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Title : ANESTHETIC REQUIREMENT IN THE "QUAKING" MOUSE

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Introduction. One approach to defining the importance of brain lipids to anesthetic action is to determine the effect of structural alterations in brain lipids on anesthetic requirement. Such an approach is used in this report, in which the anesthetic potencies of nitrous oxide, isoflurane, and enflurane are measured in the "quaking" mouse, an autosomal recessive mutant whose central nervous system myelin lipid composition differs distinctly from that of heterozygous littermate controls.[1]

Methods. Righting reflex ED_{50}s (the partial pressure of anesthetic required to abolish the righting reflex in half of the animals) of nitrous oxide, isoflurane, and enflurane were determined for quaking mice and littermate controls in a 20-liter hyperbaric chamber in the presence of 1 atm O_2. Chamber temperature was altered to maintain the temperature between 36.5 and 38.0 C in two restrained mice; a soda lime scrubber removed CO_2. Anesthetic potencies of enflurane and isoflurane were also determined by measuring the concentration required to abolish movement in response to a clamp applied to the tail. Anesthetic concentrations were measured by gas chromatography. Myelin-enriched and synaptic-plasma-membrane-enriched fractions were prepared from quaking mice and littermate controls using differential centrifugation and density gradient sedimentation techniques. Lipids were extracted from the myelin and synaptic membrane fractions and were analyzed for their fatty acid, phospholipid, and cholesterol compositions.

Results. Anesthetic requirements for the quaking mice tended to be less than for their littermate controls, but the only significant difference observed between the two groups was a 15% decrease in nitrous oxide requirement as measured by the righting reflex test (table 1). However, since quaking mice have an ataxic gait, this difference in nitrous oxide requirement might have been due to an artifact of the procedure testing the righting reflex (even though no significant differences in righting reflex ED_{50}s were observed for isoflurane and enflurane). Thus, anesthetic potencies for isoflurane and enflurane were also measured by the tail-clamp procedure. These values did not differ significantly (table 1). The myelin fatty acid composition was distinctly different for the quaking mice and controls. The most notable alterations were increased levels of stearic acid (18:0) and decreased levels of oleic acid (18:1) in quaking mouse myelin. The myelin cholesterol/phospholipid molar ratio (± SE, n = 6) in quaking mice, 0.956 ± 0.031, was significantly lower ($P < 0.005$) than the ratio in the controls, 1.132 ± 0.018 (n = 5). In contrast to the myelin lipid compositions, no significant differences in fatty acid or phospholipid content, or in cholesterol/phospholipid ratios, could be detected in synaptic membranes isolated from controls and quaking mice.

Discussion. The ability of general anesthetics to disorder lipid membranes, to decrease phase transition temperatures, and to disrupt lateral phase separations in model lipid membranes suggests that an alteration of the properties of the membrane lipid bilayer may be the basis for the action of general anesthetics. If so, altering membrane lipids and membrane physical state at the site of anesthetic action would influence anesthetic potency. The present results suggest that anesthesia is not greatly modified by alterations in myelin fatty acid or cholesterol composition.

Reference

1. Singh H, Spritz N, Geyer B: Studies of brain myelin in the quaking mouse. J Lipid Res 12: 473-481, 1971

Table 1. Anesthetic Requirements in Quaking Mice and Controls*

Anesthetic and Testing Method†	ED_{50} (mean ±SE)(atm)	
	Quaking Mice	Controls
N_2O (RR)	1.11 ± 0.05	1.30 ± 0.04‡
Isoflurane (RR)	0.00566 ± 0.00015	0.00560 ± 0.00015
Isoflurane (TC)	0.0110 ± 0.0006	0.0119 ± 0.0006
Enflurane (RR)	0.0089 ± 0.0008	0.0100 ± 0.0004
Enflurane (TC)	0.0145 ± 0.0019	0.0170 ± 0.0017

*Each value is the result from 6 to 13 mice.
†RR, righting reflex; TC, tail-clamp.
‡$P < 0.005$.