

Title: Desflurane, isoflurane and sevoflurane produce effective but limited neuroprotection in a preconditioning paradigm in neonatal hypoxia-ischemia.

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Introduction: We have previously shown that 2 hours of isoflurane (I) given 24 hours to a moderate-severe hypoxic-ischemic insult produces selective protection of striatal function in a mouse model of neonatal hypoxi-ischemia (1). Others have shown that both desflurane (D) and sevoflurane (S) are cardio-protective in a delayed preconditioning paradigm (2,3). We tested the ability of these three volatile agents to protect the brain from a moderate hypoxic-ischemic insult on post-natal day 10 (P10) in mice.

Methods: 4 mating pairs of 129T2 males and C57Bl/6 females each produced 35 F1 hybrids (total 140 mice) that were randomized to one of 5 treatments;

<u>Group</u>	<u>Preconditioning on P9</u>	<u>HI 24 hrs. later</u>
D	8.4% D in 30% O ₂ for 3 hrs	55 min
I	3.1% I in 30% O ₂ for 3 hrs	55 min
V	1.8% S in 30% O ₂ for 3 hrs	55 min
C	sham preconditioning	55 min
S	sham preconditioning	sham HI

HI signifies R common carotid ligation followed in 2 hrs by 10% O₂ in N₂. The surviving animals were tested using a battery of behavioral tests including novel object recognition, cued and hidden water maze learning with probe trial and apomorphine challenge as previously described (4). Data were analyzed using parametric ANOVA after transformation to assure normality and equality of variance were met; otherwise non-parametric methods were used. Novel object data were analyzed using paired comparisons. Differences among groups were established by using the matrix of orthogonal contrasts adjusting for multiple comparisons. Histologic outcome was assessed using Nissl stain and immunohistochemistry.

Results: There were no significant differences among all groups for mortality. Mice in groups D ($p = 0.026$), I ($p = 0.029$) and V ($p = 0.045$) performed significantly better than C on the cued maze. However groups D, I and V all performed worse than S on both the cued and hidden mazes. In contrast to the cued maze, Groups D, I and V did not perform significantly better than C on the hidden maze, or the probe trial. Groups S, D, I and V all had intact novel object recognition while C did not. Among the worst spatial learners, novel object recognition was preserved in groups D and I but not S. Groups D, I and V had reduced circling after apomorphine compared to C but circled more than S. There was no significant difference in performance on any test among groups D, I and V. There was no difference in the extent of injury in dorsal hippocampus among the HI groups; similarly there was no gross difference in post-injury neurogenesis in the DG of any HI group using BrdU-NeuN colocalization.

Discussion: The volatile anesthetics used in a delayed preconditioning paradigm provide improved cued learning and apomorphine response compared to sham preconditioning following moderate HI insult on P10. No improvement was noted in hidden maze learning but novel object recognition was preserved compared to Group C. These findings are consistent with our original **I** study (1) and suggest that the neuroprotective effectors of volatile agent preconditioning are more effective in the dorsal lateral striatum than in hippocampus. However, a hippocampus-dependent pathway (5) was preserved despite extensive loss of right hippocampus following preconditioning with D or I.

- References:**
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