D151. Intranasal Insulin Prevents Anesthesia-induced Cognitive Impairment in Juvenile Mice

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1243
IARS Poster Session
The Fairmont Queen Elizabeth
Room: Place du Canada / Square Dorchester

Description

Anesthetics administered at the extremes of age trigger long-term morphological and functional changes in the brain. Pre-clinical studies in rodents and non-human primates correlate early-life, repeated or prolonged general anesthesia (GA) with neurotoxicity and sustained neurobehavioral deficits. This is in-line with pediatric epidemiological studies that associate longer or repeated anesthesia with cognitive and behavioral problems including: neurodevelopmental delay, learning disabilities, and attention deficit/hyperactivity disorder.

Moreover, anesthetic and sedative agents were cited in 2016 and 2017 updates of the U.S. FDA Drug Safety Communication, warning they may negatively impact brain development when administered to young children.

The mammalian brain is rich in insulin receptors. Insulin administered intranasally to healthy and cognitively-impaired adults has been shown to increase regional brain perfusion, hippocampal function, and verbal memory.

We developed a mouse model to determine how early-life intranasal insulin treatment could mitigate anesthetic-induced neurotoxicity on cognition during adulthood. We hypothesized that insulin administered intranasally to juvenile mice prior to anesthesia exposure would exert a neuroprotective effect to prevent anesthesia-induced cognitive impairment during adulthood.

Learner Objectives

The study was approved by McGill Animal Care Committee according to CCAC guidelines. Juvenile C57BL6 wild-type (WT) mice were randomized by sex to 1 of 4 groups: Home Cage Control, Intranasal Vehicle+Anesthesia, Intranasal Insulin (INI)+Anesthesia, and INI Alone. We treated postnatal day 8 (PND8) mice with saline vehicle or intranasal insulin (2U Humulin®R) daily for seven days. At PND15, GA was induced by 2.0% isoflurane and maintained at 1.5% for 2h/d for three days, comparable to pediatric MAC of 1.6% to 1.8%.

Hippocampal-dependent spatial learning was evaluated at adulthood, PND65 (+/- 5), using Object Location and Contextual Fear tests.

Synaptic plasticity was assessed at adulthood by measuring the late-phase of long-term potentiation (L-LTP) in the hippocampal CA1 region.

Hippocampal slices were prepared after the last dose of anesthesia at PND17 to determine apoptosis by immunofluorescence of cleaved caspase 3 (CC3).

Key Takeaways

Juvenile mice exposed to isoflurane GA (n=13) exhibited impaired Object Location and Contextual Fear memory during adulthood ($p<0.0001$) compared to controls (n=17). Administration of insulin intranasally prior to anesthesia exposure (n=15) prevented the memory deficit in both tasks ($p<0.0001$) while intranasal insulin alone (n=10) did not improve memory compared to controls.

Intranasal Insulin prior to anesthesia exposure in young mice (n=8) prevented impairment in hippocampal synaptic plasticity in adults ($p < 0.05$) compared to vehicle and anesthesia group (n=10) while being similar to controls (n = 8).

Apoptosis in the hippocampal dentate gyrus was lower in mice given intranasal insulin prior to anesthesia exposure (n = 4, $p<0.001$) compared to vehicle and anesthesia group (n=4) while being similar to controls (n=4).

Submissions

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IARS Abstract Category

Pediatric Anesthesiology