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Research Perspective Title: Inflammation in neurodegeneration: The response of the central cannabinoid CB₂ receptor to injury, and its potential as an anti-inflammatory, neuroprotective target in Parkinson's disease.

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Neuroinflammation in neurodegeneration, and the potential of targeting the cannabinoid CB₂ receptor:

In recent times there has been an intensification of interest in the pathological role of neuroinflammation in neurodegenerative disease. Neuroprotective strategies to slow, halt or reverse neurodegeneration have not proven fruitful clinically, and the notion of a multi-hit hypothesis in the progression of neurodegenerative disease has steered focus towards other contributory pathological factors, particularly neuroinflammation. Neuroinflammation is believed to sustain the neurodegenerative pathology, forming a cyclical and self-sustaining pathological process, with dying neurons activating microglia, which, once activated, can release several factors that kill further neurons (reviewed in Blandini, 2013). Indeed, evidence of neuroinflammation has been observed around sites of neuropathological lesions in many neurodegenerative conditions including Parkinson's disease (Gómez-Gálvez et al., 2015). Furthermore, epidemiological evidence suggests that chronic administration of drugs with anti-inflammatory action, including non-steroidal anti-inflammatory drugs (NSAIDs), may reduce the risk of developing neurodegenerative conditions. With this in mind, the concept of anti-inflammatory therapy for disease-modification in neurodegenerative disease has emerged, with a view to identifying specific, novel targets to reduce inflammation in neurodegeneration. One such anti-inflammatory target that has garnered particular attention in the context of Parkinson's disease is the anti-inflammatory and immunosuppressant cannabinoid type-2 (CB₂) receptor. The endocannabinoid system has been the focus of much interest in Parkinson's disease research, initially due to the role of the CB₁ receptor in the basal ganglia neurocircuitry. Indeed, in Parkinson's disease patients, elevated levels of the endogenous cannabinoid, anandamide, and dysregulation of the central CB₁ receptor have been reported, and preclinically, targeting the CB₁ receptor has shown therapeutic benefit in treating both symptomatic and drug-induced motoric features (reviewed in Concannon et al., 2015a). In contrast, preclinical

studies targeting the CB₁ receptor have been less successful as a neuroprotective strategy, and this has led to increased interest in the CB₂ receptor for disease-modification. The CB₂ receptor has emerged as an exciting target for modulation of neuroinflammation because it is expressed on microglial cells, and when activated, has profound anti-inflammatory and immunosuppressant effects on these neuroimmune cells (Mecha *et al.*, 2016). This perspective will draw together some of the recent evidence indicating that CB₂ receptor expression is profoundly increased at sites of injury in the brain, thus supporting the concept that specific targeting of this receptor may have the potential to break the pathological cycle of neuroinflammation and neurodegeneration in neurodegenerative disease.

The response of the central cannabinoid CB₂ receptor to injury, and its potential as an anti-inflammatory, neuroprotective target in Parkinson's disease: The first evidence that the CB₂ receptor expression is altered in the diseased human brain came in 2003 when Cristina Benito, Julián Romero and colleagues (Benito *et al.*, 2003) showed that the CB₂ receptor was selectively expressed in microglia and astrocytes surrounding neuritic plaques in the *post mortem* brains of patients with Alzheimer's disease. This was the first evidence that expression of the CB₂ receptor, which was heretofore considered the "peripheral" cannabinoid receptor, was altered in the human brain in a neurodegenerative disease. Since then, upregulation of microglial CB₂ receptor expression has been reported to be associated with the degenerative pathology of many human diseases including in the degenerating substantia nigra of patients with Parkinson's disease, the degenerating striatum of patients with Huntington's disease, the degenerating cerebellum of patients with spinocerebellar ataxia, and in the demyelinated cortex of patients with multiple sclerosis (see Concannon *et al.*, 2015b, Gómez-Gálvez *et al.*, 2015, Mecha *et al.*, 2016 and references therein).

Although these studies are crucially important in that they have shown that the microglial CB₂ receptor undergoes upregulation in the diseased human brain, the key question is the role they playing in the pathophysiological cycle of neurodegeneration and neuroinflammation - is CB₂ receptor upregulation contributing to inflammation-driven neurodegeneration or is it a compensatory attempt to keep it in check? The probable answer to this question comes from a multitude of *in vitro* studies which have provided overwhelming evidence to support a role for the CB₂ receptor in attenuating the microglial neuroinflammatory response to injury and neurodegeneration (extensively reviewed in Mecha *et al.*, 2016). These studies have shown that activation of CB₂ receptors produces a less active microglial phenotype with suppressed phagocytic and antigen presentation functionality, reduced release of pro-inflammatory cytokines and other neurotoxic factors, and enhanced release of anti-inflammatory cytokines. If these *in vitro* observations are reflective of the functions of microglial CB₂ receptors in the diseased human brain, then it follows that pharmacological targeting of CB₂ receptors should reduce neuronal degeneration in conditions where this is associated with neuroinflammation.

In vivo preclinical studies provide the interface between such *in vitro* studies and the human findings, and provide a means for probing dynamic changes in CB₂ receptor expression in response to brain injury, as well as for assessing the functionality of any such changes. Moreover, valid animal models in which microglial CB₂ receptor upregulation is associated with neurodegenerative lesions (such as occurs in the human brain), will also facilitate the development of novel therapeutic strategies targeting this receptor. To this end, we have recently embarked on a series of studies investigating the change in expression of the brain's CB₂ receptor in response to neurotoxic, environmental and inflammatory stimuli in the rat (Concannon *et al.*, 2015b; Concannon *et al.*, 2016). We specifically investigated CB₂ receptor expression in response to direct intrastriatal infusion of the catecholaminergic neurotoxin, 6-

hydroxydopamine, the organic pesticide, rotenone, the bacterial inflammagen, liposaccharide (LPS), and the viral inflammagen, polyinosinic:polycytidylic acid (Poly I:C). Although chosen because of their relevance to the etiology and pathogenesis of Parkinson's disease, the inflammagens, in particular, are relevant to a wider range of neurodegenerative diseases in which neuroinflammation plays a pathological role. The toxins were also chosen because they initiate neuroinflammation and neurodegeneration in different ways: both 6-hydroxydopamine and rotenone are direct neurotoxins causing neuronal death from within the cell through oxidative stress, while LPS and Poly I:C cause inflammation-driven neurodegeneration secondary to microglial activation. Thus selecting neurotoxins with different inductive/degenerative mechanisms allowed for assessment of CB₂ receptor expression where inflammation plays a greater or lesser role in the neurodegenerative process. We found that all neurotoxins, whether direct or indirect, were associated with pronounced upregulation in CB₂ receptor expression in the rat striatum which peaked two weeks after the initial insult (Fig. 1). However, intriguingly, the upregulation in CB₂ receptor expression was substantially more pronounced in response to the bacterial and viral inflammagens, LPS and Poly I:C, respectively. These data show that, similar to the human degenerating brain, the central CB₂ receptor undergoes dynamic changes in response to brain injury, and is profoundly upregulated when the brain's innate immune system is engaged in the neurodegenerative process.

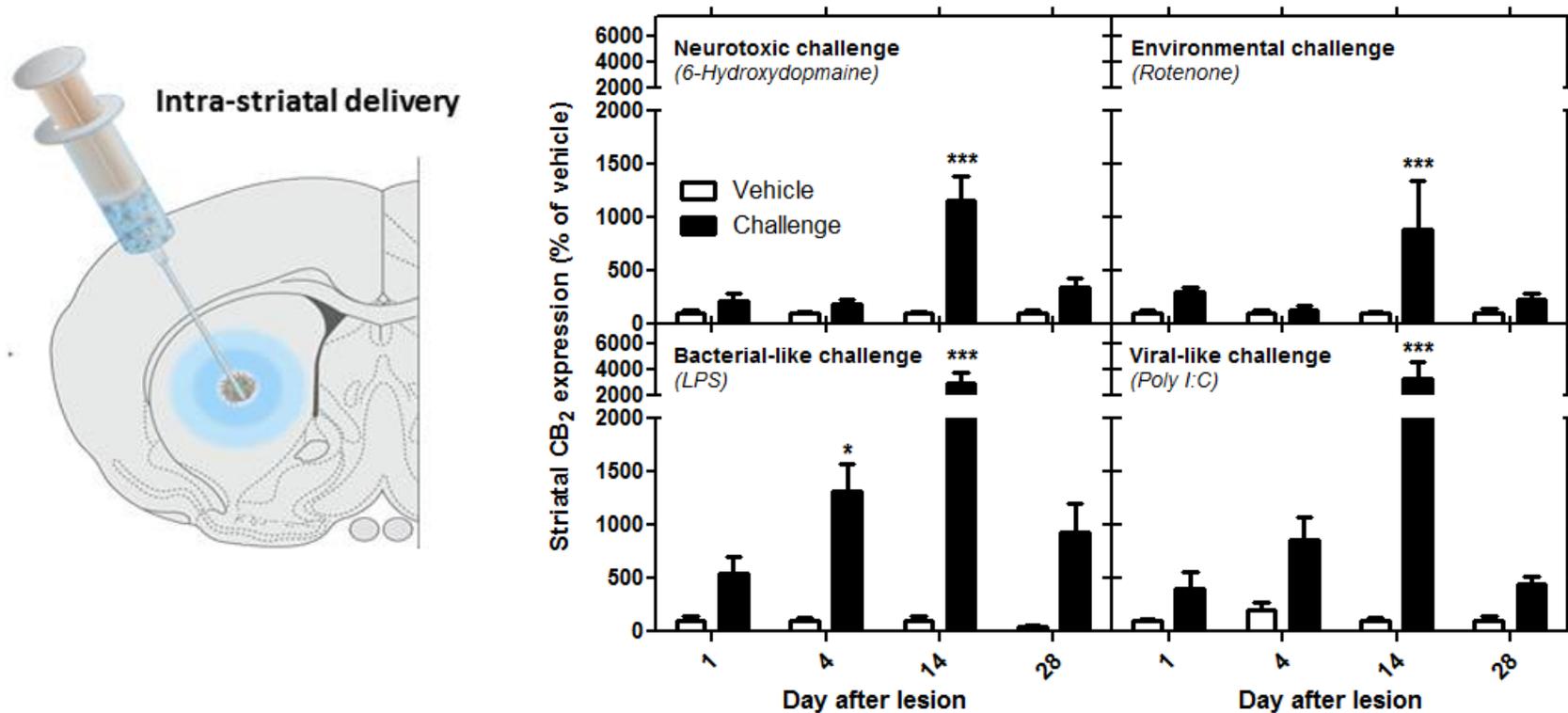


Fig. 1. The response of the central CB₂ receptor to neurotoxic, environmental and inflammatory neurodegenerative challenges. The change in expression of the CB₂ receptor was assessed using qRT-PCR in the striatum of young adult male rats after direct intrastriatal infusion of the various neurodegenerative challenges (or their corresponding vehicles). The catecholamine neurotoxin, 6-hydroxydopamine, was used to induce selective degeneration of the nigrostriatal dopaminergic system; the agritoxin, rotenone, was used to induce oxidative stress-driven striatal neurodegeneration; the bacterial endotoxin, lipopolysaccharide (LPS) was used to induce bacterial inflammation-driven neurodegeneration; and the viral mimetic, polyinosinic:polycytidylic acid (Poly I:C), was used to induce viral inflammation-driven neurodegeneration. Note that the elevation in CB₂ receptor expression was substantially more pronounced after the inflammatory challenges. * $P < 0.05$, *** $P < 0.001$ by two-way ANOVA with *post hoc* Bonferroni, $n = 6-7$ per group. Figure modified, with permission, from Concannon *et al.* 2015b and Concannon *et al.* 2016.

Other *in vivo* preclinical evidence that supports the potential of targeting the CB₂ receptor for anti-inflammatory and neuroprotective disease modification in Parkinson's disease comes from pharmacological and genetic studies. Several pharmacological studies have shown that non-selective cannabinoid drugs have anti-inflammatory and/or neuroprotective efficacy in animal models of Parkinson's disease, and these effects are mediated by CB₂ receptor activation. The first such study, reported that the non-selective cannabinoid agonist, WIN55,212-2, reduced MPTP-induced microglial marker expression in the mouse ventral midbrain, and this was blocked by the CB₂ antagonist, JTE-907 (Price *et al.*, 2009). Likewise, more recent studies using inflammation-driven mouse models of Parkinson's disease, have shown that pharmacological activation of CB₂ receptors can reduce LPS-induced microglial activation and protect the nigrostriatal pathway (García *et al.*, 2011; Gómez-Gálvez *et al.*, 2015). Several genetic studies have also revealed the functional neuroprotective capacity of the CB₂ receptor with deletion of CB₂ causing increased vulnerability to LPS-induced nigrostriatal damage (García *et al.*, 2011), and overexpression of CB₂ receptor causing less susceptibility to 6-hydroxydopamine (Ternianov *et al.*, 2012).

Thus, the emerging preclinical *in vivo* studies, taken together with the evidence from human *post mortem* reports and substantive *in vitro* indications, strongly suggest that the CB₂ receptor should be pursued as a therapeutic target to break the pathological cycle of neuroinflammation and neurodegeneration in neurodegenerative disease. Moreover, our recent studies revealing dynamic changes in CB₂ receptor expression in response to neurotoxic, environmental and inflammatory stimuli support the use of these models for validation of emerging cannabinoid therapies targeting the CB₂ receptor. In particular, these studies have shown that the CB₂ receptor may play an important role in attenuating inflammation-driven neurodegeneration, and may be of particular relevance to

neurodegenerative disease in which the brain's innate immune system is engaged in the neurodegenerative process. Although reduction of neuroinflammation will probably not be sufficient to solely halt neurodegenerative disease progression, it may serve to slow progression, and by ameliorating the inflammatory milieu it may enhance the effectiveness of current and emerging restorative treatments.

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