Chronic Metabolic Effects of Anesthesia on the Developing Rabbit Brain

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Introduction

Millions of children undergo general anesthesia each year and a growing body of literature from animals and humans suggests that exposure to anesthesia at an early age can impact neuronal development, leading to learning and memory impairments later in childhood. Although a number of studies have reported behavioural and structural effects of anesthesia exposure during infancy, the long-term metabolic manifestation of these changes has not been previously examined. The current MRS study has investigated the chronic metabolic changes in the dentate gyrus (DG) in rabbits exposed to volatile anesthetics when they were pups.

Methods

Dutch-belted rabbits were used in accordance with the NIH guidelines and NorthShore University HealthSystem Research Institute IACUC approved protocol. At postnatal days 8, 11, and 14 the kits were anesthetized individually with a nose mask with either 1 MAC of sevoflurane (SVF) or isoflurane (ISF) in air or in 80% oxygen (4 anesthesia groups and 1 control group; n=4 or 5). At three months of age, animals were implanted with restraining headbolts and were given 10 eyeblink classical conditioning sessions. The CS was delivered by deflecting two whiskers. The US consisted of air puff supplied by compressed air. After learning sessions, MRS data were acquired from awake rabbits. MR experiments were performed on a Bruker Biospec 9.4T imager. PRESS localized, water suppressed, proton spectra were acquired from 2x2x2mm^3 voxels located in the left and right DG using TR/TE 3000ms/11.7ms, spectral width 4006Hz, 8k data points and 256 averages. Spectra were analysed using LCModel analysis, and calculated metabolite to creatine (M/Cr) ratios compared between anesthesia exposed and control rabbit brains.

Results

The learning deficit in adult rabbits exposed to anesthesia in infancy was reported previously. Resonances from N-acetyl aspartate (NAA), glutamate (Glu), glutamine (Gln), GABA, creatine/phosphocreatine (Cr/PCr), choline containing compounds (Cho), taurine (Tau), and myo-Inositol (Ins) were present in the DG spectra from awake rabbits. In the left DG of the *SVF+air* group, NAA, Glu+Gln, and GABA were significantly lower than controls. While all metabolites were lower in the left DG of *SVF+O_2* group relative to control group, only decreases in GABA and Tau reached significance. ISF treated groups did not show many differences from the control group, with only Ins being elevated in the left DG of *ISF+air* group. Metabolite levels in the right DG revealed a different pattern. The *SVF+O_2* group had lower metabolite levels across the spectrum with significant decreases in Glu and Cho which were also significantly lower in the *SVF+air* group. In contrast, no significant changes in metabolite levels were detected in the *ISF+air* and *ISF+O_2* groups.

Discussion

PRESS localized metabolite spectra from the DG of rabbits showed effects of exposure to sevoflurane and isoflurane nearly 4 months after anesthesia. Decreases in NAA, Glu+Gln, GABA and Tau in the pups exposed to SVF mixed with air or oxygen suggest that SVF has long term effects on neurons, both excitatory and inhibitory neurotransmitters, and brain osmolyte. In contrast, ISF causes minimal long-term neuronal effects in the DG with increases only in Ins in the *ISF+air* group, which might indicate glial effects. The difference in the metabolic patterns between left and right DG in anesthetic-exposed animals suggests that the effects of anesthesia might be modulated by behavioural training. The effects of training are seen only on one side of the brain since eye blink conditioning was performed on one side only.

Conclusions

Exposure to volatile anesthetics in infancy has chronic adverse effects on the metabolism of the developing brain. SVF causes greater metabolic impairment than ISF. The metabolic effects of anesthesia may be modulated by behavioural training.

References: Aksenov D. et al., Physiol. Behav. 2016, 167:10-15.
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