Effects of Repetitive Exposure to Anesthetics and Analgesics in the APP Alzheimer's mouse model.

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Introduction

Isoflurane has been reported to induce apoptosis, and to increase levels of Alzheimer's disease associated amyloid protein. Most reports however, are based on single exposures and short time after it.

We have worked on evaluating the relevance *in vivo* of the repetitive use of anesthetics and analgesics in an Amyloid Precursor Protein Alzheimer's mouse model after a month.

Methods

14-18 month-old Tg7526 mice were anesthetized - sedated for 90 minutes once a week for 4 weeks. While monitoring their physiological variables (temperature, blood pressure, heart rate, weight pre and post exposure).

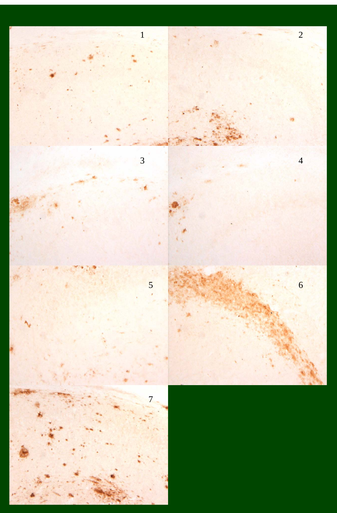

Figure 4: **Total Aβ in the CA1 region**. 1- Isoflurane 1%, 2- Propofol 26 mg/kg bolus and 2mg/kg/min infusion, 3- Diazepam 4mg/kg, 4-Ketamine 80mg/kg, 5-Pentobarbital: M 50mg/kg and F 40mg/kg, 6-Fentanyl 0.165 mgrs/kg and 7-Control group of transgenic mice non treated. Note that groups 1 through 5 show less positive staining than groups 6 and 7.
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Animals recuperated from the exposures at room air. Mice were divided into six groups as follows; Group 1 received Isoflurane 1%. Group 2 received Propofol IV. Group 3 was exposed to Diazepam IP, Group 4 received Ketamine IP. Group 5 was exposed to Pentobarbital IP and Group 6 received Fentanyl IP. Brains were harvested 8 days after the last exposure and stained for Congo Red and A-Beta.

Results

Amyloid Beta deposition patterns evidenced significant decrease ($p<0.05$) of deposition in cortex of the mice repetitively exposed to isoflurane, propofol, diazepam, ketamine, pentobarbital and Fentanyl (Fig 1).

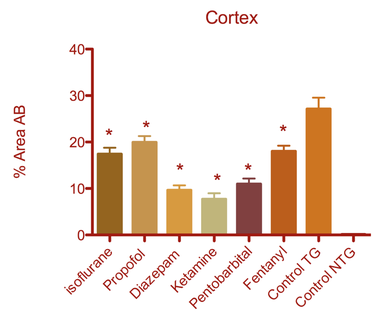

Figure 1: **Immunochemistry staining A Beta in brain Cortex**. Deposition of A beta was significantly less in all groups exposed compared to control transgenics. P<0.05.

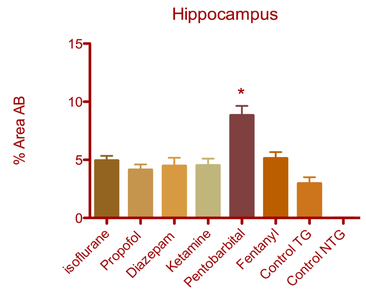

Figure 2**: Immunochemistry staining A Beta in brain Hippocampus**. When analyzing cumulative date for hippocampus Pentobarbital increases A beta when compared to transgenic controls. P<0.05.

Hippocampus showed significant increase of amyloid deposition in the mice exposed to Pentobarbital when compared to controls (Fig 2). However exposition to all agents but Fentanyl significantly reduced A beta deposition in the CA1 region (Fig 3 & 4).

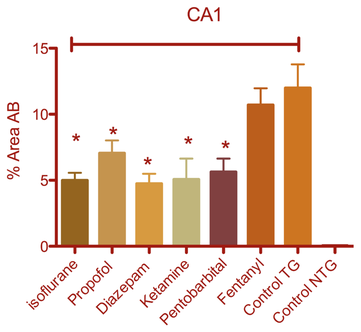

Figure 3: **Immunochemistry staining A Beta in CA1** hippocampus region. Isoflurane, Propofol, Diazepam, Ketamine and Pentobarbital showed significant decrease in A beta depositionP<0.05.

Compact Amyloid Plaque deposition evidenced with Congo Red Staining evidenced that in cortex there was a significant decrease in fibrils presence in the groups repetitively exposed to Diazepam, ketamine and Pentobarbital

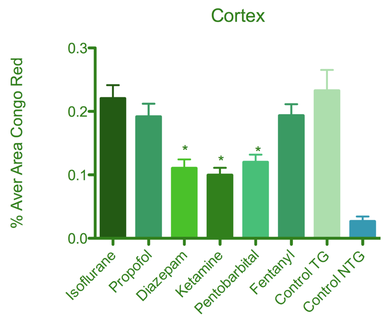

Figure 5: **Congo Red staining in brain Cortex**. Deposition of fibrils was significantly less in all groups exposed to Diazepam, ketamine and Pentobarbital compared to control transgenics. P<0.05.

In contrast Congo Red Staining in hippocampus despite of not generating an increase in deposition only the brains exposed to Diazepam exhibited significantly less fibrils deposition than that observed in the transgenic controls.

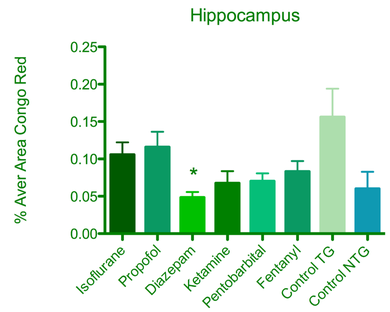

Figure 6: **Congo Red staining in Hippocampus**. Deposition of fibrils is significantly diminished in the brains of animals exposed to Diazepam when compared to control transgenics. P<0.05.

Conclusion

Our experience suggests that repetitive exposure to anesthetics and sedatives did not cause a significant detriment in the evolution of the Alzheimer's plaque's pathology in this particular model of Alzheimer's mouse.

If any effect, most agents showed a limited but favorable response . Similar protective results have been previously observed(1) related to isoflurane and explained as preconditioning protection.

References

1. Wei H, Liang G, Yang H. Isoflurane preconditioning inhibited isoflurane-induced neurotoxicity. Neurosci Lett 2007;425:59-62.