Editorial: The Behavioural Pharmacology of Cannabinoids

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Humans have been using cannabis preparations for thousands of years for a variety of purposes. The scientific study of cannabinoids has taken an impressive flight in the last few decades, fuelled by the discovery of endogenous cannabinoids and cannabinoid receptors in the brain and body. Ever since, cannabinoid pharmacology has been a very active and exciting research field, ranging from fundamental molecular to clinical work. Indeed, the endocannabinoid system has been implicated in a wide range of neural and mental disorders that you will find represented in this Special Issue. To showcase the current standing of cannabinoid research, we chose to devote this 2022 Special Issue to the Behavioural Pharmacology of Cannabinoids, and we are pleased to present you the result, containing four reviews and seven empirical papers.

The first article paper in this issue is a review paper by Moore *et al*., who present an innovative summary of vapour exposure methods in preclinical studies. Investigating the neural and behavioural effects of exposure to cannabis vapour is of great translational importance, since inhalation is the most common route of cannabis use in humans. In their review, Moore *et al*. discuss the technological state of affairs of vapour exposure systems, as well as methodological details. Furthermore, the kinetics and behavioural pharmacology of cannabis vapour are discussed and compared with other routes of cannabinoid administration, thus providing a useful survey of this methodological advance, which will be of great help to inform future research. The second review in this issue, by Asth *et al*., addresses the rewarding and addictive properties of cannabinoids. In particular, they focus on the conditioned rewarding effects of drugs, as studied using place conditioning methods, as contextual cues associated with drug effects can be strong drivers of addictive behaviour. The article presents an overview of the conditioned rewarding and aversive properties of phytocannabinoids, cannabis receptor agonists and antagonists, as well as drugs that interfere with cannabinoid metabolism. Alongside discussing the abuse potential of cannabinoids, Asth *et al*. also evaluate how cannabinoid drugs may be used for the treatment of substance addiction. What follows is an article by Bagues *et al*., who provide an extensive review of current knowledge on the use of cannabinoid drugs to counteract the adverse effects of chemotherapy. To that aim, they discuss three common adverse effects of chemotherapeutic drugs, which are nausea and vomiting, neuropathic pain, and cognitive impairments. Importantly, Bagues *et al*. note that cannabis is being used to counteract nausea and vomiting induced by chemotherapy, but that evidence that cannabinoids may be used to treat chemotherapy-induced neuropathic pain at present only exists in preclinical studies. Furthermore, the potential beneficial effects of cannabinoids on the cognitive side effects of chemotherapy remain to be investigated. In all three domains, however, the potential psychoactive effects of systemically used and centrally active cannabinoids remain an area of concern. The last review in this Special Issue is by Rodriguez *et al*., which deals with less commonly known cannabis constituents and their potential analgesic effects. That is, most studies on the analgesic effects of cannabis have focussed on Δ9-tetrahydrocannabinol (THC) and cannabidiol, the most widely known and investigated phytocannabinoids in cannabis. Importantly though, cannabis contains a wide array of molecules, such as minor cannabinoids, terpenes and flavonoids. This review presents a thorough overview of a few dozen of different cannabis constituents, making clear that some of these minor cannabinoids, terpenes and flavonoids have clear-cut analgesic effects in models of acute pain, sometimes being just as effective as common analgesics. As such, this review may provide a starting point for studies to identify novel analgesic drugs, perhaps with a more favourable profile in terms of side effects.

The next section of this Special Issue presents seven empirical studies on cannabinoid pharmacology. The first of these has a clear link to the last article in the previous section, as it deals with the role of cannabinoids in pain sensation. In their study, Gonçalves *et al*. demonstrate that stimulation of spinal CB1 and CB2 cannabinoid receptors reduces allodynia in a rat model of diabetic neuropathic pain. This observation may open a new avenue for the development of cannabinoid-based treatments for this chronic pain condition. The article that follows also focuses on the role of cannabinoids in pain. In this paper by Raoof *et al*., blockade of CB1 cannabinoid receptors in the periaqueductal grey is shown to enhance dental pulp pain, as well as the associated deficits in learning and memory. This study therefore intriguingly links peripheral pain to cognition, implicating cannabinoids in both. Next, Gatch *et al*. explore the behavioural pharmacology of five novel synthetic cannabinoids. The importance of this work lies in the fact that synthetic cannabinoids are being sold as designer

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drugs, often to avoid the legislation around cannabis use. They found that four of these five cannabinoids, just like THC, reduce locomotor activity in mice and share discriminative stimulus effects with THC, the fifth one being less potent. These drugs may therefore share abuse liability with THC. Somewhat related to the previous study, in the following article, Paronis *et al*. provide evidence that not only tolerance but also spontaneous withdrawal symptoms can be observed after daily treatment with either THC or a direct cannabinoid receptor agonist in mice. These withdrawal symptoms were seen in terms of paw tremors as well as locomotor hyperactivity. Following up on this work, the next paper from the same laboratory investigates sleep changes following cannabinoid treatment and withdrawal. This study by Missig et al. shows that exposure to a CB1 cannabinoid receptor agonist acutely alters sleep composition; these effects on sleep change with repeated treatment and withdrawal. In parallel, they show that acute cannabinoid receptor agonist treatment reduces the activity of lateral hypothalamic orexin cells, but that activity of these cells is increased during cannabinoid withdrawal. Shifting from drug abuse to mood-altering effects of cannabinoids, the study that follows by Liu *et al*. shows that acute treatment with THC but not cannabidiol had anxiolytic effects in the elevate plus maze in mice. Importantly, cannabidiol cotreatment did not alter these anxiolytic effects of THC. The penultimate article in this issue, by Brianis *et al*., ventured into a related domain, by investigating the role of periaqueductal grey cannabinoid signalling in the response to aversive events. Their data show that treatment with the endocannabinoid 2-arachidonoylglycerol (2-AG) into the periaqueductal grey reduced the expression of contextual conditioned fear as well as punished drinking in the Vogel conflict task, the latter assay being less sensitive. These effects of 2-AG depended on stimulation of CB1 and CB2 cannabinoid receptors. The last study in this issue investigated the contribution of cannabinoid signalling in cognition, more specifically, the interaction between calcium channel signalling and cannabinoid receptor stimulation. Thus, in their study, Karimi *et al*. demonstrate that repeated treatment with the calcium channel blocker verapamil impaired learning and memory in a passive avoidance setup and that this amnestic effect was attenuated by treatment with a CB1 cannabinoid receptor antagonist. These findings fit well with the notion that the secretion of endogenous cannabinoids requires activation of calcium channels.

We think that these 11 manuscripts represent important steps forward in the study of the behavioural pharmacology of cannabinoids. In particular, they highlight the breadth of contemporary cannabinoid research, by showing the variety of processes and disorders that cannabinoids play a role in. That is, cannabinoid signalling is implicated in addiction, pain, emotion and cognition, as shown by the papers in this issue. Indeed, drugs that target cannabinoid neurotransmission may therefore hold promise for the treatment of several disorders of the nervous system, keeping the side-effect profile of cannabis itself in mind of course. As editors of Behavioural Pharmacology, we definitely enjoyed reading and editing these papers, and we are proud to present this Special Issue to the readers of the journal.

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