

Strain Differences of Ether Susceptibility in Mice

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The susceptibility to ether in the following six strains of mice was tested: C57BL/6, DBA/2, BALB/c, C3H/He, ICR and ddY. Mice of 4 weeks old were exposed to a flow of air containing various concentrations of ether for 90 min and the mortalities were assessed. The C57BL/6 strain was the most resistant and the C3H/He strain was the most sensitive to the lethal effect of ether. The susceptibilities of the closed colony mice, ICR and ddY, were intermediate between those of C57BL/6 and C3H/He mice. The DBA/2 and BALB/c strains were more sensitive than these closed colony mice and made up a sensitive group with the C3H/He strain. The LD₅₀ values for ether in male mice of C57BL/6 and C3H/He were 6.0 and 3.1% atm, and in female mice of these strains were 6.6 and 3.2% atm, respectively. The ED₅₀ value of ether which was accompanied by loss of righting reflex after exposure for 10 min was also higher in male C57BL/6 mice than in male C3H/He mice.

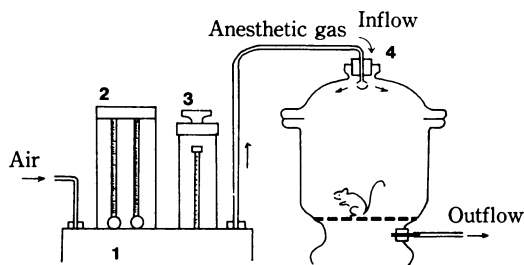
Variations have been reported among strains of mice in their response to anesthetics such as chloroform [3,5,10,22,24] and barbiturates [7,11,12,16,17,19,23]. Koblin *et al.* [14] described the selective breeding of mice for resistance and susceptibility to nitrous oxide anesthesia and suggested genetic involvement in this trait. Although ether has long been used as an anesthetic agent not only for mice but also for men and other laboratory animals, the differences in ether susceptibility among strains of mice have not been reported. In the present study, the differences in susceptibility to ether in six strains of mice were tested.

Materials and Methods

Animals: The mouse strains used were C57BL/6N Jcl, DBA/2N Jcl, BALB/cA Jcl, C3H/HeN Jcl and Jcl:ICR from CLEA JAPAN, INC., and Slc:ddY and Std:ddY

from Shizuoka Laboratory Animal Center. Mice of 4 weeks old were generally tested for their susceptibility to ether except that mice of 8–11 weeks old were also tested to determine the effect of age. Within a week before the test, the mice were fed on a commercial diet (CE-2, CLEA JAPAN, INC.) and tap water *ad libitum*, and kept in a room at a temperature of 23±1°C, relative humidity of 50±5% and 12 hours light per day.

Assessment of mortality: Male and female mice of the six strains were anesthetized with diethylether in the apparatus shown in Fig. 1. In each trial, 5 or 6 mice were exposed to ether in a 14 l glass chamber which was connected to an anesthetic machine (model F0-10, ACOMA ANESTHETIC APPARATUS, Tokyo). Ether was vaporized in the Copper Kettle and diluted with a fixed volume of air (6 l/min) to give several different concentrations. Special grade



1. Anesthetic machine (model F0-10, ACOMA ANESTHETIC APPARATUS, (Tokyo) ;
2. flowmeters for kettle and diluent flow of air ;
3. vaporizer (Copper Kettle) ;
4. glass chamber for exposure of mice.

Fig. 1 Apparatus for exposure of mice to known concentrations of ether.

diethylether from WAKO Pure Chemical Industries, LTD. (Osaka) was used. All mice were exposed to a given concentration of ether gas for 120 min, and the number of dead animals in the chamber was counted every 30 min. The mortality at each dose was obtained using 5 to 16 mice for each strain and sex. Cessation of respiration, and paleness of the paws and lips were used as indications of death. After exposure for 120 min, cessation of heart beat was confirmed on the outside of the chamber. The room was controlled at $25 \pm 2^\circ\text{C}$ throughout the experiments.

LD₅₀ estimation : The median lethal doses (LD₅₀) of ether after exposure for 90 min were determined using dose-mortality curves for the C57BL/6 and C3H/He strains. This exposure time was chosen because it was considered that the concentration of ether in the blood would then be sufficiently in equilibrium with that of the vapour mixture, and because the strain differences in susceptibility at 90 min were the clearest among the four times, *i. e.*, 30, 60, 90, and 120 min. Logarithm-probit transformation was employed for linearization of the dose-response curve. The LD₅₀ values were estimated

on the regression lines, and analysis of covariance was performed to examine the fitness of the lines and differences in susceptibility between the strains and sexes. Differences among the adjusted means of regression lines with a common slope were evaluated by the *t* test.

Susceptibility in adult mice : Male mice of the C57BL/6, Std : ddY and C3H/He strains were tested for their ether susceptibility at 8-11 weeks of age, in order to examine the effect of age. The mortalities after 90 min exposure were assessed at three different concentrations of ether. In this test, one mouse was tested in each trial and the ether gas was diluted with air of which the flow rate was 8 l/min.

Anesthetic response to ether : Male mice of the C57BL/6 and C3H/He strains were tested for their response to ether at low concentrations, in order to compare the anesthetic effect with the lethal. The same apparatus as for the assessment of mortality was used. The loss of righting reflex was observed at intervals of 5 or 10 min during 30 min of exposure. Mice which were unable to regain their feet within 5 sec after being thrown down were regarded as having lost the righting reflex. In this test, one or two mice were tested in each trial and ether gas was diluted with air of which the flow rate was 4 l/min. The median effective doses (ED₅₀) of ether were determined using the same statistical methods as for estimating the LD₅₀.

Results

(1) ***Strain differences in mortality to ether*** : The mortalities of the six mouse strains at 4 weeks of age after exposure to ether for 30 and 90 min are shown in Table 1. At a 2.7% atm concentration of ether in air, no mouse died at either time of exposure in the six strains. After exposure for 90 min, a concentration of 6.6% atm ether was sufficient to kill

Table 1. Mortalities of 4-week-old mice of six strains after exposure to diethylether for 30 and 90 min.

(a) 30 min exposure

Strain	Sex	Concentration of ether (% atm)													
		2.7	2.9	3.2	3.5	3.8	4.2	4.6	5.1	5.5	6.0	6.6	7.3	8.0	9.6
C57BL/6	male	—	—	0/10	—	—	—	0/10	0/10	0/10	0/15	0/15	0/10	2/10	0/10
	female	—	—	0/10	—	—	—	—	—	0/10	0/10	0/10	0/10	0/10	—
ddY	male	—	—	0/ 5	—	—	—	0/16	—	—	—	3/ 5	—	—	—
	female	—	—	0/ 6	—	—	—	0/16	—	—	—	1/ 5	—	—	—
ICR	male	—	—	0/10	—	—	—	0/11	—	—	—	1/ 5	—	—	—
	female	—	—	0/10	—	—	—	0/10	—	—	—	0/ 6	—	—	—
DBA/2	male	0/11	—	0/10	—	—	—	5/12	—	—	—	—	—	—	—
	female	0/ 5	—	0/10	—	—	—	3/ 6	—	—	—	—	—	—	—
ICR	male	0/11	—	0/10	—	—	—	1/11	—	—	—	—	—	—	—
	female	0/ 5	—	0/10	—	—	—	2/ 6	—	—	—	—	—	—	—
C3H/He	male	0/10	0/15	0/15	0/15	2/10	—	1/10	—	—	—	—	—	—	—
	female	0/10	0/10	0/10	0/10	0/10	0/10	0/10	—	—	—	—	—	—	—

(b) 90 min exposure

Strain	Sex	Concentration of ether (% atm)													
		2.7	2.9	3.2	3.5	3.8	4.2	4.6	5.1	5.5	6.0	6.6	7.3	8.0	9.6
C57BL/6	male	—	—	0/10	—	—	—	0/10	2/10	2/10	4/15	9/15	10/10	10/10	5/5
	female	—	—	0/10	—	—	—	—	—	0/10	3/10	5/10	8/10	10/10	—
ddY	male	—	—	0/ 5	—	—	—	8/16	—	—	—	5/ 5	—	—	—
	female	—	—	0/ 6	—	—	—	10/16	—	—	—	5/ 5	—	—	—
ICR	male	—	—	1/10	—	—	—	9/11	—	—	—	5/ 5	—	—	—
	female	—	—	0/10	—	—	—	4/10	—	—	—	6/ 6	—	—	—
DBA/2	male	0/11	—	3/10	—	—	—	12/12	—	—	—	—	—	—	—
	female	0/ 5	—	0/10	—	—	—	6/ 6	—	—	—	—	—	—	—
BALB/c	male	0/10	—	7/10	—	—	—	11/11	—	—	—	—	—	—	—
	female	0/ 5	—	5/10	—	—	—	6/ 6	—	—	—	—	—	—	—
C3H/He	male	0/10	4/15	12/15	13/15	10/10	—	10/10	—	—	—	—	—	—	—
	female	0/10	3/10	7/10	9/10	9/10	9/10	10/10	—	—	—	—	—	—	—

100% of the animals in five of the strains of mice, except the C57BL/6 strain. To obtain 100% mortality in C57BL/6 mice, a concentration of 8.0% atm or more was needed. In the case of exposure for 30 min, no mouse of the C57BL/6 strain died even at 9.6% atm which was the highest concentration of ether tested in this study.

The C57BL/6 strain was thus the most resistant and the C3H/He strain the most sensitive to ether among the six strains.

The DBA/2 and BALB/c strains were next sensitive after the C3H/He strain and together made up the sensitive group. The susceptibilities of the closed colony mice of the ICR and Slc : ddY strains were intermediate between those of the C57BL/6 strain and the sensitive group.

Mice of the C3H/He strain frequently became convulsed at induction of anesthesia, and just before cessation of respiration, fell into incontinence of the urine

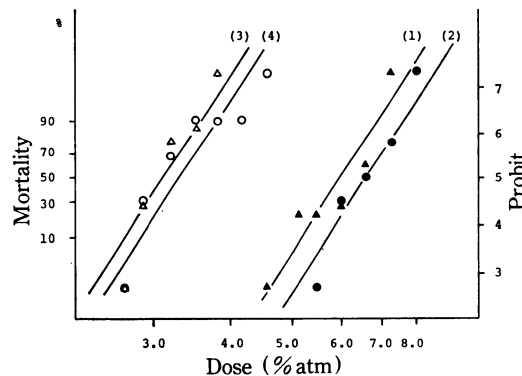
Table 2. LD₅₀ concentrations in the C57BL/6 and C3H/He strains after exposure to ether for 90 min.

Strain	LD ₅₀ (% atm)	
	male	female
C57BL/6	6.00 (5.45 – 6.61)*	6.58 (6.08 – 7.13)
C3H/He	3.13 (2.91 – 3.36)	3.24 (2.89 – 3.62)

* Confidence limits at the 95% level.

Table 3. Mortalities at 8–11 weeks of age in male mice of the C57BL/6, Std : ddY and C3H/He strains after exposure to ether for 90 min.

Strain	Concentration of ether (% atm)		
	3.2	4.6	6.6
C57BL/6	0/4	0/4	1/3
Std : ddY	0/2	—	3/3
C3H/He	5/7	7/7	8/8



(1) C57BL/6 males (▲); (2) C57BL/6 females (●); (3) C3H/He males (△); and (4) C3H/He females (○).

Fig. 2 Regression lines with a common slope in the C57BL/6 and C3H/He strains after exposure to ether for 90 min.

and feces at a high rate. On the other hand, mice of the C57BL/6 strain revealed neither convulsions nor incontinence of the urine and feces.

(2) *LD₅₀ values of ether in the C57BL/6 and C3H/He strains.*: The LD₅₀ values for male and female mice of the C57BL/6 and C3H/He strains are listed in Table 2. The LD₅₀ values of the C57BL/6 strain were approximately twice those in the C3H/He strain for each sex. The regression lines with a common slope after exposure for 90 min in both sexes of the two strains are shown in Fig. 2. The differences in gradient between the four dose-response lines were not significant by analysis of covariance. The

differences of susceptibility between the two strains were significant at the level of 0.1% in both sexes, although those between the sexes were significant at 5% in C57BL/6 mice by the *t* test.

(3) *Ether susceptibility in adult mice.*: Male mice of the C57BL/6, Std : ddY and C3H/He strains were tested for their ether susceptibility at 8–11 weeks of age. The mortalities of the adult mice are shown in Table 3. At 4.6% atm, no mouse died in the C57BL/6 strain but 100 % mice died in the C3H/He strain. These results were the same as those in the 4-week-old mice shown in Table 1 (b). The C57BL/6 strain was more resistant to ether than the C3H/He strain, and the susceptibility of the Std : ddY strain was intermediate between those of the two inbred strains.

(4) *Strain differences in anesthetic response to ether.*: Male mice of the C57BL/6 and C3H/He strains were tested for their anesthetic response. The numbers of mice losing righting reflex during 30 min exposure are shown in Table 4. At 3.2% atm, which is well known as a median anesthetic dose (AD₅₀) [21] or minimum alveolar concentration (MAC) [6,18] of ether in mice, most mice of the C3H/He strain were anesthetized and lost the righting reflex, while in the C57BL/6 strain no mouse lost the righting reflex after exposure for 15 min. After exposure for 30 min, however, no mouse showed the righting reflex in either strain.

Table 4. Numbers of mice losing the righting reflex due to ether anesthesia in male mice of the C57BL/6 and C3H/He strains.

C57BL/6	Time (min)	Concentration of ether (% atm)										
		1.9	2.0	2.2	2.4	2.7	2.9	3.2	3.5	3.8	4.2	4.6
C57BL/6	5	0/7*	0/10	0/11	0/ 6	0/ 5	0/ 5	0/ 9	0/10	0/10	0/10	1/9
	10	0/7	0/10	0/11	0/ 6	0/ 5	0/ 5	0/ 9	3/10	4/10	9/10	9/9
	15	0/7	0/10	0/11	0/ 6	0/ 5	0/ 5	0/ 9	7/10	10/10	10/10	9/9
	20	0/7	0/10	0/11	0/ 6	0/ 5	3/ 5	7/ 9	10/10	10/10	10/10	9/9
	30	0/7	0/10	1/11	5/ 6	5/ 5	5/ 5	9/ 9	10/10	10/10	10/10	9/9
C3H/He	5	0/4	0/ 8	0/13	0/11	0/11	0/10	0/12	1/11	3/10	7/10	6/7
	10	0/4	0/ 8	0/13	0/11	1/11	1/10	3/12	8/11	9/10	9/10	7/7
	15	0/4	0/ 8	0/13	0/11	5/11	6/10	11/12	11/11	10/10	10/10	7/7
	20	0/4	0/ 8	0/13	1/11	8/11	10/10	12/12	11/11	10/10	10/10	7/7
	30	0/4	0/ 8	1/13	9/11	11/11	10/10	12/12	11/11	10/10	10/10	7/7

*The denominator indicates the number of mice tested at each dose.

The ED₅₀ values of C57BL/6 and C3H/He mice after 10 min exposure were 3.8 and 3.3% atm, respectively. Thus, the ED₅₀ value of C57BL/6 mice was larger than that of C3H/He mice, although the dose-response lines of the two strains were not parallel. The ED₅₀ value after 30 min exposure was 2.3% atm in both strains.

Discussion

Differences in response to ether were demonstrated among C57BL/6, DBA/2, BALB/c, C3H/He, ICR and ddY mice at 4 weeks of age. When compared for their mortalities, the order of resistance was found to be as follows : C57BL/6>ddY=ICR>DBA/2≥BALB/c≥C3H/He. These six strains and the 4-week-old mice tested in this study have been abundantly supplied and used as laboratory animals. The present results for their ether susceptibility may thus be useful in evaluating laboratory studies. In 8-11 week old mice, the order of resistance to ether was found to be C57BL/6>ddY>C3H/He. The resistance in 8-11 week old mice thus showed the same order as that in 4-week-old mice, although the present ddY

strain (Std : ddY) was reared behind a semi-barrier and the Slc : ddY strain behind a barrier, and the numbers of adult mice used were small. Buchsbaum and Buchsbaum [1] reported that 1-8 month mice exhibited a similar behavior pattern and anesthesia and recovery times following ether anesthesia when compared with very young (0.5 month) and very old (14-18, 20 month and over) mice. Strain differences in 4-week-old mice may therefore be similar to those in adult mice except for very old mice. The strain differences in ether susceptibility in adult mice, however, must be confirmed in large numbers of mice and in other strains.

The C57BL/6 strain was the most resistant to ether and the C3H/He strain was the most sensitive among the six strains. The LD₅₀ values for C57BL/6 mice were 6.0% atm in males and 6.6% atm in females after exposure for 90 min. These values were approximately twice as large as those of C3H/He mice. At induction of ether anesthesia, male mice of the C57BL/6 strain were also more resistant than male mice of the C3H/He strain as evidenced by the righting reflex. This resistance at induction of ether

anesthesia may be related to the resistance to lethality. Such responses to ether in mice may be genetically controlled, since genetic involvement in other forms of anesthetic resistance has been reported in mice [10,14,15,24]. Further investigations into the heredity of these traits [13] are needed.

Robbins [21] and Raventós [20] reported ED_{50} (AD_{50}) and LD_{50} values for ether in mice after exposure for 10 or 30 min, respectively. However, they did not indicate the names of the mouse strains except that Robbins stated that adult male white mice had been used. The median anesthetic dose (AD_{50} , 3.2% atm) reported by Robbins was regarded as the MAC of ether in mice by Eger [6] and Miller *et al.* [18]. The ED_{50} value for C3H/He mice estimated in the present study after exposure for 10 min was close to the AD_{50} value reported by Robbins. C57BL/6 mice, however, are more resistant to ether than the mice of Robbins and Raventós, since the ED_{50} value of C57BL/6 mice was larger than that of Robbins, and because all mice of the C57BL/6 strain tested survived at 9.6% atm ether after exposure for 30 min, while the LD_{50} of Raventós was 7.3% atm.

It has been reported that the C57BL strain is resistant not only to ether but also to chloroform [5,10,24]. Thus, C57BL mice appear to be commonly resistant to ether and chloroform. However, C57BL mice are not always resistant to barbiturates [11,16].

The LD_{50} value of female mice was significantly larger than that of male mice in the C57BL/6 strain, while the sex difference in the C3H/He strain was not significant. Sex differences in susceptibility to volatile anesthetics in mice have been investigated previously by some workers (ether [1], chloroform [3,5,22,24] and fluroxene [2]). The sex differences in susceptibility to ether were not so clear as those to chloroform or fluroxene. However, it is interesting to note that

females were more resistant than males in each case referred to here when there were sex differences.

Convulsions and incontinence were observed in C3H/He mice with ether anesthesia, but were not observed in C57BL/6 mice. These differences in behavior may reflect the resistance to lethality of ether in the C57BL/6 strain. Strain differences in such phenomena have not been reported previously in ether resistant and sensitive strains of mice.

Some reports about the metabolism of ether in mice are known [4,9]. The data, however, do not include comparative physiological and biochemical information between strains with high or low resistance levels to volatile anesthetics. It is difficult therefore to explain the underlying physiological and biochemical mechanisms of anesthetic resistance in mice. Recently, Gamo *et al.* [8] reported a relationship between the anesthetic resistance and alterations in some molecular species of phosphatidylethanolamine in ether-resistant (*Eth*) and sensitive (*bw*; *st*; *sv*) strains of *Drosophila melanogaster*. Koblin *et al.* [14] reported no significant difference in synaptic membrane lipid composition in selectively bred mice which were either resistant to or susceptible to nitrous oxide anesthesia. Investigations of this type in ether-resistant and sensitive strains of mice must form a subject of future research.

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マウスのエーテル麻酔に対する反応の系統差

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マウスのエーテル麻酔に対する反応を C57BL/6N Jcl, BALB/cA Jcl, DBA/2N Jcl, C3H/HeN Jcl の 4 近交系および Jcl : ICR, Slc : ddY の 2 クローズドコロニーについて比較, 検討した。各系統マウスの 4 週齢の動物を空気で一定濃度に希釈したエーテルガスに 90 分間暴露し, その致死反応の系統差を調べた。その結果, 一般にマウス・ラットの MAC (ED_{50}) として知られている 3.2% atm では雄の C57BL/6 の死亡率は 0% であるのに対し, C3H/He は 80% と高い。また, 4.6% atm における死亡率は C57BL/6 では 0%, ddY, ICR ではそれぞれ 50%, 82%, DBA/2, BALB/c, C3H/He の 3 系統ではすべて死亡した。雌もほぼ同様の傾向を示し

た。エーテル濃度 2.7~9.6% atm を通しての結果からエーテルに対する抵抗性の順位は C57BL/6 > ddY = ICR > DBA/2 \geq BALB/c \geq C3H/He であった。最も抵抗性である C57BL/6 と最も感受性である C3H/He の 50% 致死濃度 (LD_{50} , % atm) は雄ではそれぞれ 6.0, 3.1, 雌では 6.6, 3.2 であり C57BL/6 は C3H/He の約 2 倍の値を示した。また, 麻酔導入時に, 正向反射の消失を指標として算出した 50% 有効濃度 (ED_{50}) にも C57BL/6 > C3H/He の傾向が見い出された。以上の結果から, C57BL/6 系はエーテルに対し抵抗性系統であり, C3H/He 系は感受性系統であることが明らかとなった。