The Pain Divide between Men and Women

The problem with treating pain, of course, is that no one can see it. And even though doctors are warned never to think that they know how much pain patients are experiencing, it happens all the time. "Put yourself in that position and you immediately misrepresent the patient and do them a misservice. The patient may end up undertreated," said Allan I. Basbaum, PhD, professor and chair of the Department of Anatomy at University of California, San Francisco, and editor in chief of the journal *Pain*.

Women are particularly likely to face this problem because they seek treatment for pain far more often than men. In fact, clinical pain conditions, except for back pain, occur at far higher rates in women, Basbaum said. For instance, 9 of 10 patients with fibromyalgia and 8 of 10 patients with temporomandibular disorder are women. Women are also 2 times more likely to have irritable bowel syndrome (IBS), 9 times more likely to have interstitial cystitis, and 3 times more likely to have migraine.

Exactly why women experience pain differently from men remains largely unclear. "However many people you talk to, that's how many explanations you will get. A variety of factors probably contributes to the sex differences in pain," said Roger B. Fillingim, PhD, associate professor at University of Florida College of Dentistry in Gainesville. Some pain experts postulate that the differences originated during primitive times when gender roles were more clear-cut and people's response to pain was more closely linked to survival strategies. Societal, behavioral, and psychological influences still clearly play a part in sex differences in pain.

For a long time, doctors tended to undertreat women's pain, chalking up their symptoms of pain to their being more emotional or lacking in toughness, but recent clinical studies, backed by abundant animal studies, have demonstrated that women have a lower threshold and tolerance for pain. Currently, researchers are beginning to identify specific biological underpinnings of sex differences in pain. These findings are providing clues about why women suffer more and, in doing so, are making women's reports of pain more difficult for physicians to dismiss. Continued research in this direction may lead to a day when doctors treat pain in both female and male patients more effectively.

Pain Response Differences Provided Early Clues

Pain research has focused on emerging awareness of significant sex differences in the body's opioid receptor system, which comprises μ, κ, and Δ receptors. These receptors, which are found in the brain and spinal cord, are responsible for regulating pain. Each shows an affinity for different endogenous opioid peptides—namely, endorphins, enkephalins, and dynorphins—that are released by the pituitary gland. These peptides stimulate the receptors and block painful stimuli from reaching the higher brain centers where the perception of pain occurs.

Early clues to sex differences in the opioid receptor system were anecdotal. Clinicians noticed that nalbuphine (a κ-receptor agonist) provided better pain relief for women during childbirth than morphine (a μ-receptor agonist). Men, on the other hand, tended to prefer morphine when they were in severe pain. According to a 2003 literature review of sex-based differences in clinical practice by researchers at St. Olav's University Hospital in Trondheim, Norway, women taking the same morphine dose as men experienced more respiratory-depressive side effects, while men required 30% to 40% more morphine than women to achieve similar pain relief.

Limited randomized, controlled clinical studies have so far supported the anecdotal evidence. In a recent randomized, controlled study published in the January 2004 issue of *Southern Medical Journal*, women ($n = 45$) reported statistically significantly lower pain scores after 60 minutes when given butorphanol (a κ-receptor agonist) than when given morphine. Men ($n = 49$) reported less pain with morphine, although this trend was nonsignificant. The findings led the authors to recommend κ-receptor agonists for female patients with injury-related pain.

Other researchers found that although women receiving a 5-mg dose of the κ-receptor agonist nalbuphine were relieved of postoperative dental pain, the drug was actually antianalgesic for men, who experienced more pain while receiving it than they did while taking placebo. Lead researcher Robert W. Gear, DDS, PhD, assistant research physiologist and assistant clinical professor in the Department of Oral and Maxillofacial Surgery at University of California School of Dentistry in San Francisco, discovered that adding 0.4 mg of naloxone, an opioid receptor antagonist that equally affects all 3 types of opioid receptors, to the 5-mg dose of nalbuphine resulted in significantly improved pain relief in both sexes. (When the investigators tried a similar experiment with a 2.5-mg dose of nalbuphine, they could not replicate the findings of the previous experiment.)

Gear hypothesized from his work that the body actually has 2 separate receptors for κ-receptor opioids, one that produces the analgesic effect and another that produces the antianalgesic effect. Naloxone may block the action of nalbuphene at the antianalgesic κ receptor and, in so doing, unmask the separate analgesia κ receptor, so that it is expressed completely in both men and women, Gear suggested. "The sex difference

is explained, we think, because men may have more of the antianalgesia receptors than women," said Gear. If these antianalgesia receptors could be identified, Gear added, they might provide a potent new target for new pain-killing drugs.

Mechanisms Contributing to Sex Differences

Armed with the mounting evidence of sex differences in the opioid receptor system, researchers at McGill University in Montréal, Canada, used mapping to identify a gene responsible for the sex difference in analgesia from drugs acting at the κ-opioid receptor. The gene turned out to be the melanocortin-1 receptor (*Mc1r*) gene, which is linked to red hair and fair skin in humans.

The McGill University researchers found in their 2003 Proceedings of the National Academy of Sciences study that κ-specific analgesics administered to mutant mice with an inactive variation of *Mc1r* analogous to the "redhead" variation in humans produced more analgesia than in normal mice. "Whether the melanocortin-1 receptor worked mattered for the functioning of the pain inhibition system in female mice," said Jeffrey S. Mogil, PhD, professor of pain studies at McGill. But it did not seem to matter at all with the male mice: They did not appear to use the melanocortin receptor system to modulate pain.

The McGill study included a follow-up study wherein men and women with several *Mc1r* variations, causing different hair colors and skin types, received the κ-receptor agonist pentazocine. *Mc1r* variations caused women to have a heightened response to the pain reliever, particularly redheaded, fair-skinned women, but did not produce pain relief in men. This interesting result indicated that the *Mc1r* gene has the "unexpected" role of modulating a κ-specific pain pathway that exists only in women, Mogil said.

These findings were the latest in convincing Mogil that pain response is mediated by different brain circuits in men and women, with most of the sex differences in the opioid pain modulatory system. "Not only are there sex differences in the output of pain systems, but I believe that males and females actually have separate and neurally distinct pain processing with different neurochemicals and genes," he said. "I don't think that there is anything else like this in biology," he added.

Differences in How Pain Is Processed

While Mogil continues his genetics studies, other researchers are using different tools to learn about this gender-distinct pain processing pathway. For instance, some researchers are using positron emission tomography to view the brain localization of the response to pain stimuli. Researchers studying IBS at University of California, Los Angeles, for instance, used positron emission tomography, as well as measures of autonomic system response (such as blood pressure and heart rate), to track differences in responses to pain. They found that female patients with IBS not only were generally more sensitive to gastrointestinal pain than male patients with IBS but also that their brains reacted differently. The female patients with IBS showed greater activity in the emotion-based limbic regions, whereas the men with IBS showed greater activity in the analytic cognitive regions, according to the report in the June 2003 issue of *Gastroenterology*. "This probably has something to do with the emotional response to pain. Women seem to process pain differently from men in certain situations. It may have to do with more general sex differences in stress biology," said Bruce D. Naliboff, PhD, clinical professor in the Department of Psychiatry and Biobehavioral Sciences at University of California, Los Angeles, School of Medicine and chief of the psychophysiology research laboratory at the Veterans Affairs Greater Los Angeles Healthcare System. Naliboff and his colleagues are now using functional magnetic resonance imaging to learn more about sex differences in the brain's response to pain.

Positron emission tomography has detected sex differences in the regional activation of the μ-opioid system in response to sustained pain. Researchers at the University of Michigan in Ann Arbor attached a radioactive tracer to a molecule that only binds to μ-opioid receptors to trace the localization of the activation of the μ-opioid neurotransmitter system, which mediates the effects of endorphins or enkephalins. The researchers first showed that the endorphin system became activated in the brains of 13 men and 7 women who were subjected to moderate levels of pain in their jaw muscle over 20 minutes. Endorphin-system activation corresponded in time with a drop in the volunteers' perceived pain and pain-related emotions, according to a report in the 13 July 2001 issue of *Science*.

In a follow-up report a year later, the researchers stated that the μ-opioid–mediated pain response differed by gender. According to the report in the 15 June 2002 issue of the *Journal of Neuroscience*, 14 men scanned before and during jaw pain showed increases in endorphin release in certain brain areas during the painful state, similar to the earlier results. The 14 women in the study showed a reduction in endorphin release and experienced intense pain. The women reported more pain-related negative emotions than the men. Positron emission tomography showed that, during pain, the men had more μ-opioid activation in the anterior thalamus, ventral basal ganglia, and amygdala than the women. The women also had reductions in basal-state μ-opioid activation in the nucleus accumbens, an area associated with hyperalgesia in animal experiments. The findings indicated that men and women differ in the magnitude and direction of the

μ-opioid system in distinct brain nuclei.

The Role of Sex Hormones

Sex hormones appear to be a major factor in pain. All of the women in the 2002 *Journal of Neuroscience* study were tested during the time in their menstrual cycle when levels of estrogen and progesterone were lowest, noted lead author Jon-Kar Zubieta, MD, PhD, associate professor of psychiatry and radiology at University of Michigan. Fluctuating levels of sex hormones have long been associated with changes in pain tolerance, so Zubieta and colleagues wanted to find out if the pain experienced by women differed depending on their estrogen level.

Zubieta and colleagues followed up the *Journal of Neuroscience* study by scanning healthy women once during their early follicular phase when estrogen levels are low and then again during that same phase in another month after they had worn an estrogen-releasing skin patch for a week. The patch increased their estrogen to levels normally seen in the menstrual cycle. (This design allowed the investigators to study estrogen's effect in the absence of progesterone, which normally increases along with estrogen.) Positive emission tomography performed without any painful jaw stimulus showed that more μ-opioid receptors were available in the presence of high estrogen levels. After the painful jaw injection, the women reported feeling less pain than when their estrogen levels were low, and in fact, positive emission tomography showed a much greater increase in endorphin release and activation of the receptors. The effect was seen in multiple brain areas that are known to be involved with the perception and regulation of pain.

Other research has linked low estrogen levels to impaired activation of the body's pain-response system. The risk for migraine, for instance, is highest during menstruation, when estrogen levels are low. "Our research shows that exogenous sex hormones will block the headache in women with menstrual migraine, but not the bleeding, while progestins will block the bleeding but not the headache," said Richard B. Lipton, MD, professor and vice chair of neurology and professor of epidemiology and population health at the Albert Einstein College of Medicine in Bronx, New York.

Because migraine remains almost 2 times more common in women after menopause and even past age 80 years, cyclical hormonal factors are only partly responsible for sex pain differences, Lipton noted. "It may be that estrogens produce enduring changes in the brain that set up a predisposition even after hormones stop cycling," Lipton said. "In any case, it's clear that sex hormones influence inflammation and also neural processing of pain. But the experience of pain is complex and depends on more than just the hormonal milieu," he added.

The role of estrogen is more complex than these experiments indicate because increased estrogen levels, not decreased levels, are also associated with pain activation. For instance, some research has linked increased levels of pain in women with temporomandibular disorder to increases in estrogen levels during the menstrual cycle. But human studies on the effects of sex hormones are difficult to perform because they may involve gonadectomy or administration of female hormones to men and vice versa, pain experts noted. Studies involving female rodents have indicated that high levels of estrogen are associated with decreased opioid analgesia. In a recent animal experiment involving rats without ovaries, researchers found that temporomandibular joint neurons were more excitable in rats receiving long-term estrogen replacement, an effect that was exacerbated in the presence of temporomandibular joint inflammation—suggesting increased pain for rats without estrogen. The estrogen also suppressed swelling and blood flow in the joint, an action that is known to augment tissue damage associated with persistent inflammation, said principal investigator Michael S. Gold, PhD, associate professor in the Department of Biomedical Sciences at University of Maryland Dental School in Baltimore. The results of these experiments were published in the *Journal of Neurophysiology* in March 2005. In addition, results from experiments in male rats indicated that testosterone has an effect that is just the opposite of estrogen, actually increasing swelling and blood flow but reducing the excitability of the temporomandibular joint afferents, Gold noted.

Gender-Based Pain Treatment

Research deciphering sex differences in pain is still in early development, according to pain experts, and pain remains largely mysterious. "Pain is a matrix of activity, and there is no one pain center, just like there is no one beauty center. But that doesn't mean that the matrix can't be evaluated and better understood," Basbaum said.

Although there are no biomarkers for pain yet and just a few identified pain-associated genes, researchers are hopeful that clinicians will one day be able to individualize treatment according to a patient's sex or other aspects of his or her biological profile. Drug companies may even develop a pain-relieving medication that "will literally kill pain in one sex and not in another," Mogil said.

Understanding sex differences in pain—and other differences among men and women—might advance faster if more basic research, such as animal models, included both sexes. "Although women are now included in all clinical trials, basic science research in rats and mice is still 92% males only," Mogil said. The main reason is probably habit, he said. Also, many scientists believe that the extra variability of estrous cycles would make experiments more difficult to interpret. However, when

Mogil reviewed the past decade of his research, in which he used both male and female mice, he found that males actually showed slightly more variability than females. On the basis of this finding, published in *Pain* in August 2005, Mogil said that "there are no excuses left: If you don't use both males and females, you're ignoring half the population that you're trying to model." He noted that he had identified many findings about sex differences simply because his ongoing work included both male and female subjects.

In 1993, the National Institutes of Health mandated that clinical research include women, and scientific investigation into differences in pain sensitivity and pain conditions that particularly affect women appears to have increased dramatically in recent years. Still, only a limited number of studies actually focus on this issue. Just 3% of recent National Institutes of Health grants include a hypothesis about sex or gender differences, according to a 2005 report from the Society for Women's Health Research. And although recognition of the importance of diagnosing and treating pain conditions has increased greatly, pain research overall remains a low priority. Pain accounts for more than 20% of medical visits and 10% of prescription drug sales, but just 0.6% of the National Institutes of Health budget goes to basic and clinical pain research, according to an article in the September 2003 issue of *The Journal of Pain*.

Whether drug companies are devoting adequate attention to developing new painkillers is a matter of some debate. More varied and effective pain relievers with fewer side effects would clearly be useful because most pain relievers are limited by their side effect profile, Basbaum said.

Drug companies are interested in the potential for more targeted pain therapies because there are clearly significant genetic differences in how people process pain and respond to analgesic drugs, according to Basbaum. Targeting a painkiller to a specific population would limit the potential market to, say, women only, but such a drug might also perform better in clinical trials and in the clinic because it would only be tested and used in those people it was designed to help. "If you could predict that a patient was going to be more sensitive to a particular type of analgesic drug, it would certainly be worth a lot," Basbaum said.

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