PRESIDENT’S MESSAGE

Endogenous Opioids’ Primary Role: Harmonizing Individual, Kin/Cohort, and Societal Behaviors

This is the sixth and final AAPM President’s Message of my term. Prior messages emphasized that pain and its treatment should be viewed not only as individual patient management issues, but also as public health issues related to the care of populations. The public health concept of disease combines pathophysiology, host, and environment—a framing that fits well within the multidisciplinary pain care model that AAPM has championed for decades.

This has been a turbulent time in pain medicine. During my term, the conversation about pain has understandably been dominated by the current epidemic of opioid abuse. This prominence and the reality it reflects are both catastrophic. Mass media increasingly presupposes that all pain is about opioids and all opioids are about substance abuse. From the point of view of pain treatment, we are witnessing a historic pulling back of the enthusiasm and effectiveness with which patients with pain are assessed and treated. A widespread focus on addiction has also stigmatized patients with chronic noncancer pain, particularly those treated with opioids. Across the nation, many patients—including those who have benefited from and been compliant with a stable, modest dosing regimen of opioids for chronic noncancer pain—are being tapered, discontinued, and thrown into crisis based on misapplication of the 2016 Centers for Disease Control guidelines on this topic. Several months ago, results of routine Medicare surveys by recently hospitalized patients of their inpatient pain control were delinked from pay-for-performance incentives for institutions to do well on these quality measures. The announcement accompanying this change by the Centers for Medicare and Medicaid Services (CMS) stated that CMS was “not aware of any scientific studies that support an association between scores on the pain management dimension and opioid pre-issues (e.g., crack cocaine) have been. Going forward, this is a good time to take stock of what we know about the endogenous opioid system to guide research, practice, and education. Drawing upon an abundant literature, I suggest that modulation of pain is a secondary role and that something much more important—behavioral fine-tuning to help the population as a whole survive threats beyond trauma to the individual—is primary.

My introduction to opioid research began in the late 1970s as a research fellow with colleagues in endocrinology and neurology; together, we developed an assay for beta-endorphin. Our initial clinical application of this assay had nothing to do with pain. Instead, funded by a grant to better understand impaired fertility in female athletes, we examined the effect of physical conditioning in previously sedentary women (see Carr, N Engl J Med 1981;281:560–63). We found that such training augmented the acute exercise-related increase of beta-endorphin in the bloodstream. Sensing that this finding could tie together several then-emerging actions of this morphine-like hormone, we began our report by noting that “emerging evidence suggests that endogenous opioid peptides influence diverse functions linked with the body’s energy balance including appetite, thermoregulation, lipolysis, and reproduction.” Since that publication, substantial research literatures have extended knowledge of endogenous opioids’ role in each of these linked functions.

Pain research has likewise advanced remarkably in recent decades. Among its most significant findings is the rediscovery through brain imaging and other research methods of what writers, artists, and clergy have known for millennia: Pain is not simply the experience of nociception, but also is a dysphoric state with feelings of isolation, social rejection, even stigmatization. An enormous literature on social factors in pain (see, e.g., Craig, Can Psychiatr 2009;50:22–32) resonates with what mothers instinctively know when they hug and comfort a child after a bruise or scrape, with every confidence that the resultant analgesia will be prompt and persistent. As surveyed by Krahe et al. (Front Hum Neurosci 2013; 7.386 doi: 10.3389), opioid administration appears to alleviate both bodily pain and the pain of social isolation or absence of a caregiver. Thirty years ago, Alexander and colleagues questioned whether traditional appraisals of drugs’ addictive potential using solitary rats held in small glass and steel cages were distorted. They found that housing them in spacious enclosures—“rat parks”—with painted scenery, wood shavings to roam over, toys to play with, crevices to explore, and most importantly, their mates and pups reduced or eliminated the self-administration of opioids observed in isolated rats within small bare cages.
A panoply of studies using many methods has since linked pain, the opioid system, and subjects’ degree of social connectedness (see Lieberman and Eisenberger, Science 2009;323:890–1). Naloxone blocks the analgesic effect of nearby mouse littermates in pain models (nonsibling mice do not evoke analgesia). Naltrexone reduces human subjects’ feelings of social connection. In species from chickens through monkeys, small nonbreeding doses of opioids reduce cries of distress in infants separated from their mothers. A genetic variant of the morphine receptor in humans is associated with increased activation of brain regions felt to mediate the unpleasantness of physical pain, along with heightened sensitivity to social rejection and reduced analgesic benefit from opioids (Way et al., Proc Natl Acad Sci U S A 2009;106:15079–84). Earlier this year, Oxford researchers found significant correlations between the size of subjects’ social networks and their experimental pain thresholds; they speculated on a role for endorphins but did not, for ethical reasons, sample cerebrospinal fluid to measure them. Building on many similar findings, a “brain opioid theory of social attachment” had earlier been proposed (see, e.g., Machin and Dunbar, Behaviour 2011;148:985–1035).

What if, as the modern era of opioid studies commenced in the 1960s and 1970s, history had taken another path? In this alternate universe, policy-makers alarmed by social unrest might have approved funding to investigate biological determinants of weakened or fractured societal structures and individual social bonds. They also might have been interested to support investigations of mechanisms responsible for individuals’ physiological responses to their perceptions of breakdown of their societies (cf. Tainter, The Collapse of Complex Societies. Cambridge: Cambridge University Press; 1988). In this parallel universe, researchers would uncover a family of receptors and endogenous ligands that, if blocked by antagonists or genetically engineered to be absent, profoundly disrupt maternal-infant attachment behavior to the point of starvation of newborn mouse pups due to inadequate suckling. Young knockout mice would exhibit major deficits in social behavior including deficient reward behavior reminiscent of humans with autism spectrum disorders. Adult males would show a blunted response to female vocalization, test high on anxiety surrogate measures, and be so aggressive that they could not be safely housed with other mice. Given these properties, this system might be named something like the “eusocial” system. Later, perhaps a decade or two after their discovery, an investigator might stumble onto the fact that eusocialins not only mediate behavior that reinforces social bonding, but also act as analgesics. That sequence of events would be possible because the above actions have in reality been observed in research on...the morphine (“mu”) opioid receptor! (see Nelson and Panskepp, Neurosci Biobehav Rev 1998;22:437–52; Becker et al., Neuropsychopharmacol 2014;39:2049–60).

Societal cohesiveness is an interindividual or group property, not definable in single isolated individuals. Nonetheless, processes at the individual level may be governed by parameters whose alteration on a microscale leads to substantial consequences at the macro scale. This is thought to be the case for our physical universe, in which the microscale “constants of nature” (e.g., the charge of an electron, the weak attraction between subatomic particles, weight of a proton, etc.) are no longer considered to be accidental. Altering any of them even slightly would instantly perturb, then collapse or explode, the physical universe (see, e.g., Barrow, The Constants of Nature. New York: Vintage; 2002; Siddarth, The Thermodynamic Universe. World Scientific; 2008). The stability of our physical universe reflects a harmony or resonance between the laws and forces at the microscale and those at the largest, cosmological scales. For example, if the average density of matter in the universe were to exceed a certain critical value, following the Big Bang the entire universe would over time collapse back into itself (see Rowan-Robinson, The Nine Numbers of the Cosmos. Oxford: Oxford; 1999). If the density were just at the critical value, the universe would expand to a certain volume and remain there forever. If less than the critical value, as appears to be the case for our universe, it would forever be expanding. One may draw an analogy with the intensity of social binding—below a particular value of cohesiveness, social groups fall apart; above that value they stagnate, unable to adapt. Tellingly, Hans Selye’s term for the overarching model now termed the stress (or allostatic) response was the “General Adaptation Syndrome.” Although well aware of population-level traumas such as world war, his focus was on their consequences in individuals.

Apart from maintaining the intensity of social cohesiveness at an optimal value, the endogenous opioid system mediates population-level adaptation to the energy supplies and demands of its environment. Impairing reproductive capacity during stressful, energy-expending, and/or calorie-deprived intervals, the endorphin system mediates a decline in population-wide fertility. The population will hence decline in number during intervals of poor nutrition. (The proximal site of this adaptive response—the hypothalamus—is the same target through which exogenous opioids produce hypogonadism and secondary bone loss.) The paradox that a decrease in population can illustrate its “fitness” recalls Darwin’s later thinking, in which, for example, he extended the concept of fitness from the single worker bee to the entire hive. From that perspective, the sterility of worker bees allows a shift of available nutrient energy to the benefit of the superfertile queen, thereby favoring survival of the colony as a whole. But the endogenous opioid system, along with other eusocialin gene families (e.g., oxytocin), is not just about reducing populations during caloric deprivation. Clearly, social cooperation enhances survival of the group. Stress-induced mobilization of the opioid system to provide temporary endogenous analgesia also would appear to provide a
brief respite for members of the group to successfully escape further harm after initial injury, at a minimal cost to the organism or the population.

I have presented a case for the prime importance of the non- or extra-analgesic effects of the endogenous opioid system. Using phrases such as “energy balance” or “social bonding” to encapsulate these effects intellectualizes their life-and-death importance (much like describing smothering in terms of pulmonary alveolar gas exchange). For offspring too young to feed themselves, acceptance among the nourished litter and mutual bonding with the nourishing mother are essential for survival. Based on descriptions by opioid abusers of what it feels like to be “high,” there seem to be parallels with the pleasantly warm, desire-free, and maternally cared-for state of well-fed, protected infants. Space does not permit surveying other endogenous opioid effects such as immune modulation. The special relevance of the endogenous opioid system to social bonding may offer a clue as to why individuals with opioid use disorder commonly engage in strikingly pernicious antisocial behavior. Stealing from family members or prostituting oneself departs from normal kin/cohort behavior to a degree rarely seen in other addictions such as cigarette smoking, alcoholism, or gambling. After acute detoxification, rehabilitation of those with opioid use disorder typically relies on a therapeutic group of peers to leverage social interactions and reinforce abstinence. In a parallel fashion, pain rehabilitation programs usually employ group formats and emphasize a return to social function in the family or workplace. Less obvious is the prospect that interprofessional pain treatment teams may have special merit in exposing patients to respectful, inclusive groups of people working collaboratively toward a common goal (see Carr, IASP Pain Clin Update 2009;17:1–6; Fishman et al., Pain Med 2013:14:971–81).

Given the current tendency to view all of pain as about opioids and all of opioids as about substance use disorder, it will take some time before this broader perspective is restored. As an example of the current narrow focus, a 2016 review co-authored by the director of the National Institutes on Drug Abuse about opioid abuse in chronic pain nicely balances safety and the analgesic needs of patients in pain. However, its sole figure, “location of mu-opioid receptors,” omits their presence in the hypothalamus—the key site of their inhibitory effects on reproductive function and ACTH/beta-endorphin secretion (Volkow and McLellan, N Engl J Med 2016:374:1253–63). My preceding President’s Message proposed to add an eighth “social sin” (care without compassion) to the seven popularized by Mohandas Gandhi. Recognizing the rich biology connecting endogenous opioids, social bonding, pain, and clinical phenomena such as stigmatization or the placebo response, we must as clinicians make every effort to ensure that our own interactions with patients and families are forthright, compassionate, and as nonstigmatizing as we can make them despite pressures from every side to the contrary. In doing so, we can rely on our own peer support from like-minded colleagues within the “pain community” and, especially, the American Academy of Pain Medicine.

Acknowledgments

I thank Donna Bloodworth, MD, for helping refine the “What if...” narrative construct above, and the numerous AAPM members, colleagues, and staff dedicated to the well-being of this organization and, by extension, patients with pain and those close to them.

**Daniel B. Carr, MD, DABPM, FFPMANZCA (Hon.)**
President, American Academy of Pain Medicine
Professor of Public Health and Community Medicine
Professor of Anesthesiology and Medicine
Founding Director, Tufts Program on Pain Research, Education and Policy
Boston, Massachusetts, USA