Active ingredients in marijuana found to spread and prolong pain

August 13 2009

Imagine that you're working on your back porch, hammering in a nail. Suddenly you slip and hit your thumb instead — hard. The pain is incredibly intense, but it only lasts a moment. After a few seconds (and a few unprintable words) you're ready to start hammering again.

How can such severe pain vanish so quickly? And why is it that other kinds of equally terrible pain refuse to go away, and instead torment their victims for years?

University of Texas Medical Branch at Galveston researchers think they've found at least part of the answer—and believe it or not, it's in a group of compounds that includes the active ingredients in marijuana, the cannabinoids. Interestingly enough, given recent interest in the medical use of marijuana for pain relief, experiments with rodents and humans described in a paper published in the current issue of *Science* suggest these "endocannabinoids," which are made within the human body, can actually amplify and prolong pain rather than damping it down.

"In the spinal cord there's a balance of systems that control what information, including information about pain, is transmitted to the brain," said UTMB professor Volker Neugebauer, one of the authors of the Science article, along with UTMB senior research scientist Guangchen Ji and collaborators from Switzerland, Hungary, Japan, Germany, France and Venezuela. "Excitatory systems act like a car's accelerator, and inhibitory ones act like the brakes. What we found is

that in the spinal cord endocannabinoids can disable the brakes."

To get to this conclusion, the researchers began by studying what happened when they applied a biochemical mimic of an endocannabinoid to inhibitory neurons (the brakes, in Neugebauer's analogy) on slices of mouse spinal cord. Electrical signals that would ordinarily have elicited an inhibitory response were ignored. They then repeated the procedure using slices of spinal cord from mice genetically engineered to lack receptors where the endocannabinoid molecules could dock, and found that in that case, the "brakes" worked. Finally, using electron microscopy, they confirmed that the receptors were in fact on inhibitory, not excitatory neurons. Endocannabinoids docking with them would suppress the inhibitor neurons, and leave pain signals with a straight shot to the brain.

"The next step was to make the leap from spinal slices to test whether this really had anything to do with pain," Neugebauer said. Using anesthetized rats, he recorded the spinal cord electrical activity produced by an injection in the hindpaw of capsaicin- a chemical found in hot peppers that produces a level of pain he compared to a severe toothache. Although the rats were unconscious, pain impulses could be detected racing up their spinal cords. What's more, formerly benign stimuli now generated a significant pain response — a response that stopped when the rats were treated with an endocannabinoid receptor blocker.

"Why was this non-painful information now gaining access to the spinal "pain" neurons?" Neugebauer said. "The capsaicin produced an overstimulation that led to the peripheral nerves releasing endocannabinoids, which activated receptors that shut down the inhibitor neurons, leaving the gates wide open."

Finally, the researchers recruited human volunteers to determine whether a compound that blocked endocannabinoid receptors would have an

effect on the increased sensitivity to pain (hyperalgesia) and tendency for normally non-painful stimuli to induce pain (allodynia) often reported in areas of the body near where acute pain had been inflicted. In this case, the researchers induced pain by passing electricity through the volunteers' left forearms, with the intensity of the current set by each volunteer to a 6 on a scale of 1 to 10. At a second session a month later, the volunteers who had received the receptor blocker showed no reduction in perceived acute pain, but had significantly less hyperalgesia and allodynia — a result that matched up well with the endocannabinoid hypothesis.

"To sum up, we've discovered a novel mechanism that can transform transient normal pain into persistent chronic pain," Neugebauer said. "Persistent pain is notoriously difficult to treat, and this study offers insight into new mechanisms and possibly a new target in the spinal cord ."

It also raises questions about the efficacy of marijuana in relieving acute pain, given that endocannabinoids and the cannabinoids found in marijuana are so biochemically similar. "If you had a toothache, you probably wouldn't want to treat it with marijuana, because you could actually make it worse," Neugebauer said. "Now, for more pathological conditions like neuropathic pain, where the problem is a dysfunction within the nerves themselves and a subsequent disturbance throughout the nervous system that's not confined to the pain system, marijuana may be beneficial. There are studies that seem to show that. But our model shows cannabinoids over-activating the pain system, and it just doesn't seem like a good idea to further increase this effect."

Source: University of Texas Medical Branch at Galveston (news : web)