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Studies Reveal Possible Ways to Tap Into Therapeutic Benefits of Marijuana

Natural and synthetic compounds target the same receptor as marijuana, but without the side effects

SAN DIEGO — Research released today reveals new strategies for treating chronic pain, post-traumatic stress disorder, and alcohol abuse by targeting the brain's cannabinoid system. Targeting cannabinoid receptors — which bind both natural neurotransmitters and the psychoactive ingredient in marijuana — may provide some of the therapeutic benefits of marijuana without the side effects. The findings were presented at Neuroscience 2016, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Chronic pain affects nearly 50 million American adults and sometimes leads to prescription opioid abuse; opioid abuse led to 19,000 deaths in 2014. Post-traumatic stress disorder, which affects up to 30 percent of war veterans, and alcohol abuse, which results in 2.5 million deaths each year worldwide, also lack promising and safe treatments. Marijuana can help with chronic pain and symptoms associated with PTSD, but it has its own risk of abuse and side effects.

Today's new findings show that:

- A compound that increases the effects of endocannabinoids — neurotransmitters that bind the same receptor as THC, the active ingredient in marijuana — decreases pain symptoms in mice, suggesting a novel way to target pain with few side effects (Andrea Hohmann, abstract 617.07, see attached summary).
- A drug that boosts the activity of a cannabinoid receptor lessens anxiety and inflammation in mice exposed to repeated stress, hinting at a possible new treatment option for post-traumatic stress disorder (Sabrina Lisboa, abstract 112.08, see attached summary).
- A novel therapeutic compound that increases levels of an endocannabinoid in the brain alleviates chronic pain symptoms in rats, providing hope for a way to reduce reliance on opioids (Jason Clapper, abstract 617.02, see attached summary).

Other recent findings discussed show that:

- Cannabidiol, a compound found in marijuana, decreases alcohol consumption in mice, suggesting a possible new treatment for alcohol abuse disorders (Maria García-Gutiérrez, presentation 77.01, see attached speaker summary).

"Today's findings reveal a better understanding of the body's cannabinoid system and how to modulate it," said press conference moderator Margaret Haney, PhD, of Columbia University, an expert in drug abuse. "There are now a number of ways to target this system and possibly alleviate pain and other diseases without relying on marijuana."

The research was supported by national funding agencies such as the National Institutes of Health, as well as other public, private, and philanthropic organizations worldwide. Find out more about the brain's cannabinoid system at *BrainFacts.org*.

Related Neuroscience 2016 Presentation
Special Lecture: Translational Neuroepigenetic Insights of Addiction Vulnerability
Sunday, Nov. 13, 11:30 a.m.-12:40 p.m., SDCC Ballroom 20

Abstract 617.07 Summary

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Amplifying Endocannabinoid Signaling Decreases Pain Behaviors in Mice

Compound could help treat chronic pain with few side effects and low risk of abuse

Compounds that modulate a cannabinoid receptor in the brain may help reduce chronic pain, according to new animal research released today at Neuroscience 2016, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

The most common treatment for chronic pain remains prescription opioids, but these sometime lead to addiction and overdose. Tetrahydrocannabinol (THC), the main psychoactive ingredient in marijuana, and endocannabinoids, natural compounds released by the brain, alleviate pain by binding to the CB1 cannabinoid receptor, suggesting a potential therapeutic strategy. However, THC produces the "marijuana high" and can impair motor function, among other unwanted side effects. And, increasing endocannabinoids by blocking their breakdown affects many molecules and systems in the body. Recent work has revealed an additional binding site on CB1 where other molecules, called positive allosteric modulators (PAMs), can bind and amplify the effects of endocannabinoids only at CB1 receptors.

In this study, researchers tested the effects of a PAM directed specifically at CB1 for neuropathic pain, a type of chronic pain caused by nerve damage. Researchers gave mice a chemotherapy drug known to damage nerves and cause pain, and then treated them with the PAM. After receiving the chemo drug, mice became hypersensitive to both mechanical and cold stimulations applied to the paw, consistent with increased pain. When PAM treatment followed the chemo drug, however, the mice performed like normal mice in the pain threshold tests. Moreover, while THC and an endocannabinoid breakdown inhibitor stopped working with repeated dosing, the PAM remained effective and did not produce the unwanted side effects of THC.

"We also found that the compound did not produce reward on its own, so it's unlikely that a CB1 PAM would be abused as a recreational drug," said senior author Andrea Hohmann, PhD, of Indiana University. "Our studies show that we can maintain or preserve therapeutic efficacy in ways that we haven't seen with some of the other classes of analgesics that are used in the clinic."

Research was supported with funds from the National Institute on Drug Abuse and the Linda and Jack Gill Center for Biomolecular Science.

Scientific Presentation: Tuesday, Nov. 15, 3-4 p.m., Halls B-H

17373, Positive allosteric modulation of cannabinoid CB1 receptor signaling suppresses chemotherapy-induced peripheral neuropathy
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TECHNICAL ABSTRACT: Activation of cannabinoid CB1 receptors either directly (via agonistic action) or indirectly (elevation of endocannabinoid tone through inhibitors of endocannabinoid deactivation) suppresses pathological pain. However, unwanted central 'side' effects (e.g. psychoactivity, tolerance) constrain therapeutic dosing. We hypothesized that positive allosteric modulation of CB1 receptor signaling would suppress neuropathic pain produced by chemotherapy treatment while bypassing cardinal signs associated with direct CB1 receptor activation. In addition, we sought to examine the potential for synergistic interactions between positive allosteric modulation of CB1 and inhibitors of endocannabinoid deactivation. We, therefore, compared the therapeutic efficacy of GAT211, a positive allosteric modulator of CB1 receptor signaling, with URB597, an inhibitor of fatty-acid amide hydrolase (FAAH), and JZL184, an inhibitor of monoacylglycerol lipase (MGL) using a mouse model of chemotherapy-induced peripheral neuropathy. Within-subjects dose-response curves were constructed for GAT211, URB597, and JZL184; ED_{50} values were generated and used in fixed combinations to determine if the combination treatments produced antinociceptive effects that were additive or synergistic. GAT211 produced a CB1-dependent suppression of mechanical and cold allodynia induced by the taxane chemotherapeutic agent paclitaxel. Isobolographic analysis revealed synergistic interaction of GAT211 with inhibitors of either FAAH or MGL. Moreover, GAT211 did not produce cardinal signs of cannabinoid receptor activation (hypothermia, motor ataxia, catalepsy, tail flick antinociception) in wildtype mice but produced signs of catalepsy in transgenic mice lacking either FAAH or MGL. Therapeutic efficacy of GAT211 was preserved over a dosing period of 19 days with no appreciable signs of tolerance developing to its antinociceptive efficacy. By contrast, JZL184 initially displayed therapeutic efficacy but tolerance developed with repeated dosing. Thus, positive allosteric modulation of CB1 represents a promising strategy for harnessing the therapeutic potential of the endocannabinoid signaling system to suppress neuropathic pain without producing tolerance to therapeutic efficacy or detrimental CNS side-effects observed with orthosteric CB1 agonists. Moreover, our studies also suggest that CB1 positive allosteric modulators may show greater therapeutic potential compared to sustained inhibition of MGL, as manifested by absence of both tolerance and cardinal signs of CB1 intoxication.

Abstract 112.08 Summary

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A Synthetic Cannabinoid Reduces Anxiety and Inflammation in Stressed Mice

Mimicking THC, endocannabinoids may ease post-traumatic stress disorder symptoms

Drugs targeting the endocannabinoid system may help treat post-traumatic stress disorder symptoms by modulating over-activation of the immune system, according to new animal research released today at Neuroscience 2016, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Post-traumatic stress disorder (PTSD), the fourth most common psychiatric condition, appears to result from disrupted interactions between neurotransmitters and the immune, autonomic, and endocrine systems. Researchers believe dysregulation of naturally occurring endocannabinoid neurotransmitters — which normally decrease stress, anxiety, and pain — contributes to PTSD. The active ingredient in marijuana, THC, binds to the same receptor as endocannabinoids and has been used to ease the symptoms of PTSD. However, the side effects of marijuana, including motor impairment, and the potential for drug abuse prevent its widespread use as a therapy.

To test whether synthetic cannabinoids might produce the same benefits without the side effects, researchers treated mice with a compound that binds to the endocannabinoid receptors and then exposed them to repeated stress for six days. Following the stress, mice receiving the synthetic cannabinoid displayed less anxiety and fewer inflammatory signals in brain areas implicated in PTSD compared with mice receiving no treatment. In treated animals, safe memories replaced fear memories, similar to unstressed mice: When placed in a cage that had previously shocked them, stressed treated mice quickly learned the shocks had ended and the environment was now safe while untreated mice continued to freeze long after the shocks stopped.

"Our results indicate that the effects of cannabinoid drugs, a synthetic one in the present work, in attenuating the development of anxiety and PTSD symptoms may involve dampening over-activation of the immune system after stressful and traumatic events," said lead author Sabrina Lisboa, PhD, of the University of São Paulo in Brazil, who developed the work at the Ohio State University. "A better understanding of PTSD neurobiology could tell us how cannabinoid compounds reduce its symptoms and potentially lead to new pharmacotherapies that lack the adverse effects of marijuana."

Research was supported with funds from the São Paulo Research Foundation and the National Institute of Mental Health.

Scientific Presentation: Sunday, Nov. 13, 9:45-10 a.m., SDCC 5B

11586, Short and long-term behavioral and neuroinflammatory changes induced by repeated social defeat stress in mice are attenuated by a cannabionoid receptors agonist: Implications for PTSD

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TECHNICAL ABSTRACT: The repeated social defeat (RSD) stress in mice induces peripheral immune system activation, myeloid cell trafficking, microglia activation and prolonged anxiety-like behavior. Endocannabinoid system (eCBS) molecules are expressed by immune and neuronal cells, modulating their functions. One purpose of this study was to test if cannabinoid receptors activation in mice would attenuate neuroinflammatory and behavioral effects of RSD. Stress exposure may lead to a persistent stage of low-grade inflammation and alterations in other systems, including the eCBS, which could predispose the individual to the development of psychopathology, such as the PTSD. Social stress might contribute to PTSD and, therefore, the RSD in mice would mimic some PTSD features, such as alterations in conditioned fear processing. Therefore, we also tested the hypothesis that RSD changes conditioned fear response 1 week after the end of RSD and that treatment with a cannabinoid agonist during RSD attenuates this effect. For those purposes, C57BL/6 mice have received a nonselective cannabinoid agonist, WIN55,2122 (1 mg/Kg, i.p.), 30 minutes prior to each of the six exposures to SD stress session (2h/each). The mice were tested in the morning following the last SD cycle for anxiety-like behavior and cellular/molecular alterations. Independent groups were left undisturbed and single-housed during 7 days after RSD and then were submitted to the contextual fear conditioning (CFC; 3 electrical foot-shock, 0.75 mA, 2s/each). 24h later, they were returned to the same chamber for evaluation of fear expression/ extinction acquisition (20 min session; no foot-shock presentation). Following additional 24h hours, the extinction recall was evaluated (5 min session) and the frontal cortex (FC) and hippocampus (HIP) were dissected. WIN administration during RSD attenuated anxiety-like behavior, decreased redistribution of immune system cells to the blood, spleen and brain and attenuated microglia activation in the brain. RSD induced-later fear sensitization and impaired extinction recall in the CFC were prevented by WIN administration during RSD. WIN also attenuated the observed increase in IL-1β mRNA in the FC and HIP after evaluation of extinction recall. Our data, therefore, suggest that modulation of cannabinoid system, targeting both neuronal and immunological components of stress, could be potential therapeutic intervention in stress-related disorders where inflammation is observed, such as PTSD. Moreover, they also suggest that PFC and HIP IL-1β signaling would be involved in fear sensitization after stressful events.

Abstract 617.02 Summary

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Researchers Develop Novel Compound That Alleviates Chronic Pain Symptoms in Rats

Treatment may reduce or replace need for opioids

Researchers developed a compound that increases the amount of natural cannabinoids in the brains of rats, which relieved chronic pain symptoms in the rodents, according to new research released today at Neuroscience 2016, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Chronic pain is a widespread condition that can sometimes lead to prescription opioid abuse and overdose. Marijuana has proven therapeutic benefits for people suffering from chronic pain, but its psychotropic properties and risk of abuse prevent its widespread use as a therapy. Regulating levels of natural cannabinoids, which target the same receptors as compounds in marijuana, may have similar benefits without the side effects. Previous work revealed that blocking a protein called MGLL leads to an increase in the cannabinoid neurotransmitter 2-AG and a reduction in symptoms of pain in mice.

To investigate the therapeutic potential of targeting this system, researchers developed a compound that inhibits MGLL, amplifying the effects of 2-AG. In various rat models of pain (including acute, chronic, and inflammatory pain), the compound reduced pain-related behaviors, such as licking and attending a paw that received a painful injection. Treated rats also did not display the side effects typical of marijuana treatment, such as decreased locomotor activity. Additionally, the compound enhanced the effects of a low dose of morphine, leading to pain relief similar to that produced by a high dose of morphine.

"There's a great need for non-opioid medications for treating pain," said lead author Jason Clapper, PhD, of Abide Therapeutics in San Diego. "Based on our preclinical studies, the biology that we know about the cannabinoid system, and the use of medicinal marijuana, we think this has huge potential for treating pain and potentially reducing opioid use, which could have very important health and socioeconomic implications."

Scientific Presentation: Tuesday, Nov. 15, 2-3 p.m., Halls B-H

12520, *In vivo* characterization of a selective monoacylglycerol lipase inhibitor ABD-1970 in rodents and activity in models of pain
J. R. CLAPPER, J. L. BLANKMAN, A. R. COPPOLA, A. KNIZE, G. SIMON, J. CISAR, O. WEBER, M. NIPHAKIS, C. HENRY, I. FRASER, C. GRICE, A. EZEKOWITZ, G. O'NEILL;
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TECHNICAL ABSTRACT: Monoacylglycerol lipase (MGLL) is the primary regulator of 2-arachidonoylglycerol (2-AG) an endogenous ligand of the cannabinoid (CB) receptors CB1 and CB2. Selective blockade of MGLL inhibits the hydrolytic degradation of 2-AG resulting in elevated 2-AG levels in the CNS and periphery, and CB1/2-dependent anti-nociceptive and anti-inflammatory effects. In the rodent brain and select peripheral tissues, MGLL inactivation also reduces levels of the catabolic product of 2-AG hydrolysis, arachidonic acid, a metabolic precursor to pro-inflammatory prostanoids. Here, we present a comprehensive in vivo characterization of a selective covalent inhibitor of MGLL, ABD-1970. ABD-1970 is orally active in rodents producing a rapid and potent inhibition of MGLL and elevation of 2-AG in the brain. In vivo blockade of 2-AG hydrolysis was also associated with reduced levels of arachidonic acid and prostanoids PGE_2, PGD_2 and $PGF_2\alpha$ in the brain. Using activity-based protein profiling to comprehensively profile the in vivo selectivity of ABD-1970 against other serine hydrolases, α/β-hydrolase domain-containing 6 (ABHD6) and rodent-specific carboxylesterase 1c (CES1c) were the only off-targets identified, albeit at doses above those required for in vivo pharmacological activity at MGLL. In time course experiments, MGLL activity was inversely correlated with ABD-1970 concentrations in the blood and brain with recovery of MGLL activity observed as the compound was eliminated from the body. Furthermore, ABD-1970 was efficacious in the rat incisional model of acute post-operative pain, the rat formalin and complete Freund's adjuvant models of inflammatory pain and the rat chronic constriction injury model of neuropathic pain. In the formalin model, ABD-1970 produced enhanced activity in combination with standard of care agents, pregabalin and morphine. Integrated analysis of compound exposure, brain target engagement, and 2-AG levels reveal a strong relationship between PK, central biomarkers and efficacy in models of pain. Importantly, acute administration of ABD-1970 lacked effects on total exploratory activity in an open field test. These results identify ABD-1970 as a highly potent and selective in vivo active inhibitor of MGLL and underscore the therapeutic potential of selective MGLL inhibitors for the treatment of acute and chronic pain.

Speaker Summary (77.01)

Speaker: Maria S. García-Gutiérrez, PhD +34 (965) 919252
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Cannabidiol Mediated Regulation of Alcohol Consumption
Saturday, Nov. 12, 1-2 p.m., Halls B-H

Our study indicates that cannabidiol (CBD), one of the main compounds present in the plant *Cannabis sativa*, reduced the consumption of ethanol in mice.

Alcohol use disorders (AUD), including alcohol dependence and harmful use or alcohol abuse, represents a serious public health problem worldwide. According to the World Health Organization, approximately 2.5 million deaths per year are attributable to alcohol. In the U.S., society problems related with AUD cost approximately $185 billion annually. These costs result from the increased health risks associated with problematic alcohol use and from the social harms caused by alcohol. Also, AUD are linked to considerable disability.

Although patients receive pharmacological treatment and psychosocial therapies, the clinical outcome is poor, with up to 70 percent of patients resuming drinking within one year. Therefore, it is necessary to invest much effort and resources in identifying new therapeutic drugs to improve the efficacy of the treatment of alcoholism.

In the U.S., CBD is currently classified as a Schedule 1 controlled substance, according to United Nations Single Convention on Narcotic Drugs and the Controlled Substance Act of United States (CSA, 1970). A Schedule I controlled substance is defined by the CSA as a substance presenting "no currently accepted medical use, a lack of accepted safety for the use under medical supervision, and a high potential for abuse." However, in European Union, CBD is considered as a drug with no potential for abuse. Interestingly, during the past years, several studies demonstrated that CBD presents properties that make it an ideal candidate for reducing anxiety and depression and also that it has neuroprotective activity. These properties suggested that CBD may be useful for treating multiple pathologies associated with AUD.

In this study we evaluate the potential effects of CBD on ethanol consumption. To this aim, we selected mice with high consumption of ethanol in two animal models. CBD significantly reduced the ethanol consumption and also the motivation to drink and relapse.

Another innovative aspect of our study is the use of a new formulation of CBD that provides a continuous controlled release of CBD during 14 days. The results revealed that one administration of this formulation was able to reduce ethanol consumption and motivation to drink during 14 days.

Taken together, these results point out CBD as a promising new drug for the treatment of AUD. The next step will be the evaluation of this new CBD formulation in a clinical study in alcoholic patients.

Research was supported with funds from Instituto de Salud Carlos III, Plan Nacional Sobre Drogas, and Ministerio de Economía y Competitividad of Spain.