Outstanding Questions

How can authors and journals more clearly detail the contribution of all team members, and how far should lists of contributors reach (e.g., lab technicians)?

Can laboratories and institutions facilitate skill specialization and team-science approaches organically, that is, without the encouragement of funding agencies?

If neuroscience is to become increasingly collaborative, should this be reflected in increasingly standardized procedures and formats for data acquisition, preservation and sharing?

opportunity to do justice to the complexity of future scientific questions.

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Science & Society

Cannabidiol: Swinging the Marijuana Pendulum From 'Weed' to Medication to Treat the Opioid Epidemic

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Epidemics require a paradigm shift in thinking about all possible solutions. The rapidly changing sociopolitical marijuana landscape provides a foundation for the therapeutic development of medicinal cannabidiol to address the current opioid abuse crisis.

Curbing an Epidemic

In an unprecedented report, the US Surgeon General recently released their first state of the science on substance use, addiction, and health to fully recognize substance use and addiction as significant and substantial public health challenges [1]. As emphasized in the report, a major component of the current substance use crisis is the misuse and abuse of opioid drugs. The numbers are alarming. In the United States, approximately 2.5 million people have been diagnosed with an opioid use disorder (OUD). Over 80 people die each day from opioid overdose; that number was even higher the past few years before many lives were saved due to the recent availability of the overdose-reversing agent naloxone. Disconcertingly, four in five new heroin users started out misusing opioid prescription painkillers. This has significant implications for the current course of the opioid epidemic because over 200 million opioid painkiller prescriptions are still written each year, a number closely approximating the entire adult population in the United States. While the burden of OUDs for the individual, their families, and communities is enormous, so are the economic costs, currently estimated at US$78 billion yearly. The current opioid epidemic has gripped every community in the United States and crossed political party lines such that there is for the first time complete agreement about the critical need to limit production and consumption of opioid medications. It is my opinion that bold steps are also required to escalate the pipeline in developing creative and innovative treatments to help curb this epidemic.

The Changing Sociopolitical Pendulum of Medicinal Marijuana

The predominant pharmacological treatments currently prescribed for OUDs are methadone, buprenorphine, and naltrexone, which directly target the opioid system. These medications have been of significant clinical value but also have their own challenges (often associated with strict governmental regulations governing their use). One emerging solution showing potential therapeutic properties is cannabinoids. States with legalized marijuana laws have reported a reduction in opioid use, as evidenced by lower number of prescriptions for opioid painkillers, reduced number of opioid overdoses, and lower opioid-positive screens associated with car fatalities [2]. The reasons for these associations have not been established, despite speculations regarding the potential for medicinal properties of marijuana to reduce opioid use.

The scientific community has been largely missing from most conversations and policymaking regarding the legalization of marijuana for medical purposes. Indeed, it is clear that the legalization of marijuana has outpaced the science; this is one of the first times in US history that the question of whether a plant (or any drug) is an effective medicine has been decided at

the ballot box. Contrary to the normal course of medication development, it is the general public and politicians, not scientists and physicians, determining the medical value of marijuana in states where marijuana use has been legalized for medicinal purposes. Normally, preclinical models provide the foundation for clinical trials, and then – after years of rigorous, structured, investigations – accrued evidence is evaluated by federal agencies to determine whether a particular compound should be approved for the treatment of specific symptoms/disease, with any potential side effects clearly noted to thoroughly inform the public. For marijuana, such a bar has not been met; elections across the country have been driven in large part by anecdotal reports and lobbying efforts by a growing marijuana industry.

Despite this growing movement, prescribing the medical use of a plant within our existing clinical structure still has tremendous challenges, but specific constituents of the plant could be more easily developed for medicinal indications. Of the cannabinoids found in the marijuana plant, cannabidiol (CBD) is the phytocannabinoid with perhaps the greatest potential for development as a therapeutic strategy for substance use disorders. There are some early indications from a few experimental studies, most of which are in the initial phases in the development pipeline, supporting the benefits of CBD for treating certain behaviors both associated with addiction and relevant to OUD. This, together with the changing medical marijuana landscape, provides an impetus to more seriously and expeditiously consider the potential of CBD as a therapeutic agent.

Making the Case for CBD As a Treatment for Opioid Addiction

There is a strong scientific basis for considering CBD as a therapeutic intervention for OUDs. First, in contrast to most current opioid medications, there is minimal concern about diversion to the black market. In contrast to Δ^9-tetrahydrocannabinol (THC), the prominent psychoactive component of marijuana, CBD is not rewarding [3,4] and as such has limited misuse and diversion potential. In addition, CBD has very low lethality, thus alleviating concerns about potential overdose. Moreover, when combined with a strong opioid agonist, CBD retains its safe profile and does not induce severe adverse effects. CBD has been studied in various *in vitro* systems, *in vivo* animal models, and human studies across a broad dose range (even up to 50 mg/kg/daily in humans) with minimal side effects or any toxicity reported [5,6]. This strong safety profile has made it even suitable for use in children, as evidenced by the recent epilepsy clinical trials with CBD (Epidiolex) [5].

Another important consideration in the development of medications for addictive disorders is the complexity of the illness (i.e., one medication cannot treat all aspects of the disorder). Addiction is a chronic illness characterized not just by the intoxication associated with acute drug use, but by disturbances of cognition and negative emotional states that trigger craving and relapse, perpetuating the insidious cycle of drug use. Thus, although not a panacea, a medication that specifically modulates behaviors relevant to craving and relapse could have significant medicinal benefits. A highly reproducible and indisputable finding based on human studies and animal models is the ability of CBD to modulate anxiety [7], a core behavioral feature of addiction that often triggers craving and promotes relapse. The neurobiological mechanisms underlying anxiety have been well studied and key anatomical and cellular components of such networks are highly influenced by CBD, as emphasized in the following section.

CBD to Treat Opioid Addiction: Neurobiological Considerations

The endogenous cannabinoid [endocannabinoid (eCB)] system has been well documented to contribute to the stress responsivity and negative emotional states that dominate substance use disorders [8]. The eCB system is composed of G-protein-coupled receptors, including the cannabinoid receptor type 1 (CB1R) (prominent subtype expressed in the central nervous system) and CB2R (mainly expressed in the periphery); small neuromodulatory lipid ligands [*N*-arachidonylethanolamide (anandamide; AEA) and 2-arachidonoylglycerol (2-AG)]; as well as biosynthetic and metabolic enzymes for the synthesis and degradation [(fatty acid amide hydroxylase (FAAH) and monoacylglycerol lipase for AEA and 2-AG), respectively] of the ligands [9]. Unlike THC, CBD is not a potent agonist at the CB1R. Rather, CBD has a broad profile in its pharmacological actions, which are not fully established and thus remain controversial. One important feature of CBD's actions that is not debated and highly relevant to its anxiolytic properties is its ability to enhance AEA (through inhibition of FAAH and potentially through inhibition of the putative AEA transporter). The weak agonist properties of CBD at the CB1R and its potentiation of AEA, which also has low efficacy at the CB1R, is an important consideration for its therapeutic potential, because robust engagement of CB1R signaling normally evokes reward and can induce psychosis. Instead, enhanced eCB tone under closer physiological ranges is associated with reduced anxiety. Thus, CBD's ability to discretely modulate eCB ligands to mediate its actions potentially contributes to its wide therapeutic dose range since it lacks direct potent receptor effects.

Currently, the most consistent pharmacological and behavioral evidence relating to CBD effects on anxiety, negative affective states, and emotional memory processing pertains to its modulation of the 5-HT1A (5-hydroxytryptamine 1A subtype) receptor [10]. CBD is an indirect agonist of 5-HT1A receptors and many effective anti-anxiety drugs have partial agonist properties at 5-HT1A receptors. Along with its effects on 5-HT1A signaling, the spectrum

of CBD's modulatory actions at multiple other neuromodulator/neurotransmitter systems highly implicated in anxiety and negative affect is of significant importance for its therapeutic properties.

Neuroanatomically, some of the strongest evidence observed regarding CBD's actions directly pertains to brain regions highly implicated in negative affect and addiction. The amygdala is a critical structure mediating anxiety and fear and has been well established to mediate stress response and encode the processing of conditioned cues associated with drug memories that elicit drug-seeking behavior. Animal models have shown that systemic administration of CBD specifically decreases the number of c-Fos-positive neurons (a marker of neuronal activity) in the central nucleus of the amygdala and direct CBD infusion into this amygdala nucleus reduces anxiety-like behaviors [11]. Importantly, neuroimaging studies have shown that administration of CBD to humans reduces activation of the amygdala during negative emotional processing [12]. Moreover, other anxiety-related mesocorticolimbic neural circuits, such as the prefrontal cortex, which mediates decision making and cognitive control, and the striatum, which regulates goal-directed behavior, motivation, and habit formation, are directly linked to addiction psychopathologies and shown to be affected by CBD.

The Crosstalk between CBD and Opioid Addiction

What initially made a cannabinoid strategy intriguing to consider for opiate addiction is the tight crosstalk and often reciprocal interactions that exist between the endogenous opioid and eCB systems. For example, (i) animals deficient in CB1R have reduced opioid reward, (ii) opioids regulate the release of eCBs and eCBs alter opioid peptide levels, (iii) eCB and opioid receptors are expressed in the same cells in discrete neuronal pathways highly implicated in addiction, and (iv) because they are both coupled to inhibitory $G_{i/o}$ proteins, opioid and cannabinoid receptors share similar intracellular signaling cascades. As such, the significant convergence for opioid/cannabinoid interactions opens up opportunities to assess potential cannabinoid interventions for OUD. Since THC is not a suitable treatment option, given that it can even enhance opioid reward self-administration and induce other psychopathologies, CBD is the most optimal phytocannabinoid candidate.

Accumulating evidence supports this contention. Preclinical animal models have long demonstrated that, in addition to reducing the rewarding properties of opioid drugs and withdrawal symptoms [13], CBD directly reduces heroin-seeking behavior [14]. Importantly, these effects are related to conditioned cue-induced reinstatement of heroin-seeking behavior, an effect that was evident weeks after CBD was initially administered. This long-lasting effect is an important consideration in developing practical strategies for substance use disorders, in which drug craving increases over the course of the drug abstinence phase. Interestingly, CBD normalizes heroin-induced impairment of the CB1R and glutamate receptors in the striatum, suggesting that it normalizes synaptic plasticity in this region [14]. Importantly, a pilot human investigation also documented findings consistent with those observed in the animal model, demonstrating that CBD reduced heroin-related cue-induced craving in heroin abusers [15]. Moreover, similar to the protracted effects seen in the animals, CBD's attenuation of general craving lasted even a week after its last administration. Interestingly, CBD's strongest effects were on the attenuation of the anxiety induced by heroin cues. Unfortunately, one small clinical study is not sufficient to make sweeping conclusions about the potential efficacy of CBD to inhibit heroin craving and drug use in addicted individuals. However, it serves as an important foundation, along with accumulating evidence in animal models, to warrant expedited efforts for additional clinical studies to evaluate the potential therapeutic benefits of CBD as a treatment for OUDs.

Concluding Remarks … So Where Do We Go from Here?

It is important to move with a deep sense of urgency to leverage the opportunity presented by increased legalization of medical marijuana to expedite the development of CBD for therapeutic interventions for OUDs, thus curbing the opioid epidemic. Clinical trials must be of the highest priority to establish the most appropriate formulations, entourage effects with other cannabinoids, routes of administration, and treatment regimens for the use of CBD by individuals with OUDs. Although significant momentum in the general public has moved the pendulum regarding marijuana, the scientific and medical communities now need to play a more leading role via evidence-based studies. In this way, scientific and medical evidence will once again serve to inform the public and to develop efficacious and safe therapies. However, such advances will require significant and immediate actions to be taken by the National Institutes of Health and other federal agencies to help develop a structure for fast-tracking the clinical use of 'medical CBD'.

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Spotlight

Neuronal Adaptation: Tired Neurons or Wired Networks?

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Neuronal adaptation – time-dependent modulation of sensory responses following sequential stimuli – is thought to be a consequence of synaptic plasticity. But recent, empirically-grounded, modeling by Quiroga and colleagues demonstrates that the adaptation of visual cortical responses can be described by recurrent network connections with fixed synaptic weights.

A fundamental goal of systems neuroscience is to determine the neural mechanisms that govern perception. These mechanisms can be broadly divided into two classes: changes in the strength of individual synaptic connections and circuit-wide changes in the pattern of neuronal population activity. Given the large difference in scale between synaptic plasticity and network dynamics, it may be surprising that one mechanism could be mistaken for the other. Yet recent work by Quiroga and colleagues [1] suggests that neuronal adaptation, often thought to be a form of sensory response modulation dependent on synaptic plasticity [2,3], can be carried out via recurrent neuronal connections with constant synaptic weights (Figure 1). This result provides insight into one of the most ubiquitous mechanisms of sensory encoding and highlights a promising, reliable avenue of investigation for researchers interested in relating brain function to local circuitry.

Neuronal adaptation is a general term that encompasses a variety of response profiles that depend on recent stimulus history. Quiroga *et al.* [1] focused on one of the best-described forms of adaptation, orientation adaptation in primary visual cortex (V1) [4]. Using an established model of thalamocortical processing in the mammalian visual system, the researchers first built a recurrent network that incorporated orientation-specific thalamic inputs to cortical neurons. The network's parameters were fit to ensure that basic response properties such as the response latency and orientation selectivity of individual neurons, as well as the breadth of excitatory and inhibitory connections between neurons, approximated previously reported experimental values. Importantly, the two species-specific models (cat and monkey) were constrained to fit the relevant experimental data before they were tested for adaptation.

Without changing the synaptic weights between neurons and relying solely on the recurrent connectivity between cortical neurons, Quiroga *et al.*'s models exhibited a remarkable number of response properties associated with

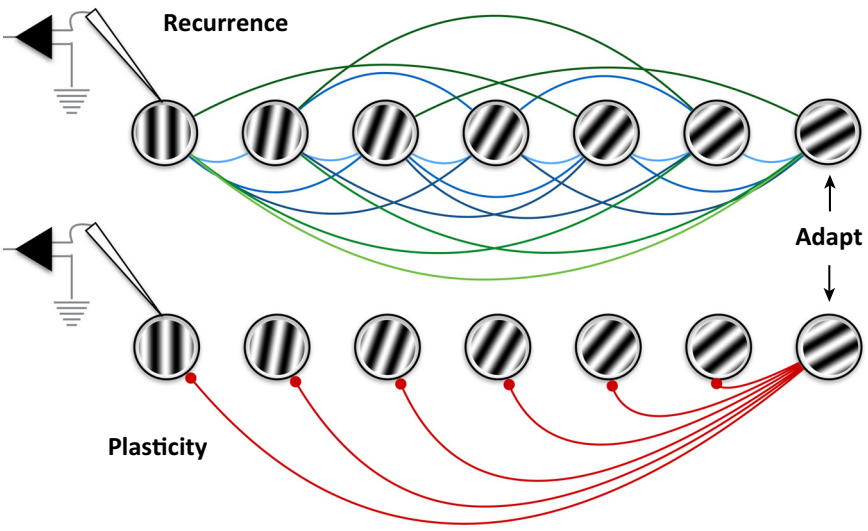

Figure 1. Illustration of Candidate Adaptation Mechanisms. Adaptation has often been proposed to occur through synaptic plasticity (bottom); a recorded neuron (leftmost circle) with a preference for vertical orientation could undergo a tuning curve shift away from the adapted orientation due to a loss of excitatory input. Quiroga *et al.*'s results demonstrate that the same tuning curve shift can occur through the temporal dynamics of recurrent network connections (top, nearby connections in blue and distant connections in green). Each circle represents a population of similarly tuned V1 neurons.