POSSIBLE PROTECTIVE EFFECT OF GLUTAMINE IN AD

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Introduction: Glutamine is categorized as non-essential amino acid because cells contain necessary synthetic enzymes, but under conditions of stress it can become essential. The relevance to AD is heightened by studies showing a significant anti-inflammatory effect of glutamine supplements. Chronic inflammation has been well established as a central pathogenic feature. Depletion of glutamine from brain has been documented in LPS-induced inflammation in human subjects. De novo expression of glutamine synthetase in neurons in AD also suggest a loss of glutamine in affected region.

Results: In culture, glutamine is essential for the survival and proliferation of N2a cells. Withdrawal of glutamine induces morphological differentiation. This morphological change is ATM dependent; an ATM specific inhibitor blocks the effect of glutamine deprivation on these cells. This interaction is bi-directional as the ATM-mediated DNA damage response is greatly reduced, and cell death increased in N2a cells deprived of exogenous glutamine. By contrast, loss of exogenous glutamine stimulates primary neurons to up-regulate glutamine synthetase. This blocks the cell death seen in N2a cells, but over time DNA damage accumulates. We next tested the in vivo protective effects of glutamine supplementation in mouse models of AD (R1.40 and APP8.9 - 4% glutamine in drinking water for 10 days). When mice were administered a low dose of LPS, both the DNA damage response and inflammation-induced neuronal cell cycle activation was reduced.

Conclusions: Taken together, these observations suggest that glutamine has neuroprotective effects that may be lost in AD where its extracellular levels likely decline.