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Cannabinoid receptor antagonism augments the valproic acid induced attenuation of neural stem cell proliferation, an effect not dependant on IL-1β

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Introduction: Interactions between the endocannabinoid (EC) and immune system have been demonstrated to influence neurogenesis and neurodevelopment [1]. However, it is unknown if these same interactions apply in neurodevelopmental conditions such as Autism Spectrum Disorder (ASD). Clinically, pregnant mothers taking the epileptic treatment valproic acid (VPA), have a greater risk of having a child with an ASD [2]. VPA is a histone-deactylase inhibitor which results in epigenetic modifications and alterations in gene expression and has been shown to alter neurogenesis [3].

Aims: The aim is to examine the effects of VPA on the proliferation of neural stem cell (NSC)s, the expression of components of the EC system, and the impact of IL-1β deletion on such effects. A further aim was to examine the effect of cannabinoid receptor antagonism on VPA-induced modulation of NSC proliferation.

Methods: NSC cultures were prepared from the cortex of embryonic day 12 (ED12) C57BL6 mice (wildtype, WT) or IL-1β knockout (KO) mice. Cells were treated with VPA (0, 10, 50, 100, 500, 1000μM) for 72 hours and MTT and LDH assays conducted to determine cell proliferation and cell death (n=3). Cell pellets were examined for expression of CB1, CB2 and FAAH genes. In a separate experiment, NSCs were pre-treated with CB1 (AM281; 1μM) or CB2 (AM630; 1μM) antagonists, 45 minutes later with VPA, and MTT and BrdU assessed 72 hours later (n=2).

Results: VPA concentration dependently reduced NSC proliferation in WT cells ($P<0.001$) without inducing cytotoxicity. While a similar trend for VPA to decrease cell proliferation was observed in IL-1β KO NSCs, this failed to reach statistical significance. VPA treatment significantly increased the expression of the CB1 receptor and FAAH. CB1 and CB2 receptor antagonism significantly reduced NSC proliferation and BrdU incorporation, an effect potentiated by VPA (1000μM) treatment ($P<0.001$). Similar effects were observed in IL-1β KO NSCs.

Conclusion: The data demonstrate that VPA attenuates NSC proliferation and alters expression of components of the ECS. Cannabinoid receptor antagonism further enhances the anti-proliferative effect of VPA in NSCs, an effect independent of IL-1β. Taken together this data suggests a possible interaction between the ECS and VPA in neurogenesis which may have implications for understanding the pathogenesis of neurodevelopmental disorders such as ASD.

References:

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