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Title : ANESTHETIC REQUIREMENT IN MICE SELECTIVELY BRED FOR DIFFERENCES IN ETHANOL SENSITIVITY

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Introduction. Through selective breeding procedures, two lines of mice have been obtained which differ in their ethanol-induced sleep times.[1] These mice are termed "long-sleep" (LS) and "short-sleep" (SS) mice, the SS mice being more resistant to the hypnotic effect of alcohol. The different ethanol-induced sleep times of LS and SS mice result from differences in their central nervous systems, since both lines of mice have identical rates of ethanol elimination and the SS mice awaken at higher blood alcohol concentrations. Our study demonstrated that this resistance to alcohol was associated with a higher requirement for general anesthesia. We also determined whether such cross-tolerance was associated with differences in synaptic membrane lipid composition in LS and SS mice.

Methods. Measurements of nitrous oxide, enflurane, and isoflurane ED_{50} (the partial pressure of anesthetic required to abolish the righting reflex in half of the animals) for LS and SS mice were performed using a 20-liter hyperbaric chamber. Chamber temperature was altered to maintain the rectal temperatures of two additional restrained mice between 36.5 and 38.0 C. We also determined the concentration of isoflurane required to abolish movement in response to a clamp applied to the tail. For all measurements, the observer was unaware of the identity (SS or LS) of the animals. Synaptic plasma membranes were isolated from LS and SS mice using differential centrifugation and density gradient sedimentation techniques; and the fatty acids, phospholipids, and cholesterol/phospholipid ratios of these membranes were determined.

Results and Discussion. Although our results qualitatively support the hypothesis that SS mice are more resistant to the effects of anesthetics, some quantitative differences cannot be entirely explained (table 1). The greatest difference between the anesthetic requirement for SS and LS mice was seen with isoflurane using the tail-clamp test. The smallest difference also was seen with isoflurane using the righting-reflex test (table 1). In part, this discrepancy may have resulted from the different sensitivities or reflex arcs assessed by the two tests. However, the negative results for the righting reflex with isoflurane contrast with the significant results seen with nitrous oxide and enflurane. Synaptic plasma membrane fatty acids, phospholipids, or cholesterol/phospholipid ratios did not differ between the LS and SS mice. That is, these differences in anesthetic requirement cannot be explained by alterations in synaptic membrane lipid composition, and the molecular basis for the altered sensitivities of LS and SS mice remains to be determined.

Reference

1. McClearn GE, Kakihana R: Selective breeding for ethanol sensitivity in mice. Behav Gen 3:409-410, 1973

Table 1. Anesthetic Potencies of Inhaled Agents in Long-sleep (LS) and Short-sleep (SS) Mice

Anesthetic and Testing Method	ED_{50} ± SE (% atm)	
	LS Mice	SS Mice
Nitrous oxide (RR)*	123 ± 2.5†	165 ± 3.2
Enflurane (RR)	1.24 ± 0.02†	1.49 ± 0.03
Isoflurane (RR)	0.60 ± 0.01	0.61 ± 0.02
Isoflurane (TC)	1.18 ± 0.10†	1.64 ± 0.08
	n = 17	n = 19

*RR = righting reflex test; TC = tail-clamp test.

†Anesthetic potencies in long-sleep mice are significantly different from those of short-sleep mice at levels of $P < 0.001$.