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Title : CONVULSIONS IN MICE SELECTIVELY BRED FOR RESISTANCE AND SUSCEPTIBILITY TO NITROUS OXIDE ANESTHESIA

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Introduction. We selectively bred two lines of mice ("HI" and "LO") that differ in their resistance to nitrous oxide anesthesia.[1] Nitrous oxide requirement in the HI strain is approximately 0.6 atm above that of the LO strain. If the increase in anesthetic requirement found in the HI mice results from a generalized increase in central nervous system excitability, then the HI mice should exhibit an increased sensitivity to convulsants. We therefore examined the convulsive effects of high pressure and pentylenetetrazole in these mice.

Methods. We used seventh- and eighth-generation HI and LO mice. For studies of high pressure, groups of four mice were placed in a 20-liter hyperbaric chamber, and helium was added at a rate of 1 atm/min in the presence of 1 atm $O_2$. Chamber temperature was adjusted to maintain rectal temperatures between 36.5 and 38.0 C in two additional restrained mice. We recorded the pressures at which coarse tremors, convulsions, and death occurred. For studies of pentylenetetrazole, mice were given an intraperitoneal injection of the drug (range, 40 to 90 mg/kg) and were examined for 30 min after the injection for clonic convulsions (defined as the loss of the righting reflex), tonic extensions, and death. The doses of pentylenetetrazole that produced convulsions ($ED_{50}$) and death ($LD_{50}$) in 50% of mice were calculated by quantal analysis. All measurements were performed in a blind fashion, the observer being unaware of which strain of mice was being studied.

Results. The pressure thresholds for onset of coarse tremors and convulsions were significantly less in the HI mice (table 1). The HI mice died at a pressure that was 17 atm below the pressure at which LO mice died. Tonic convulsion $ED_{50}$ and $LD_{50}$ values in mice injected with pentylenetetrazole were approximately 15% less in the HI group than in the LO group (table 2). No significant difference in pentylenetetrazole-induced clonic convulsion $ED_{50}$s could be detected between the HI and LO mice (table 2).

Discussion. Mice selectively bred for their resistance to $N_2O$ anesthesia (HI mice) are more sensitive to high-pressure- and pentylenetetrazole-induced convulsions than mice bred for their susceptibility to $N_2O$ anesthesia (LO mice). This result supports our hypothesis that the higher anesthetic requirement in HI mice is due to a generalized increase in central nervous system excitability. However, the decrease in convulsion thresholds for the HI mice represents about a 15% shift in the dose-response curve, whereas the difference in $N_2O$ requirement between the HI and LO mice represents about a 40% shift in the curve. The structural alterations in the central nervous system that give rise to these differences in anesthetic requirements and convulsion thresholds remain to be elucidated. If our studies are extrapolated to clinical practice, they suggest that certain patients may be unexpectedly sensitive to the convulsant effects of some anesthetic agents (e.g., enflurane or fentanyl).

Reference

1. Koblin DD, Dong DE, Deady JE, et al: The breeding of mice resistant to and susceptible to nitrous oxide anesthesia. Anesthesiology 51(3S):S17, 1979 (abstract)

Table 1. Pressure Thresholds (Mean ± SE, atm) at Which High-Pressure Nervous Syndrome Occurs in HI and LO Mice (n = 6)

| Mice | Coarse Tremors | Convulsions | Death |
|---|---|---|---|
| HI | 73 ± 0.6 | 77 ± 1.7 | 108 ± 3.4 |
| LO | 80 ± 1.0* | 89 ± 3.1** | 125 ± 3.4** |

*P < 0.005.
**P < 0.01.

Table 2. Clonic Convulsion (CC) $ED_{50}$, Tonic Convulsion (TC) $ED_{50}$, and $LD_{50}$ after Pentylenetetrazole Injections in HI and LO Mice (mean ± SE, mg/kg)

| Mice | n | CC $ED_{50}$ | TC $ED_{50}$ | $LD_{50}$ |
|---|---|---|---|---|
| HI | 44 | 53.3 ± 2.2 | 62.5 ± 2.9 | 64.4 ± 3.3 |
| LO | 71 | 53.3 ± 2.7 | 73.9 ± 2.0* | 76.6 ± 1.9** |

*P < 0.005.
**P < 0.001.