduction

With the introduction of immunocytochemistry in anatomical studies of the nervous system, significant progress has been made in our understanding of CNS circuitry. By simultaneously performing retrograde tracing studies with immunocytochemistry, it is now possible to identify the cytochemistry of projection systems. When this is combined with a functional analysis of a given pathway, e.g., the spinothalamic tract, it is possible, for the first time, to characterize the likely transmitter content of specific neuronal systems. The importance of such information cannot be overemphasized. For example, if one knows the neurotransmitter that is involved in the central transmission of nociceptive messages, it should be possible to develop receptor antagonists that block the action of that neurotransmitter. That approach could lead to the development of very specific analgesic drugs.

That goal has, of course, not yet been obtained. Attempts are, however, presently being made to develop antagonists to some of the substances that have recently been identified in components of the pain transmission pathway. In this review I will discuss the organization of pain transmission and control networks, focussing specifically on their cytochemistry. Unfortunately, our knowledge of the cytochemistry of the second and third order neurons in the pain transmission system is extremely limited. Thus, for example, there is little information on the neurotransmitter content of spinothalamic and spinothalamic tract neurons. Although there are data indicating that some ventroposterolateral thalamocortical neurons contain the amino acid, aspartate, it is not at all certain that those are nociceptive neurons. It is likely that most are part of the nonnociceptive, lemniscal projection system. This review will, therefore, focus on the region of the nociceptive system where there is the most complete information, namely the spinal dorsal horn.

I will organize the discussion around the projection neurons of the dorsal horn, namely the nociceptive spinothalamic tract and reticulothalamic tract neurons of laminae I and V. Most of the discussion, in fact, will focus on the cytochemical organization of the superficial dorsal horn, the region which contains the highest concentration of most of the neuroactive peptides yet discovered. Three systems converge onto these neurons, the primary afferents, the local spinal interneurons and the descending projection neurons which modulate the output of the dorsal horn projection neurons.

Primary Afferents

There is much new information about the cytochemistry of the primary afferents. Dorsal root ganglion (DRG) cells have been subdivided according to the peptide content (Dodd et al. 1984). Among the many peptides associated with the DRGs are Substance P, CCK, VIP, somatostatin and calcitonin-gene related peptide (CGRP) (Rosenfeld et al. 1983). There is also recent evidence that the opioid peptide, dynorphin is found in some primary afferent fibers (see below).

CGRP is of particular interest since it is found in a large population of the small DRG cells, some of which also contain Substance P (Wiesenfeld-Hallin et al. 1984). The finding of co-occurrence of two or more putative neurotransmitters in the same neuron is now a common finding in the periphery and in the CNS, but, with rare exception (Jan and Jan 1982, Agnati et al. 1983) the different roles of the coexisting compounds have not been characterized. In the case of CGRP and SP there are interesting data which suggest that the former enhances the effect of Substance P (Wiesenfeld-Hallin et al. 1984, Gamse and Saria 1985). By itself, CGRP has little effect.

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Although it has been argued that the evidence for these primary afferent peptides being neurotransmitters is weak, the case for some of the peptides is, in fact, quite strong. Substance P, for example, is localized in small diameter primary afferents and is found in large dense-cored vesicles of synaptic terminals of lamina I, outer II and V of the dorsal horn (Hokfelt et al. 1977, Barber et al. 1979). Substance P is released by intense peripheral nerve stimulation (Yaksh et al. 1980) and iontophoresis of SP near spinal cord neurons excites these neurons (Henry 1976). Intrathecal injection of SP elicits behaviors suggestive of the animal experiencing pain (Hylden and Wilcox 1983). Of particular interest are the attempts to block the effects of SP with receptor blockers. Unfortunately, the specificity of the antagonists is not adequate, so the long sought “specific analgesic” is not yet available.

Sectioning the dorsal root, as expected, results in a significant drop in the content of the dorsal horn SP (Hokfelt et al. 1976, 1977). Perhaps more significantly, peripheral nerve damage results in an equally profound drop in the level of spinal SP (Jessell et al. 1979). This observation runs counter to the long taught doctrine that central (spinal cord) changes only result from injury proximal to the DRG. In fact, even slight damage to the peripheral branch of the primary afferent results in significant and probably clinically relevant central changes. Not only are there central anatomical changes, but correlated physiological changes can be detected, some of which may contribute to the neurogenic pains seen with peripheral nerve injury.

Despite the emphasis on the central actions of primary afferent derived peptides, it is now clear that the DRG synthesizes compounds and directs them to the peripheral terminal of the primary afferents. For example, about 90% of DRG derived SP is transported to the distal terminal, where it is stored and can be released (Brimijoin et al. 1980, Olgart et al. 1977). The normal contribution of the peripheral peptides is not known, but effects on local microcirculation and on other nonnervous elements, e.g., mast cells and immunocompetent cells are likely. The clinical relevance of these peripheral peptides is suggested from studies indicating that SP contributes to neurogenic inflammation (Lembeck and Holzer 1979). More recently, SP has been implicated in the severity of experimental arthritis in the rat (Levine et al. 1984).

Studies of the effects of capsaicin, a peripheral C fiber neurotoxin, have been critical to the understanding of the contribution of these peripheral peptides. Pretreatment with capsaicin not only eliminates, or significantly reduces neurogenic inflammation (Janse et al. 1968), but it reduces arthritis as well (Colpaert et al. 1983). Thus, the primary afferent peptides are not only involved in the central transmission of nociceptive messages by small diameter primary afferent fibers, but also in the contribution of the nervous system to peripheral inflammatory mechanisms.

**Descending Projections**

Perhaps the most detailed analysis of CNS cytochemistry in pain-related circuitry concerns the organization of brain stem spinal control systems. The majority of studies have focussed on the mechanisms through which electrical brain stimulation and opiate injection generates analgesia. Our own laboratory has been involved in this analysis for several years (Basbaum and Fields 1978, 1984). Figure 1 illustrates a model of the brain stem spinal controls that operate in these analgesia mechanisms. It is a three-tiered model that incorporates the midbrain periaqueductal grey (PAG), the rostral ventral medulla and the spinal dorsal horn. Systemic opiates are thought to act by binding to receptors in the PAG. This results in the activation of a PAG output neuron that excites spinally projecting neurons of the medulla, a large component of which are serotonin-containing neurons of the midline nucleus raphe magnus (NRM). The 5HT neurons, in turn, project to and inhibit nociceptive neurons of the dorsal horn. This inhibitory control system can be activated by electrical stimulation through electrodes implanted in the PAG, a technique which has proven useful for the treatment of intractable pain in humans (Hosobuchi et al. 1977).

Although there are numerous compounds found in the rostral ventral medulla, the bulk of the evidence has implicated descending 5HT control systems. Thus, for example, antagonism of 5HT systems counteracts the analgesic action of narcotics as well as that produced by electrical brain stimulation (see Basbaum et al. 1983 for review). Treatment with tryptophan, a serotonin precursor, reduces the tolerance that develops with repeated electrical stimulation, in both animals (Oliveras et al. 1975) and humans (Hosobuchi et al. 1980).

The simplest model of the organization of descending pain control systems at the level of the spinal cord would have a SP-containing primary afferent fiber excite a spinal nociceptive projection neuron that also receives a convergent descending serotonergic inhibitory projection from the medulla. In fact, there is evidence that 5HT systems directly inhibit spinal
Fig. 1. Schematic illustration of the brain stem and spinal neural substrate that contributes to the analgesic action of electrical brain stimulation and systemic morphine injection.

Neurons of the periaqueductal grey (PAG) are activated through an implanted electrode or by opiate injection. These neurons project to and excite neurons of the medullary nucleus raphe magnus (NRM), some of which are 5HT-containing. The latter project to the spinal cord via the dorsolateral funiculus (DLF) and inhibit the firing of spinal cord nociceptive neurons of laminae I and V. Some of the spinal nociceptive neurons are presumed to have an excitatory input from small diameter substance-P containing (sp) primary afferents and to project axons into the spinothalamic tract (STT).

Although there is direct postsynaptic inhibition of some nociceptors of the cord, there is also evidence that some of the descending 5HT axons exert their effects via synaptic interaction with enkephalin interneurons (starred cell bodies) of the dorsal horn.

The figure also indicates that there is a complicated contribution of the noradrenergic (NE) neurons of the brain stem. Some of these project to and inhibit the raphe-spinal control system and others project to the cord and inhibit the spinal nociceptors. Some NE neurons send an axon to both the raphe and the spinal cord. Finally, the diagram indicates that there is another endorphin link within the PAG, however, how it interacts with the PAG projection neuron is not known.

nociceptive neurons. Anatomical studies have established that 5HT synapses contact projection neurons and iontophoresis of 5HT most profoundly inhibits those neurons which are inhibited by raphe stimulation (Hoffert et al. 1983). Furthermore, the density of 5HT synapses on neurons not affected by raphe stimulation is much lower than on neurons which are inhibited.

There is also evidence for a norepinephrine control of spinal nociceptive neurons, and thus our original model included a descending projection from norad- renergic cell groups of the locus coeruleus and parabrachial region. Although it is not certain that those sites are indeed the origin of the NE in the spinal dorsal horn, recent studies have, in fact, established that the NE contribution is particularly important. Not only is the inhibitory effect of NE iontophoresis particularly potent (Headly et al. 1978, Wilcockson et al. 1984), but intrathecal injection of clonidine, a NE agonist, generates a potent analgesia (Reddy et al. 1980). More importantly, the analgesia produced by clonidine is not reversed by the opiate antagonist naloxone and shows no cross tolerance with epidurally-produced morphine analgesia. With a view to reducing the doses of morphine required to elicit adequate analgesia in humans, recent studies are directed at combined administration of narcotics and alpha adrenergic agonists.

Norepinephrine has also been implicated in the controls exerted by electrical stimulation of the medulla. For example, the analgesic action of raphe stimulation is not completely blocked by spinal administration of the 5HT antagonist methysergide, but requires simultaneous administration of an alpha-2 blocker, e.g., yohimbine (Barbaro et al. 1985). Complete antagonism of the analgesia produced by morphine injected into the PAG similarly requires simultaneous spinal administration of 5HT and NE blockers (Yaksh 1979). Since there are no NE cell bodies in the raphe (Dahlstrom and Fuxe 1964), the observation that the analgesic action of raphe stimulation can be partially blocked by injection of NE antagonist into the cord was surprising. The source of the NE involvement was unclear. Hammond et al. (1980) partially clarified the problem when they demonstrated that microinjection of the alpha antagonist phentolamine into the raphe produced a significant hypoalgesia. The authors concluded that noradrenergic inputs to the raphe exert a tonic inhibition of the bulbospinal 5HT control of nociceptive neurons.

This observation was intriguing since it indicated that a given neurotransmitter, i.e., norepinephrine, apparently exerts opposing actions on the output of spinal nociceptive neurons. At the level of the spinal cord, NE blocks the transmission of nociceptive messages. At the brain stem level, NE antagonizes the controlling effects exerted by the 5HT neurons of the raphe. These data may explain why systemic injection of NE agonists are not effective in eliciting analgesia. Unlike direct spinal injection, a systemic route would bring into play both the agonist spinal and antagonist supraspinal sites.
Since there are very limited sites from which the NE control of the raphe and the cord could arise, we were interested in the possibility that some brainstem NE neurons project both to the cord and to the raphe. To this end we performed a triple labeling study of the projections of brainstem NE neurons. (Basbaum and Menetrey, unpublished observations). First a retrograde dye tracer, “true blue”, was injected into the spinal cord. This labeled all brainstem neurons which project to the cord. At the same time, a second cell group, which is located just dorsal and lateral to the Kolliker-Fuse cell group and in the A5 norepinephrine cell group, which is located just dorsal and lateral to the superior olive.

These data indicated that there is obviously very subtle fine tuning of the descending control systems and that noradrenaline cell groups of the brain stem are critical to adjusting the gain of those controls. A single NE neuron sends an axon to the spinal cord where it can potentially block the transmission of dorsal horn, pain related messages. Via an axon collateral that terminates in the midline raphe, the same neuron can simultaneously modulate the descending controls exerted by bulbospinal 5HT systems.

There are numerous other cytochemically characterized medullary cell groups that project to the spinal cord, including substance P and enkephalin-containing cells (Bowker et al. 1981). The function of these other descending systems is unknown, however, they have attracted considerable attention because almost all of these peptide-containing cells contain a coexisting transmitter, usually one of the two biogenic amines, 5HT or NE (Hokfelt et al. 1980). It has been suggested that the coexisting peptide facilitates the action of the amine. There is also some evidence that antagonistic effects could arise from the cooccurring neurotransmitters. It is of particular interest for example, that the putative nociceptive transmitter, substance P, is found not only in small diameter primary afferent fibers, but also in the 5HT-containing raphe-spinal neurons which are known to control the transmission of spinal nociceptive neurons (Hokfelt et al. 1978).

Fig. 1 illustrates the growing complexity of the inputs to the spinal projection neuron. There are convergent excitatory SP and inhibitory 5HT and NE inputs. In addition, the known interactions between the two aminergic systems in the rostral medulla are illustrated. This simple diagram, however, is very understated. Still to be included are the extensive local circuit interactions that exist in the dorsal horn itself.

**Spinal Endorphins**

**A. Enkephalin**

One of the first clues to the contribution of the endorphins to descending controls was, of course, the observation that injection of the narcotic antagonist, naloxone, could block both the analgesic effects of morphine and of electrical brain stimulation of the PAG (Akil et al. 1976). Until recently the site of the naloxone antagonism of SPA was not known. Zorman et al. (1982) however, demonstrated that intrathecal injection of naloxone could antagonize the analgesic action of microstimulation in the raphe magnus. The latter observation provided support for our early suggestion (Basbaum and Fields 1978) that the descending 5HT systems, in part, exert their effects via the local enkephalin neurons which are found in large numbers in the superficial dorsal horn.

In fact, there is a significant overlap in the distribution of the opiate receptor (Atweh and Kuhar 1977), of enkephalin (Hokfelt et al. 1977, Glazer and Basbaum 1981), substance P (Barber et al. 1979) and of the descending terminals from the raphe (Basbaum et al. 1978) in lamina I and II of the spinal dorsal horn, and in its medullary homologue, the trigeminal nucleus caudalis (TNC). To provide anatomical support for the hypothesis that 5HT neurons interact with local spinal enkephalin neurons, we performed an ultrastructural double labeling study in which immunocytochemistry was used to localize immunoreactive enkephalin neurons and dendrites and autoradiography was used to localize tritiated serotonin that was infused into the cisternal CSF (Glazer and Basbaum 1984). This study established that some spinal 5HT axons (all of which originate in the medulla) indeed synapse on enkephalin dendrites and cell bodies of the superficial dorsal horn (Fig. 2). This observation indicated that the control of spinal nociceptive neurons by the medullary raphe is not only exerted directly on the projection neurons, but is also exerted indirectly, via an endorphin link in the cord.

The next question addressed the synaptic mechanisms through which the spinal enkephalin neurons
control the projection neurons. We were influenced by the elegant *in vitro* (Jessel and Iversen 1977) and subsequent *in vivo* (Yaksh *et al.* 1980) studies which examined the effect of morphine on the release of Substance P from primary afferent fibers. In the *in vitro* studies, Substance P release from slices of trigeminal nucleus caudalis was generated with high K⁺ in the bath. In the *in vivo* studies, SP release from lumbar cord into the CSF was evoked by high intensity “painful” electrical stimulation of the sciatic nerves in the cat. These authors found that morphine and other narcotic or opioid peptide ligands blocked the release of substance P. Since there was good evidence that a large fraction of the spinal opiate receptor distribution is located on primary afferent fibers (La Motte *et al.* 1976, Hiller *et al.* 1978, Fields *et al.* 1980) many of which are probably unmyelinated (Gamse *et al.* 1979), these authors proposed that local enkephalin neurons of the dorsal horn presynaptically control the release of substance P from nociceptive primary afferent fibers.

This provocative model received considerable attention in immunocytochemical studies which searched (in many species) for the anatomical substrate that would underly such a presynaptic control. What was sought was an axoaxonic synapse in which enkephalin terminals are presynaptic to another vesicle-containing profile (which presumably would contain substance P). Despite extensive analyses, however, this synaptic arrangement has never been found (Aronin *et al.* 1981, Glazer and Basbaum 1983, Hunt *et al.* 1980, Sumal *et al.* 1982, La Motte and de Lanerolle 1983). On the other hand, there is considerable physiological evidence for direct postsynaptic control of spinal neurons by local enkephalin neurons (Ziegglansberger and Tulloch 1979, Willcockson *et al.* 1984, Yoshimura and North 1983). In fact, spinothalamic tract neurons of lamina I and V receive direct enkephalin synaptic inputs (Ruda 1982, Ruda *et al.* 1984). Presumably that latter arrangement underlies a direct postsynaptic inhibition of the nociceptive projection neurons of the dorsal horn.

Despite the absence of anatomical support for the Jessel and Iversen presynaptic model, it is possible that enkephalin is released in a somewhat nontraditional fashion. In fact, there is evidence that some peptide neurotransmitters are released from synaptic terminals and can act at a relatively long distance from the release

Fig. 2. This photomicrograph illustrates the synaptic interaction between a serotonergic synapse (labeled by high affinity uptake of tritiated 5HT) and a large immunoreactive enkephalin dendrite in the substantia gelatinosa of the trigeminal nucleus caudalis. Adapted from Glazer and Basbaum (1984)
site (Jan and Jan 1982). This so-called “nonsynaptic” transmission could result in the presynaptic control of substance P-containing primary afferent P by enkephalinergic dorsal horn neurons.

B. Dynorphin

With the discovery of the dynorphin class of endorphins (Goldstein et al. 1979) the nature of the contribution of spinal opioid peptides to the segmental and supraspinal pain control systems has become significantly more complicated. Dynorphin is synthesized on a precursor that differs from that which produces the enkephalin peptides (Kakidani et al. 1982). After preliminary studies of the immunocytochemical distribution of dynorphin revealed its presence in the spinal cord (Vincent et al. 1982, Khatchaturian et al. 1982), we initiated a detailed study of its anatomical distribution. It should be emphasized that since the dynorphin molecule contains the leucine-enkephalin sequence, previous studies with antisera directed against the pentapeptide opioid may also have revealed the distribution of dynorphin, as a result of antibody cross reactivity. To overcome this problem, we used antisera that did not recognize the enkephalin sequence. Those studies demonstrated significant differences in the distribution of the two opioid peptides in the spinal dorsal horn and trigeminal nucleus caudalis (Cruz and Basbaum 1985).

A major feature of the dynorphin distribution is that there is much less terminal staining than for enkephalin. That which was found was almost exclusively associated with regions of the dorsal horn which process nociceptive information, i.e. lamina I and V. To determine the distribution of dynorphin cell bodies, we also examined tissue from animals treated with colchicine (which blocks axoplasmic transport and thus builds up peptide levels in the cell bodies). That study revealed a large concentration of dynorphin-immunoreactive cells in laminae I and V of both the spinal dorsal horn and trigeminal nucleus caudalis. Quantitative analysis revealed that almost 82% of the dynorphin cells are found in lamina I and V. Fig. 3 is from the TNC and illustrates the very restricted distribution of immunoreactive dynorphin and the comparison with that of enkephalin.

Although enkephalin cells and terminals are also found in high concentration in similar regions of the dorsal horn, it must be pointed out that enkephalin is also located in regions not associated with nociceptive processing. In fact, the densest terminal enkephalin staining is found in the inner part of the substantia gelatinosa, a region which receives nonnoxious inputs via small diameter afferents and which contains cells which respond to nonnoxious peripheral stimulation (Bennett et al. 1980, Light et al. 1979) (Fig. 4). Large numbers of enkephalin cell bodies are also found ventral to the substantia gelatinosa, in lamina III, the neurons of which are also predominantly responsive to nonnoxious stimulation.

When we examined the sacral spinal cord, we found another feature of the dynorphin distribution that differs significantly from that of enkephalin. The pattern of dynorphin terminal staining was very characteristic of that seen with antisera directed against vasoactive intestinal polypeptide, a compound known to derive, in large part, from primary afferent fibers (Basbaum and Glazer 1983; Honda et al. 1983, Kawatani et al. 1985). For example, there is a dense concentration of labeled fibers in the tract of Lissauer, which is made up predominantly of afferent fibers of small caliber (Fig. 4). In some cases, we also found staining of fibers within dorsal rootlets that remained attached to the spinal cord section. The terminal distribution in the cord included the marginal zone. A second branch of fibers curved around the lateral aspect of the dorsal horn and penetrated the spinal grey in the region of lamina V.

This characteristic pattern of staining suggested that at least part of the terminal spinal dynorphin staining pattern derives from primary afferent fibers, an hypothesis consistent with earlier observations (Botticelli et al. 1981, Sweetnam et al. 1982). To examine this possibility, we assayed the spinal DRG by radioimmunoassay and found significant levels of immunoreactive dynorphin in all ganglia tested. The highest levels were found in the sacral ganglia. As a final test that some primary afferent fibers contain dynorphin, we unilaterally sectioned dorsal roots L 5 to S 4 in the cat (Basbaum et al. 1986). Seven days later the spinal cord was examined for dynorphin by immunocytochemistry. As expected, the distribution of substance P was decreased ipsilateral to the rhizotomy. Enkephalin staining, if anything, increased ipsilateral to the deafferentation. Consistent with dynorphin deriving from primary afferents, however, we found a significant decrease in dynorphin staining in the dorsal horn ipsilateral to the rhizotomy (Fig. 5).

The functional significance of these observations is difficult to evaluate. One possibility of course, is that dynorphinergic neurons are the source of the presynaptic opioid input to the primary afferent opiate receptor. A review of the behavioral effects of dynorphin after
Fig. 3. These photomicrographs illustrate the difference in the distribution of immunoreactive enkephalin and dynorphin cells in the trigeminal nucleus caudalis. The enkephalin cells are difficult to visualize within the dense terminal distribution, however, they are found in all layers of the dorsal horn. Note the absence of staining in the magnocellular layers (mag). In contrast, the dynorphin cells are concentrated almost exclusively in laminae I and V. The substantia gelatinosa (sg) has almost no dynorphin staining.

Fig. 4. These two photomicrographs illustrate the difference in the spinal cord distribution of immunoreactive enkephalin and dynorphin. The enkephalin terminal staining pattern (left) is far more widespread but the dynorphin (right) terminals are more concentrated in those regions of cord that are associated with the transmission of nociceptive messages. Arrows point to dynorphin fibers in the Lissauer’s tract. Arrow heads indicate dorsal and lateral bundles of dynorphin fibers. Adapted from Cruz and Basbaum 1985.
Fig. 5. This figure illustrates the effect of unilateral multiple dorsal rhizotomy on the distribution of immunoreactive dynorphin in the sacral spinal cord of the cat. The rhizotomy was on the right side. Note that there is a dramatic loss of dynorphin staining ipsilateral to the rhizotomy, indicating that the staining derives, in large part, from primary afferents.

Intrathecal injection, however, raises the intriguing possibility that dynorphin exerts an effect opposite to that generated by the enkephalins. The first reports of the effects of intrathecal administration of dynorphin were, in fact, controversial. Some reports found very prolonged analgesic effects, often lasting more than twenty-four hours (Han and Xie 1982). In some cases, however, the necessary dose to produce this effect was very high (Basbaum et al. 1983). Tung and Yaksh (1982) were, in fact, emphatic that dynorphin was without analgesic effect when given by intrathecal injection. One complication that is difficult to control after spinal injections of dynorphin is that often there results a concomitant flaccid paralysis. This, of course, makes assessment of the analgesia difficult. More recently, Schmauss and Yaksh (1984) suggested that dynorphin may produce an analgesia specific for tests of visceral pain. The latter observation is of particular interest since there appears to be an especially high concentration of dynorphin in primary afferents entering the sacral cord and these distribute in a pattern that is indistinguishable from that of pelvic visceral afferents (Morgan et al. 1981).

Despite the disagreement concerning the spinal analgesic effects of dynorphin, there are quite consistent data on the effects of intracerebral injection. In contrast to morphine, beta endorphin or the enkephalins, dynorphin does not produce analgesia. To the contrary, there is evidence that dynorphin can antagonize the analgesia produced by morphine or beta endorphin, at least in the opiate naive animal (Tulunay et al. 1981, Walker et al. 1982).

In light of the striking localization of dynorphin cells and terminals in those regions of the dorsal horn associated with nociceptive transmission and particularly the presence of dynorphin in some primary afferents, the following hypothesis is presented. It is possible that dynorphin, rather than controlling the output of spinal nociceptive neurons, is part of the input system to those neurons. Conceivably the observations of analgesia produced by intrathecal dynorphin are a result of feedback inhibition (segmental and possibly supraspinal) in response to activation of spinal nociceptive neurons. This might account for the requirement of high doses to produce analgesia. The particular association of dynorphin with visceral pain, in fact, would be expected from its preferential location in the sacral cord.

The observation on the effects of intracerebral dynorphin injection are also consistent with this view. Increased afferent drive produced by dynorphin could result in a functional antagonism of morphine or beta endorphin analgesia. That is, the shift to the right in the morphine dose response curve would result because a greater “afferent” input must be overcome to produce an equivalent level of analgesia. Importantly, there is no evidence that the antagonistic effect of dynorphin involves competition with morphine at the opiate receptor, which, of course, is consistent with the proposed mechanism.

Obviously numerous studies have to be performed to determine the contribution of dynorphin to pain control and/or transmission systems. Given how different its anatomical distribution is from that of the enkephalins, it is certain that significant functional differences between the different opioid peptides will be found. Perhaps more importantly, since dynorphin is considered the endogenous ligand for the kappa opiate receptor (Chavkin et al. 1982), new antagonists will no doubt be developed which can block the effects of dynorphin. With those drugs available, the effects of the individual opioid peptide families will be independently assessable. Hopefully, that approach will lead to highly selective and more effective analgesic agents.

Conclusions

It must be emphasized that this review has focussed on a very small number of the neurotransmitter substances which contribute to the pain control and transmission circuitry in the spinal cord. Numerous other compounds have been identified in the same region. These almost certainly also influence the output
of the nociceptive projection neuron. In the next few years a better understanding of how those other compounds fit into the circuit diagram will be made available. Although the complexity of the “pharmacological” circuit map of the dorsal horn will grow considerably, there should be a parallel growth in the number of analgesic drugs that are designed as a result of those anatomical developments. Significant improvements in the treatment of pain should follow.

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Neuronal Mechanisms of Pain with Special Emphasis on Visceral and Deep Somatic Pain*

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Summary

Pain has several dimensions: the sensory-discriminative, the motivational-affective, the cognitive and the motor and autonomic dimension. Each dimension can be roughly identified with certain brain areas. The sensory-discriminative dimension is also called the “nociceptive dimension” or, briefly, “nociception”.

1. Noxious stimuli applied to the skin appear to be encoded quite specifically by certain types of nociceptive afferent units with group III (Aδ) and IV (C) fibers. The impulse activity of these cutaneous primary afferents converges on spinal “nociceptive-specific” neurones, most of which seem to be located in lamina I of the dorsal horn, and together with the nonnociceptive information from the skin on “wide-dynamic range” (multisensory) neurones in the grey matter, most of which are situated in lamina V, but some also in adjacent laminae and lamina I.

2. Many of these “nociceptive-specific” and “wide-dynamic range” neurones project with their axons through the anterolateral tract to the nucleus ventralis posterolateralis (VPL) of the thalamus and also to other thalamic nuclei, to the mesencephalon and to the reticular formation of the brain stem. In the VPL of the thalamus, most neurones with nociceptive input have a wide-dynamic range property, very few are nociceptive-specific.

3. Noxious events leading to deep somatic pain are encoded by thin myelinated (Aδ) and unmyelinated afferent fibers (e.g., from skeletal muscle, tendon and joint capsule). Besides these deep somatic “nociceptive” afferent units, other nonnociceptive deep somatic afferent units with fine afferents have been claimed to exist and it is believed that these are involved in functions other than nociception. The specificity of responses of these afferents, with respect to the natural stimuli, is only relative.

4. For the viscera nociceptive spinal visceral afferents, which are only activated when injurious or potentially injurious events in the visceral domain (which may lead to pain) occur, cannot be unambiguously shown to exist. It seems more likely that the activity in the same population of spinal visceral afferents is involved in nociceptive as well as in nonnociceptive sensory functions, in the regulation of visceral organs and in various types of reflexes.

5. No neurones in the spinal grey matter have been found which specifically transmit and process information from fine deep somatic and spinal visceral afferents. This information seems to converge not only on many “wide-dynamic range” (multisensory) spinal neurones but also on some “nociceptive-specific” neurones. Only very limited information on thalamic neurones, with respect to the deep somatic and visceral afferent inputs, is available.

6. With the experimentally evaluated knowledge available, it seems unlikely that the “specificity theory” of Müller and von Frey can be applied to the generation of deep somatic and visceral pain; however, it seems more likely that “intensity” and “pattern mechanisms” are rather more important for the generation of these two types of pain. The way in which the impulses from deep somatic and visceral structures, which are associated with deep somatic and visceral pains, are processed by neuronal mechanisms in the spinal cord, brain stem and thalamus is unknown. It appears probable that “wide-dynamic range neurones obtaining convergent input from deep somatic structures and viscera are involved in referred pain.

7. Finally, it should be kept in mind that the experimental work on the problem of the biology of pain is taking place essentially at three methodological levels: the structure and location of the neurones involved, the physiology of the synaptic events and the impulse in these neurons and the psychology of pain behaviour. Results obtained with these different approaches leads to the description of three classes of associated but not causally linked phenomena. For example, the activity of “nociceptive-specific” neurones does not cause pain but may be associated with it.

Introduction

Pain is a complex event with several dimensions: sensory-discriminative, affective-motivational, cognitive, and motor and autonomic (Melzack and Casey 1968). The term “sensory-discriminative” describes the ability to identify the type (mechanical, thermal, chemical) of injurious stimulus and its temporal, spatial and intensive aspects. The term “affective-motivational” describes the complex avoiding and escaping behaviour and the associated unpleasant and aversive feelings elicited by the noxious stimulus. The term “cognitive” describes the ability cognitively to control affective-
motivational behaviour and motor and autonomic components. The motor and autonomic dimension describes the motor and autonomic reflexes and reactions elicited by an injurious stimulus. Each dimension, which can be identified and measured in humans and—with limitations—also in animals, can be roughly assigned to certain brain structures, as exemplified in Fig. 1. The motor and autonomic components are, of course, not limited to the spinal cord; the spinal circuits serve as final motor and autonomic programmes (Baldissera et al. 1981, Jänig 1985a, b, 1986) for expressing the adequate behavioural reactions. Fig. 1 illustrates that virtually the whole brain is involved in the generation of the complex event “pain” and that all dimensions belong together. In this sense, it is not correct to talk of pain fibers, pain neurones and pain centers etc.

Up to now most experimental neurobiological work performed in the field concerned here has concentrated on the analysis of the peripheral and central neuronal mechanisms of the sensory-discriminative dimension of cutaneous pain, i.e. on cutaneous nociception (Wall and Melzack 1984, Willis 1985, Albe-Fessard et al. 1985). Based on the general conception that pain is a primary afferent sensation with its own peripheral receptors and central pathways and that noxious physical and chemical stimuli can be applied to the skin with relative ease, a rigorous analysis of peripheral and central neurones, which are probably involved in cutaneous pain, has been performed during the last 15