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MITOCHONDRIAL DYSFUNCTION IN REYE'S SYNDROME: MECHANISMS AND METABOLIC CONSEQUENCES, A REVIEW OF THE LITERATURE

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Reye's syndrome is a rare but severe and potentially fatal pediatric disorder characterized by acute noninflammatory encephalopathy and hepatic steatosis, described by Australian pathologist R.D.K. Reye in 1963. It has been established that RS is linked to viral infections and aspirin use, but any substance containing a salicylate moiety bismuth subsalicylate, choline salicylate, methyl salicylate, magnesium salicylate are food additives that can cause RS.

The pathophysiological mechanism of RS includes multiple steps:

1. Preceding viral infection, most commonly influenza A/B and chickenpox
2. Use of substances containing a salicylate moiety
3. Salicylate directly inhibits long chain 3-hydroxyacyl CoA dehydrogenase, disrupting fatty acid β-oxidation
4. Salicylates are triggers for mitochondrial permeability transition (MPT) which occurs due to opening of mitochondrial permeability transition pore (MPTP) this happens because salicylates increase mitochondrial Ca^{2+} and ROS
5. Inner mitochondrial membrane becomes leaky, and the proton gradient needed for ATP synthesis is violated, stopping of oxidative phosphorylation leads to ATP depletion

The involvement of viruses is as follows: viral endotoxins amplify mitochondrial damage by increasing cytokine concentrations, further impairing energy metabolism. Liver and brain cells are most affected because they heavily rely on mitochondria function for energy, this leads to fatty degeneration in hepatocytes (microvesicular steatosis), liver impairment leads to hypoglycemia. Hyperammonemia occurs due to urea cycle dysfunction (due to mitochondrial failure) which leads to ammonia buildup and crossing into the BBB, astrocytes convert ammonia to glutamine leading to osmotic swelling (cerebral edema). Lactic acidosis develops due to activation of anaerobic metabolism, the combination of these manifestations leads to stupor, disorientation, combativeness, delirium

While less than 0.1% of children who took aspirin developed Reye syndrome, more than 80% of children diagnosed with RS had taken aspirin in the preceding 3 weeks, and during the 1979-1980 influenza outbreaks the U.S reported 555 cases of RS with 97% of cases linked to aspirin use, a study from 2008 found that 71% of RS cases had an underlying metabolic disorder, another study of 58 children with RS found fatty acid oxidation defects in 41% of the children, these defects include

1. MCAD deficiency: inability to break down fatty acids leads to energy crisis during fasting/viral illness which is exacerbated by aspirin use
2. LCHAD deficiency
3. OTC deficiency: prevents ammonia detoxification which leads to hyperammonemic encephalopathy

In conclusion, modern research is showing that RS occurs due to an underlying, undetected metabolic mitochondrial disease that is only exacerbated with the use of aspirin in a viral infection due to their heavy effect on mitochondria, future research should be aimed towards using MPT inhibitors as potential therapy for RS and genetic testing in RS patients to check for genetic metabolic disorders