26485 - THE AMNESTIC AND SEDATIVE-HYPNOTIC PROPERTIES OF ETOMIDATE IN MICE CAN BE DISSOCIATED BASED ON GABA(A) RECEPTOR SUBTYPE PHARMACOLOGY.

Beverley Orser PhD MD, Beverley Orser, MD PhD; Loren Martin, MSc; Victor Cheng, John MacDonald, PhD; Sunnybrook And Women's College HSC, Toronto, ONTARIO, Canada

Introduction: Our aim is to elucidate the mechanisms underlying the amnestic properties of anesthetics. GABA(A) receptors containing the $\alpha 5$ subunit ($\alpha 5$ GABA(A)Rs) are predominantly expressed in the hippocampus, a brain region that is critically involved in learning and memory. $\alpha 5$ GABA(A)Rs have been implicated in memory processes, as $\alpha 5$ null mutant ($\alpha 5^{-/-}$) mice exhibit improved performance in certain hippocampal-dependent learning tasks (J Neurosci 22(13):5572). Further, behavioral studies showed that $\alpha 5^{-/-}$ mice are resistant to the amnestic effects of etomidate (Society for Neuroscience Abstracts, 2006: 611.11). The aim of this study was to determine whether $\alpha 5^{-/-}$ mice exhibit a generalized insensitivity to etomidate by measuring sedation and hypnosis.

Methods: Experiments were approved by the local animal care committee. The sedative-hypnotic properties of etomidate were tested in $\alpha 5^{+/+}$ and $\alpha 5^{-/-}$ mice using the classical loss of righting reflex (LORR) paradigm. The LORR was measured for a wide range of etomidate doses (5-15 mg/kg). A quantal dose-response plot was constructed and fitted with a logistic equation. The time to LORR was also quantified. Experimenters were blinded to the mouse genotype.

Results: The dose of etomidate that caused half the maximal response was similar in WT and $\alpha 5^{-/-}$ mice (9.6 and 9.2 mg/kg, $n=35$ and $n=34$ respectively, $P>0.05$). The time to LORR also showed no difference between WT and $\alpha 5^{-/-}$ mice.

Conclusions: Behavioral endpoints that are commonly used as surrogate measures for sedation and loss of consciousness were studied and showed that $\alpha 5^{-/-}$ mice did not exhibit a non-specific generalized resistance to etomidate. Thus, $\alpha 5^{-/-}$ mice exhibited reduced sensitivity for amnesia but not sedative-hypnotic effects indicating different components of the anesthetic state can be dissected based on GABA(A) receptor subtype.