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Editorial

A new dawn in cannabinoid neurobiology: The road from molecules to therapeutic discoveries

There is likely no greater timely topic in biomedical and clinical research today than discussions surrounding the utility of active chemicals found in marijuana and how they interact with the body's own homeostatic systems to elicit beneficial or potentially deleterious effects. Various preparations of the plant *Cannabis sativa* have been used for medicinal and religious purposes for millennia. These were initially used as for a wide variety of therapeutic effects including (but not limited to) antiemetic, anticonvulsant, antibiotic, anti-inflammatory, analgesic, anesthetic, antispasmodic, diuretic, digestive, appetite stimulant, antitussive, expectorant and even aphrodisiac.

Although the chemical isolation of the two most widely studied phytocannabinoids; e.g. those derived from *Cannabis* (Δ^9-THC and cannabidiol), occurred in the 1960s, there is a renewed need for more mechanistic understanding on how these lipid molecules impact neuronal functions in the brain. In fact, the precise molecular mechanisms of action of *Cannabis*' main phytocannabinoids and the endogenous signaling molecules that they interact with (endogenous cannabinoids) were only described starting in the early and mid-1990s with the cloning of cannabinoid receptors and the chemical isolation of their best known endogenous ligands, highly diffusible arachidonic acid derived lipid messengers, aptly termed anandamide (from the Sanskrit word "*ananda*" meaning bliss) and 2-arachidonoyl glycerol.

Cannabinoid receptors are some of the most densely expressed G protein-coupled receptors the brain. While the extent of their influence on neuronal processing has been described at an explosive pace for the past two and a half decades there are many questions that remain to be answered. Such insights are an essential foundation for the rational development of therapeutic interventions. This *Neuropharmacology* Special Issue, which coincides with the 2017 Gordon Research Conference on Cannabinoid Function in the CNS, provides a series of reviews by world experts who examine in detail the many facets of cannabinoid receptor signaling ranging from basic and canonical pharmacological and physiological tenets to complex mechanisms underlying psychiatric and neurological disorders such as addiction, schizophrenia, chronic pain and neurodegeneration.

The first contribution to this exciting Special Issue (Khurana et al., 2017), discusses a new frontier in cannabinoid pharmacology, namely the ability of allosteric modulators to selectively engage specific transduction pathways, which can be potentially used to produce tailored therapeutic strategies depending on the condition to be treated. These allosteric ligands bind to sites different than those targeted by the endogenous ligand, and can thus modulate receptor activity in novel and predictable ways.

One of the first demonstrations of endogenous cannabinoid activity in the brain occurred in the early 21st century, when a series of elegant reports clearly and unambiguously demonstrated that endogenous cannabinoid signaling is one the most widespread negative feedback modulators of neurotransmitter release and of certain forms of synaptic plasticity. Here, Araque and collaborators (Araque et al., 2017), provide a unifying update on novel mechanisms of synaptic plasticity that recruit signaling at CB1 receptors on targets as varied as neurons, astrocytes and even mitochondria.

The next two contributions focus on two of the most commonly reported anecdotal effects of acute *Cannabis* consumption: disrupted memory mechanisms and alleviation of pathological states such as epilepsy through hippocampus dependent mechanisms (Lupica et al., 2017) as well as enhanced appetite for palatable food (Lau et al., 2017). Lupica et al., in particular, focus on the synaptic basis for these conditions and guides the reader through a series of cogent transitions to phenomena that may underlie higher order neural interactions such as theta oscillations. Lau et al., center their review on the interaction between energy sensing neural nodes in the hypothalamus and reward-related relays within the mesocorticolimbic system, with a special emphasis on interactions with feeding peptides and dopaminergic mechanisms.

This is then followed by the work of Covey et al. (2017) who revisit the different ways that dopaminergic pathways in the brain can be modulated via cannabinoid receptor signaling (CB1 and CB2) and the implications for motivational processing in general and for related disorders such as addiction in particular.

A critical topic in the current debates surrounding the legalization of marijuana relates to addiction, both in regard to the potential for cannabis abuse and for cannabinoids to serve as novel therapeutic strategies for treating substance use disorders. Melis et al. (2017) review preclinical models of *Cannabis* use disorders including the nuances of cannabinoid self-administration strategies. They explore the contribution of non-neuronal cells underlying the neural actions of cannabinoids and the mechanisms associated with the long-term impact of prenatal *Cannabis* exposure on the developing brain. Subsequently, Sloan et al. (2017) provide the reader with an integrative overview of human clinical trials carried out with conventional and novel pharmacotherapies targeting the endocannabinoid system as potential interventions for substance use disorders.

The clinical considerations of cannabis continue with an in-depth evaluation by Mizrahi et al. (2017) of *Cannabis* use on cognition. Focusing on preclinical mechanisms and human neuroimaging in *Cannabis* users, they highlight the fundamental role of CB1 receptor signaling in regulating human cognition.

For decades, the relationship of *Cannabis* and mental illness has been particularly linked to psychosis and schizophrenia. Murray

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et al. (2017) provides a strong foundation educating readers about psychotic symptoms and psychotic disorders and then weaves through an intriguing and comprehensive array of human laboratory and neuroimaging studies regarding the acute and long-term effects of cannabis. They provide a comprehensive outlook on the status of the endogenous cannabinoid system in schizophrenia to highlight factors important for psychosis vulnerability.

The Special Issue culminates with reviewing the medical use of *Cannabis* for a condition that has been documented since ancient times, namely pain relief. Woodhams et al. (2017) details the endogenous cannabinoid system in sensory, emotional, and cognitive aspects of pain. They leverage information obtained from preclinical data to effectively inform the challenges and promise of translating cannabinoids into successful clinical treatments.

In addition to the review articles, there are a number of original publications relevant to the topic of this Special Issue that emphasize the important role of the endocannabinoid system in (1) neuroendocrine and behavioral response to stress (Henricks et al., 2017), (2) exercise-induced anti-nociception linked to specific downstream signaling mechanisms (King-Himmelreich et al., 2017) and (3) modulation of the output of retinal ganglion cells via specific calcium channels regulated by CB1Rs and CB2Rs (Qian et al., 2017). Finally, original evidence is also provided underscoring the druggable potential of the endocannabinoid system by demonstrating that targeting an endocannabinoid enzyme that enhance the neuroprotective and anti-inflammatory cannabinoid may be exploited therapeutically for neurodegenerative diseases such as amyotrophic lateral sclerosis (Pasquarelli et al., 2017).

Overall, the presented series of papers spanning from basic mechanisms to the clinical and therapeutic potential of cannabinoids emphasize the incredible depth of the exponentially expanding cannabinoid field and its critical interactions with multiple biological functions that underlie a myriad of brain disorders.

We dedicate this Special Issue to our dear cannabinoid colleague Dr. Loren “Larry” Parsons whose outstanding research helped shape the field and who will be greatly missed.

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