Study raises caution on new painkillers

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A new class of painkillers that block a receptor called TRPV1 may interfere with brain functions such as learning and memory, a new study suggests. The experiments with rat brain found that the TRPV1 receptor regulates a neural mechanism called long-term depression, which is believed to be central to establishing memory pathways in the brain.

The researchers said their findings also suggest that the function of TRPV1 in neural tissue may explain reported side effects of the anti-obesity drug Acomplia, widely used outside the U.S. While Acomplia has been approved in Europe, the FDA denied U.S. approval because of concerns that the drug increases risk of depression and suicide. The researchers, led by Julie Kauer, published their findings in the March 13, 2008, issue of the journal *Neuron*, published by Cell Press.

TRPV1, or "transient receptor potential vanilloid 1," is a pain receptor whose activation causes the pain in inflammation. The receptor is also triggered by noxious chemicals such as the chili pepper compound capsaicin.

Drug companies have been testing TRPV1 receptor blockers to treat the pain of inflammation and nerve damage in the peripheral nervous system (PNS). However, besides being expressed in the PNS, TRPV1 is expressed in areas of the central nervous system (CNS), including the hippocampus, the brain's learning center. However, its function in the brain was not well established.

In their experiments with rat brain slices, Kauer and colleagues explored

whether TRPV1 plays a role in long-term depression (LTD), which is a weakening of the signaling between neurons that takes place at the connections called synapses. LTD, and the counterpart strengthening of connections, called long-term potentiation, are key to the formation of neural pathways in learning, a process called plasticity.

The researchers found that they could block LTD in the brain slices using drugs that block TRPV1. Also, they could induce LTD using the TRPV1-activating compound capsaicin.

What's more, they found that genetically knocking out the TRPV1 receptor in mice drastically reduced LTD in the animals.

"In this study, we show for the first time that TRPV1 receptors are necessary and sufficient for a novel form of long-term depression at excitatory synapses," concluded the researchers. "The broad distribution of TRPV1 receptors in the brain suggests that these receptors could play a similar role in synaptic plasticity throughout the CNS."

The researchers said their findings suggest that drugs targeting TRPV1 could act not only on pain receptors in the PNS, but in the brain as well. They also wrote that their findings and those of other researchers "indicate that drugs that bind to CNS TRPV1 receptors are likely to influence more than just pain-related functions."

"Further work will help to ascertain whether hippocampal TRPV1 receptors could provide novel drug targets for neurological disorders," they wrote.

What's more, they concluded that their findings suggest a mechanism for the reported side effects of the anti-obesity drug Acomplia.

"A large percentage of patients stop taking this drug as a result of

psychiatric side effects, and our findings suggest the possibility that some of the central effects of [Acomplia] result from the antagonism of TRPV1 receptors …," they wrote.

"The results from this study have important implications for the development of drugs targeting TRPV1," wrote Benedict Alter and Robert Gereau in a preview of the paper in the same issue of Neuron. They wrote that the Kauer study as well as others indicating widespread expression of the TRPV1 receptor, "cloud the prospects of TRPV1-targeted analgesics. If TRPV1 is important in hippocampal synaptic plasticity, as this study suggests, then systemic TRPV1 antagonists may interfere with many processes thought to rely on hippocampal synaptic plasticity, such as learning and memory."

However, wrote Alter and Gereau, "there is a silver lining to this cloud." Drugs targeting TRPV1 in both the peripheral and pain-processing regions of the central nervous system "actually produced greater analgesia than antagonists thought to primarily act in the periphery." Also, they noted, targeting TRPV1 may be useful in treating other neural disorders, such as epilepsy.

"Regardless of the uncertain future of TRPV1-targeted therapeutics," they wrote, such studies "are important not only for drug development but also for expanding our knowledge of synaptic function."

Source: Cell Press