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# Contemporary Research in Pain and Analgesia, 1983

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • Alcohol, Drug Abuse, and Mental Health Administration

# Contemporary Research in Pain and Analgesia, 1983

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National Institute on Drug Abuse

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A RAUS Review Report

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# Contemporary Research in Pain and Analgesia, 1983

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# Preface

The Research Analysis and Utilization System (RAUS) is designed to serve four functions:

- Collect and systematically classify the findings of all intramural and extramural research supported by the National Institute on Drug Abuse (NIDA)
- Evaluate the findings in selected areas of particular interest and formulate a state-of-the-art review by a panel of scientific peers;
- Disseminate findings to researchers in the field and to administrators, planners, instructors, and other interested persons;
- Provide a feedback mechanism to NIDA staff and planners so that the administration and monitoring of the NIDA research program reflect the very latest knowledge gleaned from research in the field.

Since there is a limit to the number of research findings that can be intensively reviewed annually, four subject areas are chosen each year to undergo a thorough examination. Distinguished scientists in the selected field are provided with copies of reports from NIDA-funded research and invited to add any information derived from the literature and from their own research in order to formulate a comprehensive view of the field. Each reviewer is charged with writing a state-of-the-art paper in his or her particular subject area. These papers, together with a summary of the discussions and recommendations which take place at the review meeting, make up a RAUS Review Report in the NIDA Research Monograph series.

In Fiscal Year 1583 the subject of new advances in pain research was chosen as an area for a RAUS review. This subject has selected for a comprehensive review because research in the area is funded by several different NIH and ADAMHA Institutes and there was a need to bring the findings on the subject together; further, there have been significant advances in both basic and clinical research on analgesia but there is a general perception that these have not been followed by significant advances in general clinical practice. Finally, there is the basic administrative question as to whether or not NIDA should continue to fund pain research.

The results of these reviews are presented in this monograph. Drs. Roger Brown and Theodore Pinkert served as the scientific moderators of the meeting and the final chapter of this monograph is their summary of the discussions which took place at the meeting and the recommendations from the attendees.

# Contents

# Executive Summary

Jacqueline P. Ludford, M.S.

Within recent years significant strides have been made in the area of the neurobiology of pain and analgesia. In particular, the discovery of endogenous opiates and their receptors has contributed immeasurably to our understanding of pain transmission and modulation. At its RAUS review meeting on January 19-20, 1983, NIDA invited reviewers to discuss:

| | |
|---|---|
| o Anatomy and Physiology of Pain | Dr. Howard Fields<br>University of California, San Francisco |
| o Neurochemical Basis of Pain | Dr. Gerald Gebhart<br>University of Iowa |
| o Comparative Clinical Studies in Analgesia and Pain Management | Dr. Raymond Houde<br>Sloan-kettering Institute for Cancer Research |
| o Behavioral and Psychological Components of Pain Management | Dr. Charles O'Brien<br>Veterans Administration Medical Center, Phila. |
| o Biobehavioral Approach to Studying Pain Mechanisms | Dr. David Mayer<br>Medical College of Virginia |

Dr. Fields' presentation focused on pain transmission and pain modulating systems with particular attention to the role of endogenous opioid peptides. He reviewed the "families" of endogenous opiates and current knowledge regarding their anatomical sites of act ion. The probable mechanisms of action of exogenous opiates were discussed and related to their likely connection with the mode of action of endogenous opiates. Dr. Fields concluded that understanding pain modulating systems has greatly contributed to our understanding of the neural basis of opiate action and vice versa.

Dr. Gebhart's presentation, also in the area of basic neuroscience, extensively reviewed recent research relative to stimulation-versus opioid-produced antinociception, starting with the results of focal electrical stimulation and direct administration of opioids into the midbrain (1970s). He also reviewed the discovery of opiate receptors and endogenous opioids and the state-of-the-art in our knowledge about them as well as the possible implications for analgetic mechanisms, neuroendocrinologic control, memory, and learning. It is likely that pain control involves not only endogenous opioid systems but nonopioid endogenous systems as well, and there was considerable discussion on this subject. Finally, Dr. Gebhart reviewed research on the brainstem organization of descending systems of antinociception. He cited the need for an integrated approach to pain research, that is, linking behavioral studies with neurochemical and electrophysiologic investigations.

Dr. houde, who discussed comparative clinical studies in pain management, has been unable to provide a paper for this monograph. Dr. Houde focused on the problems of the management of chronic clinical pain in cancer patients and emphasized the need for better phannacokinetic studies to determine the optimum balance for dose effectiveness vs. unwanted effects.

Dr. O'Brien pointed out the paucity of controlled outcome studies to evaluate the effectiveness of treatment. The significant advances in understanding the physiology and biochemistry of pain have not yet been translated into improved pain management at the clinical level. Dr. O'Brien reviewed the behavioral and psychological aspects of pain and the potential for some of the less conventional treatments, including classic conditioning, biofeedback, hypnosis, psychotherapy, patient-controlled analgesia, antidepressants, and neuroleptic drugs.

Dr. Mayer reported on basic research in the area of behavioral mechanisms of pain transmission, particularly the environmental activation of an analgesic system. Using a "footshock" model in rats, intriguing research has been performed delineating the neural circuitry and mechanisms involved in pain transmission.

Finally, in the last chapter of this monograph, Drs. Brown and Pinkert have summed up the discussions that took place over the course of the two-day meeting and the recommendations for future research.

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# Recent Advances in Research on Pain and Analgesia

Howard L. Fields, M.D., Ph.D.

The past two decades have witnessed remarkable progress in our understanding of pain mechanisms. Research breakthroughs have kindled renewed interest in the subject among both neuroscientists and clinicians. This has produced a marked expansion in the number of research projects related to the problem of pain. The increased knowledge and active research in pain have been complemented by similar progress in investigations of the mechanisms of opiate action. It is a particularly encouraging sign that a broad cross-section of the biomedical community has been recruited to the effort. Thus, anatomists, pharmacologists, neurophysiologists, psychologists, and biochemists as well as clinicians are now actively involved. In a sense, a new field of research has developed.

Progress has been made in two general areas: pain transmission and pain modulation. I would like just briefly to mention active research related to transmission and then focus on pain modulation.

**PAIN TRANSMISSION**

Research has focused on understanding both peripheral and central mechanisms. It is well established that, in peripheral nerves, pain is transmitted by small diameter myelinated and unmyelinatea nerve fibers whose central projections terminate primarily in the superficial layers of the spinal cord dorsal horn.

The circuitry of the superficial dorsal horn is an area under active investigation. There is evidence that small diameter primary afferents terminate on both second-order sensory projection cells (such as spinothalamic tract cells) and intrinsic interneurons. Some of the interneurons are probably excitatory relay cells (Bennett et al. 1979) and others are probably inhibitory interneurons (Gobel 1978). There are numerous interneurons in this region which contain enkephalin-like immunoreactivity and may be inhibitory (Hunt et al. 1981).

Another important area of research involves the immunocytochemical study of primary afferents to determine whether they contain putative peptide neurotransmitters. Small dorsal root ganglion cells and the superficial layers of the dorsal horn in which they terminate nave been shown to contain immunoreactive substance P, somatostatin and vasoactive intestinal peptide (Hokfelt et al. 1980). These findings raise the auestion of whether a particular peptide is associated with pain-transmitting primary afferents. In fact, there is an extensive body of evidence indicating that substance P is contained in nociceptive primary afferents (Henry 1976).

Other recent work has provided evidence identifying particular classes of primary afferent or central projection neurons as pain-transmitting using a combination of physiological and behavioral studies in primates combined with human psychophysical studies (Lamotte and Campbeli 1978). Unfortunately, a complete review of the subject is beyond the scope of this paper.

**PAIN MODULATION AND THE MECHANISM OF OPIATE ANALGESIA**

Accumulated experimental evidence has established that there is a network Within the brain that functions to selectively inhibit pain transmission. This network includes neurons at midbrain, medullary, and spinal levels, some of which contain opioid peptides. This analgesia system can be activated by narcotic analgesics such as morphine which presumably mimic the action of endogenous opioia peptides at synapses where they are normally released. Thus it is auite clear that advances in our understanding of the neural mechanisms of pain modulation and opiate analgesia are closely related.

For example, the identification of the opiate receptor depended on establishing that there is a similar relationship, in a series of compounds, between binding-affinity to brain membranes, efficacy on a bioassay (guinea pig ileum or mouse vas deferens), and analgesic potency in man (Kosterlitz 1977). Without a consistent and selective biological effect to guioe research it would not have been possible to extract and purify the first endogenous opioid peptides.

On the other hand, once these compounds had been discovered and sequenced (Hughes et al. 1975, Mains et al. 1977), antibodies to them were used to map their precise distribution in the brain and to serve as a guide to the study of pain-modulating systems. This approach will be discussed in more detail below.

In addition to this direct interdisciplinary interplay between the study of pain mechanisms and of the action of opiates, the pain modulation pathway can serve as a model for the cellular-neurophysiological mechanisms of opiate action. For example, evidence, to be discussed below, indicates that there are

both presynaptic and postsynaptic. opiatergic synapses that function in pain modulation. Certainly, tolerance to the analgesic action of opiates ooes occur and must involve these modulating systems. As the precise circuitry of these is elucidated, more sophisticated questions about in vivo tolerance can be posed. Although it is not certain where future scientific breakthroughs may come, it is clear thdt research into the neural mechanisms of opiate action will overlap extensively with that on pain modulation.

**Descending Pathways That Control Pain (see previous review, Fields and Basbaum 1978)**

In rats, electrical stimulation of the midbrain periaqueductal gray (PAG) suppresses pain-related behavior. This suppression appears to be selective for pain since, during stimulation, the animals are ambulatory and respond to other types of environmental stimuli. The existence of this selective pain-suppression system has been confirmed in a variety of species, but perhaps the most spectacular confirmation was in human subjects with severe, intractable pain. Electrical stimulation of the caudal diencephalon and midbrain PAG, which are analogous to analgesia sites in animals, produces a dramatic and often complete reduction of pain. The pain suppression in patients, as in animals, is highly specific. Most patients note no effects of stimulation besides analgesia, i.e., no arowsiness, no projected sensation, and no seizures or motor signs unless the electrode was near oculomotor pathways. The close anatomical correlation between the effective sites for pain suppression in man and other species and the Similarity in behavioral effects of stimulation again suggested that the study of the animal model would prove highly relevant to human pain.

What is the mechanism of this analgesia? Modulation of pain transmission could take place at any point from spinal cord to cortex. Since the spinothalamic tract, or, for that matter, any proven pain transmission pathway, does not pass throuogh the PAG, it is unlikely that the suppression actually occurs at the site of stimulation in the PAG. In fact, lesions restricted to the PAG or injection of local anesthetic into the PAG does not impair pain sensation. Thus stimulation of the PAG must cause <u>active inhibition</u> of pain transmission at some <u>other</u> point in the nervous system.

These observations established that there is an identifiable pain suppression system and served as the impetus to search for the anatomy and physiology of pain suppression. One of the earliest observations bearing on this problem was that stimulation of midbrain sites effective for analgesia inhibited spinal pain-transmission neurons. This indicated that a descending pathway from brainstem to spinal cord was involved in the pain suppression. This hypothesis was confirmed by the observation that partial lesions of the spinal cord at midthoracic levels blocked analgesia below the lesion. In rats, the effective lesions are restricted to the dorsolateral funiculus (DLF) (Barton et al. 1980). A large proportion of DLF axons originate in the

ventromedial medulla, including the nucleus raphe magnus and the adjacent reticular formation, and we showed that cells in this region project specifically through the DLF to terminate in precisely those regions of the spinal dorsal horn which contain the neurons responding maximally to painful stimulation (Basbaum and Fields 1978, Basbaum and Fields 1979). Electical stimulation of the medullary raphe nuclei powerfully and selectively inhibits pain transmission neurons in the spinal cord dorsal horn and produces behavioral analgesia. Thus these raphe nuclei in the medulla oblongata are a crucial direct link for the modulation of pain. Subseauent studies have aemonstrated a direct, excitatory connection from the PAG to the raphe magnus (Behbehani and Fields 1979). More recently, large inputs from frontal cortex, amygdala am hypothalamus to tne PAG have been demonstrated (Hardy and Leichnetz 1981, Beitz 1982).

**Endogenous Opioid Peptides (Cox 1982)**

Endogenous opioid substances are compounds that are synthesized in the body and have actions similar to narcotic analgesics such as morphine. The best characterized of the endogenous opioias are the pentapeptides leucine (leu) and metnionine (met) enkephalin (enk) and the 30 amino acid compound, beta-endorphin. Leu and met enk were the first endogenous opioids to be discovered (Hughes et al. now known to be present in the gut, adrenal medulla, and autonomic 1975). They were first extracted from the brain, although they are flervous system. Beta-endorphin (BE) was first discovered in the pituitary but has subsequently been shown to be present in the hypothalamus as well.

Both BE and the enkephalins bind with high affinity to opiate receptors and both produce analgesia When injected into the ventricular system. BE is a potent analgesic as are metabolically stable synthetic enkephalin analogs (e.g. D-Ala-D-leu enk) (Morley 1980).

Peptide transmitters are usually derived from larger precursor molecules that are synthesized in the cell body. BE is derived from a large molecule (pro-opiomelanocortin) that is also a precursor for at least two other biologically active peptides (ACTH and $\alpha$-MSH) (Mains et al. 1977). Although BE contains the sequence for met-enk (figure 1), it is <u>not</u> a precursor for the shorter peptide. The enkephalins have a different precursor (proenkephalin). BE is present in a single contiguous population of cells in the diencephalon. Although wiaely distributed in the brain, neither leu- or met-enk is present in this population of BE-containing cells.

On the other hand, leu- and met-enk overlap almost completely in their anatomical distribution. In fact, there is biochemical evidence, in the adrenal medulla, that leu- and met-enk are derived from a common precursor (Jones et al. 1982). If this is also the case in the brain, antibodies to either met- or leu-enk

FIGURE 1

SEQUENCES OF ENDOGENOUS OPIOID PEPTIDES

INVOLVED IN PAIN MODULATION

| | |
|---|---|
| Leucine-enkephalin | Tyr-Gly-Gly-Phe-Leu-OH |
| Methionine-enkephalin | Tyr-Gly-Gly-Phe-Met-OH |
| ß-endorphin | Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys-Asn-Ala-Ile-Val-Lys-Asn-Ala-His-Lys-Gly-Gln-OH |
| Dynorphin | Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Try-Asp-Am-Gln-OH |
| α-neoendorphin | Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Tyr-Pro- |

might label all cells that contain the precursor. whether both enkephalins are released from the same nerve terminals and act post-synaptically at the same receptor remains an open question.

Another opioid peptide, dynorphin, has recently been discovered (Goldstein et al. 1981). Dynorphin is a 17 amino acid peptide, the first five residues of which are leu-enk. Dynorphin is derived from a third endorphin precursor which also gives rise to alpha-neoendorphin (Kakidani et al. 1982). Though there is some overlap (see below), dynorphin's anatomical aistribution is largely distinct from that of either BE or the enkephalins.

In summary, there are at least three distinct families of endogenous opioid peptides. They are coded by separate genes, occur in different cell groups in the brain, and may have distinct biological functions. We will focus on the evidence that links endogenous opioid with the modulation of pain below.

**Opiate Receptor and Analgesia**

Prior to the characterization of opiate binding sites in the brain, synthetic modification of the opiate molecule had produced compounds with a broad range of analgesic potency. Knowledge of structure-activity relationships, especially of rank-order of potencies for a number of these opiate agonists, was used to establish that particular binding sites in the brain were involved in opiate analgesia (Kosterlitz 1977). Thus it was determined that the opiate binding site relevant to analgesia is stereospecific and of high affinity.

It was subsequently demonstrated that brain membrane preparations show just such high-affinity, saturable, stereospecific binding sites for opiate agonist and antagonists. Moreover, among a group of narcotic analgesics there is a positive correlation between binding affinity and analgesic efficacy. Dextrorotary isomers of opiates neither bind with high affinity to these sites nor have any biological activity.

There is now evidence for at least two, and possibly three, biologically significant binding sites. The two best characterized binding sites, '"mu" and "delta" (d), are defined primarily by differences in rank order of potency of various opioids to displace a high affinity labeled ligand from one or the other binding site (Chang and Cuatrecasas 1979). Available ligands show, at best, only relative specificity for mu and delta binding sites. Autoradiographic methods indicate that there is significant anatomical overlap of mu and delta binding sites (Herkenham and Pert 1980). It has in fact been suggested that the two binding sites are physically linked, i.e., that there is a single, two site receptor (Lee and Smith 1980). Part of the solution of this problem of linkage of the two binding sites lies in the development of more specific mu and delta ligands. It could then be determined whether the location of the two binding sites is identical. Except

for the demonstration that certain types of neuroblastoma cell cultures contain only delta binding sites, it has not been possible to show clearly that the two binding sites are totally separate.

If there are two binding sites and possibly two distinct receptors, are their functions different? There is evidence that mu ligands are potent analgesics. Whether the delta receptor is related to analgesia is more complex. Both potent analgesia and antagonism of opioid analgesia have been reported after intracerebroventricular administration of d ligands. Tung and Yaksh (1982) have recently shown that, in morphine-tolerant rats, D-ala-D-leu-enkephalin (a relatively specific delta ligand) remains a potent analgesic. This suggests that both mu and delta sites are relevant to analgesia.

The existence of the kappa (k) receptor was originally proposed by Martin (1976) on the basis of distinct actions of the prototype k agonist, ketocyclazocine. In the chronic spinal dog both morphine and ketocyclazocine produce miosis and depression of nociceptive reflexes with sedation, but only morphine causes hypothermia and bradycardia. With repeated administration, tolerance to both drugs occurs, and all of these effects are blocked by the antagonists naltrexone and naloxone. However, when morphine-tolerant dogs are withdrawn from morphine, ketocyclazocine does not supress the morphine abstinence syndrome, indicating that the two drugs act at separate receptors. Further confirmation that the k and mu receptors are distinct has recently been provided by studies aemonstrating high affinity selective kappa binding sites (Kosterlitz and Patterson 1980). Perhaps the most fascinating aspect of k agonists is that they may have a distinctly higher analgesic potency on tests of nociception that use mechanical stimuli (Upton et al. 1982, Tyers 1980). This contrasts with mu agonists which are more effective than k agonists on tests emloying noxious heat as the painful stimulus. Perhaps the different receptor-mediated systems control different modalities of pain sensation or different types of responses to noxious stimulation. Support for this hypothesis comes from studies showing that k agonists produce analgesia largely through a direct spinal action, whereas systemic morphine's effect (see below) on spinal nociceptors has both a supraspinal and a spinal component (Wood et al. 1981).

**Relationship Between Endogenous Opioids and the Intrinsic Analgesia System (Fields 1982)**

The intrinsic analgesia system can be thought of as a discrete anatomical entity running from the frontal cortex and limbic system through the periaqueductal gray and ventromedial medulla to the superficial layers of the dorsal horn. With the possible exception of the cortex, endogenous opioid peptides are present at all levels in this system. Enk is present in either cell bodies, terminal fields, or both, in amygdala, hypothalamus, midbrain periaqueductal gray, ventromedial meduila (including the serotonergic nucleus raphe magnus), and in the superficial layers of the dorsal horn.



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Opiate receptor is also present in high concentrations in all these regions (with the possible exception of the ventromedial medulla (Herkenham and Pert 1980). BE runs from cell bodies in the hypothalamus to the amygdala, midbrain periaqueductal gray, locus coeruleus, and ventromedial medulla.

In recent work Watson and coworkers (1982) have been able to demonstrate in the rat that although the anatomical distribution of aynorphin immunoreactivity largely parallels that of leu-enk in the pain-modulating system, it does differ in some respects. Dynorphin has a more ventral location in the PAG, and dynorphin cell bodies are not present in the nucleus raphe magnus or n. reticularis paragigantocellularis. Whether dynorphin and leu-enk coexist in some cells is, at present, unknown. Thus all three known classes of opioid peptides are found in one or more sites known to be part of the intrinsic analgesia system.

The anatomical association of opioid peptides and opiate receptor with this pain suppression system taken together with the well-known analgesic action of opiate alkaloids suggests that the opioid peptides are crucial for pain modulation under "physiological" conditions. A major effort has been directed at confirming this concept and determining how opioid peptides act to produce analgesia. Experimental strategies have been developed at several levels; cellular/biophysical, ultrastructural, behavioral, clinical (subjective), and neurophysiological. A unifying conceptual thread has been tne use of anatomy, immunocytochemistry, and pharmacology to relate findings from different types of experiments.

Microstimulation and microinjection for mapping analgesia-producing sites. Stimulation-produced analgesia (SPA) gave the first clue that there is an intrinsic analgesia system. The first region stimulated was the midbrain periaqueductal gray, which is rich in enkephalins, BE, and opiate receptor. The midbrain region effective for SPA extends rostrally into the medial diencephalon. There is strong evidence that the endogenous opioids in this region are involved in analgesia; first, SPA from this region is blocked by the opiate antagonist naloxone. Second, this region is very sensitive to the analgesia-producing action of locally microinjected opioids. Third, in man, SPA is associated with a marked rise in CSF BE-like immunoreactivity (Hosobuchi et al. 1979). Thus, endogenous opioias produce analgesia when injected into the PAG; they are normally present in the PAG and are released concomitant with SPA. Further, SPA is blocked by naloxone.

Activation of cells in tne PAG excites cells in the medulla that, in turn, project to the spinal cord to produce analgesia by inhibition of pain-transmission neurons (Fields and Basbaum 1978, Behbenani and Fields 1979). It is of interest that the medullary region, which contains the pain-modulating relay neurons, is rich in enk terminals and also has enk-containing cells that project to the spinal cord (Bowker et al. 1981). Furthermore, in single

neurons of this region, coexistence of 5HT with either substance P or enk has been aemonstratea by double-labeling techniques (Hokfelt et al. 1978).

If the system outlined above does produce analgesia and if the enkephalinergic neurons are involved, it should be possible to produce analgesia by activation of these neurons. We have employed the method of monopolar microstimulation to produce SPA in the rostral ventromedial medulla (RVM) (Zorman et al. 1982). In lightly anesthetized rats, the tail-flick reflex to noxious heat is present at normal latency and can be blocked by stimulation of the RVM at intensities of 10 μA (50 Hz, 400 μs pulses, continuous). Using stimulating currents this low it is possible to state that the behavioral effects are due to activation of neural elements within RVM. When low threshold SPA sites in the rostral RVM are plotted, they overlap with the location of cells projecting via the DLF to the superficial layers of the dorsal horn.

The use of the microstimulation technique gives a very fine-grained map of RVM SPA sites, but electrical stimulation is nonselective, in that any type of locally excitable neural element may be activated. One approach to this problem is to chemically activate local neurons. This is done by stereotaxically implanting cannulae near the target neurons and microinjecting small volumes of fluid. Opiate microinjection in the RVM does produce potent analgesia (Akaike et al. 1978, Azami et al. 1982). This strongly suggests that the anatomically demonstrated enk in the RVM does play a role in the descending pain-modulating systems.

A very important new approach to experimental studies of pain modulation was developed by Yaksh and Rudy (1976). They showed that an intrathecal cannula could be placed at any point along the spinal cord. Since the descending pain-modulating system could be activated in brainstem and its action manifest at spinal levels, the possibility arose of studying the pharmacology of the pain-modulating system at its output end.

Autoradiographic, immunohistochemical, and biochemical studies have shown that the superficial layers of the dorsal horn are densely packed with enk terminals and opiate receptors. Most of the enkephalin-containing terminals in the superficial dorsal horn derive from local interneurons. Some of these enkephalin interneurons have been shown to synapse onto identified spinothalamic tract cells (Ruda 1982). Opiate microinjection directly on the cord produces analgesia in animals (Yaksh and Rudy 1976) and in man (Wang et al. 1979). Furthermore, iontophoresis of morphine or enkephalin into the superficial dorsal horn selectively inhibits noxious input to dorsal horn cells (Duggan et al. 1976).

There is evidence that opiates produce analgesia, in part, by acting on opiate receptors located on the terminals of nociceptive primary afferents. In support of this concept is the observation that opiates reduce substance P release from dorsal horn tissue in vitro (Jessell and Iversen 1977) and from cultured dorsal root

ganglion cells (Mudge et al. 1979). As of this writing, however, there are no reports of opioid peptide-like immunoreactivity in the presynaptic element of an axo-axonic synapse in the dorsal horn of the spinal cord.

We have proposed tnat medullospinal neurons activate enkephalinergic interneurons which in turn inhibit pain transmission (Basbaum and Fields 1978). We recently tested this hypothesis by using the specific opiate antagonist naloxone applied directly to the spinal cord co reverse SPA from the RVM. A low dose (15-20 μg) of naloxone reverses SPA when applied to the lumbosacral cord but not when appliea to the cervical cord. Lumbosacral naloxone also effectively blocks the analgesia produced by morphine injected into the fourth ventricle (Levine et al. 1982).

To summarize briefly, endogenous opioid peptiaes are closely associated with the pain-modulating network at diencephalic, midbrain, meoullary, and spinal levels. Opiate microinjection at any one of these levels produces analgesia as does electrical stimulation of the rostral sites. Several observations indicate tnat tnis network is activated by systemically administered opiates to produces analgesia. First, naloxone injected into brainstem sites reverses the analgesic action of systemically administeted morphine (Azami et al. 1982). Second, spinal (Barton et al. 1980) or brainstem (Prouafit and Anderson 1975) lesions markedly reduce morphine analgesia. Finally, this hypothesis is strongly supported by the work of Yeung and Rudy (1980) who showed that whereas microinjection of morphine at either brainstem or spinal cord produced submaximal analgesia, simultaneous microinjection of virtually ineffective doses at both sites produces a potent analgesia. Not only are both structures implicated but this observation implies that they are interconnected. These results also imply that understanding the network properties of the intrinsic analgesia system will be crucial to elucidating the neural mechanisms of opiate analgesia.

The general approach outlined above has been to study the behavioral consequences of electrical stimulation of anatomically defined pathways, and then identify histochemically the component neurons of the pathway. The final steps are to activate the system and selectively block peptiaergic neurons by local injection of antagonists or to mimic their action by local application of agonists. The results strongly implicate particular groups of opioid peptide-containing neurons in pain modulation.

Electrical or chemical stimulation of groups of medullary neurons may or may not produce behavioral events that are of physiological significance. Further information on this question can be derived from recording the activity of neurons in SPA-producing regions. We have used a technique originally developed for studies of the motor system (Asanuma et al. 1968). Briefly, using the preparation described above, the metal micro-electrodes can be used for mapping SPA sites and then for extracellular recording of neurons at those sites.

We have mapped receptive fields for neurons in analgesia-producing sites in RVM using physiological stimuli such as brushing, tapping, pinching with toothed forceps, and noxious heat. The activity of most of the cells in this region is significantly affected by intense stimuli (either increasing or decreasing their discharge), and many increase or decrease their discharge when morphine (5mg/kg) is injected systemically (see Gebhart 1982 for review).

It is now clear that in awake-behaving rats noxious stimuli or stress can activate the opioid-mediated descending analgesia network. This indicates that the system can act under "physiological" conditions. It would be important to show that the activity of RVM neurons is increased under various conditions that produce analgesia; for example, during stress and when morphine is given.

**ENDOGENOUS OPIOIDS AND PAIN MODULATION IN MAN**

It is important to demonstrate that the endorphin-mediated analgesia system is operative in man under physiologica conditions. The usual experimental approach to this problem has been to give the opiate antagonist naloxone and look for a worsening of pain. Lasagna (1965) presented the first data suggesting that naloxone causes hyperalgesia, out conflicting reports appeared (El-Sobky et al. 1977, Grevert and Goldstein 1977). The method of pain evaluation that we have used is very simple: subjective pain is reported using the visual analog scale (a 10 cm line with 0 pain on the right and "worst pain ever" on the left.) Using this method and a double-blind crossover design produces a significant increase in reported pain severity compared to placebo (Levine et al. 1978a). The effect in this clinical situation requires a relatively higher dose of naloxone (8 mg i.v. per patient) than is usual for treating narcotic overdose (0.4-0.8 mg) .

Although the naloxone hyperalgesia described above is seen when data from indiviauals are pooled, more striking changes are revealed when subjects are categorized. Thus, we have presenteo evidence that naloxone produces significant hyperalgesia in placebo responders, but has no effect in placebo non-responders (Levine et al. 1978b). Furthermore, consistent with our neuropnysioioglcal studies, there is some evidence that a positive placebo response (which may represent activation of the endorphin-mediated analgesia system (EMAS) ) is more likely to occur in patients reporting more severe pain levels just prior to receiving a placebo (Levine et al. 1979).

Other manipulations whicn have been reportea to produce naloxone-reversible analgesia include acupuncture (Mayer et al. 1977) and transcutaneous electrical stimulation (Sjolund and Eriksson 1979).

It should be stressed that the use of naloxone provides only indirect evidence that a function is mediated by endogenous opioid peptides. Naloxone may have actions unrelated to opiate

antagonism. Other approaches that can be used are to look for cross-tolerance between opiates and the analgesic manipulation in question, to look for endogenous opioid peptide release concomitant with analgesia, and to determine whether the anatomical substrate that underlies the analgesia produced by that manipulation is associated with endogenous opioid peptides.

## CONCLUSION

The past decade has seen major advances in our understanding of pain. Most of this advancement has been due to the related discoveries of an endogenous pain-modulating system and of the endogenous opioid peptides that contribute to its function. The explosion of knowledge in this field is the result of a convergence of different approaches and scientific disciplines to a set of related problems that involve the neural mechanism of opiate action.

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# Recent Developments in the Neurochemical Bases of Pain and Analgesia

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**BACKGROUND**

Several developments in the recent past have been germinal to the rapid growth in our understanding of the central sites and mechanisms of nociception and antinociception. In the early 1970's, focal electrical stimulation and opioids given directly in the midbrain were demonstrated to be antinociceptive. The second major advance was the demonstration in the central nervous system of opiate receptors and the subsequent discovery of endogenous opioids.

**Stimulation- and Opioid-Produced Antinociception**

The initial stimulus for the recent past productive research activity in mehanisms of antinociception can be traced to the report by Reynolds (1969) that focal electrical stimulation in the midbrain periaqueductal gray matter (PAG) produced an antinociception in rats. The nature of this "stimulation-produced analgesia" (SPA) was subsequently characterized in non-human animals in other laboratories (e.g., Gebhart and Toleikis 1978, Lewis and Gebhart 1977a, Mayer and Liebeskind 1974, Oliveras et al. 1974) and shortly thereafter extended to and successfully employed in man for the relief of pain (e.g., Hosobuchi et al., 1977). Stimulation in the PAG also inhibits the ncciceptive responses of spinal cord dorsal horn neurons (Carstens et al. 1979, 1980, Liebeskind et al. 1973, Oliveras et al. 1974) and it is generally held that such descending inhibition is necessary to the antinociception evoked in the brain stem (cf. Fields and Basbaum 1978). In both the behavioral and electrophysiologic studies, the data have been generally interpreted to provide evidenoe for the selectivity of the effects of electrical stimulation for ncciception and nociceptive neurons, respectively. There is some disagreement on this point, however, since stimulation at sites in and around the PAG which inhibit spinal

nociceptive responses do not produce an antinociception or are aversive in the behaving animal. For example, Liebeskind et al. (1973) reported early on that the distribution of stimulation sites in the midbrain of the cat which inhibit spinal nociceptors was wider than the distribution of stimulation sites from which an antinociception could be produced, including two sites in the midbrain which produced aversive responses when stimulated. In the behaving animal, SPA is generally considered not to produce a generalized sensory, motivational, attentional or motoric deficit (Mayer et al. 1971, Mayer and Liebeskind 1974, Yeung et al. 1977); that is, the antinociception is considered to be selective. This interpretation is supported by reports indicating that SPA is often expressed as an anatomically restricted field of hypoalgesia (Mayer and Liebeskind 1974, Soper 1976, Soper and Melzack 1982) and also that animals are capable of performing other motivated behaviors during SPA (Soper 1976).

Tsou and Jang (1964) were the first to report that an opioid (morphine) microinjected into brain tissue produced an antinociception. After a delay of several years (and after the initial report on SPA), other laboratories characterized the distribution of sites in the brain where opioids were antinociceptive (e.g., Lewis and Gebhart 1977a, Yeung et al. 1977) and it was established that the antinociception produced by morphine microinjected into the PAG was a specific opioid effect. The microinjection of other non-opioid, central nervous system depressants (e.g., pentobarbital, chlordiazepoxide) and of local anesthetics was found not to influence nociceptive behavior in a variety of analgesiometric tests (Lewis and Gebhart 1977a, Yaksh and Rudy 1978). Following these reports, the antinociception produced by stimulation and opioids given in the PAG was compared and it was demonstrated that stimulation-produced and opioid-induced antinociception shared many common characteristics (cf. Mayer 1975, Mayer-and Price 1976, Watkins and Mayer 1982):

- antinociceptive tolerance to the repetitive administration of morphine or stimulation in the PAG (cf. Mayer and Price 1976);
- development of cross-tolerance between stimulation and morphine given in the PAG (Mayer and Hayes 1975; however, see Lewis and Gebhart 1977b);
- partial antagonism of SPA by the opioid antagonist naloxone (cf. Watkins and Mayer 1982); and
- additivity of sub-antinociceptive doses of morphine with SPA (Samanin and Valzelli 1971).

Reports of these findings spawned neuroanatomic and neurophysiologic investigations revealing that there existed only limited direct spinopetal efferents from the PAG and that the ventromedial medullary raphe nuclei and adjacent areas were important to the antinociception and descending inhibition evoked from the PAG. Thus, it was generally believed that the effects of morphine and stimulation given in the PAG were exerted via a relay in the medulla; the medullary area most prominently implicated was the nucleus raphe magnus (NRM) (cf. Basbaum and Fields 1978,

1980, Fields and Basbaum 1978, 1979). It was demonstrated that focal electrical stimulation in the NRM produced an antinociception (Oliveras et al. 1975, 1979) and, like stimulation in the PAG, also inhibited the nociceptive responses of spinal cord dorsal horn neurons (Deal) et al. 1976, Fields et al. 1977, Guilbaud et al. 1977). Further, it was demonstrated that neurons in the NRM were excited by morphine, glutamate, and electrical stimulation given in the PAG (Behbehani and Fields 1979, Fields and Anderson 1978, Lovick et al. 1978, Mohrland and Gebhart 1980a). This led to proposals that the PAG and NRM were nodal points in an endogenous antinociception-producing system, and that the antinociception evoked in the PAG relied on a medullary relay in the NRM. The ultimate expression of the antinociception fmn the brain stem was considered to be dependent upon the spinopetal efferents of the NRM carried in the spinal cord dorsolateral funiculus (DLF) (cf. Fields and Basbaum 1979). Since the NRM, like other raphe nuclei, is rich in serotonin-containing neurons, and since there are serotonergic projections from the PAG-dorsal raphe to the NRM (cf. Fields and Basbaum 1979, Gebhart 1982, Willis 1982), serotonin was considered to be the primary transmitter involved in this descending antinociceptive system. This interpretation was consistent with a large earlier body of literature implicating serotonin in the antinociception produced by morphine (cf. Messing and Lytle 1977) and also with data suggesting the modulation by serotonin of SPA (cf. Besson et al. 1981). Further, because the opioid antagonist naloxone attenuated the antinociception produced by stimulation either in the PAG or NRM (e.g., Zoman et al. 1981, 1982), an enkephalinergic synapse was believed to be present between the PAG and NRM or in the spinal cord dorsal horn between descending serotonegic raphe-spinal fibers and primary afferent nociceptive input.

The preceedihg is a superficial overview of events leading up to the topic of this essay. The material is reviewed in greater depth in several other sources (e.g., Gebhart 1982, Mohrland 1982, Willis 1982).

**Opiate Receptors and Endogenous Opioids**

The second major development in this field was the demonstration, in the central nervous system, of selective, stereospecific, saturable and reversible binding sites for opiates (Pert and Snyder 1973, Simon et al. 1973, Terenius 1973). Although then already called "opiate receptors," it was not until more recently that these binding sites have been accepted to be in fact receptors; that is, that a pharmacologic effect results fran the binding of an opioid to these sites. These receptors were demonstrated to be localized in areas of the central nervous system important to nocieption/antinociception (as well as in other areas of the central nervous system and in smooth muscle associated with the non-analgetic effects of opioids). It is now believed that there are as many as six subclasses of opiate receptors, the more important ones are named mu, delta

and kappa. These different opiate receptors are heterogeneously distributed in the central and peripheral nervous systems and are considered to subserve different roles for different opioid agonists. Further discussion is beyond the scope of this essay; specific information is available elsewhere (e.g., Miller 1981, Wood 1982).

Complementing the demonstration of opiate receptors in the mammalian CNS was the discovery of endogenous opioid-like peptides in brain (Hughes 1975, Simantov and Snyder 1976). These pentapeptides were subsequently characterized and named methionine-enkephalin and leucine-enkephalin. It is now believed that there are at least 3 different families of endogenous opioids: the.enkephalins, endorphins and dynorphins/neo-endorphins. The endorphin family is derived fran the large precursor proopiamelanocortin which is also the parent protein for adrenocorticotropin and melanocyte-stimulating hormones. The cell bodies of origin of the endorphins are localized in the medial basal hypothalamus which, in addition to giving rise to intracerebral endorphinergic fibers (to the PAG, for example), send the majority of fibers to the pituitary fran which the endorphins are liberated (cf. Miller 1981). Although the pentapeptide methionine-enkephalin sequence is contained within the 91 amino acid ß-endorphin peptide, leucine- and methionine-enkephalin are derived fran a separate pro-enkephalin precursor and not as breakdown products of ß-endorphin. The enkephalins, moreover, are distributed differently fran the endorphins and exist separately. For example, hypophysectomy will significantly reduce levels of endorphins, but fails to affect the central nervous system content of enkephalins (Krieger et al. 1977). The final endogenous opioid family, the dynorphins/neo-endorphins, is less well understood at present than either the endorphins or enkephalins. The leucine-enkephalin sequence is present at the N terminus of dynorphin-(1-13) and -(1-17), but the enkephalins are not considered to be derived from the dynorphins. Dynorphin-(1-13) is a very potent opioid in some systems (Goldstein et al. 1979), but unlike the enkephalins and endorphins it does not produce an antinociception when administered directly in the PAG (Walker et al. 1980). The function of the dynorphins, and for that matter the enkephalins and endorphins, is not well understood at present. It has been hypothesized that the enkephalins participate generally in the inhibition of release of a variety of other neurochemicals (e.g., acetylcholine. substance P. thyrotropin-stimulating hormone and that this enkephalinergic modulation occurs via an inhibitory interneuron acting presynaptically in the central nervous system (cf. Nicoll et al. 1980).

**CURRENT UNDERSTANDING OF THE NEUROCHEMICAL MEDIATION OF ANTINOCICEPTION**

It is presently clear that endogenous enkephalins and the monoamines norepinephrine and serotonin are involved in the antinociception evoked in the brainstem either by stimulation or the microinjection of morphine. Further, there appear to be

multiple systems for the production of "analgesia" in which the same as well as other neurochemicals may be involved (Watkins and Mayer 1982, Mayer, this volume). The remainder of this essay will discuss the neurochemicals possibly involved in the antinociception evoked from the brainstem and recent develop ments in our understanding of the organization in the brainstem of descending systems of antinociception.

**Neurochemicals and Antinociception**

The conclusion drawn from initial studies was that descending fibers of the serotonin-containing neurons of NRM were necessary to morphine induced antinociception. This conclusion was based on studies in which the NRM was destroyed electrolytically; the antinociceptive efficacy of systemically administered morphine was significantly attenuated in these studies (Chance et al. 1978, Proudfit and Anderson 1975, Yaksh et al. 1977). Recent investigations, however, have questioned the role played by the NRM and serotonergic raphe-spinal neurons in the antinociception produced by morphine (e.g., Proudfit 1980, Proudfit and Hammond 1981). Thus, it has been suggested that serotonin in the NPM may not be necessary for the expression of morphine-induced antinociception. This is further supported by reports that the neurotoxic (5,7-dihydroxytryptamine) destruction of the serotonin-containing neurons in the NRM does not affect morphine-induced antinociception in some analgesiometric tests (e.g., tail-flick), while the efficacy of morphine in the hot-plate test is unaffected (Mohrland and Gebhart 1980b, Pert et al. 1980). It is now clear that morphine exerts central antinociceptive actions at both the spinal and supraspinal levels (cf. Yaksh and Rudy 1978, Yaksh 1981) and thus the central level of organization of the response to nociceptive input is important to the results reported. Alternatively, transmitters of raphe spinal neurons other than serotonin are important. Initially, serotonin and substance P ware shown to co-exist in the same neurons in the NRM (Chan-Palay et al. 1978, Hokfelt et al. 1978). Consequently, consideration was given to the involvement of substance P in the antinociception evoked fron or through the NRM. Supportive evidence was provided by the report that systemically administered morphine increased the content of substance P in the NRM, but did not affect the content of either serotonin or its metabolite, 5-hydroxyindole acetic acid (Lakoski et al. 1980). It was suggested, therefore, that morphins had a selective effect on different types of neurons in the NRM. Additional support for a role for substance P in antinociception is provided by reports that substance P produces an antinociceptive effect when given systemically, intraventricularly, intrathecally or in the PAG (Doi and Juma 1982, Malick and Goldstein 1978, Mohrland and Gebhart 1979). The role of substance P in a descending antinociceptive system remains uncertain, however, and is complicated by convincing data suggesting that substance P is a transmitter of small diameter primary afferent (nociceptive) fibers in the spinal dorsal horn (cf. Jessell 1981).

The picture is further complicated by recent reports of the presence of other peptides in the medial medulla, some existing independent of and others existing together with serotonin. It has been recently estimated that 85% of the neurons of the raphe-spinal system of the rat CNS contain serotonin; approximately half of those serotonin-containing neurons also contain substance P, while approximately 15% contain thyrotropin-stimulating hormone or enkephalin in addition to serotonin (Rocker et al. 1982). It is estimated that the remaining 15% of the neurons of the raphe-spinal system contain either substance P, thyrotropin-stimulating hormone, enkephalin, acetylcholine, or other peptides, but not serotonin. The distribution of these peptides is not homogeneous in the medulla, and it is concluded from such anatanical evidence that multiple transmitter complexes exist in the medulla, the functions of which are presently unknown

In addition to serotonin and peptides in the medulla, norepinephrine is also present in descending systems from the brainstem to the spinal cord and is implicated in the modulation of nociceptive processing (cf. Yaksh et al. 1981). For example, norepinephrine as well as serotonin is released in the lumbar spinal CSF by morphine and electrical stimulation given in the PAG (Yaksh 1979, Yaksh and Tyce 1979). Further, both norepinephrine and serotonin produce an antinociception when administered intrathecally (Reddy and Yaksh 1980, Yaksh and Wilson 1979) and also significantly attenuate the noxious-evoked responses of dorsal horn neurons when administered iontophoretically (Belcher et al. 1978, Headley et al. 1978, Randic and Yu 1976). Monoaminergic involvement in nociception/antinociception in the spinal cord is also supported by studies employing pharmacologic antagonism of presumably post-synaptic monoaminergic receptors. The intrathecal administration of serotonergic (e.g., methysergide) or noradrenergic (e.g., phentolamnine) antagonists partially attenuates the antinociception produced by morphine microinjected in the PAG (Yaksh 1979, Yaksh et al. 1976). That both norepinephrine and serotonin independently play a role is supported by the complete antagonism of morphine's effect when both antagonists are given concurrently (Yaksh 1979). Additional data suggesting a separate role for norepinephrine include reports that **α**-adrenergic agonists (e.g., clonidine) are antinociceptive when administered in the NRM (Sagen and Proudfit 1982) and intrathecally (Reddy and Yaksh 1980, Reddy et al. 1980). The antinociception produced by serotonin and **α**-agonists is not antagonized by the opiate antagonist naloxone (cf. Yaksh et al. 1981). Additionally, the antinociception produced by the intra-NRM administration of the noradrenergic antagonist phentolamine was antagonized by the intrathecal administration of the serotonergic antagonist methysergide (Hammond et al. 1980). Taken together, such data indicate that both norepinephrine and serotonin are involved in antinociceptive mechanisms at both spinal and supraspinal levels and may function independently of enkephalinergic "systems." Indeed, Tyce and Yaksh (1981) suggest that norepinephrine and serotonin

participate in an intrinsic non-opioid system capable of modulating nociceptive transmission. This hypothesis derives from studies in the cat where peripheral nerve stimulation at intensities activating high threshold Aδ and C "pain" fibers was demonstrated to significantly increase the content of both monoamines in superfusates of the spinal cord; "non-noxious" peripheral nerve stimulation was without effect on the contents of norepinephrine and serotonin in the spinal cord superfusates. The effects of somatic stimulation were unaltered by naloxone, again indicating that monoaminergic systems which may be involved in the processing of nociceptive information may exist independently of, as well as perhaps in concert with, opioid-mediated systems.

Data from studies examining SPA suggest a similar conclusion. Focal electrical stimulation in both serotonin- and norepinephrine-containing cell groupings in the brainstem has been repeatedly reported to be antinociceptive (cf. Besson et al. 1981, Oliveras et al. 1979, Willis 1982). Not only have norepinephrine, serotonin, and endogenous opioids been implicated in SPA evoked from the PAG, dopamnine has also been suggested to contribute to the antinociception produced by stimulation in the PAG (Akil and Liebeskind 1975). Stimulation in the NPM produces an antinociception which can be antagonized by metysergide (Satoh et al. 1980) as well as by naloxone, whether administered systemically (Zorman et al. 1981) or intrathecally (Zorman et al. 1982). Stimulation in the medullary nucleus paragigantocellularis in the rat, an area lateral to the NRM, produces an antinociception which can be blocked by an α-adrenergic antagonist (Satoh et al. 1980). Thus, like the antinociception produced by morphine administered in the brainstem, norepinephrine, serotonin, and opioid-containing systems have all been implicated in the modulation of SPA, suggesting a complex, perhaps overlapping organization of descending systems of inhibition of nociceptive transmission (also see later section).

In summary, it is clear that norepinephrine as well as serotonin plays an important role in the modulation of nociception. The role of peptides, particularly those which might descend from supraspinal levels, is less clear. Although there are some descending enkephalinergic fibers from the medulla to the spinal cord (Hokfelt et al. 1979), the contents of enkephalins in the spinal cord dorsal horn are not significantly changed by spinal cord transection, indicating that the majority of enkephalinergic interneurons and/or terminals in the spinal cord dorsal horn arise from neurons intrinsic to the cord. Thus, the involvement of peptides may arise locally in the medulla or spinal dorsal horn. Further, many other putative modulators of nociceptive processing have not been considered in this essay. For example, GABA and/or glutamate may be involved in nocicep tion and antinociceptive mechanisms in the PAG (Sherman and Gebhart 1975, 1976). Lovick and Wolstencroft (1983) recently suggested that GABA is involved in the actions of the NRM in suppressing the responses of reticular neurons to noxious



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stimulation. There is also a literature detailing the role $Ca^{++}$ plays in the antinociception induced by morphine; the intracerebroventricular administration of $Ca^{++}$ reportedly antagonizes morphine-induced antinociception (Hano et al. 1964; Harris et al. 1975), and the content of $Ca^{++}$ in selected brain sites is increased during the development of tolerance to morphine's antinociceptive effect (Harris et al. 1976, Yamamoto et al. 1978). Thus, while we know far more today about neurochemical mediators "participating" in the antinociception induced by morphine and stimulation, we are still far fran fully understanding the mechanisms involved.

**Brainstem Organization of Descending Systems of Antinociception**

Until now I have focused upon the NRM as the bulbar relay between the PAG and the spinal cord responsible for the antinociception and descending inhibition of spinal nociceptive responses evoked fran the midbrain. However, efferents from the PAG also distribute to sites both dorsal and lateral to the NRM in the medulla (cf. Gebhart 1982). As stimulation in the NRM is antinociceptive and also capable of inhibiting spinal nociceptive neurons, so too does stimulation lateral to the NRM produce an antinociception or inhibition of noxious-evoked activity of dorsal horn neurons (Fields and Anderson 1978, Fields et al. 1977, Gerhart et al. 1981, Satoh et al. 1980). While transection of the DLF significantly attenuates the effects of stimulation in the NRM, transections of the DLF do not attenuate the effects of stimulation lateral to the NRM (Haber et al. 1980, McCreery et al. 1979). Therefore, it is apparent that at least two medullary systems of descending spinal inhibition exist. This helps to explain data suggesting that morphine and stimulation in the PAG may not be affecting the same system of descending inhibition, but rather affecting different systems similarly- For example, lesions bilaterally placed in the medullary reticular formation on either side of the NRM blocked the antinociception produced by morphine administered in the PAG but not that produced by stimulation at the same site in the PAG (Mohrland et al. 1982). In addition, depletion of serotonin and norepinephrine in the spinal cord failed to affect the efficacy of SPA evoked fran the PAG, but prevented expression of the antinociception produced by morphine microinjected in the PAG (Johannessen et al. 1982).

Stimulation in the PAG can also apparently activate two different systems of antinociception: stimulation in the ventral PAG-dorsal raphe produces an antinociception which can be antagonized by naloxone, while stimulation in the dorsal PAG produces an antinociception which is not antagonized by naloxone (Cannon et al. 1982). This result helps clarify confusion in the earlier literature regarding the controversy over whether naloxone antagonized SPA. Regardirg inhibition of nociceptive responses of dorsal horn neurons, lesions in the NRM alone do not affect the efficacy of stimulation in the PAG, and recent electrophysiolgic studies suggest that the descending inhibition evoked

from the PAG courses in a diffuse manner through the medulla medially and laterally (Gebhart et al. 1983, Gebhart and Sandkühler 1983). Thus, the functional organization and the neurochemical composition of the antinociception-producing/descending inhibitory system(s) is more complex than previously believed. Collectively, recent reports clearly question the notion of a single, selective system of descending antinociception and inhibition. They support, instead, the existence of multiple functionally heterogeneous antinociceptive and inhibitory influences (see also Mayer, this volume). A significant failing in earlier studies in this field was the absence of behavioral correlates to either the neurochemical or electrophysiologic indices examined. More investigations are currently correlating the neurcchemical and electrophysiologic data with behavioral measures of antinociception. Such integrated approaches to research problems in this field will help clarify what now appear to be contradictions or inconsistencies in the literature.

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# Behavioral and Psychological Components of Pain Management

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In recent years there have been significant advances in our understanding of the physiology and biochemistry of pain perception. Many of these are reviewed elsewhere in this monograph. However, these advances have thus far not been translated into improved treatment for the pain patient, particularly the chronic pain patient. On the whole, our review indicates that most chronic pain patients are treated by a combination of behavioral and psycholcgical tehniques which have not been objectively evaluated for efficacy. Moreover since the syndrome of chronic pain lacks a generally agreed upon classification system and severity rating system, it is difficult to reliably test new treatments as they are generated from the research labs. In this paper, we will review some of the techniques currently in use and comment upon the need for further research and evaluation.

**BEHAVIORAL**

Operant conditioning is believed to underlie a large part of pain-related behavior. The pain patient receives reinforcement in the form of attention and sympathy when he indicates the presence of pain. Fordyce and Steger (1979) nicely describe thee developement of pain-related behaviors in patients by an operant mechanism. In a sense the behaviors (moans, grimaces, limps) can be shaped by the people in the patient's environment. By the time the patient arrives at a pain clinic these behaviors may be central to the patient's life. A recommended treatment strategy in many pain clinics is to utilize operant conditioning to reshape the patient's behavior. This involves reward or reinforcement of "pain-incompatible behaviors" and nonreinforccment of pain-related behaviors. Treatment may take the form of a combined effort by all staff in a day treatment center and it should involve the training of family members to change their behavior relative to the patient with pain.

The approach to pain as a learned behavior is reported to be quite effective in several reports. The treatment has a well developed rationale and it is widely practiced in many pain

clinics. However, in our review we were not able to find any controlled treatment outcome studies that demonstrated efficacy.

We were not able to find evidence that classical conditioning is being used in the treatment of pain even though there is considerable evidence that the effects of opiate drugs are influenced by classical conditioning. Abraham Wikler (1973) described what he called counter-adaptive effects which were learned with reputed exposure to drugs. More recent investigations have shown that tolerance to opiates follows the rules of classical conditioning with environmental stimuli as the complex conditioning stimulus. Thus, Siegel (1978) has shown that opiates given repeatedly in the same environment (so that environmental cues reliably predict the onset of opiate effects) produce more tolerance than opiates given in a novel environment (so that environmental cues fail to predict the onset of opiate effects). Other investigators (O'Brien et al. 1977) have showm that opiate withdrawal effects can be conditioned and that, in some cases, opiate-like effects can be conditioned. others have shown that both alcohol and neuroleptics can also produce conditioned effects. Thus it is likely that the effects of many drugs used in the treatment of pain are influenced by conditioning. Conditioning is an area of research which has been well supported by NIDA over the years, probably because of its potential relationship to drug dependence. This phenomenon also has a relationship to the therapy of pain, but the principles of classical conditioning have yet to be investigated for potential usefulness in this area.

**BIOFEEDBACK**

The feedback of information concerning visceral or somatic responses, using a visual or audio analog, has been shown to enable human subjects to gain some degree of control over such responses. In the treatment of pain, electromyographic (EMG) biofeedback and temperature biofeedback have been the two modalities generally used. EMG biofeedback has been reported to facilitate the learning of muscular relaxation and this has been reported in several studies to be beneficial in such conditions as tension headaches, low back pain and temporomandibular joint pain. Case reports and small patient series are often found in the literature. For example, Peck and Kraft (1977) reported significant reduction of pain in twelve of eighteen patients with tension headaches and in one of eight back pain patients. They also reported improvement in three headache patients, three back and shoulder pain patients, and two patients with tempormandibular joint pain. This interesting report is typical of the biofeedback and pain literature. Unfortunately, there is no control group and no attempt to classify patients other than by the location of their pain.

Biofeedback has been used in contexts other than treatment of pain. For example it has been used in the treatment of anxiety and phobias as an aid to muscular relaxtion. It has also been used in the treatment of opiate withdrawal. Some research on these conditions has utilized control groups using noncontingent or "false" biofeedback. In these studies it has been found that there is a very potent nonspecific or placebo effect of biofeedback (Khatami et al. 1982). Moreover, it has been determined that many people can learn to relax their muscles without the aid of a biofeedback instrument.

Our review indicated that EMG biofeedback appears to be widely used in pain clinics throughout this country and it is generally believed to be effective (Khatami et al. 1979). However, controlled studies to prove efficacy are lacking. Temperature biofeedback has also been recommended for the treatment of migraine headaches. In this treatment, warming of the peripheral skin of a digit has been reported to be associated with improvement in headaches. Using the biofeedback technique the patient can learn to warm his skin and thus, possibly indirectly, affect the blood vessels within the brain. It should be noted that there appear to be significant placebo or nonspecific effects in this treatment and the actual efficacy remains uncertain. Of course, placebo effects can be quite useful in the treatment of pain and if it is determined that the use of elaborate and impressive biofeedback equipnent results in enhanced placebo effect, this is not necessarily a bad result. Unfortunately the literature seems to contain mainly anecdotal reports rather than controlled studies. Thus, distinctions between placebo effects and specific effects are difficult to make.

**HYPNOSIS**

Hypnosis is another technique which is frequently used as part of a comprehensive treatment program for the management of pain. There is ample evidence, from numerous experiments over the years, that hypnosis can relieve pain at least temporarily. The mechanism is uncertain, but two studies (Goldstein and Hilgard 1975; Barber and Nayer 1977) have found that naloxone failed to reverse hypnotic analgesia, suggesting that the endorphin system was not involved in those cases. In one report, naloxone did reverse hypnotic analgesia (Stephenson 1978). The role of hypnosis in the management of chronic pain is also not clear. Several authors have indicated that it is a useful technique in "good hypnotic subjects," particularly those who can be taught the technique of self-hypnosis (Barber 1982). Here again, evidence consists mainly of clinical case reports.

**PSYCHOTHERAPY**

Comprehensive pain clinics usually include a wide variety of psychotherapeutic techniques. In addition to individual psychotherapy, some form of family or marital therapy is often included. It is generally thought by clin!icians that the treatment of the pain patient should involve the patient's entire support system. Family conflicts often can be recognized which may have resulted from the disability produced by the pain or in some cases may have antedated the pain. These conflicts may produce anxiety and depression which aggravate the pain syndrome. In either case, family or marital therapy would be indicated as part of the comprehensive pain treatment program.

While psychotherapy is generally a part of the program, the type of psychotherapy is usually not well specified. Modern psychotherapy research often utilizes manual-guided psychotherapy so that each patient is receiving a known standard treatment technique. Manuals are available for supportive psychotherapy and cognitive-behavioral psychotherapy, two treatments which appear to be used in many pain clinics. Unless manuals are used, it cannot be certain that a standard treatment is being administered.

**PSYCHOTHERAPY OF THE PRESCIPTION OF ANALGESICS**

It is widely lamented in the medical literature (Angell 1982) that pain, particularly acute pain, is often undertreated by physicians. Perhaps many physicians have an aversion to spending time with patients in pain, trying to understand the nature of pain and the response or lack of response to treatment. Many physicians report a fear of producing addiction even in terminally ill cancer patients. These patients, therefore, are often undertreated so that they experience unnecessarily severe pain in their final days. On the other hand, one sees chronic pain patients who are, perhaps, too readily given potent analgesics without proper medical management. Clearly there is a great need for physician education regarding the treatment of pain.

A recent technical advance which utilizes many of the behavioral principles involved in pain management is the use of patient-controlled analgesia (Tamsen et al. 1982). In this method, patients suffering from acute pain are outfitted with a programable electric pump which controls intravenous infusions of morphine or another rapidly acting opioid. The patient is then able to activate the pump at will, causing the injection of a small quantity of opioid as needed. There is a tilt-in latency period, usually five to ten minutes, between injections

to prevent the possibility of overdose. Experience thus far with this technigue indicates that it usually results in a highly satisfactory level of pain relief. Total daily dosage is less than would occur with the usual"prn intramuscular" dosing, which is generally controlled by the nurse rather than the patient. Under the prn system, the patient may request a dose of analgesic when the nurse comes by, not because medication is really required, but because he recognizes that the nurse may be too busy to come promptly later when the medication is really needed. Controlled evaluations of patient-controlled analgesia are currently in progress.

The use of analgesics in the treatment of chronic pain presents quite different problems from usage in acute pain. Many of the patients presenting at chronic pain clinics already are quite tolerant to and dependent upon opioid drugs. In these cases the drugs may be providing relatively little in the way of pain relief, but they may be perpetuating their use through the onset of withdrawal symptoms as early as 4-6 hours after the last dose was received. The withdrawal symptoms create discomfort which is translated into a desire for drug. It is generally felt by pain clinics that detoxification is helpful in these cases (Taylor et al. 1980). One can switch the patient to a long acting opioid such as methadone. Methadone provides analgesia for no more than 4-6 hours, but it prevents the onset of withdrawalfor at least 24 hours. A common practice is to utilize a liquid form of methadone and then graduadlly reduce the dose while keeping the volume constant. Thus, the patient is not aware of the timing of each dose decrement although he generally realizes that one of the goals of treatment is detoxification. Using this method, there are many case reports indicating that success is often accompanied by an increase in the patient's feeling of well-being and even reduction in his concern about pain. While NIDA has supported several excellent studies on detoxification procedures from methadone maintenance programs, we were not able to find any controlled studies of the effects of detoxification in chronic pain clinics.

**PSYCHOACTIVE MEDICATION**

Antidepressant drugs, particularly amitriptyline and doxepin, are frequently used in the management of chronic pain. There is significant overlap between the syndromes of depression and chronic pain. several studies have found that 60-65% of depressed outpatients complain of physical pain (Ward et al. 1982). In pain clinics, a significant minority of patients show elevated depression scores on various psychological tests, but we were unable to find any systematic assessment of pain patients utilizing modern psychiatric nosology such as DSM-III or RDC

(Research Diagnostic) criteria. It is possible, therefore, that some of the patients in pain clinics who appear to be helped by antidepressant medication are really responding to treatment of their depressive syndromes. However,there are other postulated mechanisms.

There is a significant body of literature showing potentiation of the analgesic effect of opioid drugs by tricyclic antidepressants (TCA). Early work concentrated on antinociceptive activity of the TCA. Charpentier demonstrated high analgesic activity produced by TCA in animals in visceral, skin, and trigeminal areas. Sarnivaara and Mattila (1974) noted that tertiary tricyclics were inferior to morphine, but superior to secondary amine TCA in antinoceptive effect. They concluded that this effect was due either to a local anesthetic effect or a central serotonergic mechanism rather than any adrenergic or adrenolytic activity. Chapman and Butler (19781, working with human chronic pain patients, tested the hypothesis that doxepin has analgesic properties. Among their conclusions, they stated that the prompt efficacy of TCA "... is probably not due to the relief of reactive depression since positive responses are observed inexplicably early..." Other studies demonstrated enhancement of propoxyphene analgesia by doxepin (Tofanetti et al. 1977), potentiation of morphine analgesia by amitriptyline (Liu and Wang 1981), and enhancement of analgetic effects of morphine and pentazocine by TCA (Lee and Spencer 1980).

Theories on the mechanism of enhancement were proposed by Malseed and Goldstein (1979). Antidepressant effects and local analgetic effects were discounted as major mechanisms (Chapman and Butler 1978; Malseed and Goldstein 1979; Liu and Wang 1981). Possible biochemical effects would include:

a. Reduction of synaptic release of acetylcholine in the brain, thereby enhancing the ability of morphine to interfere with central cholinergic activity.

b. Although the roles of central moncamines in nociception are not clear, one possiblity is that TCA may have their effect by interfering with presynaptic uptake and increasing synaptic concentrations of serotonin, thereby augmenting the effects of opioids in the central pathways involved in nociception and enhancing analgesia.

c. TCA are biotransformed by the cytochrome P-450 system in rat liver, as are morphine and methadone. Further, desmethylimipramine has been shown to inhibit N-demethylation of methadone in rat liver (Goldstein et al. 1982). Malseed and Goldstein (1979) have suggested that retardation of hepatic biotransformation of



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morphine by amitriptyline and nortriptyline may occur. Goldstein et al. (1982) demonstrated increased morphine plasma levels as a direct outcome of pretreatment with desmethylimipramine. Such pretreatment also increased peak intensity and duration of antinociceptive effects of morphine in rats (Liu and Wang 1981). They proposed that the enhanced analgesia is directly related to higher plasma levels of morphine causing higher brain concentrations, since both the plasma level and analgesia increases occurred simultaneously.

In summary, TCA have been useful in the management of chronic pain, probably for a variety of reasons. While controlled studies in nondepressed patients are lacking, clinicians generally agree that TCA reduce pain or potentiate other analgesics.

**NEUROLEPTICS DRUGS**

Nonsedating neuroleptics such as fluphenazine and haloperidol have been recommended in the treatment of chronic pain. The mechanism of action here is not at all clear. These drugs have some antianxiety effect and one point of view is that they assist in the management of pain by reducing the anxiety component . They have the advantage of producing less tolerance than anxiolytic drugs, but they have the disadvantage of having other more serious potential side-effects. These drugs are dopamine antagonists and they carry the risk of producing tardive dyskinesis. This risk is very small when the drugs are given in low doses, as they are typically used in pain clinics, but it is still a risk which must be considered.

**MINOR TRANQUILIZERS**

Minor tranquilizers, particularly the benzodiazepines, are generally not recomended in the treatment of pain. While these drugs do relieve anxiety, which should thus be helpful to pain patients, tolerance develops to many of their effects. Physical dependence has been demonstrated in response to all of the minor tranquilizers that have been studied in this regard. While the abuse potential of these drugs is low compared to other sedating drugs such as barbiturates, they do lead to abuse in some patients.

**RESEARCH NEEDS**

It is clear from our review of the literature that there are nUmerous treatments for pain which are being utilized in the absence of evidence for efficacy. The problem is most noticeable in the area of chronic pain. While it can be argued that pain

is a complex problem which resists the application of controlled outcome methodology, other equally complicated conditions such as drug dependence, alcoholism, neurosis, and other psychiatric disorders have been amenable to treatment outcome research. The complex treatment programs which are currently applied in the management of pain wntain many independent elements which could be studied objectively. If the pattern developing in other areas applies also to the area of pain, it will be found that there are some patients for whom a particular treatment element is very helpful, others for whom it is neutral, and others for whom the treatment element actually worsens their condition.

In order to correct this situation, we would like to make two main recommendations. First, research should be supported which leads to the development of a classification system for pain patients. This will involve the development of diagnostic categories and severity rating scales. These scales will have to be subjected to reliability and validity testing utilizing large populations of patients and several different investigators. A classification system, however, is necessary in order to accomplish controlled outcome studies.

A second recommendation is that research support be directed toward conducting controlled outcome studies. The current treatment literature on chronic pain is based on clinical experience and reports of interesting cases. The large sums of money being spent currently on long and complicated treatments will eventually have to be justified. Controlled prospective treatment studies can lead to the selection of the right treatment for a given patient and to the discarding of treatments which are found to be ineffective. This is also the method by which potential new treatments coming out of basic research can be properly evaluated.

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# Biobehavioral Modulation of Pain Transmission

David J. Mayer, Ph.D.

It has been well known for millenia that the perception of pain is highly vulnerable to environmental manipulations. It is only within the past few years, however, that systematic examination of the neurobiological consequences of various environmental manipulations has generated intense interest. This renewed interest is probably attributable to major interacting new discoveries in the fields of pain research and opiate pharmacology. First I will review the evidence which gave rise to the concept of an endogenous opiate analgesia system. This includes stimulation-produced analgesia, the discovery of endogenous opiate peptides, and the primary neural structures involved (periaqueductal gray matter, ventral medulla, dorsolateral funiculus, spinal cord dorsal horn). Then I will discuss the development of experimental attempts to activate this system with environmental manipulations. These experiments have shown that painful and/or stressful stimuli are potent modulators of the transmission of nociceptive stimuli. A detailed description of the neuroanatomical and neurochemical circuitry involved in analgesia produced by electrical footshock in the rat will follow. This work has demonstrated the existence of multiple pain modulatory systems. Finally an attempt to organize the rather confusing data in this field will be made, and the implications of this work for the role of narcotics in the treatment of clinical pain will be discussed.

A simple invariant relationship between stimulus intensity and the magnitude of pain perception is often not present. This concept was explicitly embodied in early models of pain perception despite the lack of direct evidence to support it (Melzack and Wall 1965; Noordenbos 1959). The impetus for a renewed interest in the detailed study of pain modulatory circuitry resulted from the observation that electrical stimulation of the brain could powerfully suppress the perception of pain (Mayer et al. 1971; Reynolds 1969). Further investigation of stimulation-produced analgesia (SPA) provided considerable detail about the neural circuitry involved. Importantly, several similarities were recognized between these observations and information emerging from a concomitant resurgence of interest in the mechanisms of opiate

analgesia. The most important parallel facts revealed by these studies were: 1) Effective loci for both opiate analgesia (OA) and stimulation-produced analgesia (SPA) lie within the periaqueductal and periventricular gray matter of the brain stem (Mayer and Price 1976); 2) OA and SPA are both mediated, at least in part, by the activation of a centrifugal control system which exits from the brain via the dorsolateral funiculus of the spinal cord (Basbaum et al. 1977; Murfin et al. 1976); and 3) The ultimate inhibition of the transmission of nociceptive information occurs at the initial processing stages in the spinal cord dorsal horn and homologous trigeminal nucleus caudalis by selective inhibition of nociceptive neurons (Bennett and Mayer 1979).

In addition to these correlative observations, studies of SPA produced direct evidence indicating that there are mechanisms extant in the central nervous system which depend upon endogenous opiates (Mayer 1980): 1) Subanalgesic doses of morphine were shown to synergize with subanalgesic levels of brain stimulation to produce behavioral analgesia (Samanin and Valzelli 1971); 2) Tolerance, a phenomenon invariably associated with repeated administration of opiates, was observed to the analgesic effects of brain stimulation (Mayer and Hayes 1975; Sessle et al. 1975)); 3) Cross-tolerance between the analgesic effects of brain stimulation and opiates was demonstrated (Mayer 1975); and 4) SPA could be at least partially antagonized by naloxone, a specific narcotic antagonist (Akil et al. 19763). This last observation, in particular, could be most parsimoniously explained if electrical stimulation resulted in the release of an endogenous opiate-like factor (Mayer 1975). Indeed, naloxone antagonism of SPA was a critical impetus leading to the eventual discovery of such a factor (Hughes 1975).

Coincidental with work on SPA, another discovery of critical importance for our current concepts of endogenous analgesia systems was made. Several laboratories, almost simultaneously, reported the existence of stereospecific binding sites for opiates in the central nervous system (Hiller et al. 1973; Pert and Snyder 1973). These "receptor" sites were subsequently shown to be localized to neuronal synaptic regions (Pert et al. 1974) and to overlap anatomically with loci involved in the neural processing of pain (Pert et al. 1975). The existence of an opiate receptor again suggested the likelihood of an endogenous compound with opiate properties to occupy it. Hughes and Kosterlitz (1974) reported the isolation from neural tissue of a factor (enkephalin) with such properties. An immense amount of subsequent work has characterised this and other neural and extraneural compounds with opiate properties (Adler 1980). Importantly, as with the opiate receptor, the anatomical distribution of endogenous opiate ligands shows overlap with sites involved in pain processing (Hughes 1975). Table 1 provides a summary of the most critical facts supporting the existence of an endogenous opiate analgesia system.

The demonstration of a well-defined neural system capable of potently blocking pain transmission suggests, but by no means

proves, that the function of this system is to modulate the perceived intensity of noxious stimuli. If, in fact, this system has such a physiological role, then one might expect that the level of activity within the system would be influenced by impinging environmental stimuli. If environmental situations could be identified which produce analgesia, that would give credibility to the idea that invasive procedures, such as brain stimulation or narcotic drugs, inhibit pain by mimicking the natural activity within these pathways.

*TABLE 1*

*Major Anatomical Structures Involved in Analgesia*

| Neural Area | Manipulation: STIMULATION | LESION | RECORDING | OPIATES | OTHER |
|---|---|---|---|---|---|
| PAG | ELECTRICAL MORPHINE CHEMICAL | PARTIAL BLOCK OF MORPHINE | ↑↓ ACTIVITY | RECEPTORS; ENKEPHALINS; PARTIAL NALOX BLOCK OF SPA; PARTIAL X-TOL | |
| BULBAR RAPHE | ELECTRICAL MORPRINE | BLOCKS MORPH BLOCKS SPA? | MORPRINE →↑ | ENDORPHINS; NALOX BLOCKS SPA | RECEIVES INPUT FROM PAG |
| DLF | | BLOCKS SPA AND MORPHINE | | | PROJECTS FROM BR TO DORSAL HOE |
| DORSAL HORN | | | SPECIFIC INHIBITION OF WDR NEURONS | RECEPTORS; ENKEPHALINS | DIRECT EFFECTS OF OPIATES |

*Summary of available data on analgesia for the major anatomical structures known to be involved. PAG = periaqueductal gray matter; DLF = dorsolateral funiculus of the spinal cord; BR = bulbar raphe which includes nucleus raphe magnus, nucleus reticularis magnocellularis and other associated ventral medullary nuclei; SPA = stimulation produced analgesia; X-Tol = cross tolerance; Nalox = Naloxone; Morph = Morphine; WBR = Wide Dynamic Range.*

The first evidence for the environmental activation of an endogenous opiate analgesia system was provided by Mayer et al. (1976, 1977). They showed that acupuncture analgesia in humans can be reversed by the narcotic antagonist naloxone. They suggested that such a result could be explained if acupuncture produced analgesia by the release of endogenous opiates.

A systematic search for environmental stimuli which activate pain inhibitory systems in animals was begun by Hayes et al. (1976,1978a). They discovered that potent analgesia could be produced by such diverse stimuli as brief footshock, centrifugal rotation, and injection of intraperitoneal saline. These effects appeared to be specific to pain perception in that normal motor behavior, righting and corneal reflexes, vocalization, startle responses, and response to touch remain unimpaired (Hayes et al. 1978a). Two important additional concepts emerged from this work. First was the conclusion that exposure to stress was not sufficient to produce analgesia. Although all environmental stimuli which produce analgesia are stressors (Hayes et al. 1978a), the failure of classical stressors, such as ether vapors and horizontal oscillation, to produce pain inhibition indicated that stress was not the critical variable responsible (Hayes et al. 1978a). The second concept resulted from the rather unexpected finding that the opiate antagonist, naloxone, did not block environmentally induced analgesias (Hayes et al. 1978a). Therefore, it appeared that non-opiate systems must exist, in addition to the opiate system described earlier.

Although the stimuli studied by Hayes et al. (1978a) did not appear to activate an opiate system, subsequent investigations found clues that brain endorphins might be involved in at least some types of environmentally induced analgesias. Akil and coworkers (1976a) studied the analgesic effects of prolonged footshock. In contrast to the results of Hayes et al. (1978a), naloxone did partially antagonize the analgesia. This initial indication of opiate involvement led Akil and coworkers to look for biochemical evidence that footshock caused brain opiates to be released. They found that changes in brain opiate levels did indeed parallel the development of footshock induced analgesia (FSIA) (Akil et al. 1976a). When tolerance developed to the analgesic effects of footshock, brain opiate levels returned to control values (Akil et al. 1976a). In agreement with these results, $^{3}$H-leu-enkephalin binding has been reported to decrease as analgesia increases (DeVries et al. 1979).

The controversy over the involvement of opiates in footshock-induced analgesia was resolved, in part, by Lewis et al. (1980). They noted that the duration of footshock used by Hayes et al. (1978a) and Akil et al. (1976a) differed greatly and wondered whether this variable might explain the difference in their results. By comparing the effects of naloxone on analgesia produced by brief (3 min) vs. prolonged (30 min) footshock, Lewis et al. (1980) showed that only the latter could be blocked by naloxone. This suggested that different analgesia systems become active as the duration of footshock increases.

Concurrent with this work of Lewis et al. (1980), we made the observation that brief shock restricted to the front paws produced a naloxone-reversible analgesia as measured by the tail flick assay (Watkins and Mayer 1982). We thought that this was rather puzzling since Hayes et al. (1978a) and Lewis et al. (1980) found that brief shock produced non-opiate analgesia. This led us to test whether naloxone had different effects on analgesia produced by front paw vs. hind paw shock. We found that naloxone does indeed have markedly different effects depending upon the body region shocked. An opiate system appears to be activated by front paw shock since low doses (0.1 mg/kg) of naloxone antagonize this analgesia. In contrast, even high doses (20 mg/kg) of naloxone failed to reduce hind paw shock induced analgesia (Fig. 1). Therefore, a non-opiate system seems to be-involved in this response.

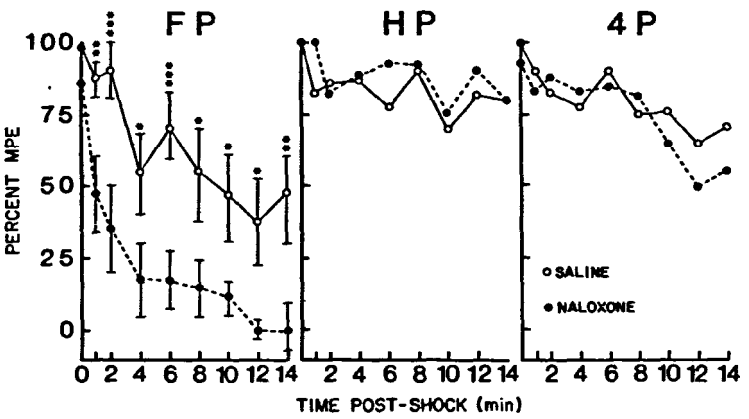



*FIGURE 1*

*The effect of naloxone (2 i.p. injections of 10 mg/kg) on analgesia induced by shock delivered to the front paws (FP), hind paws (HP) or to all four paws (4P). As measured by the tail flick test, naloxone significantly antagonized front paw FSIA (left) but had no effect on either hind paw FSIA (center) or four paw FSIA (right). *=p<0. 05; **p<0.005; ***p<0.001. MPE=Maximal Possible Effect. From Watkins et al. 1982a. Copyright 1982, Elsevier Biomedical Press. Reprinted by permission.*

Definitive conclusions about opiate involvement in neural systems are tenuous when based exclusively on the effects of narcotic antagonists. Narcotic antagonists are known to have effects on non-opiate systems as well (Hayes et al. 1977; Pert and Walter 1976). Thus, additional lines of evidence are required to infer opiate involvement. To meet this criterion, we reasoned that if opiates are involved in front paw footshock-induced analgesia(FSIA), then front paw FSIA should also be reduced in rats which have been made tolerant to opiates. To test whether such cross-tolerance

exists between morphine analgesia and front paw FSIA, we continuously infused rats with either morphine or saline for six days (Watkins et al. 1982a). At this time, the rats given morphine were tolerant to this opiate since 10 mg/kg morphine no longer produced analgesia. When the rats were tested for front paw FSIA, analgesia was greatly reduced in morphine-tolerant rats. Since front paw FSIA shows cross-tolerance with morphine and is antagonized by naloxone, the involvement of an endogenous opiate system in this type of analgesia stands on firm ground.

Using this same procedure, rats were tested to see whether cross-tolerance could be observed between morphine analgesia and hind paw FSIA. No cross-tolerance occurred. The fact that hind paw FSIA is not affected by either high doses of naloxone or morphine tolerance demonstrates that this manipulation activates an independent non-opiate analgesia system. Since identical shock parameters were used in the hind paw FSIA and front paw FSIA experiments, these results show that factors other than exposure to stress determine whether non-opiate or opiate systems are activated.

We have studied front paw FSIA and hind paw FSIA in order to define how these opiate and non-opiate environmental analgesias are produced. In the following sections, the results of this *work* will be presented. The opiate analgesia produced by front paw shock will be discussed first. As will be seen, several similarities exist between the opiate analgesias produced by front paw shock and morphine.

The fact that endogenous opiates are involved in front paw FSIA does not prove that this effect is mediated by the same circuitry as morphine analgesia. A critical question was whether front paw FSIA could be accounted for by release of opiates from the pituitary or sympathetic-adrenal medullary axis since footshock has been shown to cause opiate release from these sites (Mayer and Watkins 1981). Hypophysectomy failed to reduce front paw FSIA. This shows that pituitary ß-endorphin is not necessary for front paw FSIA. Since adrenalectomy and sympathetic blockade actually potentiated front paw FSIA, our results also clearly show that this analgesia is not produced by opiates from the sympathetic nervous system. These data strongly suggest that front paw FSIA, like morphine analgesia, is effected via opiate pathways within the central nervous system (Watkins et al. 1982a).

Based on these results, we began to search for the neural pathways involved in front paw FSIA. We found that front paw FSIA is abolished by lesions of the dorsolateral funiculus (DLF) of the spinal cord (Fig. 2). Furthermore, we have shown with brain lesion studies that, for front paw FSIA as well as morphine analgesia, the

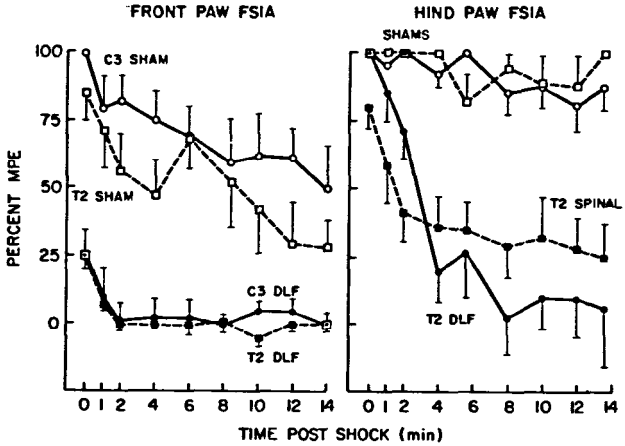
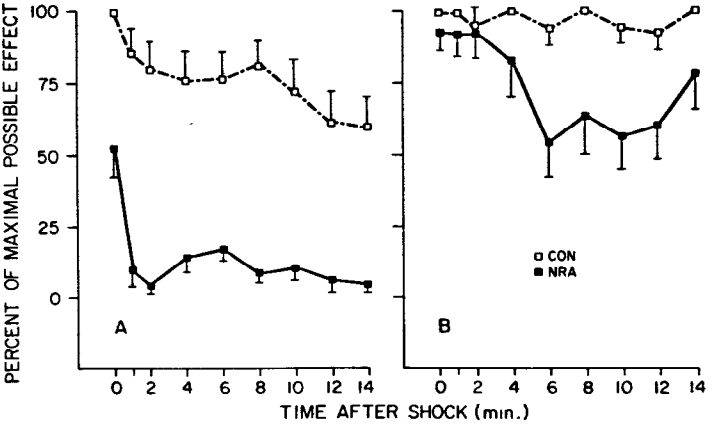



*FIGURE 2*

*Effect of bilateral dorsolateral funiculus (DLF) lesions and spinal transection on front paw FSIA and hind paw FSIA. Left: Bilateral DLF lesions at either the second thoracic (T2) or third cervical (C3) vertebral 1evels virtually abolish front paw FSIA. Since DLF lesions at C3 leave intact all potential intraspinal connections between the level of stimulus input (front paws) and the lumbosacral cord (controlling the tail flick response), direct intraspinal pathways cannot be involved in this analgesic response. Pain inhibition must be mediated by supraspinal sites which inhibit pain via descending pathways within the DLF. Right: Bilateral DLF lesions at T2 greatly attenuate, but do not abolish, hind paw FSIA. Immediately after shock termination (0 min), profound analgesia is observed, which then slowly dissipates. No further significant reduction in analgesia is observed following T2 spinalization; spinalized rats remained analgesic through 12 min after hind paw shock. These results imply that descending pathways involved* in *hind paw FSIA only exist within the DLF, and that intraspinal pathways account for the remaining potent analgesia. MPE=Maximal Possible Effect. From Watkins and Mayer 1982. Copyright 1982, The American Association for the Advancement of Science. Reprinted by permission.*

descending DLF pathway arises from the nucleus raphe alatus (NRA - n. raphe magnus and n. reticularis paragigantocellularis) (Fig. 3). In addition, we have shown that all of the critical circuitry for this analgesia effect exists below the level of the mesencephalon, since midcollicular decerebration has no effect on the analgesia (Watkins and Mayer 1982).

At this point, then, front paw FSIA has been characterized as being a neural, opiate-mediated phenomenon. Analgesia is produced by activating brain sites which inhibit pain by way of descending pathways within the DLF. Yet none of this information pinpoints where the opiate synapse is located. To determine whether a spinal cord site of action is involved, intrathecal catheters were implant-




*Effect* of *NRA lesions* on front *pm FSIA (A) and hind paw FSIA (B). Compared to controls (open squares), NRA lesions (filled squares) significantly reduced both* front *paw FSIA and hind paw FSIA. Since this lesion reduced front paw FSIA (A) to a degree comparable to that caused by bilateral DLF lesions (Fig. 2), it appears that the NRA is the origin* of *this descending pain inhibitory pathway. contrast, NRA lesions attenuated, but did not abolish, hind paw FSIA (B).*

ed so that the tips ended at the lumbosacral enlargement. In this manner, naloxone could be delivered to the spinal cord level controlling the tail flick reflex which was the behavioral measure used to assess the pain threshold. Immediately prior to front paw shock, rats were injected either with saline or 1 µg naloxone. Spinal naloxone significantly antagonized front paw FSIA (Fig. 4). This effect is not due to spread of the drug to the brain since the same dose delivered to high thoracic cord (further from the level controlling the tail flick reflex yet closer to the brain) failed to reduce front paw FSIA. These experiments demonstrate that an opiate synapse critical to the production of front paw FSIA exists within the spinal cord (Watkins and Mayer 1982).

One intriguing aspect of this naloxone effect is that naloxone can prevent, but cannot reverse, front paw FSIA (Watkins and Mayer 1982). If this opiate antagonist is injected onto the lumbosacral spinal cord immediately after the brief (90 sec] shock, analgesia is -not reduced. Naloxone is effective only if it is delivered before the induction of analgesia. This implies that brief activation of this system produces a perseverative activity within the spinal cord which is no longer dependent upon continued opiate release. These results lead us to speculate that these endogenous



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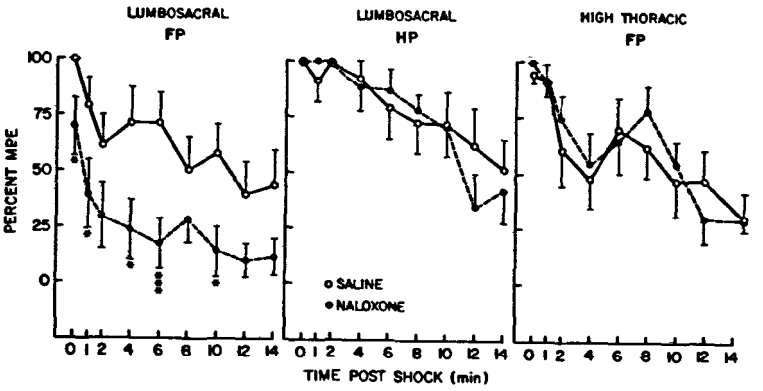


*FIGURE 4*

*The effect of intrathecal naloxone on front paw and hind paw FSIA. As measured by the tail flick test, 1 μg of naloxone delivered to the lumbosacral cord significantly antagonized analgesia induced by front paw shock (left). In contrast, this same dose of naloxone failed to attenuate hind paw FSIA (center). The observed antagonism of front paw FSIA by intrathecal naloxone demonstrates that a critical opioid site exists within the spinal cord. This result cannot be explained by spread of the antagonist to supraspinal sites since naloxone delivered to high thoracic cord (right) fails to attenuate front paw FSIA. *=p<0.05; ***=p<0.005. MPE=Maximal Possible Effect. From Watkins and Mayer. Involvement of spinal opioid systems in footshock-induced analgesia: Antagonism by naloxone is possible only before induction of analgesia. Brain Research, 242:309-316, 1982, Copyright 1982, Elsevier Biomedical Press. Reprinted by permission.*

spinal opiates may act as neuromodulators of postsynaptic activity, rather than as classical neurotransmitters.

A parallel series of experiments examined the non-opiate analgesia produced by hind paw shock. This work indicated that this effect is also neurally, rather than hormonally, mediated since analgesia was not reduced by removal of the pituitary or the adrenal glands (Watkins et al. 1982d). Spinal lesion studies showed that this effect, like front paw FSIA, is mediated via descending pathways within the DLF (Watkins et al. 1982c). However, since lesions of the nucleus raphe alatus failed to abolish hind paw FSIA (Fig. 3), the neural substrate of this effect is distinct from front paw FSIA at the level of the medulla (Young et al. 1981). A further difference between the analgesias produced by front paw and hind paw shock is that hind paw FSIA is only reduced, not abolished, by DLF lesions. Therefore, it seemed possible that the existence of a second descending pathway could account for the potent analgesia

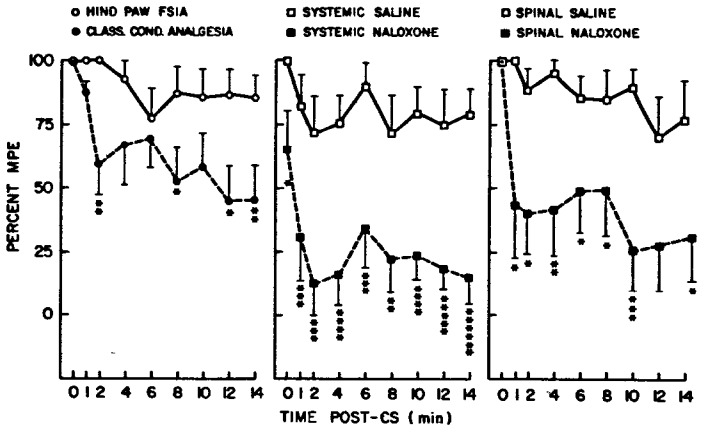


*FIGURE 5*

*Naloxone reversibility of analgesia classically conditioned to hind paw shock. Hind paw shock (Day 1) produced profound analgesia, as measured by the tail flick test (left, open circles). This single exposure to shock was sufficient to classically condition analgesia, since placement of the rats on the non-electrified grid on Day 2 was sufficient to invoke significant analgesia (left, filled circles). Although hind paw FSIA has previously been demonstrated to be mediated by non-opiate systems, analgesia classically conditioned to hind paw shock does indeed appear to involve endogenous opioids. Compared to saline test days (center and right, open squares), both 10 mg/kg systemic (center, filled squares) and 1 μg lumbosacral (right, filled squares) naloxone significantly antagonized analgesia classically conditioned to hind paw shock. *=p<0.05; **=p<0.01; ***=p<0.005; ****=p<0.001; *****=p<0.0005; ******=p<0.0001. MPE= Maximal Possible Effect. From Watkins et al. 1982b. Copyright 1982, Elsevier Biomedical Press. Reprinted by permission.*

which remained. However, a comparison of hind paw FSIA in spinalized and DLF lesioned animals indicated that an intraspinal, rather than descending, pain inhibitory system is responsible for the analgesia observed following DLF lesions, since spinalization failed to further reduce the pain inhibitory effects of hind paw shock (Fig. 2). Thus, segmental circuitry and descending pathways within the DLF account for the entire analgesic response to hind paw shock. As with front paw FSIA, the supra-spinal component of hind paw FSIA is mediated below the level of the mesencephalon, since it is unaffected by decerebration (Young et al. 1981).

An intriguing aspect of FSIA is that plasticity exists in the neural circuitry. Using a Pavlovian classical conditioning paradigm, Hayes et al. (1976) found that rats readily associated environmental cues with the delivery of shock, such that they learned to activate their endogenous pain inhibitory systems when these cues were presented. In this study, the non-electrified

shock chamber served as the conditioned stimulus (CS), grid shock delivered to all four paws served as the unconditioned stimulus (UCS) and tail flick inhibition served as the unconditioned response (UCR). Following CS-UCS pairings, exposure to the non-electrified grid reliably induced analgesia.

Since we have no demonstrated that front paw FSIA is mediated via a well defined centrifugal opiate pathway, we used brief front paw shock as the UCS in a classical conditioning paradigm to determine whether plasticity exists in opiate systems. The following section summarizes the evidence that animals can learn to activate their endogenous opiate systems to inhibit pain.

Exposure to the nonelectrified grid (CS) became capable of producing potent analgesia after this CS was paired with front paw shock (Fig. 5). That this effect is true classical conditioning is demonstrated by the observations that it shows extinction but cannot be produced by sensitization, backward conditioning, or pseudoconditioning (Watkins et al. 1982b). The fact that we have observed classically conditioned analgesia to be antagonized by systemic naloxone (Fig. 5), spinal naloxone (Fig. 5), and morphine tolerance (Watkins et al. 1982b) strongly suggests that animals are learning to activate an endogenous opiate system. Intriguingly, maintenance of the analgesic state again appears to be independent of continued opiate release.

Like the situation previously discussed for front paw FSIA, we have observed that naloxone can prevent, but cannot reverse, classically conditioned analgesia (Watkins et al 1982b).

Although, as described above, opiate (front paw) and non-opiate (hind paw) FSIA can be differentially elicited, classically conditioned analgesia appears to always involve opiate pathways regardless of the body region shocked during conditioning trials. Classically conditioned analgesia can be antagonized by naloxone regardless of whether front paw or hind paw shock is used as the UCS.

The opiate analgesia produced by these classical conditioning paradigms appears to be neurally, rather than hormonally mediated, since it is not attenuated by either hypophysectomy or adrenalectomy (Watkins et al. 1982d).

Classical conditioning involves supraspinal circuitry since our studies have shown that conditioned analgesia is abolished by bilateral DLF lesions (Watkins et al 1982b). Again, as with front paw FSIA, nucleus raphe alatus lesions abolish the effect. However, as might be expected with a higher order behavior, decerebration abolishes the effect as well (Watkins and Mayer 1982). Finally, the role of the periaqueductal gray matter in the neural circuitry of endogenous analgesia systems is beginning to be understood because lesions of this structure reduce the conditioned effect but not the acute effects of footshock. Fig. 6 provides an overview of the neural circuitry of these systems.

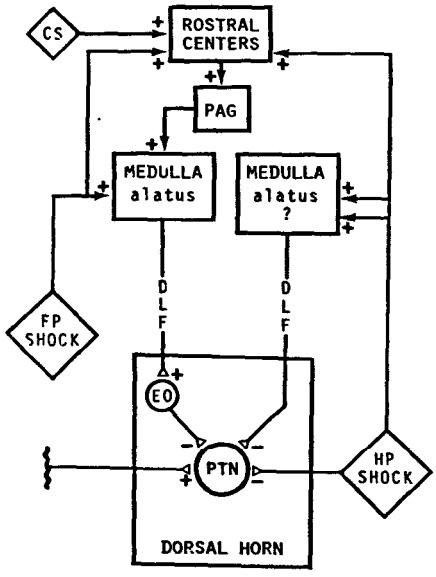


*FIGURE 6*

*Summary of the neural circuitry mediating front paw (opiate) FSIA, hind paw (non-opiate) FSIA and classically conditioned (opiate) analgesia. Front paw (FP) shock leads to activation of the nucleus raphe alatus (NRA) within the ventral medulla. This nucleus sends a descending projection through the dorsolateral funiculus (DLF) to the dorsal horn of the spinal cord. In turn, endogenous opiates (EO) are released, resulting in inhibition of pain transmission neurons (PTN). Hind paw (HP) shock leads to inhibition of pain transmission neurons via two non-opiate pathways: an intraspinal pathway and a descending DLF pathway. The latter originates from the nucleus raphe alatus and from some other yet unidentified medullary area(s). Classically conditioned (opiate) analgesia appears to result from activation of the same output pathway as front paw (opiate) FSIA. Following conditioning trials in which the conditioned stimulus (CS) is paired with either front paw shock or hind paw shock (the unconditioned stimulus), the CS becomes capable of activating rostral centers in the brain. In turn, this leads to activation of the periaqueductal gray (PAG) and subsequently to activation of the nucleus raphe alatus. This results, via a descending DLF pathway, in release of endogenous opiates within the dorsal horn, producing analgesia. From Watkins and Mayer 1982. Copyright 1982, The American Association for the Advancement of Science. Reprinted by permission.*

In another series of experiments we have begun to examine the neurochemical bases of pain modulation. One approach was motivated by the observation that cholecystokinin (CCK) has effects opposite those of opiates on a number of behaviors. We have made a number of striking observations about CCK and analgesia: (1) CCK (5 µg/kg, i.p.) greatly reduces analgesia produced by 10 mg/kg morphine (Fig. 7) (Faris et al. 1983). (2) CCK (as little as 1.5 µg/kg, i.p.) reduces environmentally produced opiate analgesias (front paw FSIA,

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Since we have now demonstrated that front paw FSIA is mediated via a well defined centrifugal opiate pathway, we used brief front paw shock as the UCS in a classical conditioning paradigm to determine whether plasticity exists in opiate systems. The following section summarizes the evidence that animals can learn to activate their endogenous opiate systems to inhibit pain.

Exposure to the nonelectrified grid (CS) became capable of producing potent analgesia after this CS was paired with front paw shock (Fig. 5). That this effect is true classical conditioning is demonstrated by the observations that it shows extinction but cannot be produced by sensitization, backward conditioning, or pseudoconditioning (Watkins et al. 1982b). The fact that we have observed classically conditioned analgesia to be antagonized by systemic naloxone (Fig. 5), spinal naloxone (Fig. 5), and morphine tolerance (Watkins et al. 1982b) strongly suggests that animals are learning to activate an endogenous opiate system. Intriguingly, maintenance of the analgesic state again appears to be independent of continued opiate release.

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experiments examining the role of spinal monoamines in various analgesia systems.

In one series of experiments, the effects of spinal cord serotonin depletion or combined serotonin and norepinephrine depletion on analgesia elicited by electrical stimulation of, or morphine microinjection into, the periaqueductal gray were tested (Johannessen et al 1982). Spinal cord serotonin was depleted by intrathecal injection of 5,7-dihydroxytryptamine (5,7-DHT), preceded by systemic desipramine, while 5,7-DHT alone was used to deplete both norepinephrine and serotonin. Selective serotonin depletion had no effect on analgesia induced by either method at 24 hrs, one week, or two weeks after treatment. Depletion of both monoamines had no effect on stimulation-produced analgesia 24 hrs and one week after treatment, but produced a slight attenuation two and three weeks after treatment. In contrast, depletion of both monoamines drastically attenuated morphine analgesia 24 hrs after treatment. Thus, although total c.n.s. depletion of serotonin can reduce both stimulation-produced analgesia and morphine analgesia, medullospinal serotonin systems do not appear to be involved.

Although this lack of involvement of medullospinal serotonin systems may at first glance appear perplexing, a series of anatomical studies we have done makes this result more coherent. A critical fact concerning the organization of supraspinal neural systems which control pain is that the output pathway from the brain appears to descend to the spinal cord by way of the dorsal lateral funiculus (DLF). DLF lesions greatly reduce or abolish analgesia produced by brain stimulation, systemic morphine, and morphine microinjection (Mayer 1980). Thus, we felt it was of particular importance to describe carefully the origins of this pathway before undertaking behavioral and neurophysiological studies of brain centers involved in analgesia. Several studies utilizing a new horseradish peroxidase gel technique developed in our laboratory (Griffin et al. 1979) have examined the problem. We have shown that the population of neurons in the medullary raphe region contributing to the DLF consists of cells in nucleus raphe magnus (NRM) and reticularis magnocellularis (Rmc) and roughly corresponds to the serotonergic cell group B3. We have named this region the nucleus raphe alatus (NRA), and this work has redefined the anatomical organization of the medullary raphe nuclei which contribute to the DLF (Watkins et al. 1980). The medullary nucleus raphe alatus, which gives rise to fibers which descend in the DLF, is a sensitive site for the production of analgesia by electrical and pharmacological methods (Mayer 1980). Indirect evidence suggests that descending serotonergic fibers from area B3 may play a role in descending inhibition. The cells of B3 show a similar distribution to those of NRA, however, there is no direct evidence that serotonergic fibers from B3 descend in the DLF.

In order to examine this question, we performed a study in which the cell bodies of NRA were labelled retrogradely with HRP by implanting a small piece of HRP-gel unilaterally into the cervical

DLF. Two days later, the method of Bowker et al. (1981) was used to simultaneously visualize both retrogradely labelled cells and cells exhibiting serotonin-like immunoreactivity (SLI). Extremely few double-labelled cells were seen (Johannessen et al. 1981). Retrogradely labelled cells of NRA exhibited a different distribution than SLI cells. The SLI cells of B3 lie ventral to NRA (Fig. 8). Some intermingling of retrogradely labelled cells and SLI

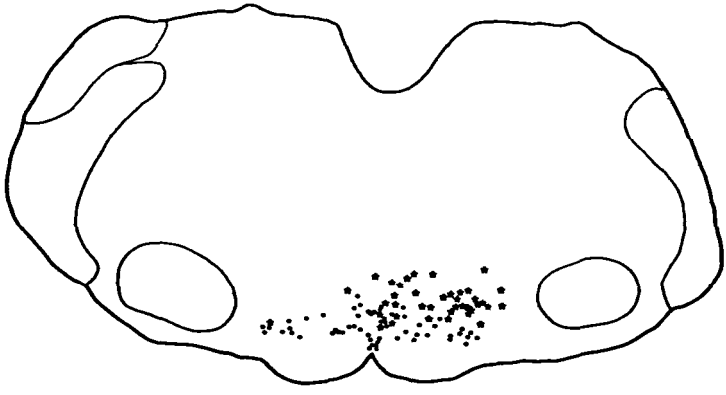

*FIGURE 8*

*Composite of cells retrogradely labelled from the right dorsolateral funiculus (DLF) (stars) and cells exhibiting serotonin-like immunoreactivity (filled circles) at the level of the n. raphe magnus. No double labelled cells were seen in this section. Note intermingling of DLF projecting cells and serotonin cells near the midline.*

cells was seen, especially near the midline. At the level of the facial nucleus, 25 retrogradely labelled cells and 55 SLI cells were seen in a typical hemisection, while no more than two double-labelled cells could be identified. These results suggest that serotonin is not a major component of the DLF projection which originates in the NRA. This is consistent with evidence indicating that a descending serotonergic projection is unnecessary to elicit some types of analgesia.

A study examining the effects of these same monoamine manipulations on footshock induced analgesia has been conducted. Interestingly, while hind paw FSIA is unaffected by monoamine depletions, front paw FSIA is reduced by selective spinal cord serotonin depletion (Fig. 9). This study has complex but important implications. Since (1) the DLF is necessary for front paw FSIA, (2) the n. raphe alatus is necessary for front paw FSIA, and (3) serotonergic output

from NRA does not descend via the DLF, these results indicate that a synergism of serotonergic and non-serotonergic descending pathways may sometimes be necessary to produce analgesia.

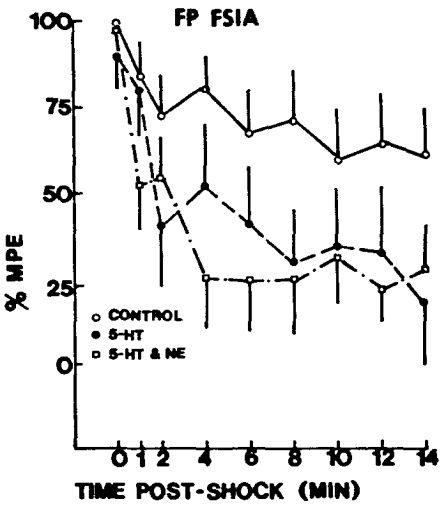


*FIGURE 9*

*Effect of spinal cord serotonin depletion (5HT) or combined sero-*tonin and norepinephrine *depletion (5HT & NE)* on front paw *FSIA. Compared to controls (open circles), both 5HT (closed circles) and 5HT & NE (open squares) depletion reliably reduced analgesia induced by brief front paw shock. Since* intrathecal *BC 105 (5HT antagonist) and intrathecal phentolantine (NE antagonist) also reduce front* paw *FSIA, NE and 5HT appear to be involved in the production of this analgesia at the level of the spinal cord. MPE=Maximal Possible Effect.*

These studies of front paw FSIA, hind paw FSIA, and classically conditioned analgesia provide strong support for the existence of multiple endogenous pain modulatory systems within the central nervous system. At least three systems have been identified (Fig. 7). The first two pathways mediate the neural non-opiate analgesia

observed following hind paw shock. These consist of an intraspinal pathway and a descending DLP pathway with supraspinal origin. The third is a neural opiate analgesia which is produced by front paw shock or by classical conditioning using front paw or hind paw shock as the UCS. This opiate analgesia is effected solely via descending pathways within the spinal cord. Thus, front paw FSIA and classically conditioned analgesia provide the first unequivocal demonstrations of neural opiate pathways activated in response to environmental stimuli.

However, a review of the literature indicates that even these three systems do not account for all of the pain inhibitory responses which have been reported. As summarized in Table 2, presently available evidence indicates that four classes of analgesia exist: neural/opiate, hormonal/opiate, neural/non-opiate, and hormonal/non-opiate. The criteria used to classify analgesia as opiate include naloxone reversibility and cross-tolerance to morphine. Hormonal analgesia is characterized as being attenuated either by adrenalectomy, adrenal demedullation, or hypophysectomy. These latter criteria were chosen since all environmental stimuli which produce analgesia activate the pituitary-adrenal cortical and sympathetic-adrenal medullary axes. Brain stimulation is listed in two classes, neural/opiate and neural/non-opiate since it can apparently activate both opiate and non-opiate pain inhibitory pathways. Regarding the neural substrates of these various analgesic responses, the most comprehensive data are available on the effect of dorsolateral funiculus (DLF) lesions, nucleus raphe alatus (n. r. alatus) lesions and periaqueductal gray (PAG) lesions. As can be seen, DLF lesions attenuate all analgesic manipulations which have been tested, suggesting that the DLF may form the final common pathway for endogenous pain inhibitory systems. (Akil et al. 1976a; Mayer 1980; Mayer and Price 1976.)

At this point, I would like to make some parallels between our work in rats and experimental and clinical studies in humans. This will be done in order to highlight the potential relevance of this work to the very difficult problem of treating pain syndromes in man. Throughout this discussion, it will be important to bear in mind that a number of distinct modulatory systems have been identified under controlled laboratory conditions. In the more naturalistic circumstances of clinical research, it is likely that more than one of these systems may be active at any given time, which may account for the variability and controversy in the clinical literature.

There are at least two situations available for study in which endogenous pain modulatory systems may be active in man. The first involves the basal, tonic activity within these systems and allows the experimenter to assess whether pain inhibition occurs continuously, at least to some degree. The second involves clinical manipulations which attempt to activate pain inhibitory systems.

Attempts have been made to determine whether pain modulatory systems are tonically active. The assumption made by these studies

TABLE 2

*Summary of Currently Available Data on Endogenous Analgesia Systems*

| CLASSES OF ANALGESIA: | SIMILARITY TO OPIATES: SYSTEMIC NALOXONE | SIMILARITY TO OPIATES: INTRATHECAL NALOXONE | SIMILARITY TO OPIATES: MORPHINE TOLERANCE (X TOL) | SIMILARITY TO OPIATES: PLASMA OPIATE LEVELS | SIMILARITY TO OPIATES: CNS OPIATE LEVELS | ENDO. LESIONS: ADRENALECTOMY | ENDO. LESIONS: ADRENAL DEMEDULLATION | ENDO. LESIONS: HYPOPHYSECTOMY | NEURAL LESIONS: DLF LESIONS | NEURAL LESIONS: NRA LESIONS | NEURAL LESIONS: PAG LESIONS | NEURAL LESIONS: DECEREBRATION | NEUROCHEM. EFFECTS: 5HT (CNS) | NEUROCHEM. EFFECTS: 5HT (SPINAL) | NEUROCHEM. EFFECTS: NE (CNS) | NEUROCHEM. EFFECTS: NE (SPINAL) | NEUROCHEM. EFFECTS: ACH | NEUROCHEM. EFFECTS: CCK-8 | NEUROCHEM. EFFECTS: HISTAMINE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NEURAL/OPIATE | | | | | | | | | | | | | | | | | | | |
| BRIEF FRONT PAW SHOCK | ↓ | ↓ | ↓ | | | ↑ | | 0 | ↓ | ↓ | 0 | 0 | | ↓ | | ↓ | 0 | ↓ | |
| CONDITIONING TO FOOTSHOCK | ↓ | ↓ | ↓ | | | ↑ | | 0 | ↓ | ↓ | ↓ | ↓ | | 0 | | 0 | ↓ | ↓ | |
| SYSTEMIC MORPHINE | ↓ | ↓ | ↓ | 0 | ? | ↑ | 0 | ↑ | ↓ | ? | ? | 0 | ? | | ? | ↓ | ? | ↓ | |
| INTRACEREBRAL MORPHINE | ↓ | 0 | ↓ | | | 0 | ● | 0 | ↓ | ↓ | ? | ● | | 0 | | | | ↓ | |
| INTRATHECAL MORPHINE | ↓ | ↓ | ↓ | | | ● | ● | ● | ● | ● | ● | ● | | 0 | | 0 | | | |
| BRAIN STIMULATION | ↓ | ↓ | ↓ | | ? | | | | ↓ | ? | ? | ● | ↓ | 0 | ↑ | ↓ | | | |
| NEURAL/NON-OPIATE | | | | | | | | | | | | | | | | | | | |
| BRIEF HIND PAW SHOCK | 0 | 0 | 0 | | | 0 | ● | 0 | ↓ | ↓ | 0 | 0 | | 0 | | 0 | ↓ | 0 | |
| BRIEF 4 PAW SHOCK | 0 | ● | 0 | | ↑ | 0 | 0 | ↑ | ↓ | ↓ | | | | | | | 0 | | ↓ |
| 2-DEOXY-D-GLUCOSE | ? | | ↓ | | | | | 0 | | | ? | | | | | | | | |
| BRAIN STIMULATION | 0 | ● | 0 | 0 | | | | | | | | | | | | | | | |
| HORMONAL/OPIATE | | | | | | | | | | | | | | | | | | | |
| ACUPUNCTURE | ↓ | | 0 | ↑ | ↑ | | | ↓ | | | | | ↓ | | ? | | ↓ | | |
| PROLONGED 4 PAW SHOCK | ↓ | | ↓ | | 0 | ↓ | ↓ | ↓ | ↓ | 0 | | | | | | | ↓ | | |
| IMMOBILIZATION | ↓ | | | ↑ | | | | ↓ | | | | | | | | | | | |
| CONDITIONED HELPLESSNESS | ↓ | ↓ | ↓ | | | ↓ | | ↓ | ↓ | | | | | | | | | | |
| PROLONGED TAIL SHOCK | ↓ | | | | | ↓ | | | ↓ | | | 0 | | | | | | | |
| HORMONAL/NON-OPIATE | | | | | | | | | | | | | | | | | | | |
| COLD WATER SWIMS | 0 | ● | 0 | | | | | ↓ | | | 0 | | | | | | | | |
| BRIEF TAIL SHOCK | 0 | ● | | | | ↓ | | | ↓ | | | 0 | | | | | | | |
| UNKNOWN/OPIATE | | | | | | | | | | | | | | | | | | | |
| TNS (LOW FREQ/HI INT) | ↓ | | | ↑ | | | | | | | | | | | | | | | |
| FOOD DEPRIVATION | ↓ | | | | | | | | | | | | | | | | | | |
| PLACEBO | ↓ | | | | | | | | | | | | | | | | | | |
| DEFEAT | ↓ | | | | | | | | | | | | | | | | | | |
| HYPERTENSION | ↓ | | | | | | | | | | | | | | | | | | |
| ANXIETY (HUMAN) | ↓ | | | | | | | | | | | | | | | | | | |
| VAGINAL PROBING | ↓ | ↓ | ↓ | | | | | | ↓ | | | | | ↓ | | ↓ | | | |
| UNKNOWN/NON-OPIATE | | | | | | | | | | | | | | | | | | | |
| TNS (HI FREQ/LOW INT) | 0 | | | | | | | | | | | | | | | | | | |
| HYPNOSIS | 0 | | | | | | | | | | | | | | | | | | |
| VAGINAL PROBING | 0 | | 0 | | | | | | | | | | | | | | | 0 | |
| ACUPUNCTURE | 0 | | | | | | | | | | | | | | | | | | |
| CENTRIFUGAL ROTATION | 0 | | | | | | | | | | | | | | | | | | |
| HORMONAL/UNKNOWN | | | | | | | | | | | | | | | | | | | |
| INSULIN | | | | | | | | ↓ | | | | | | | | | | | |
| UNKNOWN | | | | | | | | | | | | | | | | | | | |
| SEXUAL BEHAVIOR | | | | | | | | | | | | | | | | | | | |

↑ = *potentiation,* ↓ = *attenuation,* 0 = no effect, ? = *conflicting data exist indicating either no* effect or *attenuation, blank = no data are available,* • = *inappropriate category.*

has been that administration of opiate antagonists should alter the perception of pain if opiate systems are tonically active. This change in pain perception would be recorded either as a decreased pain threshold or an increased level of ongoing pain. In general, however, naloxone has failed to affect pain thresholds of normal human volunteers (El-Sobky et al. 1976; Grevert and Goldstein 1978; Mayer et al. 1977). In contrast to these negative results, Buchsbaum et al. (1977) found that naloxone lowered the thresholds on subjects with naturally high pain thresholds, yet had no effect in subjects with low pain thresholds.

Naloxone appears to be more consistently effective when delivered to experimental subjects who are experiencing some level of clinical pain. Therefore, circumstances have been observed in which spontaneous activity of an endogenous opiate analgesia system occurs. Importantly, ongoing pain is one factor that appears to activate this system. In this regard, these results are consistent with the animal studies described above in which pain was observed to be a powerful activator of endogenous analgesia systems.

A number of manipulations are known to have some degree of clinical efficacy for the reduction of pain. Most of these procedures were developed before the recent explosion of information about endogenous pain control systems. Indeed, many of them evolved from theoretical approaches which are now outdated or incorrect. Nevertheless, the procedures are efficacious. It may be informative to re-examine them in the light of current knowledge.

The belief that an acute painful stimulus can be used to alleviate ongoing pain has been held since antiquity and is known as counter-irritation. This procedure has a great deal in common with acupuncture and TNS. All use the application of somatic stimuli, either noxious or innocuous, to obtain relief from pain. Importantly, pain relief persists beyond the period of treatment in all cases. The site of treatment in relation to the painful area is highly variable, ranging from the painful dermatome, itself, to a theoretically unpredictable constellation of points in classical Chinese acupuncture. Lastly, the duration of treatment varies from less than a minute to hours. All of these factors, as we have seen, are important determinants of the effects produced by footshock in animals. Thus, the highly variable effects observed in the clinic would be predicted from animal research. Nevertheless, human data suggest the involvement of the same systems described above.

The involvement of an opiate system in these types of analgesia was first suggested by Layer et al. (1977) who showed that the increased pain thresholds produced by traditional acupuncture in man could be completely reversed by naloxone. Other investigators (Chapman and Benedetti 1977) found that naloxone only partially reduced electroacupuncture analgesia. The differences in the magnitude of the effects seen in these studies is particularly enlightening considering the animal studies described above. Mayer et al (1977) used the ho-ku points in the hands to induce analgesia in the teeth, an acupuncture point far removed from the painful region. In contrast, Chapman and Benedetti (1977) stimulated the

face to produce analgesia in the teeth and saw only a very small effect of naloxone. Thus, it seems likely that, as in animal experiments, stimulation of regions adjacent to the painful area activate non-opiate analgesia systems, whereas stimulation of distant dermatomes activates opiate systems.

Other parameters of stimulation also appear to be critical in determining whether opiate or non-opiate systems are involved. Sjolund and Eriksson (1979) have recently shown that high frequency/low intensity and low frequency/high intensity nerve stimulation can both alleviate clinical pain. However, only the analgesia produced by low frequency/high intensity stimulation could be reversed by naloxone. From this work, it appears that noxious stimulation is required for the activation of opiate inhibitory systems. In fact, that acupuncture and TNS should be painful to produce maximal effects has been pointed out by several workers (Fox and Melzack 1975; Mann 1974; Melzack 1976).

In-conclusion, acupuncture and TNS appear to be forms of counter-irritation which activate both opiate and non-opiate systems. The variable clinical outcomes observed following these treatments probably result from differential recruitment of segmental, extrasegmental, opiate and non-opiate pain inhibitory systems, all of which are now known to be activated by these types of stimulation in animals.

Naloxone has also been used to examine whether endogenous opiates are involved in placebo analgesia. Levine and coworkers (1978a and b) reported that naloxone antagonized placebo effects. Although this conclusion has been questioned on technical grounds (Karczyn 1978) , no conflicting data have been published, and the possibility that opiates are involved in some aspect of placebo analgesia appears particularly reasonable considering the fact that footshock analgesia can be classically conditioned in rats. Placebo analgesia can easily be conceived of as a classical conditioning paradigm wherein the placebo manipulation (i.e., injections, pills) serves as the conditioned stimulus and prior medication or treatment serves as the unconditioned stimulus.

Although explanations of this sort are clearly speculative, they are indicative of the wealth of concepts from experimental pain research now available for clinical evaluation. Our increasing knowledge of pain modulatory systems has the potential not only of providing explanations of current therapies but of suggesting new approaches for the control of pain. The preponderance of current pain therapies involve either the surgical destruction of neural tissue or the use of addictive drugs. Such procedures offer great difficulties for the prolonged treatment of chronic pain. If multiple pain inhibitory systems could be activated pharmacologically or otherwise in an alternating sequence, the problems of tissue destruction and addiction could be circumvented.

A primary conclusion of the present research as well as much other research in this area is that there are numerous "analgesia systems" (Watkins and Mayer 1982; Lewis et al. 1980). The concept

of an "analgesia system," however may be more an artifact of our desire to control pain than a true reflection of the evolutionary development and normal functioning of the nervous system. That the nervous system evolved even one, much less numerous "analgesia systems" is contradicted by several observations: (1) Many of these systems seem to be activated by only the most extreme of naturally occurring conditions such as intense pain or stress. Under such conditions in nature, animals would be unlikely to survive. (2) The major somatosensory pathology is the presence of pain without apparent cause, not its absence. If all of this circuitry existed to produce analgesia, one would expect the opposite.

Although some or all of these systems may exist for the specific purpose of modulating the flow to consciousness of information about tissue damage, we feel it may be more heuristic to examine such circuitry in the broader context of somatosensory processing. It should be understood that the evaluation of tissue damage versus other somatic inputs presents a distinct dilemma to the nervous system. The nervous system must be designed to evaluate and escape from tissue damaging stimuli as rapidly as possible. Yet, physical contact with the somatic environment is obviously useful to the organism in numerous realms. Thus it seems likely that complex neural systems would evolve to mitigate this conflict between somatic-informational systems and somatic avoidance (pain) systems. Viewing somatosensory systems in this light has no less profound implications for the practical applications to pain treatment and may provide a more comprehensive understanding of sensory processing.

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# Mechanisms of Pain and Analgesia as Revealed by Opiate Research: Summary and Recommendations

Roger M. Brown, Ph.D., and
Theodore M. Pinkert, M.D., J.D.

Historically, the National Institute on Drug Abuse (NIDA) and its predecessors in the Public Health Service have been deeply committed to research in the area of analgesic drugs and analgesia. This commitment has extended through the years to become an elemental part of almost all of NIDA's programs, from basic research to treatment and services research to the public dissemination of those research findings through publications and professional meetings. This Research Analysis and Utilization Systems (RAUS) review is a part of a continuing process of evaluation of current research findings in this area, and an attempt to discern the most promising areas of study for the future investment of effort.

The search for a remedy from acute and chronic pain is centuries old. Only recently, however, has the phenomenon of pain and analgesia been subjected to rigorous experimentation and systematic study. The observation of the remarkable analgesic properties of the opiate drugs revolutionized the treatment of pain from an empirical point of view. Unfortunately, opiates were soon recognized as also possessing the liability of producing euphoria, tolerance, and physical dependence. These properties of the then-known analgesic drugs led to drug dependence among the afflicted, even when the source of pain could be successfully treated. This led to a search which continues today for new pharmacological entities which possess the analgesic properties of the classic drugs in this field, while diminishing the risks of drug dependence or abuse. A corresponding scientific inquiry into the physiology, anatomy, biochemistry, and psychology of pain began at a later point in time. and has proceeded much more slowly, only gradually beginning to reveal the secrets of nociception in research conducted over the last two decades.

It should not have been surprising that one of the major outgrowths of drug abuse research has been the elucidation of nociceptive and antinociceptive mechanisms and the micro-architecture of pain in the neural substrate. Mood changes, the development of tolerance to increasing doses, and physical dependence are shared properties of many drugs of abuse and of most of the drugs which are effective in

pain relief. Therefore, progress in understanding addictive processes is inextricably tied to (and inseparable from) advances in research in pain and analgesia.

A direct result of NIDA-funded opiate research over the past 10 years has been the discovery of endogenous systems of pain modulation and control. The neuroanatomy of pain pathways is no longer restricted to discussion of main afferent "trunk" lines coursing UP the spinal cord, but now additionally focuses on discrete microanatomical locations designated as opiate receptors. At these locations, previously unknown endogenous compounds (endorphins, enkephalins, and other peptides) have been shown by ingeniously designed experimentation to be intimately involved in the modulation of pain perception. Functional investigations have demonstrated localized sites of pain modulation in both the brain and spinal cord. In addition to the opioid systems, studies in non-primate species have revealed the presence of non-opiate modulated pain pathways the significance of which is not yet apparent for man. Clinical studies of both the classical opiate compounds and the new synthetic opioid and non-opioid analgesics have established their relative potencies, frequency and type of side effects, and pharmacokinetic/pharmacodynamic models which help to explain some of the idiosyncratic properties associated with a particular drug or drug family. Other clinical investigations have systematically explored non-chemotherapeutic approaches to pain, including such widely disparate modalities as acupuncture, behavior modification, and psychotherapy.

**OVERVIEW**

Dr. Fields presents an anatomical picture of the pain suppression systems as they are currently understood, and points to the neuroanatomical overlap between pain modulation and opiate action. The endoqenous opioid systems which are closely associated with pain modulation occur at the level of the diencephalon, midbrain, medulla, and soinal cord. Two important loci at which analgesics act are presented and discussed. First, they act within the spinal cord to block impulse transmission through the dorsal horn. Secondly, they act within the brain itself to alter the perception of and resoonse to painful stimuli. The cellular, ultrastructural behavioral, and clinical neurophysiological strategies which have been applied to test this concept of pain modulation are presented in this chapter to develop the current model of pain suppression systems.

Dr. Gebhart reviews the neuropharmacology and neurochemistry of nociception/antinociception. In addition to peptidergic systems, other neurotransmitter/neuromodulator systems are important in mediating pain pathways, and these include serotonin, norepinephrine, and gamma-aminobutyric acid, among others. Dr. Gebhart points out the importance of behavioral correlates to either neuropharmacological or neurophysiological measures of analgesia so that earlier contradictions in the literature can be clarified, and so that multiple mechanisms involved in pain suppression and inhibition can be resolved.

Dr Houde (who was unable to prepare a written report for this monograph) reviewed the clinical study of opiate and non-opiate analgesics. His work has systematized the study of the analgesic effectiveness of a broad variety of classical analgesic compounds and provided a scientific basis for the selection of an analgesic regimen which may limit or postpone the development of tolerance and dependence in pain patients. In addition, Dr. Houde's studies comparing the analgesic effectiveness of equianalgesic doses of morphine and heroin have put to rest some of the popular misconceptions of the superiority of heroin over other analgesic drugs.

Dr. O'Brien and Dr. Weisbrot discuss pain treatment and review current methods which include behavior modification, classical conditioning, biofeedback, hypnosis, and psychotherapy. The difficulty with pharmacotherapy is discussed, and there is emphasis throughout the chapter on the importance of research in evaluating treatment efficacy and outcome.

Finally, environmental influences are well known to influence pain processing. For example, chronic pain is influenced by acute pain. Dr. Mayer reviews behavioral evidence for the existence of multiple pain suppression systems---both opioid and non-opioid in nature. A functional analysis of analgesic mechanisms indicates important differences in the physiological responses to noxious stimuli that are aversive in their own right, as opposed to those stimuli which have become aversive through learning. These differences are important because, unlike the acute pain patient, the chronic pain patient-can potentially develop extensive amounts of learned pain behavior.

## NEW DIRECTIONS

The members of the review panel were asked to present their ideas for future research which would build upon our current knowledge base. Most of the question and answer sessions following the oral presentation of each paper as well as most of the discussion session at the end of the meeting centered on this issue. The following is a distillation of the highlights of some of their recommendations, which is not intended as, and should not be considered to be, an exhaustive list.

Recognizing that not all drugs are abused, there needs to be a search for those shared or unifying factors that abused substances have in common. One essential step is an enhanced understanding of the underlying neural mechanisms of drug-seeking behavior. This would provide a window for understanding how certain special characteristics of all abused substances create, or are a cause for, their being abused.

In addition to further exploration of the microanatomical neurocircuitry and the neurochemistry involved in opiate analgesia, the search for normal physiological pain suppression systems needs to be expanded. This would include characterization of the activity

occurring at non-opiate synapses after stimulation; the development of immunocytochemical methods for the study of putative non-opioid pain suppression systems; and further studies of the functional meaning of concentrations of particular types of opiate receptors. and their chemical transmitters at different locations within the nervous system which may operate in concert with non-opioid pain modulation.

The search must be continued for neurotransmitter substances which are as yet undiscovered, as well as a more complete characterization of the effects of those which are known. What are the changes in the neuronal cell membranes caused by transmitter activity? What is their effect on conductance? What are the events leading to termination of the action of opioid peptides in the brain (via "enkephalinase-like" activity?), and what are the implications of derangements in this system for the development of tolerance? Do peptide fragments from opioid precursors have biological and practical functions? Do differences in central nervous system (CNS) opioid metabolism explain why certain individuals become (or remain) drug abusers?

There is a great deal more that must be learned about the activities of neurotransmitters and the sites at which they are active. What is their anatomical distribution, and what is the functional effect of that distribution? Are the actions of a particular neurotrans-mitter characteristic (e.g., GABA is generally inhibitory), or does the result of a transmitter action depend on how a neuroreceptor site is activated, or its location within ascending or descending pathways?

Another issue requiring further study is an examination of the true nature of "high-affinity" vs. "low affinity" opiate binding sites. Is it a subtle change in the tertiary structure of the receptor that is responsible for an alteration in subsesuent binding, or are the receptors "anatomically" different, but located in functionally similar locations? Another unresolved issue is the "true" anatomical relationship between opiate receptor sites, i.e., a determination as to whether the identified receptors are distinctly set apart or just different parts of one large receptor complex. There is a need to develop better animal models for the study of chronic pain. Studies conducted to date have been based primarily on time-limited noxious events which do not have the capacity for demonstrating the neuroanatomical and neurochemical consequences of chronic exposure to pain, or chronic administration of analgesics. This gap in our knowledge is paralleled in clinical studies, in which there exists the need for further evaluations of analgesic drugs after they have achieved steady-state levels.

More time and effort will also be required to understand the pharmacodynamic/pharmacokinetic properties of a large group of analgesic drugs which have not been studied using these methods. The effects of opioids and other drugs on patients with previous narcotic exposure needs to be elucidated in well-controlled studies, as well as the related issue of measuring interindividual variations

in the general clinical response to analgesic drugs. Previous studies have shown statistically significant differences in analgesic drug responses that have been related to age, sex, race, etc., but there may be other important intrinsic factors that remain to be sorted out.

New opioid and non-opioid analgesic drugs are continually being developed (including drugs of the mixed agonist/antagonist type), and these must be studied for their capacity to produce tolerance and dependence before they can be safely released for general use. An unexpected bonus that might be derived from such studies would be the discovery that one or more of these drugs potentiate an opiate's analgesic action without potentiating the development of tolerance. This would have important implications for the treatment of chronic pain, as well as for an understanding of the mechanism(s) of drug tolerance itself.

There is also a need for further research to develop a better taxonomy of pain. An improved classification of pain, and pain syndromes, would lead to a better understanding of the natural history, prognosis, and most efficacious treatment for particular pain syndromes. If this led to an improvement in the care received by pain patients, we would undoubtedly prevent a significant amount of drug abuse and misuse caused by the inadequate or inappropriate treatment of chronic pain patients.

## CONCLUSIONS

NIDA'S support of opiate research was a natural outgrowth of its concern with the rising tide in the abuse of these substances in the late '60s and early '70s. The discovery of a complex internal system which was stimulated by, and then subsequently modulated by, the organism's own responses to both exogenous stimuli and analgesic drug administration was to have important implications for the study of drug abuse per se, and to drastically change our understanding of pain and analgesia. The concept of a specific receptor (or receptors) which is activated to produce characteristic organismic responses for particular drugs is opening new research frames of reference for the study of non-opiate drugs of abuse. Some of the methodologies developed for the study of pain and analgesia have become imoortant for the study and measurement of other drugs of abuse, for the understanding of antagonist groups of drugs, and for reducing the potential of developing drug dependence inadvertently in the treatment of pain patients.

Research that adds to our understanding of the physiological, behavioral, and psychological mechanisms of opiate abuse will continue to have important implications for the study of pain and analgesia and vice versa. Clearly, this cross-fertilization between two closely related species of research has borne abundant fruit. It is important that NIDA maintain its vigorous support of research in this field to ensure continued advances.

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