

Neonatal Isoflurane Anesthesia Does Not Impair Neurocognitive Function And Behavior In The Same Mice In Adulthood

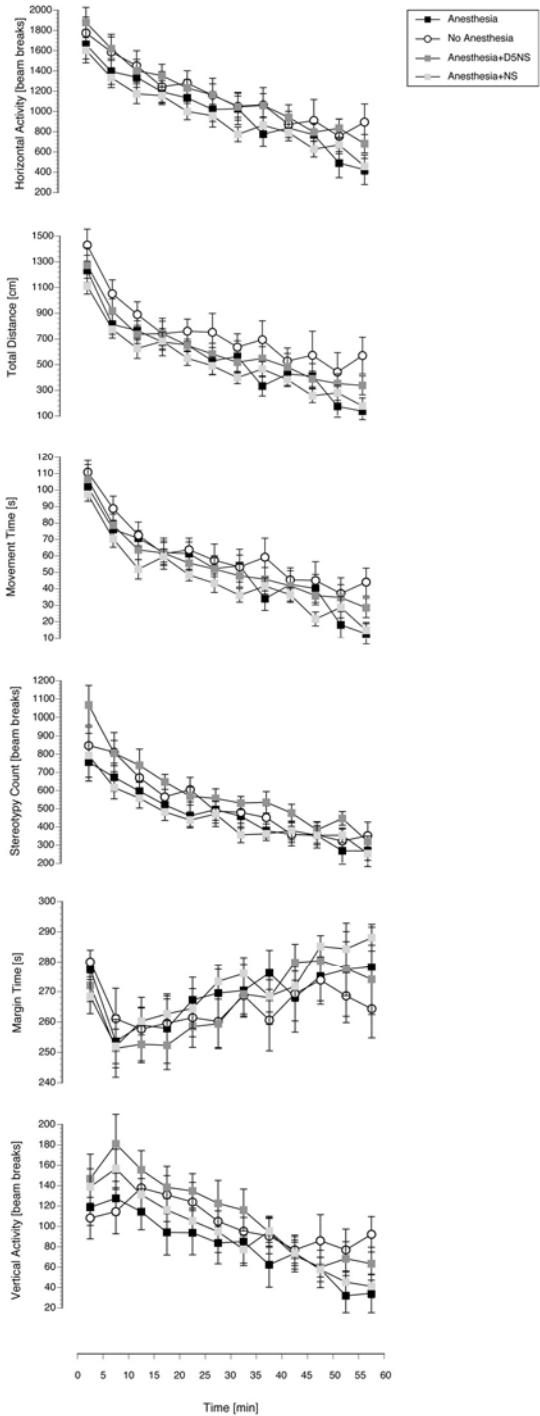
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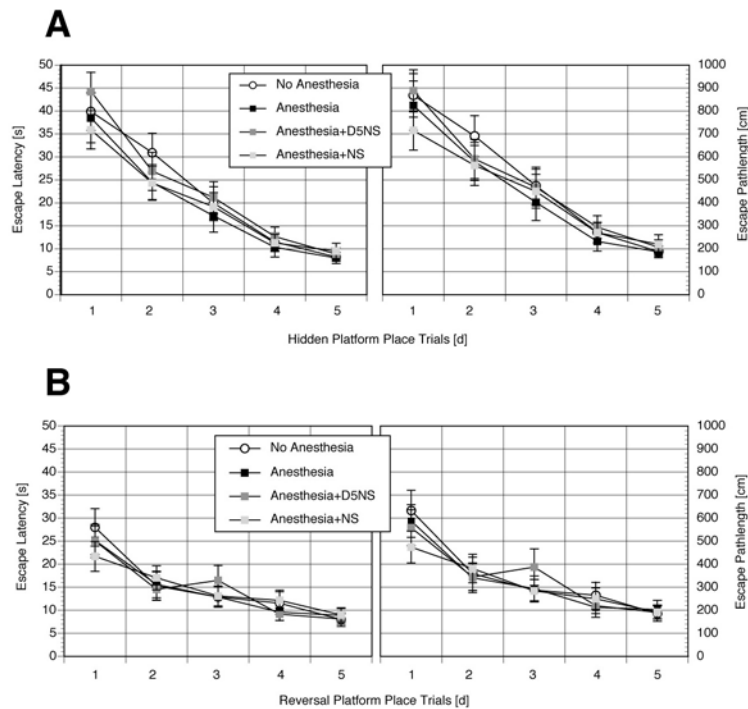
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Introduction: Volatile anesthetics are widely used for general anesthesia in adults, infants, and neonates. However, their safety for the developing brain has recently been questioned. A 6-hour isoflurane exposure in seven day-old (P7) rats was associated with widespread neurodegeneration leading to long-lasting functional impairment in adult rats exposed to anesthesia as neonates. (1) Based on this data the authors hypothesized that anesthetics pose a significant risk of damaging the developing human brain. (2) We have recently documented isoflurane-induced hypoglycemia in neonatal mice. (3) Therefore, it remained unknown whether the neurological impairment after isoflurane anesthesia is species specific to rats or whether it is related to hypoglycemia. The present study in neonatal mice examined the effects of isoflurane exposure and blood glucose on behavior and neurocognitive function in adulthood.

Methods: After IACUC approval, mouse pups (n=99) were randomly assigned on P7 to one of four study groups. For 6 hours, mouse pups were either exposed to isoflurane 1.5% in 30% oxygen with subcutaneous injections of 5% dextrose in normal saline (Anesthesia+D5NS), normal saline (Anesthesia+NS) or without injections (Anesthesia); a control group was exposed to room air without injections (No Anesthesia). Following emergence from anesthesia, animals were returned to the dam and survived for 10 weeks. Arterial blood gases and glucose were measured in a separate non-survival cohort. Beginning during week 10 of life, open-field spontaneous locomotion was measured for 60 minutes, followed by Morris water maze testing, which requires the animals to navigate within a circular pool filled with opaque water using visual cues on the walls to find a submerged escape platform (hidden platform). Animals were allowed 4 daily place trials for 5 days, while the time (escape latency) and distance traversed (escape pathlength) to reach the platform were recorded. On the sixth day, after removal of the platform, a probe trial was performed, in which the animals were introduced into the pool in the quadrant opposite to the initial platform position and the percentage of time spent in the platform quadrant and the number of times each animal crossed the original platform location (platform transitions) were recorded. During the following week, a reversal trial was conducted as described above with a smaller platform introduced in a different quadrant, followed by a probe trial on day 6. Data were compared using ANOVA and repeated measures general linear models, where appropriate, with post-hoc analysis for multiple comparisons.

Results: Isoflurane anesthesia for 6 hours caused hypoglycemia (blood glucose = 38 ± 11 mg/dl), compared with baseline (134 ± 9), Anesthesia+D5NS (105 ± 1) and No Anesthesia (93 ± 5). Figure 1 demonstrates spontaneous locomotion (mean \pm SEM) in an open field, including horizontal activity, total distance traversed, movement time, stereotypical behavior, time spent in the margins of the observation box, and rearing activity; there were no significant differences between the groups. Figure 2 shows escape latency on the left and path length on the right (mean \pm SEM) for the hidden platform (figure 1A) and reversal platform (figure 2B) Morris water maze. There were no significant differences in performance between the groups at any time point ($P > 0.3$). There were also no differences seen between any of the groups during both the hidden and reversal platform probe trials (data not shown).





Discussion: The developing mammalian brain is considered to be exquisitely sensitive to pharmacologic interference during the brain growth spurt phase. However, contrary to previous results in the Morris water maze in a neonatal rat model, a six-hour isoflurane anesthetic in neonatal mice failed to impair neurocognitive and spatial memory function in the same animals in adulthood. Isoflurane-induced hypoglycemia during neonatal anesthesia had no influence on adult neurocognitive performance. These results suggest that neurologic dysfunction in adulthood after neonatal anesthesia may not be a universal phenomenon for all mammalian species.

References: 1. *J Neurosci* 2003;23:876, 2. *Trends Pharmacol Sci* 2004;25:135, 3. *Anesth Analg* 2006;102:75,