Natural 'high' could avoid chronic marijuana use

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Replenishing the supply of a molecule that normally activates cannabinoid receptors in the brain could relieve mood and anxiety disorders and enable some people to quit using marijuana, a Vanderbilt University study suggests.

Cannabinoid receptors are normally activated by compounds in the brain called endocannabinoids, the most abundant of which is 2-AG. They also are "turned on" by the active ingredient in marijuana.

Sachin Patel, M.D., Ph.D., and his colleagues developed a genetically modified mouse with impaired ability to produce 2-AG in the brain. The mice exhibited anxiety-like behaviors, and female mice also displayed behaviors suggestive of depression.

When an enzyme that normally breaks down 2-AG was blocked, and the supply of the endocannabinoid was restored to normal levels, these behaviors were reversed, the researchers reported on Nov. 26 in the online edition of the journal *Cell Reports*.

If further research confirms that some people who are anxious and depressed have low levels of 2-AG, this method of "normalizing 2-AG deficiency could represent a viable ... therapeutic strategy for the treatment of mood and anxiety disorders," they concluded.

However, this approach has not been tested in humans, they cautioned.

Relief of tension and anxiety is the most common reason cited for chronic marijuana use. Thus, restoring depleted levels of 2-AG also "could be a way to help people using marijuana," added Patel, the paper's senior author and professor of Psychiatry and of Molecular Physiology and Biophysics.

Chronic use of marijuana down-regulates cannabinoid receptors, and thus paradoxically increases anxiety. This can lead to a "vicious cycle" of increasing marijuana use that in some cases leads to addiction.

Patel and his colleagues previously have found cannabinoid receptors in the central nucleus of the amygdala of the mouse. The amygdala is a key emotional hub in the brain involved in regulating anxiety and the flight-or-fight response.

They also have found that chemically modified inhibitors of the COX-2 enzyme they developed relieve anxiety behaviors in mice by activating natural "endocannabinoids" without gastrointestinal side effects. Clinical trials of some of these potential drugs could begin in the next several years.

Cyclooxygenase (COX) enzymes produce pro-inflammatory prostaglandins and are the target of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs), used to relieve pain and inflammation. It has been known for several years that COX-2 inhibition also activates endocannabinoids.

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