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COMMENTARY

High hopes for CB_2 receptors in neurogenesis

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During life, new neurons are continually added to hippocampal circuitry, with evidence suggesting that these adult-born neurons are functionally linked to cognition and emotion. The mammalian brain contains actively dividing neural stem cells in discrete regions, including the subventricular zone of the lateral ventricles and the subgranular zone of the dentate gyrus. Once mature, these neurons integrate into neuronal networks, forming synaptic connections with interneurons, mossy cells and CA3 pyramidal cells

LINKED ARTICLE
This article is a commentary on Avraham *et al.*, pp. 468–479 of volume 171 issue 2. To view this paper visit http://dx.doi.org/10.1111/bph.12478

Abbreviations
NPCs, neural progenitor cells; NSCs, neural stem cells; SGZ, subgranular zone; SVZ, subventricular zone; Tg, transgenic

The fate of neural stem cells (NSCs) in the adult brain is influenced by a variety of signalling molecules present in their microenvironment, including neurotransmitters (Song *et al.*, 2012), growth factors (Fournier *et al.*, 2012), cytokines (Vallieres *et al.*, 2002) and elements of the endocannabinoid system (Galve-Roperh *et al.*, 2013). Cannabinoids include the products of the cannabis plant (*Cannabis sativa* L.), the endogenous cannabinoids (endocannabinoids) and the synthetic cannabinoid ligands. Cannabinoids elicit a wide range of effects via two classes of G protein-coupled cannabinoid receptors, CB_1 and CB_2 (receptor nomnelcature follows Alexander *et al.*, 2013), the expression of which has been localized on glia, immune cells and neurons (Howlett *et al.*, 2002). CB_1 receptors are expressed at high levels throughout the brain, whereas expression of CB_2 receptors is restricted to glia, with some evidence of functional CB_2 receptors in neurons (Van Sickle *et al.*, 2005; Onaivi *et al.*, 2008; Xi *et al.*, 2011). The endocannabinoid system is linked with all aspects of human physiology and has an emerging neuromodulatory role in adult neurogenesis.

In a recent issue of the *British Journal of Pharmacology*, Avraham *et al.* (2014) examined the link between the endocannabinoid system and neurogenesis, using a model of HIV-associated dementia. The authors used GFAP/Gp120 transgenic (Tg) mice, a model that mimics the cognitive deficits observed in HIV-1 patients, with associated neuronal degeneration and deficits in hippocampal neurogenesis. They presented comprehensive evidence that treatment (for 20 days) of GFAP/Gp120 Tg mice with the CB_2 receptor-specific agonist, AM1241 (greater than 100-fold selectivity for CB_2 over CB_1), prevented deficits in neurogenesis in the hippocampal subgranular zone. They also presented a significant body of *in vitro* data demonstrating that AM1241 promoted the proliferation and differentiation of human NSCs, and furthermore prevented DNA fragmentation induced by administration of the HIV-1 glycoprotein Gp120.

Taken together, the results in this article demonstrated the neuroprotective role of CB_2 receptors against impaired neurogenesis, with relevance to the cognitive deficits seen in HIV-1 patients. The findings are consistent with earlier studies, indicating that NSCs and neural progenitor cells (NPCs) in the adult brain express both CB_1 and CB_2 receptors (Jiang *et al.*, 2005; Molina-Holgado *et al.*, 2007), and that CB_2 receptor agonists enhance proliferation of embryonic NSCs (Molina-Holgado *et al.*, 2007) and hippocampal NPCs (Palazuelos *et al.*, 2012). Indeed, studies in CB_2 receptor knockout mice have confirmed the role of this receptor in hippocampal proliferation (Palazuelos *et al.*, 2006). The

findings of Avraham *et al*. (2014) are novel. What remains unclear however are the intracellular signalling mechanisms governing these CB_2 receptor-mediated effects. AM1241 blunted astrogliosis in GFAP/Gp120 Tg mice, representing the strong possibility that one neuroprotective mechanism by which AM1241 could modulates neurogenesis was blocking inflammatory pathways. Indeed, neuroinflammation impairs neurogenesis (Monje *et al*., 2003), and evidence from Marchalant *et al*. (2009) (cited by the authors) has strongly linked cannabinoid receptor activation with decreased neuroinflammation and the restoration of hippocampal neurogenesis in aged rats. This certainly represents a worthwhile avenue for further investigation in the GFAP/Gp120 Tg model.

The link between cannabinoids and HIV-1 viral infection is a relatively uncharted area of research, and the article by Avraham *et al*. (2014) also provides advances in this area. The results described in this article supplement previous evidence that cannabinoids inhibit HIV-1/Gp120-induced neuronal damage (Kim *et al*., 2011; Hu *et al*., 2013) and that HIV-1/Gp120 enhances endocannabinoid degradation (Maccarrone *et al*., 2004). Neurological impairment afflicts a large proportion of HIV-1 patients, and the findings of Avraham *et al*. (2014) point to the existence of a strong link between the endocannabinoid system and neurogenesis, with relevance to HIV-associated neuropathology. Taken together, this article further strengthens the rationale for the development of CB_2 receptor-specific agonists as a class of therapeutics, acting as promising candidates to target NPC proliferation and neurogenesis, bypassing the undesired psychoactive effects of neuronal CB_1 receptor stimulation.

Conflict of interests

None.

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