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EDITORIAL VIEWS

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Multiple Mechanisms of Pain Inhibition Intrinsic to the Central Nervous System

IN THE LAST DECADE, and within that period at an ever accelerating rate, remarkable advances have been made to improve our understanding of the neurochemical basis of pain and pain inhibition. These discoveries have not only ignited worldwide scientific interest, but have also, thanks to an enriching dialogue now taking place between pain scientists and therapists, begun to pay dividends in the field of pain management. Certainly, the greatest harvest of clinical applications has yet to be reaped. The findings reported in the article by Yaksh and Reddy[1] appearing in this issue encourage the belief that the harvest's greatest bounty will be yielded soon.

Much recent evidence[2–4] suggests that the central nervous system possesses a substrate involving opiate receptors and opioid peptides whose normal physiologic role is pain inhibition. For example, electrical stimulation of the brain stem can cause dramatic analgesia in laboratory animals and in humans. The opioid basis of this analgesia has been inferred both from its susceptibility to naloxone antagonism and from the measurement of opioid peptide release during or after brain stimulation. Certain other pain therapies and hypalgesic states (including acupuncture, acupuncture-like transcutaneous nerve stimulation, placebo analgesia, and congenital insensitivity to pain) also appear to rely on activation of this intrinsic opioid system. The critical involvement of descending paths from brain stem to spinal cord is suggested by the inhibitory action of electrical or opiate stimulation of the brain stem on spinal nociceptive mechanisms, and by the absence of such effects following division of specific cerebrospinal tracts.

Recently, it has become clear that other important endogenous mechanisms of pain inhibition exist, some of which may be intrinsic to the spinal cord and hence independent of descending influences from the brain. Yaksh and Reddy[1] appropriately review this literature, including the telling fact that opiates delivered directly to the spinal cord via intrathecal injections are powerfully analgesic in laboratory tests and in clinical trials. Because opiate receptors are widely distributed in the nervous system and different opioceptive neural substrates appear to mediate different opiate actions, direct application of narcotics to one site can evoke a given narcotic action in the absence of others. Of particular clinical significance, Yaksh and Reddy point out that intrathecal injections of opiates cause analgesia without accompanying respiratory and motor depression or other undesirable narcotic signs.

It is also now clear that there are independent opioid and nonopioid analgesia substrates in the central nervous system. For example, although acupuncture analgesia in humans is antagonized by naloxone, hypnotic analgesia is not.[4] Moreover, the analgesic effect of prior footshock stress in rats can have either an opioid or nonopioid basis depending only on the temporal parameters of footshock.[5] In their article, Yaksh and Reddy[1] perform a pharmacologic dissection of analgesia substrates in the primate spinal cord, selectively activating opiate, α-adrenergic, and baclofenergic receptor systems. Earlier, Yaksh and Rudy[6] proposed that spinal and supraspinal sites of opiate

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analgesia can interact in a synergistic fashion. Here, Yaksh and Reddy report a comparable synergy within the cord but across receptor types: Sub-analgesic doses of morphine and an α-adrenergic agonist injected together intrathecally cause robust analgesia. Of particular interest, this effect did not manifest tolerance over a 3-week observation period. Just as using the intrathecal route was seen to prevent occurrence of unwanted opiate effects, so the use of this combination of drugs appears to circumvent the problem of drug tolerance.

Although technically feasible, the eventual clinical utility of intrathecal or extrathecal drug administration for long-term pain management remains doubtful. Problems related to the chronic implantation of a drug delivery system and the effects on spinal tissue of repeated or continuous drug infusions are among those still needing to be resolved. The ultimate hope shared by all workers in this field is that noninvasive means can be found to activate endogenous substrates of analgesia. Relatively unexplored to date are higher neural control systems that may play upon brain stem and spinal centers of pain inhibition. Behavioral experiments demonstrating cognitive, emotional, and situational factors influencing pain responsiveness are legion and suggest that the pain-inhibitory circuits of the brain are accessible to environmental controls. It does not seem unreasonable to expect, therefore, that behavioral technology may one day provide the most benign but effective anodyne in the pain therapist's arsenal. Selective pharmacologic control of spinal pathways offers enticing new prospects for anesthesiology, but detailed pharmacokinetic data on such questions as transdural passage and intrathecal binding are urgently needed if orderly exploitation is to proceed.

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Pharmacokinetic Modelling of Thiopental

ANESTHESIOLOGISTS have classically conceptualized the distribution and elimination of inhalational and intravenous anesthetics using physiologically-based models. In this issue, Morgan *et al.*[1,2] have used pharmacokinetic modelling to characterize the distribution and elimination of thiopental. This editorial will compare and contrast physiologic and pharmacokinetic models. Physiologic models (also called perfusion models) attempt to characterize drug behavior in the body using anatomic and physiologic concepts, assigning average organ size, average organ blood flow, mean blood:tissue drug partitioning and observed rates of enzyme reactions. In physiologic modelling, body tissues are grouped together into comparisons on the basis of similar blood perfusion and drug solubility characteristics. Highly perfused tissues are termed the vessel-rich or viscera group. Muscle and skin form a lean or muscle group, while fat is considered as a separate compartment. Finally, bone, ligamentous and cartilaginous tissues comprise a vessel-poor group that usually have minimal influence on drug distribution and elimination. Eger[3] and others have successfully used this approach to explain the uptake and distribution of the inhalational anesthetics.

These same concepts have been used to attempt to explain the distribution and elimination of intravenously administered thiopental. The complexity of the physiologically-based models for thiopental have