Preclinical Work Leading to the Development of Spinal Analgesia

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Advances in medical practice sometimes hinge on the development of simple models, such as the ability to routinely catheterize the rodent spinal canal. In the early 1970s, we were considering mechanisms by which opiates produced their analgesic actions. My colleagues and I had completed a number of microinjection studies in primates and rodents, which emphasized the actions of opiates in the periaqueductal gray on nociceptive behavior. A photograph is available on the Anesthesiology web site at http://www.anesthesiology.org. In the summer of 1972, I was at the University of Wisconsin, Madison, Wisconsin, in the School of Pharmacy collaborating with Thomas A. Rudy, Ph.D., on matters pertaining to thermoregulation and I had decided to address this issue of whether morphine could alter spinal sensory function. Although our predisposition was that morphine’s analgesic action was mediated supraspinally, an important control was to show that a spinal action of morphine had no effect on supraspinally organized pain behavior.

To perform the “control” experiment, it seemed necessary to show only that spinally delivered morphine had no effect on pain behavior. The problem was how to give the drug in the unanesthetized rat, our behavioral model of choice. The veterinary literature described cisternal and lumbar taps in larger animals but nothing in the rat. Moreover, because we wanted to deliver several injections, a catheter seemed appropriate. The only certain avenue available was the cisterna magna. The approach was realistic, but the likelihood of success seemed low, i.e., passing a catheter to the lumbar space.

Actually, after several weeks of vacillation, one afternoon, I just decided to try it. I anesthetized the rat with pentobarbital, placed it in a stereotaxic head holder, tilted its head forward and made an incision to expose the cisternal membrane. Through a transverse nick, I passed a length of polyethylene tubing, which to my absolute surprise, went in without resistance. I was totally unprepared for this and had not even measured the tubing length. Still I guessed it to be 8 to 9 cm. The animal’s respiration had not been altered and there had been no motor signs. I sutured the incision and externalized the catheter. The second surprise was that, after recovery from the anesthetic, the rat showed normal ambulation and there were no signs of motor dysfunction. The next morning the rat was normal in all respects, except for a length of polyethylene tubing exiting the scalp. All responses and thresholds were normal.

At that moment I realized that by some stroke of luck I had managed to atraumatically catheterize the spinal canal of a rat. Immediately, I injected 5 μg of morphine. There was no catalepsy, loss of pinnae or blink reflexes (signs of supraspinal drug action) and no evidence of motor dysfunction. This absence of a motor effect was a surprise inasmuch as considerable literature has reflected the effects of morphine in hyperpolarizing motor neurons. Despite the lack of change in motor function, the tail flick reflex was blocked. Still, that was not entirely unexpected. Ample literature dating back to the 1930s emphasized the ability of morphine to block spinal reflexes in transected animals. After taking the animal to the hot plate, it became immediately apparent that in the absence of any evident dysfunction, the animal failed to behave as if the surface were hot. It was not until the surface temperature was checked that I realized the failure to respond was not due to an inadequate stimulus and that this rat was truly “analgesic.” An injection of

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naloxone immediately reversed all the effects. I realized then that this first rat had unequivocally shown that morphine, with an action limited to the spinal cord, in an unanesthetized animal, could induce a potent analgesic state without an effect on motor function. Subsequent work confirmed that the technique was repeatable and permitted generation of large numbers of rats in which multiple intrathecal injections could be made. Of course, the importance was not the technique itself, but what it permitted one to do.

This work led to the method paper and the published report in Science, along with several others immediately thereafter. At this time we had written a small National Institutes of Health grant to undertake brainstem recording and the effects of opiates. For reasons I will never understand, this little proposal led to a site visit in 1975 by Lou Harris, M.D. (Chair of Pharmacology at Virginia, Charlottesville, Virginia), Dominic Purpura, M.D. (Editor of Brain Research), and Frederick Kerr, M.D. (Professor of Neurosurgery at Mayo Clinic, Rochester, Minnesota). We had little to show in terms of recording, but I nervously presented the rat intrathecal data. In the course of the site visit, Dr. Kerr asked if I thought the spinal morphine was “safe,” as he was convinced at the outset that this phenomenon had clinical relevance. My response was yes, in rats and primates, but at the time I was moderately skeptical of its utility, given my lack of appreciation of the common practices of epidural and intrathecal routes for anesthetic delivery usage. Dr. Kerr took a copy of the Science manuscript and played the instrumental role in fostering the effort that led Josef Wang, M.D., and colleagues to report the effects of bolus intrathecal morphine and Burton Onofrio, M.D., to initiate the chronic intrathecal infusion of morphine in cancer patients at Mayo. As regards the grant, we did not get funded, but that site visit led to an enduring friendship with Fred Kerr and my moving to the Mayo Clinic, Rochester, Minnesota, in 1977.

For my own part, much of what subsequently followed in research was made possible by the same simple model. By the early 1980s we had defined the spinal effects of enkephalins/endorphins and proposed pharmacology consistent with spinal µ and δ opiate receptors. Work included attention to a number of systems, including those for γ-aminobutyric acid and α2-adrenergic agonists, cannabinoids, N-methyl-D-aspartate antagonists, calcium channel blockers, and cyclooxygenase inhibitors, and delta-opioid agonists. These preclinical studies and others like them served two purposes. First, they provided insights into the pharmacology of spinal systems that processed nociceptive information and the relevance of these systems to behaviorally defined pain states (as opposed to reflex or single unit activity in an anesthetized animal). This work, emphasizing spinal mechanisms in pain processing, converged with the increasing focus by physiologists on the spinal connectivity associated with the encoding of nociceptive information. Second, the rat intrathecal model proved to be a robust tool in characterizing the effects of spinal drugs and initially serving to define the safety profile of these drugs, even to the point of demonstrating that spinal opiates would not impede delivery in rats and rabbits. These early studies focusing on the pharmacology of spinal pain processing led more or less directly to the clinical implementation of not only other opiates (meperidine, methadone, β-endorphin, fentanyl, alfentanil and sufentanil) but also to a variety of pharmacologically novel agents, including clonidine, neostigmine, adenosine agonists, N-type calcium channel blockers and N-methyl-D-aspartate receptor antagonists. A simple model indeed!

References