Investigating Bone Morphogenetic Protein 4 as a Potential Regulator of the Age Related Increase in Risk for Alzheimer's Disease: The Regulation of the Unfolded Protein Response and Apolipoprotein E Expression in Astrocytes

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Alzheimer's disease (AD) and other related neurodegenerative disorders are some of the most prevalent and debilitating conditions affecting elderly populations. Previous research has indicated that the concentrations of BMP4 increase dramatically as individuals age, and that such increases in BMP4 expression may play a role in the pathogenesis of AD. Therefore, this project sought to determine a possible mechanism by which BMP4 may affect the aging brain. BMP2 has been shown to upregulate the unfolded protein response (UPR) and the expression of the AD associated protein Apolipoprotein E (APOE) in non-neural tissues. In order to determine the effects of BMP4 on UPR and APOE expression in the brain, primary murine astrocyte cultures were treated with high concentrations of either BMP4, Noggin (a BMP antagonist), Brefeldin A (a protein transport inhibitor), PERK inhibitor (a UPR inhibitor), or some combination of the preceding reagents for 24 hours. Following treatment, the levels of GRP78, a UPR marker, and APOE were evaluated by western blot, and the levels of APOE, GRP78, and lipid droplet formation were evaluated by immunocytochemical staining. The results indicated that, not only can BMP4 induce UPR in astrocytes, but the induction of the astrocytic unfolded protein response is somewhat dependent on BMP signaling. Additionally, it was demonstrated that BMP4 is able to induce lipid droplet formation, as a result of UPR, and that increased BMP4 signaling can upregulate APOE expression, independent of the UPR pathway. Together, these results suggest that BMP4 may play a role in the pathological cascades of neurodegenerative disease through the induction of the unfolded protein response and the upregulation of APOE expression.

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