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# Cannabinoid signalling and IL-1β are critical mediators regulating omega-3 PUFAs neural stem cell fate decisions

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The endocannabinoid (eCB) system acting through CB1 and CB2 receptors has been demonstrated to play a key role in regulating neural development and adult neurogenesis, which has direct impact on many events including memory formation, pain, neurodegeneration and inflammation. Emerging evidence links endocannabinoid signalling to brain repair, but in terms of producing therapeutic interventions, research has yet to show an effective treatment to reverse/repair the damage caused by neurodegeneration, although much has been learnt about the causes of the damage to the brain. Compelling *in vivo* and *in vitro* evidence now indicates a complex and dynamic interplay between the endocannabinoid system, omega-3 polyunsaturated fatty acids (PUFAs), the immune system and neural stem cells (NSC) in the promotion of brain self-repair. The central nervous system is highly enriched in omega-3 PUFAs, and an adequate intake is essential for brain development and function. Furthermore, there is increasing evidence that omega-3 PUFAs such as eicosapentaenoic acid (EPA) and docohexaenoic acid (DHA) may possess therapeutic potential in a variety of neurological and neurodegenerative conditions. Consequently, the aims of this study were to investigate the effects of EPA or DHA on NSC fate and the potential role of CB1/CB2 receptor signalling pathways in these effects. Experiments were performed in NSC from wild type mice (C57BL6/J, WT) and interleukin-1β knock-out (IL-1β KO) mice. Serial dilution assays were used to identify the effects of EPA and DHA on NSC fate. It was found that EPA, but not DHA significantly increase cell proliferation (EPA: $P<0.001$ vs. Control; DHA: $P=1.000$ vs. control) in NSC from WT mice. Specifically, addition of EPA (10nM, t=7 days) to the NSC resulted in a significant increase in proliferation of approximately 46%. Our results indicate that low doses of EPA, but not DHA, significantly increase NSC proliferation *in vitro*. This is in agreement with previous literature, which has identified that EPA stimulates neurogenesis, suggesting that DHA plays a vital role in differentiation. Furthermore, proliferation assays were used to identify the relationship between EPA and DHA and the eCB system in regulating neurogenesis. By blocking CB1 (AM251, 1µM t=7 days) and/or CB2 (AM630, 1µM t= 7 days) receptors we observed a modulation of the proliferative effects of EPA on NSC (EPA vs. EPA+CB1: $P<0.001$; EPA vs. EPA+CB2: $P<0.001$), suggesting that EPA influence NSC proliferation via the CB1 and CB2 receptors and their subsequent signalling pathways. In addition, we have found new evidence for a cross-talk between the IL-1□ and the omega-3 PUFA signalling pathways that is required to stimulate NSC proliferation. Our results show that the effects of EPA are ablated in NSC from IL-1βKO mice, suggesting that EPA induced NSC proliferation is dependent on endogenous IL-1β. Further elucidation may provide a crucial insight into the regulatory role of IL-1β as a key mediator in the cell cycle. Furthermore, our data highlights the therapeutic potential of this cross-talk between omega-3 PUFAs and eCB in neurogenesis and reveals a dynamic interplay between these players in brain repair.

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