

# The effect of isoflurane on the ontogenetic development of the GABA<sub>A</sub> alpha-2 subunit composition

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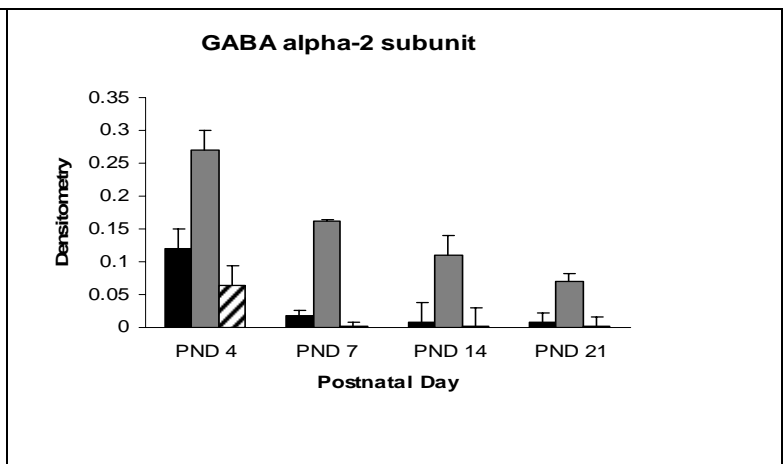
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**Introduction:** Anesthetics act via gamma-amino butyric acid (GABA<sub>A</sub>) receptors. These receptors undergo subunit composition changes during development. We hypothesize that the ontogenetic development of the GABA receptor predisposes the developing brain to isoflurane-induced neurodegeneration.

**Methods:** Using organotypic hippocampal slices (OHS) prepared from rat pups of differing postnatal age (PND 4,7,14 and 21), 7 days in culture (DIV7) we evaluated the GABA<sub>A</sub> alpha-2 subunit composition with and without a 5 hour exposure to 1.5% isoflurane. This data was compared to GABA<sub>A</sub> alpha-2 subunit composition of non-cultured hippocampi from respective PND age rat pups.

**Results:** As expected, we demonstrated the normal ontogenetic development of the GABA<sub>A</sub> alpha-2 subunit is preserved in our OHS. The GABA<sub>A</sub> alpha-2 subunit composition decreases as a function of increasing age. The GABA<sub>A</sub> alpha-2 subunit is decreased by the prolonged administration of 1.5% isoflurane (**Figure 1**).

**Figure 1:** These experiments demonstrate the effect of culture and a 5 hour exposure to 1.5% isoflurane on the GABA alpha-2 subunit composition using western blot analysis. The *black* bars represent DIV 0, the *grey* bars DIV 7 and the *diagonal stripe* bars, a 5 hour exposure to 1.5% isoflurane. The data are represented as ratio to  $\beta$ -actin.



**Discussion:** OHS provide a useful model for evaluating the developmental responses of the GABA<sub>A</sub> receptor to isoflurane exposure. Furthermore, the model enables control of variables such as pH, temperature and oxygen concentration as opposed to in vivo models. It is assumed that the developmental decrease in the GABA<sub>A</sub> alpha-2 subunit at PND7 places this developmental age at risk for isoflurane-induced neurodegeneration.

**References:** J Neurosci 14(9): 5302-24, 1994.  
Anesth Analg 100(3); 651-7, 2005.