

Chronic Pelvic Pain: Opening the Black Box

Dr. Anthony Schaeffer

Dr. Anthony Schaeffer is the Herman L. Kretschmer Professor and Chairman of the Department of Urology at Northwestern University in Chicago, Illinois. Dr. Schaeffer has led pioneering work in basic and clinical studies of urinary tract infections and prostatitis, involving novel concepts regarding the cause and treatment of these conditions. Dr. Schaeffer has also made major contributions to the management of post-prostatectomy incontinence through the implementation of a mobile urethral sling procedure. Dr. Schaeffer earned his M.D. from the Feinberg School of Medicine at Northwestern University and interned at the Chicago Wesley Memorial Hospital, after which he pursued a surgery residency at McGaw Medical Center of Northwestern University and a urology residency at Stanford University Medical Center in California. Dr. Schaeffer has been an NIH-supported researcher for the past 30 years, including research support from NIDDK for at least 20 of those years. At the September 2010 meeting of the National Diabetes and Digestive and Kidney Diseases Advisory Council, Dr. Schaeffer presented on urologic chronic pelvic pain, sharing some new insights into what this condition might be.

Urologic chronic pelvic pain encompasses two major pain syndromes—interstitial cystitis/painful bladder syndrome, which primarily affects women, and chronic prostatitis/chronic pelvic pain syndrome, which only affects men. Both syndromes, however, share the characteristics of severe pain below the abdomen, often with urinary frequency and urgency, and in both cases their cause remains unknown. Research is revealing that millions of people worldwide may have symptoms of urologic chronic pelvic pain syndromes, with attendant suffering akin to patients with serious chronic illness. As fully effective treatments are elusive and there is no cure, people with these syndromes

suffer and can also incur high medical costs for themselves and the health care system. Dr. Schaeffer described research suggesting that urologic chronic pelvic pain syndromes may be mediated by novel adaptations of well-known host-bacteria interactions, as well as evidence that the central nervous system can be permanently altered by these interactions—thus suggesting that these syndromes might actually be a disease of infectious origin.

Quest for a Possible Infectious Origin

Dr. Schaeffer related that, in many cases of urologic chronic pelvic pain, there appears to be an infectious beginning. In his experience, patients will recall contracting a urinary tract infection (UTI) prior to the onset of chronic pain symptoms. However, most of these people, when seen by a doctor later in life, have no detectable evidence of infection, and many of them do not have inflammation. So, how could a UTI, which is usually associated with acute, or short-term, pain, possibly trigger or transition into a chronic pain condition?

While one candidate might be the inflammation that results from infection, patient data suggest that there is a disassociation between infection, inflammation, and the presence of pain. For example, patients with urologic chronic pelvic pain syndrome may have pain but no current evidence of infection or inflammation. Also, whereas most patients with UTI experience pain that has long been assumed a natural consequence of infection-associated inflammation, some people have pain-free bacterial infections (*i.e.*, asymptomatic) who nonetheless also have inflammation. That is, there is evidence of inflammation, such as infection-fighting white blood cells in the urine, but no pain. So, Dr. Schaeffer and his colleagues performed experiments in animal models to determine if there

SCIENTIFIC PRESENTATION

are differences between the bacteria that cause the acute, painful UTIs and those that are involved in asymptomatic infections. They did this by placing the different strains of bacteria—those from patients with either acute UTI or from patients with an asymptomatic infection—into mouse bladders, and then monitoring the pain the mice experienced over the course of an infection. They found that, indeed, only infection with the acute UTI strain caused pain. However, similar to observations in humans, other experiments showed that both strains were capable of causing inflammation—suggesting that the difference in their ability to incite pain lay elsewhere.

Searching for bacterial factors that could contribute to this difference, Dr. Schaeffer's team focused on lipopolysaccharide, or LPS. The LPS molecule, a large lipid-sugar molecule found on the surface of bacteria, is a so-called “virulence factor” that helps to optimize bacterial infection of a host. It is known to contribute to inflammation and shock, suggesting it might also somehow contribute to pain. Experiments with cells and in animal models revealed that LPS from either strain incited inflammation. When placed in mouse bladders, however, only LPS from the acute strain caused pain, and did so much more rapidly even than the acute infection itself. Dr. Schaeffer and his colleagues determined that the typical interaction between this molecule and a receptor on host cells, called Toll-like receptor 4, was indeed involved in mediating the pain response—a potential new function for this interaction, which typically mediates inflammation.

Molecular Studies and Potential Clinical Relevance

Through further analysis of the LPS molecule, Dr. Schaeffer and his team have uncovered some intriguing findings that suggest that a specific alteration in this molecule between different bacterial strains is somehow responsible for whether a bacteria induces an acute infection that can lead subsequently to chronic pain after the infection is cleared, or whether it only causes acute pain

at the time of infection. Moreover, they now have evidence for how the LPS molecule may be used therapeutically. Shortly following infection with an acute UTI strain, mice were given either a mock treatment or LPS from asymptomatic bacteria. The LPS from the asymptomatic bacteria significantly reduced the pain associated with the UTI, implying a therapeutic response.

Dr. Schaeffer noted that they have found similar responses in mice in which they have caused interstitial cystitis-like symptoms using a herpesvirus. In other studies, bacteria isolated from a person with chronic prostatitis were transferred to the prostates of mice. These mice developed pain symptoms similar to human chronic prostatitis. Interestingly, the ability to cause pain symptoms also depended on the mouse model used in the experiments, suggesting that there are host-specific differences in susceptibility to pain. Moreover, Dr. Schaeffer and his team have observed in this spectrum of studies the same type of dissociation between inflammation and pain and infection as seen with the UTI and pain models.

Neuro-Mechanisms and the MAPP Network

In 2008, the NIDDK established the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network to enable multiple laboratories and investigators around the country to work collaboratively on novel ways of looking at these enigmatic syndromes. While the Network's focus is on two major forms of urologic chronic urologic pelvic pain syndromes, interstitial cystitis and chronic prostatitis, researchers are also exploring the possible relationship between these and other pain syndromes, including irritable bowel syndrome, fibromyalgia, and chronic fatigue syndrome. Through this Network, Dr. Schaeffer's group has begun to work with neurophysiologists and neuroimaging experts, using an imaging technology called functional magnetic resonance imaging (fMRI) to look at chronic pain states. For example, using a computerized system originally developed

SCIENTIFIC PRESENTATION

by a back pain researcher to directly correlate a person's experience of pain with what is going on in the brain, their fMRI studies have shown some intriguing differences in brain activity between people experiencing acute pain from heat exposure, people with chronic back pain, and people with chronic prostatitis. These studies in people are made all the more intriguing by new studies in mouse models suggesting that, when instilled into the mouse bladder, UTI bacteria that cause chronic pain can also cause a persistent change in electrical signaling by part of the central nervous system.

In addition to apparent functional changes in the brain, Dr. Schaeffer and collaborators have examined changes in the brain structure of people with urologic chronic pelvic pain syndromes. These imaging studies reveal an apparent correlation between the intensity and duration of pain and the density in the brain's gray matter in different brain regions. Interestingly, some of the brain areas that appear to be affected by urologic chronic pelvic pain are

important in human function and behavior, particularly in emotional decision making.

Summary and Future Directions

Dr. Schaeffer noted that the studies he presented provide evidence that there may be an infectious basis for the chronic pain experienced by people with urologic chronic pelvic pain syndromes, and that this pain persists well after the initial infection and inflammation has cleared. At a cellular level, host Toll-like receptors appear to be acting as novel "nociceptors" for pain in a way that is independent of inflammation. The bacteria appear able to modulate the pain response via differences in LPS, and there appears to be involvement of the central nervous system. Building on some of these new findings and other studies, Dr. Schaeffer's team is now exploring "designer bacteria" or bacterially based molecules that could be administered to alter the pain response in patients, providing hope that a better understanding of the genesis of pain in these conditions could lead to new treatments.