Common Anaesthetic and Sedative Agents Cause Persistent Mitochondrial Dysfunction and mtDNA Damage

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Introduction

Mitochondrial dysfunction is implicated in many acute and chronic neurological diseases. Anaesthetic agents are known to interact with mitochondrial proteins but the effects and consequences of these interactions are not known. Recent clinical and laboratory data show that exposure to anaesthetic agents induces neuronal apoptosis and neurofunctional dysfunction in animal models and possibly adverse neurocognitive and neurobehavioral changes in children.

We hypothesize that anaesthesia-induced mitochondrial dysfunction causes gross cellular dysfunction in a clinically-relevant time frame and in clinically-relevant concentrations. This mitochondrial damage will have more impact on mitochondria-rich tissue, such as neurons, and the resultant neuronal-dysfunction may be responsible for the adverse effects of anaesthetics in the paediatric population.

Objectives

(1) Investigate how common drugs given in paediatric anaesthesia affect mitochondrial function.
(2) Determine if anaesthetic drugs can cause long-term changes in mitochondrial dysfunction.
(3) Develop a high-throughput assay to measure mitochondrial function that could be used to discover new therapeutics.

Materials & Methods

Using clinically established effect site concentrations1, cells in culture (HeLa (Gold standard) and HepG2 (mitochondria rich)) were exposed to each of isoflurane, propofol, ketamine, midazolam and morphine for the clinically relevant time frame and in clinically-relevant concentrations. This mitochondrial damage will have more impact on mitochondria-rich tissue, such as neurons, and the resultant neuronal-dysfunction may be responsible for the adverse effects of anaesthetics in the paediatric population.

Results

Mitochondrial Membrane Potential: A reduction in functional mitochondria was also noted for all anaesthetic agents with the biggest percent reduction occurring within the first hour (Fig. 3).

Mitochondrial Morphology: Changes in morphology indicate acute cellular stress and loss of functional capacity. All anaesthetics tested adversely affected mitochondrial morphology and induced changes from networked mitochondria to small, more punctate and less functional units (Figs 1 and 2).

Mitochondrial Biomass: Mitochondrial biomass was reduced after the first hour, and only with isoflurane exhibited a modest recovery by the fourth hour (Fig. 4).

Mitochondrial DNA Mutations: MtDNA mutations cause a persistent mitochondrial dysfunction. An increase in the number of mitochondrial DNA mutations was consistent with the increasing concentrations of anaesthetic agents to which the cells were exposed (Fig. 5).

Conclusions

Our research shows that common anaesthetic and sedative agents interact with mitochondria; altering their morphology, reducing their function and damaging their DNA. These changes occur at concentrations of the anaesthetic and sedative agents that are used clinically and occur within the time frame of common surgical procedures. This data contributes to a growing body of evidence linking anaesthetic induced neuronal damage to mitochondrial dysfunction. Future investigation into the precise mechanism by which this occurs and the efficacy of mitochondrial protective strategies in reducing these effects is required.

References