Thinking the pain away?

August 24 2005

Study shows the brain's painkillers may cause 'placebo effect'

Just thinking that a medicine will relieve pain is enough to prompt the brain to release its own natural painkillers, and soothe painful sensations, a new University of Michigan study finds.

The study provides the first direct evidence that the brain's own pain-fighting chemicals, called endorphins, play a role in the phenomenon known as the placebo effect -- and that this response corresponds with a reduction in feelings of pain.

Previous studies at U-M and elsewhere have shown that the brain reacts physically when a person is given a sham pain treatment, which they believe will help them.

But the new study is the first to pinpoint a specific brain chemistry mechanism for a pain-related placebo effect. It may help explain why so many people say they get relief from therapies and remedies with no actual physical benefit. And, it may lead to better use of cognitive, or psychological, therapy for people with chronic pain.

The results will be published in the August 24 issue of the Journal of Neuroscience by a team from the U-M Molecular and Behavioral Neurosciences Institute (MBNI). The research was funded by the National Institutes of Health.

"This deals another serious blow to the idea that the placebo effect is a

purely psychological, not physical, phenomenon," says lead author Jon-Kar Zubieta, M.D., Ph.D., associate professor of psychiatry and radiology at the U-M Medical School and associate research scientist at MBNI. "We were able to see that the endorphin system was activated in pain-related areas of the brain, and that activity increased when someone was told they were receiving a medicine to ease their pain. They then reported feeling less pain. The mind-body connection is quite clear."

The findings are based on sophisticated brain scans from 14 young healthy men who agreed to allow researchers to inject their jaw muscles with a concentrated salt water solution to cause pain. The injection was made while they were having their brains scanned by a positron emission tomography (PET) scanner. During one scan, they were told they would receive a medicine (in fact, a placebo) that might relieve pain.

Every 15 seconds during the scans, they were asked to rate the intensity of their pain sensations on a scale of 0 to 100, and they gave more detailed first-person ratings after the experiment. The researchers correlated the participants' ratings with their PET scan images, which were made using a technique that reveals the activity of the brain's natural painkilling endorphin chemicals, also called endogenous opioids.

Endogenous opioids bind to brain cell receptors called mu-opioid receptors, and stop the transmission of pain signals from one nerve cell to the next. Besides the brain's own chemicals, drugs such as heroin, morphine, methadone and anesthetics also act on the mu opioid receptor system to reduce pain.

Because the endorphin system naturally tries to quell pain whenever it occurs, the researchers slowly increased the amount of concentrated salt water being injected in the muscle as the scans continued, in order to keep the participants' rating of their pain within the same point range throughout the experiment. The placebo, a small amount of hydrating

solution, was then given intravenously every four minutes.

As the researchers alerted participants that the placebo was coming, and injected the placebo dose, the amount of additional concentrated salt water needed to maintain participants' pain over time increased -- indicating a reduction in pain sensitivity that the subjects were not aware of. In other words, thinking they were getting a pain drug actually allowed the participants to tolerate even more pain-inducing concentrated salt water than before.

After each scan, the researchers asked the participants more questions about their mood, emotions and other aspects of how they felt during the scans. There were significant differences between post-scan ratings given by participants after the scan in which they received the placebo, and after the scan during which they received the jaw injection alone.

Nine of the participants were classified as "high placebo responders" because they had more than a 20 percent difference between pain and placebo scans in their average pain ratings per volume of salt water infused -- in other words, the placebo effect was strong. The other five were classified as "low placebo responders."

These subjective ratings are consistent with previous findings, Zubieta notes. But the simultaneous imaging of the participants' endogenous pain-reducing opioid systems sheds new light on why the placebo effect occurs.

The imaging method used in the study involves tiny doses of a medicine called carfentanil that is attached to a short-lived radioactive form of carbon, which releases subatomic particles known as positrons. These positrons are detected with the PET scanner, which acts like a photographic camera to capture those particles. It then determines exactly which part of the brain they originated from, and how many of

them are coming from each brain region. The researchers also made MRI scans of the participants' brains, which they cross-registered with the PET scans to give accurate information on exactly which brain regions were active.

Because carfentanil competes with the brain's natural endogenous opioid painkillers for space on nerve cell receptors, the PET scans can be used to see how active the opioid system and mu-opioid receptors are. The stronger the positron signal from a particular brain region, the less active the mu opioid system, and vice versa.

All of the participants showed an increase in the activation of their mu opioid endorphin system after they were told that the "medicine" was coming and the placebo was given. The most pronounced differences were seen in four areas of the brain known to be involved in complex responses to, and processing of, pain: the left dorsolateral prefrontal cortex, the pregenual rostral right anterior cingulate, the right anterior insular cortex and the left nucleus accumbens.

When the researchers correlated the mu opioid activity changes with the participants' own ratings of their pain and emotions, they also observed that the placebo-induced activation of the opioid system was correlated with various elements of the experience of pain.

For example, activity in the dorsolateral prefrontal cortex was associated with the expectation of pain relief reported by the volunteers. In other areas, that activation was associated with relief of the intensity of pain, how unpleasant it was, or even how the individuals felt emotionally during the pain experience.

Because the new study was done only in healthy men between the ages of 20 and 30, further research will be needed to determine whether the effect occurs in women and in people with various illnesses. The power

of placebos to ease pain symptoms has been well-documented in many groups of subjects and illnesses, but the researchers started with healthy young males to rule out the impact of chronic pain, mood disorders and hormone variations, which can also affect the endorphin system.

In addition to Zubieta, the research team included MBNI members Joshua Bueller, Lisa Jackson, David Scott and Janyun Xu; radiology professor Robert Koeppe, Ph.D.; Thomas Nichols, Ph.D., an assistant professor of biostatistics in the U-M School of Public Health; and Christian Stohler, formerly of the U-M School of Dentistry and now at the University of Maryland School of Dentistry.

Source: University of Michigan Health System