Cholesterol Deficiency as a Mechanism for Autism: A Valproic Acid Model

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Autism spectrum disorders (ASD) is a heterogeneous group of complex neurodevelopmental disorders characterized by impairment in social interaction, including verbal and non-verbal communication challenges, as well as patterns of restricted and repetitive behaviors.

The etiology of ASD is largely unknown, but numerous studies have shown that a low level of cholesterol is linked to autism and autism-related disorders. It is clear that brain cholesterol balance and metabolism are crucial for normal development of the brain, as it is essential for neuroactive steroid production, myelin sheath formation, etc.

Administration of valproic acid (VPA) to pregnant mice results in neuroanatomical and behavioral changes in the offspring that are consistent with autism. Mice exposed to VPA in-utero have:
- Altered expression of cholesterol metabolizing genes in the brain
- Changes in cholesterol/isoprenoid homeostasis in certain areas of the brain
- Hypomyelination in certain areas of the brain
- Decreased oligodendrocytes

Furthermore, children with fetal valproate syndrome caused by in-utero exposure to valproic acid have a higher chance of developmental problems such as decreased cognitive function, learning difficulties and ASD.

This study examines the link between VPA and cholesterol homeostasis in cultured human neuroblastoma and microglial cells.
Methods

- SHSY-5Y human neuroblastoma cells and HMC3 human microglial cells were exposed to VPA at 0, 250, 1000 and 5000 μM for 24h, N=3 per condition.

- Expression of critical genes that regulate cholesterol transport were quantified by RT-PCR using specific primers for each.

- These include:
  - The efflux proteins ABCA1, ABCG1, 27-hydroxylase (27-OHase) and 24-hydroxylase (24-OHase)
  - The influx scavenger receptor CD36

- Expression of these target genes was normalized to concurrently measured GAPDH mRNA levels.
Results

SHSY-5Y neuroblastoma cells:
- VPA increases the expression of all three transporters (ABCA1, ABCG1, CD36) in a dose-dependent manner.
- Expression of 27-OHase was increased in a dose-dependent manner.
Results

HMC3 microglial cells:
- VPA exposure caused a concentration-dependent increase in ABCG1 (80-fold at highest dose) and a reduction in ABCA1 and an increase in CD36.
- VPA exposure caused a dose-dependent increases in 24-OHase.
Discussion and Conclusion

This study shows that VPA has a dramatic hypocholesterolemic effect on two key cell types that compose the developing brain. The net impact of the changes observed in these cholesterol-related genes would be outflow and metabolism.

Furthermore, enhanced 27-OHase activity produces an oxysterol metabolite with neurotoxic effects that includes downregulating synaptic proteins and decreasing neurite number and length.

Together, our results indicate that VPA may impair brain cholesterol homeostasis, possibly explaining the relationship between VPA and ASD.

A better understanding of the involvement of cholesterol in the mechanisms by which VPA leads to ASD may translate into novel preventative therapies for this serious disorder.