[N-77] Hippocampal Dentate Gyrus Anesthetic-Induced Apoptosis Does Not Effect Context Pre-exposure Facilitation Effect in Mice

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Introduction: Anesthesia is used to facilitate surgical and radiological procedures in millions of children every year, but has repeatedly been shown to case extensive apoptotic cell death in developing and more recently mature animals. Despite overwhelming histological evidence that exposure to anesthesia can cause neuronal cell death, the clinical consequences of this phenomenon remain unknown. Previous studies have shown anesthetic exposure to postnatal day (PND) 21 mice caused extensive hippocampal dentate gyrus apoptosis. In order to examine the possible clinical consequences of this damage we used a hippocampal learning paradigm that isolates the hippocampus-dependent aspect of the fear conditioning task from context-shock association. Context Pre-exposure Facilitation Effect (CPFE) guarantees a focus on the hippocampus and is not confounded by the possibility of other neural systems maintaining behavior.

Methods: PND 21 mice (n=34) were either fasted in room air or exposed to isoflurane anesthesia for 6 hours. One week later the animals were subjected to a 3 day CPFE paradigm. Day 1 the animal was placed in the context environment for 5 minutes. Day 2 the animal was placed in the context, given a shock at 0.5mA for 2 seconds and removed from the context 30 secs later. On Day 3 the animal was returned to the context and freezing behavior was recorded for 5 minutes.

Results: Using t-test analyses, no statistical difference for total freezing episodes, total time freezing, or latency to start of the first freezing episode was observed between the two groups.

Discussion: Retrospective human studies looking at the possible consequences of anesthetic exposure and long term learning and behavior outcomes in children have given inconclusive results and are unable to separate surgical and anesthesia related outcomes. Numerous previous studies in animals have repeatedly demonstrated that exposure to anesthesia causes apoptotic neuronal cell death but have shown conflicting results about what clinical effects this damage may or may not cause. In this study we merged a specific anesthetic neuronal damage pattern (hippocampal dentate gyrus) with a specific behavior paradigm that evaluates isolated hippocampal damage effects (CPFE) in an attempt to link the phenomenon with a specific clinical outcome. Despite immunohistochemical staining evidence that showed significant neuronal cell damage, no significant CPFE behavior changes were detected. These results suggest 3 distinct possibilities: 1) That anesthesia-induced apoptosis at the observed level in the dentate gyrus does not cause a clinically significant learning deficit in rodents. 2) The clinical consequences of this neuronal destruction occur outside of our testing window or 3) CPFE is not sensitive enough to detect the clinical consequences of the anesthesia damage observed. Translating the combined results of different rodent testing paradigms and CPFE in particular, any clinical deficit or behavior change that may be caused in our pediatric population may likely be small and need a very specific and sensitive testing battery to detect.
