Could Cannabis Lead the Way to Safer Painkillers?

Christine Heiner, BA, *Scientific Writer* and Sandra Hirsch, MBA, *Research and Training Coordinator*

Chronic or persistent pain affects 76.2 million Americans, more people than cancer, heart disease, and diabetes combined (1-5). In the U.S., it is estimated that chronic pain accounts for $100 billion annually in healthcare costs and lost income and productivity. Continuous analgesic medications are the common treatment for chronic pain. These drugs, including narcotics, non-steroidal anti-inflammatory drugs (NSAIDs), and anti-depressants, all come with risks of side effects and dependency (6). They are among the most abused prescription drugs in this country. Opioid prescriptions have increased ten-fold over the last 20 years, and opioid addiction, dependence, and overdose is now more prevalent than ever. A Columbia University study found that opioid addiction tripled between 1991-2002, and Americans reporting dependency and abuse increased from .1% to .3% of the population. Prescription painkillers now kill twice as many people as cocaine and five times as many people as heroin (7).

Over the past decade, cannabinoids targeting the endocannabinoid system have emerged as an effective therapy for pain and numerous other medical conditions (8). Unfortunately, the medical benefits of cannabinoids are hampered by adverse side effects such as cardiovascular disease and impaired respiratory function (if smoked). The most widely known of the cannabinoids, Δ9-tetrahydrocannabinol (THC), is the primary ingredient of cannabis (marijuana), which causes many psychoactive side effects, including poor cognitive function, poor memory, paranoia, anxiety, psychotic symptoms, poor motor-coordination, impairment of attention span, and an increased risk of developing depression and psychiatric disorders (9). Cannabis use also carries the risk of dependence and is viewed as a "gateway" drug to addiction. In the U.S., Canada, and Australia, cannabis dependence is the third most common drug dependence disorder after tobacco and alcohol and affects 4-8% of adults in their lifetime (9-11). The 2*010 World Drug Report* (12) cites cannabis as "the most widely used illicit substance in the world." Cannabis users have a 9% risk of developing dependence during their lifetime, and the risk increases to one in six for those who starting using cannabis during adolescence (11).

Those who suffer from chronic pain are clearly in need of potent analgesics without being exposed to the risks of abuse or dependency. In a study published in *Nature Chemical Biology* last year (13), a team of investigators led by Dr. Yan Xu, Professor and Vice Chairman for Basic Sciences in our department, in collaboration with scientists at the National Institute of Alcohol Abuse and Alcoholism (NIAAA), uncovered the potential to harness THC's analgesic powers without psychoactive side effects. These investigators identified a novel drug-binding site in the transmembrane (TM) domain of the human glycine receptor (GlyR) critical for the potentiation action of THC on GlyR. Experimental evidence suggests that the site and the action of cannabinoid potentiation critically contribute to the cannabis-induced analgesic effect. The study pointed to a way to separate THC's psychoactive effects via the cannabinoid type 1 (CB1) receptors from its analgesic power by acting on the GlyRs. This discovery with high-resolution structure information sets the stage for future research to identify small, drug-like molecules which target a specific binding site in GlyR, thereby producing an analgesic effect without the psychoactive side effects associated with THC and many of its derivatives. The ultimate goal is to develop a new class of drugs with an optimal analgesic and side-effect profile.

In a second study published this year in *Journal of Experimental Medicine* (14), the same team of investigators found that systemic and intrathecal administration of cannabidiol (CBD), a major nonpsychoactive component of marijuana, and its modified derivatives significantly suppress chronic inflammatory and neuropathic pain without causing apparent analgesic tolerance in rodents. The cannabinoids significantly potentiate glycine currents in the dorsal horn neurons in rat spinal cord slices. The analgesic potency of 11 structurally similar cannabinoids is positively correlated with cannabinoid potentiation of the α3 subunit of GlyRs. In contrast, the cannabinoid analgesia is neither correlated with their binding affinity for CB1 and CB2 receptors, nor with their psychoactive side effects. Nuclear magnetic resonance analysis reveals a direct interaction between CBD and S296 in the third TM domain of purified α3 GlyR. The cannabinoid-induced analgesic effect is absent in mice lacking α3 GlyRs. These important findings suggest that α3 GlyRs mediate glycinergic cannabinoid-induced suppression of chronic pain. These cannabinoids may represent a novel class of therapeutic agents for the treatment of chronic pain and other diseases involving GlyR dysfunction.

References:

1. *American Academy of Pain Medicine: Facts and Figures on Pain.* (2011).

2. American Cancer Society: *Prevalence of Cancer: How Many People Have Cancer?* (2011).

3. American Diabetes Association: Diabetes Statistics (2011).

4. American Heart Association: Heart Disease & Stroke Statistics (2011).

5. National Institutes of Health. *NIH guide: New Directions in Pain Research*, Sept. 4. (1998).

6. American Chronic Pain Association: *2011 Consumer Guide to Pain Medication and Treatments*. (2011).

7. Painkillers fuel growth in drug addiction. Opioid overdoses now kill more people than cocaine or heroin. *Harv Ment Health Lett*,. 27(7): p. 4-5. (2011).

8. Pacher P, Batkai S and Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacol Rev* 58(3): 389-462. (2006).

9. Hall W and Degenhardt L. Adverse health effects of non-medical cannabis use. *Lancet* 374(9698): 1383-91. (2009).

10. Hall W and Pacula RI. *Cannabis Use And Dependence: Public Health And Public Policy*. Cambridge, UK, Cambridge University Press. (2003).

11. Anthony JC. The epidemiology of cannabis dependence. *Cannabis dependence: its nature, consequences and treatment*. R.A. R and R.S. S. Cambridge, UK, Cambridge University Press. (2006)

12. United Nations Office on Drugs and Crime. *World Drug Report: 2010*: 198. (2010).

13. Xiong Wei, Cheng KJ, Cui T, Godlewski G, Rice KC, Xu Y, Zhang L. Cannabinoid Potentiation of Glycine Receptors Contributes to Cannabis-Induced Analgesia, *Nat Chem Biol*, 7(5):296-303. (2011).

14. Xiong W, Cui T, Cheng K, Yang F, Chen SR, Willenbring D, Guan Y, Pan HL, Ren K, Xu Y, Zhang L. Cannabinoids suppress inflammatory and neuropathic pain by targeting α3 glycine receptors, *Journal of Experimental Medicine*, May 14. (2012).