

Title: KETAMINE PROLONGS THE REFRACTORINESS OF NEUROMUSCULAR TRANSMISSION

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**Introduction.** General anesthetics (diethyl ether, fluoroene, halothane, methoxyflurane) significantly prolong the refractoriness of neuromuscular transmission (RNMT), probably by depression of the re-excitability of the postjunctional membrane.<sup>1</sup> Prejunctional neuromuscular (NM) block by magnesium markedly shortens the RNMT, probably because impairment of acetylcholine (ACh) release makes the NM transmission dependent upon double nerve stimuli to accumulate enough ACh to transmit once. Curariform relaxants slightly shorten the RNMT, probably by a similar but less significant impairment of ACh release. Ketamine is a general anesthetic with weak but demonstrable NM effects.<sup>2</sup> Its mechanism and site of NM actions are controversial. This study demonstrates its postjunctional site of action in vivo by measuring its effect on the RNMT.

**Methods.** The study met institutional approval. Seven adult monkeys (*Macaca cyclopis*, 5-6 kg) were anesthetized with pentobarbital 30 mg/kg i.m. followed by i.v. infusion of 5 mg/kg/hr. The trachea was intubated without use of any relaxant. Ventilation was controlled at PaCO<sub>2</sub>=30-40 torr. Blood gases and pressure were determined via an arterial line. Core temperature was 35-36°C. ECG was continuously monitored. Hydration was maintained with 5% dextrose in water at 5 ml/kg/hr. The ulnar nerve was stimulated at the wrist using two Grass EEG needles, with 0.2 ms supramaximal pulses from a Grass S88 stimulator and an SIU5 stimulus isolation unit. Twin pulses with increasing inter-stimulus intervals ranging from 0.5 to 10 ms were applied with at least 20 seconds of rest between any two applications. The neurally evoked compound electromyogram (ncEMG) was measured from the dorsum of the hand over the first interosseous muscle using another needle electrode. Two other electrodes served as reference and ground. The ncEMG was unipolar and single-peaked, except when twin pulses evoked two peaks R<sub>1</sub> and R<sub>2</sub>. These were analyzed and processed for instantaneous display and recording. RI<sub>50</sub> was defined as the interstimulus interval when the NM transmission was refractory to the extent that the R<sub>2</sub> was 50% of R<sub>1</sub>, i.e. when R<sub>2</sub>/R<sub>1</sub>=0.5. RI<sub>0</sub> was the largest interstimulus interval when R<sub>2</sub> was still zero. After the control, ketamine was injected i.v. in increments of 2, 3 and 5 mg/kg, totalling 2, 5 and 10 mg/kg cumulatively. The RNMT study was repeated at each dose level. The monkey was allowed to recover after the study. Data are mean ± SEMs, p < 0.05 by Wilcoxon signed rank test being considered significant.

To confirm the previous report of Epstein and Jackson on the effect of inhalational anesthetics on the RNMT,<sup>1</sup> we additionally repeated the above study in the same manner except that the anesthetic regimen was changed to methohexital 10-15 mg/kg i.m. for premedication and halothane 0.5-1% for maintenance during the study.

**Results.** Ketamine consistently increased the RNMT in a dose-dependent manner, \*indicating p < 0.05:

ketamine dose (mg/kg)	RI <sub>0</sub> (ms)	RI <sub>50</sub> (ms)
0	1.18 ± 0.14	2.40 ± 0.15
2	1.40 ± 0.18*	2.68 ± 0.18*
5	1.48 ± 0.18*	2.88 ± 0.20*
10	1.66 ± 0.20*	3.00 ± 0.21*

Halothane anesthesia also increased the RNMT, to values significantly greater than control values obtained under pentobarbital anesthesia:

	RI <sub>0</sub>	RI <sub>50</sub>
Pentobarbital	1.18 ± 0.14	2.40 ± 0.15
Halothane	1.46 ± 0.10*	2.80 ± 0.32*

When R<sub>2</sub>/R<sub>1</sub> values were plotted against the corresponding interstimulus intervals, a refractory curve was obtained. In each instance, the curve was shifted by ketamine in a dose-dependent manner indicating increasing refractoriness.

**Discussion.** Depression of the re-excitability of the NM postjunctional membrane is a sensitive sign of generalized depression of membrane excitability by inhalational anesthetics.<sup>1</sup> In other words, the RNMT is prolonged before inexcitability ensues. By contrast, impaired release of ACh (prejunctional) by curariform relaxants shortens the RNMT. The reduced refractoriness is "paradoxical" and not indicative of increased excitability. In other words, postjunctional membrane desensitization prolongs the RNMT while the prejunctional impairment of ACh release shortens it. Since ketamine clearly prolongs the RNMT, we conclude that it depresses membrane excitability postjunctionally more than it impairs ACh release prejunctionally. NM mechanism of action of ketamine in vivo is therefore mainly postjunctional.

Work on frog NM preparation in vitro demonstrating ketamine blockage of the ACh-activated ionic channels in the open conformation<sup>3</sup> concurs with our results in the primate. Such ionic channel block would allow passage of the first impulse but impede the passage of the second impulse following immediately, thus making NM transmission more refractory.

#### References.

1. Epstein RA, Jackson SH: The effect of depth of anesthesia on the neuromuscular refractory period of anesthetized man. *Anesthesiology* 32:494-499, 1970
2. Johnston RR, Miller RD, Way WL: The interaction of ketamine with d-tubocurarine, pancuronium and succinylcholine in man. *Anesth Analg* 53:496-501, 1974
3. Malique MA, Warnick JE, Albuquerque EX: The mechanism and site of action of ketamine on skeletal muscle. *J Pharmacol Exp Ther* 219:638-645, 1980