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Special issue editorial: Cannabinoid signalling in the brain: New vistas

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Abstract

The endocannabinoid system is widely expressed both in the brain and in the periphery. This system regulates a plethora of physiological functions and is composed of cannabinoid receptors, their endogenous ligands, and the enzymes involved in their metabolic processes. In the last few years, the development of new imaging and molecular tools has demonstrated that these receptors are distributed in many cell types (e.g., neuronal or glial cells) and intracellular compartments (e.g., mitochondria). Interestingly, cellular or molecular effects are differentially mediated by cannabinoid receptors according to their specific localization in different cell-types or in different subcellular locations. Moreover, the endocannabinoid system is also expressed throughout the body where it can serve to modulate the connection between the brain and the periphery. Finally, better understanding of the cannabinoid receptors structure and pharmacology has led researchers to propose interesting and new allosteric modulators of synaptic communication. The latest advances and innovative research in the cannabinoid field will provide new insights and better approaches to improve its interesting potential therapeutic profile. This special issue intends to bring together a series of empirical papers, targeted reviews and opinions from leaders in the field that will highlight the new advances in cannabinoid research.

1 | INTRODUCTION

The finding of cannabinoid signalling in our body and brain can be classified amongst the most exciting discoveries of the last decades. Cannabinoid research has continuously evolved allowing the field to go beyond "dogmatic" and "classical" views. The endocannabinoid system (ECS), which is the main target of cannabinoid-related drugs, is composed of cannabinoid receptors, their endogenous ligands, and the enzymes involved in their metabolism. The ECS is widely present in both brain and peripheral tissues, where it controls an impressively broad spectrum of pathophysiological functions. These include brain development, learning and memory, motor behaviour, energy balance, body temperature, pain perception, and inflammation, among many others (Araque et al., 2017). Moreover, the ECS is involved in various psychiatric, neurological, and neurodevelopmental disorders (Araque et al., 2017). The involvement of the ECS in all these functions and pathological conditions is due to its distribution in many different tissues, cell types (e.g., neuronal or glial cells) and intracellular compartments (e.g., mitochondria, endosomes) (Busquets-Garcia et al., 2018). Indeed, behavioural, cellular, or molecular effects are differentially mediated by cannabinoid receptors according to their specific localization (Busquets-Garcia et al., 2015). The cannabinoid field is constantly accumulating new advances and innovative research findings, which provide new insights and better approaches to improve its interesting potential therapeutic profile.

The aim of this special series is to provide new opinions and experimental observations regarding (endo)cannabinoid signalling in the brain in order to open new perspectives on the complexity of this signalling and its participation in brain functions and behaviour. This Cannabinoid Signalling Special Collection consists of 13 articles: seven presenting original research data and six reviewing specific aspects of the field. The different manuscripts reflect recent progress in our understanding of (i) pharmacology of the ECS, (ii) the importance of cell-type specific mechanisms depending on the localization of cannabinoid receptors, (iii) the roles of the ECS in synaptic functions or developmental processes, and (iv) the involvement of cannabinoid signalling in pathological conditions. Interestingly, the research shown in this collection of articles uses different animal models, several experimental approaches, and focuses on different pathophysiological aspects of the central nervous system.

2 | PHARMACOLOGICAL TOOLS TARGETING THE ECS

The characterization of pharmacological compounds acting at different components of the ECS, including cannabinoid receptors or the enzymes involved in the metabolism of endocannabinoids, is a continuously evolving field. Different endogenous or exogenous, natural or synthetic, orthosteric, or allosteric ligands of CB1 receptors have been described in the last decades (Pertwee, 2015). Brunt and Bossong (2020) provide an outline of the neuropharmacology of several orthosteric cannabinoid receptor ligands, including endocannabinoids, herbal cannabis components and synthetic cannabinoids. By detailing their mechanisms of action and their impact on other neurotransmitter systems, the authors describe their therapeutic potential and adverse effects. Indeed, several orthosteric CB1 receptors ligands might induce important side effects (Volkow et al., 2014). Thus, putative allosteric binding sites of CB1 receptors represent new targets for novel cannabinoid pharmacology. Indeed, several CB1 receptor allosteric modulators, both of natural and synthetic origin, have been proposed (Gentry et al., 2015; Morales et al., 2016). Collectively, these might represent the basic chemical structures for the development of new cannabinoid drugs.

By definition, the ECS not only includes the cannabinoid receptors but also the proteins responsible for the biosynthesis, transport, and degradation of endocannabinoids, which can also be pharmacologically targeted. The first two identified and most studied endocannabinoids are AEA and 2-AG (Ligresti et al., 2016), whose levels are controlled by well-described enzymes responsible for their main metabolic pathways. The two major enzymes responsible for the inactivation of AEA and 2-AG are fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively (Ligresti et al., 2016). These enzymes are responsible for the degradation of AEA and 2-AG and the subsequent production of metabolites (arachidonic acid and ethanolamine or glycerol, respectively), and they represent important therapeutic targets in the cannabinoid pharmacology field. Accordingly, Gianessi et al. (2021), by using pharmacological strategies to inhibit FAAH and MAGL, show a key role of CB1 receptor signalling in the formation of habitual operant behaviour. Thus, augmenting endocannabinoid levels through the inhibition of their metabolic enzymes may have clinical value by preventing aberrant habit formation, which is a common feature in substance use disorders.

3 | CELL-TYPE MECHANISMS AND CANNABINOID SIGNALLING

Early studies on the characterization of brain CB1 receptors provided strong evidence on how they can control neurotransmitter release through their presynaptic localization (Kano et al., 2009). However, more recent advances proposed that the postsynaptic localization of CB1 receptor cannot be discarded (Bacci et al., 2004; Maroso et al., 2016). Besides its localization at the synapse, an important concept in the cannabinoid field is the different neuronal and non-neuronal expression of CB1 receptors, which has a clear impact on their role in brain functions and behavioural responses (Busquets-Garcia et al., 2015, 2018). This wide and differential expression in the brain reflects the complexity of the ECS and can explain its variety of functions. According to this, De Giacomo et al. (2020) use an elegant genetic approach to show the opposing role of the CB1 receptors on exploratory behaviour depending on their localization in dorsal telencephalic glutamatergic or forebrain GABAergic neurons. In line with this, Warren et al. (2021) present a perspective review on the synergistic role between the endocannabinoid and noradrenergic systems in regulating fear extinction. This review, together with previous findings that directly show the functional presence of CB1 receptors in noradrenergic cells (i.e., DBH-positive cells) (Busquets-Garcia et al., 2016), further strengthens the potential role of cannabinoid signalling in the regulation of noradrenergic transmission, which might have important pathophysiological functions for conditions such as posttraumatic stress disorder.

4 | CANNABINOID SIGNALLING, SYNAPTIC PLASTICITY, AND DEVELOPMENT

At the synaptic level, the main and classical function of the ECS is to act as "circuit breaker" in order to maintain synaptic homeostasis (Katona & Freund, 2012). Thus, once released from postsynaptic cells, endocannabinoids act at presynaptic CB1 receptors to decrease the probability of neurotransmitter release. Obviously, from this general function as circuit breaker to the regulation of brain functions and behaviour, there is a big gap where several synaptic processes might be involved (Busquets-Garcia et al., 2015, 2018). Besides the hippocampus, the synaptic roles of cannabinoid signalling have been largely explored in other cortical areas. A review by Durieux et al. (2021) describe in detail how cannabinoid signalling contributes to cortical plasticity throughout life, including during different critical periods of development. Importantly, they acknowledge the lack of mechanistic studies detailing the exact role of cannabinoid receptors in excitation and/or inhibition depending on the developmental stage. Thus, more research in this direction is required to improve the current knowledge of cannabinoid actions. Besides the role of CB1 receptors in shaping synaptic plasticity at different developmental windows, previous studies showed that cannabinoid signalling is also required for the establishment of proper axonal projection patterns in developing neurons (Roland et al., 2014). Interestingly, Elul et al. (2022), by using *Xenopus laevis* tadpoles, assess the effects of cannabinoid signalling on growth cone filopodia and axonal projections of retinal ganglion cells. This study confirms and extends the importance of cannabinoid signalling in developing neuronal circuits. Another important brain region where CB1 receptors have been involved in the regulation of synaptic events is the olfactory bulb (Soria-Gomez et al., 2014). In this regard, Heinbockel et al. (2021) nicely review the role of endocannabinoids as signalling molecules in the olfactory system and the relevance of CB1 receptors for synaptic plasticity in this particular brain region.

5 | CANNABINOID SIGNALLING IN DISEASE

Given the widespread distribution of CB1 receptors, it is expected that its repertoire of actions might be implicated in many (dys)functions (Pacher et al., 2006). Evidence pinpoints the ECS as an excellent therapeutic target that may prove efficient either alone, in addition to current treatments and/or as valuable diagnostic biomarker for several pathologies. Indeed, cannabinoid signalling is known to be strongly involved in various brain disorders, including depression, schizophrenia, obesity, stroke, multiple sclerosis, neurodegeneration, epilepsy, addiction, and many others (Araque et al., 2017). Moreover, ECS alterations also characterize peripheral pathological conditions, including pain, cardiovascular alterations, inflammation, cancer, and liver and musculoskeletal disorders (Maccarrone et al., 2015). In this special issue, the modulation of cannabinoid signalling is provided as an ensemble of potential novel and well-established therapeutic avenues. Kilinc et al. (2020) use a rat model of migraine to propose selective ligands targeting CB1 and CB2 receptors as novel and effective treatment strategies against this disease. In particular, they showed how CB1 and CB2 receptors are involved in the release of calcitonin gene-related peptide in migraine-related brain and in the degranulation of dural mast cells, respectively, two processes crucially involved in the pathogenesis of

migraine. In addition, Pereira et al. (2020) review recent literature on the pathophysiology of the burning mouth syndrome and highlight the potential therapeutic value of cannabis-based therapies in managing patients affected by this syndrome. Finally, according to previous findings, two experimental manuscripts further underline ECS therapeutic potential in Alzheimer's disease and epilepsy. Rodrigues et al. (2020) provide an optimized spectrophotometric assay that reveals increased activity of MAGL in a rat model of Alzheimer's disease. Notably, the optimization of this ex vivo technique for the quantification of the enzymatic activity involved in 2-AG metabolism in brain samples represents an important advance not only for the research on Alzheimer's disease but also for other animal models of neurodegenerative diseases. On the other hand, Roebuck et al. (2020) investigate how common phytocannabinoids, such as Δ^9-tetrahydrocannabinol and cannabidiol or the exposure to smoke from two different chemovars of cannabis, impact spike and wave discharges. Notably, these processes are associated with absent epileptic events and might be useful to better understand brain epileptic processes.

The expression of different components of the ECS remarkably fluctuates in many pathological conditions and might be exploited in the future as biomarkers for specific diseases. Thus, Joaquim et al. (2021) present convincing data on how plasmatic endocannabinoid levels are decreased in subjects with a high risk of psychosis. These results suggest that endocannabinoid levels might be imbalanced before the appearance of psychotic events, indicating that they could be considered as potential biomarkers to identify individuals in a prodromic phase before the onset of psychotic events. Future research will confirm if this can also be the case in other neuropsychiatric conditions. Moreover, in relation with neuropsychiatric disorders, Jung et al. (2020) reviewed the relevant literature on the potential link between cannabinoids (especially cannabidiol), omega-3 fatty acids, and peroxisome proliferator-activated receptors in the regulation of neuropsychiatric alterations. Specifically, they propose how this relationship might be involved in the modulation of dopaminergic abnormalities often associated with neuropsychiatric symptoms.

6 | CONCLUDING REMARKS

This series of manuscripts on cannabinoid signalling represents an additional step taken in the effort to better understand the complexity and the diversity of the roles of (endo)cannabinoids and their therapeutic potential. By including original research and review articles, this collection provides new insights into cannabinoid pharmacology, cannabinoid-dependent cell-type specific mechanisms controlling behaviour, the important role of cannabinoid signalling in synaptic plasticity and developmental processes, and finally, new evidence of the crucial role of cannabinoid signalling in pathological mechanisms and its therapeutic potentials. Much more is to be discovered, but the cannabinoid field is very lively and surprising discoveries are for sure ahead of us. Not only this will take part in a more thorough understanding of the ECS but it will also help in a better appreciation of how our body and brain work and in assessing new therapeutic strategies against several central and peripheral disorders.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

PEER REVIEW

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