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INTERACTION OF AGING AND LIFELONG ETHANOL INGESTION ON ETHANOL-RELATED BEHAVIORS AND LONGEVITY

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Abstract — The interactions of aging and long-term voluntary ethanol consumption were studied in the alcohol-preferring AA (Alko Alcohol) rats. The mean daily ethanol intake was 6.45 ± 0.31 g/kg/day (mean ± SE) at the beginning of the exposure at 3 months of age. The control animals were given only food and water ad libitum. There was no difference in survival or weight gain between the control and ethanol groups. When tested for voluntary ethanol intake at the age of 24 months, the rats in the ethanol group consumed significantly more ethanol than the controls. The two groups did not differ in ethanol-induced motor impairment, sleep-time, or hypothermia, nor in the rate of ethanol elimination. The 24-month-old animals, however, showed higher sensitivity to ethanol than the 3–4-month-old rats in the sleep-time test. It is concluded that the feeding regimen used in this study did not produce any detectable interactions between ethanol and the aging processes in the AA rats.

Key Words: ethanol, chronic treatment, aging, ethanol sensitivity, ethanol consumption

INTRODUCTION

EFFECTS OF prolonged consumption of ethanol across the life span and the effects of ethanol in the aged individuals have received little attention (Wood, 1980; Hartford and Samorajski, 1984). The major problem in studying human alcoholism in relation to the life span is the poor control over the life-history variables. Age-associated declines can be explained in terms of life style, habits, diet, and an array of psychosocial factors extrinsic to the aging processes (Rowe and Kahn, 1987). It is well established that chronic alcohol abuse is related to pathological processes in most organ systems, especially in the central nervous system (cf. Tavares *et al.*, 1985; Arendt *et al.*, 1989; Pietrzak *et al.*, 1989). Whether or not this is due to "premature aging," as suggested by Courville (1955), remains to be

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clarified with an animal model relating the long-term effects of ethanol on selected markers commonly used in the study of neurobiology of aging (Finch and Schneider, 1985).

In order to study the interactions between aging and chronic exposure to ethanol, a feeding regime was designed for a lifelong ethanol ingestion based on voluntary ethanol intake and the AA (Alko Alcohol) line of rats consuming voluntarily high amounts of ethanol (Eriksson and Rusi, 1981).

MATERIALS AND METHODS

Ethanol consumption

Male rats of the alcohol-preferring AA line (generations F_{46}, F_{48}, F_{49}, F_{52}, F_{53}, F_{54}, and F_{55}) were used for the study. This line was originally produced along with the alcohol-avoiding ANA (Alko Non-Alcohol) line by selective outbreeding for high and low levels of voluntary ethanol consumption, respectively (Eriksson and Rusi, 1981). These lines have been used extensively to study factors controlling voluntary ethanol consumption (Sinclair *et al.*, 1989).

The rats were housed in group cages (six per cage) in a colony room with a cycle of 12 h light, 12 h darkness. The rats had free access to standard R3 rat food (Ewos, Södertälje, Sweden). The ethanol group (EtOH + H_2O group) was continuously given a free choice between tap water and 10% (vol/vol) ethanol in two drinking tubes fitted to the front wall of the cage. Only water was served to the control group (H_2O group). The intake of water and ethanol was measured at the beginning of the study by giving the rats a free choice between water and ethanol solution in individual cages for 3 weeks at the age of 3 months. After the initial test of preference, ethanol intake was monitored monthly in the ethanol group in the group cages. The individual measurements were repeated in both groups at the age of 24 months. The measurements of food intake and body weight were taken simultaneously with the measurements of ethanol intake. New groups were introduced to the feeding regimen every 6th–12th month during 5 years. The results for each of the seven cohorts were similar and were pooled together.

The rats were introduced to ethanol at the age of 3 months, which has been a typical age for "young adult" rats in previous age- and ethanol-related studies (see Wood and Armbrecht, 1982; York, 1983; Finch and Schneider, 1985; Ott *et al.*, 1985; Pentney and Quigley, 1987). At this age rats are usually considered mature, but there is some evidence that developmental processes may not be complete in the central nervous system (Ford, 1973; Bayer, 1982) at that point. Such late maturational changes may thus have some effect on the results obtained.

The survival of the animals was carefully monitored, because the possible shifts in the survival curve were expected to show the possible impact of the treatment on the life expectancy (Schneider and Reed, 1985).

Ethanol sensitivity

After testing individual ethanol consumption at the age of 24 months the rats were withdrawn from ethanol. After an abstinence of 5–7 days the sensitivity of the rats to ethanol was estimated by measuring ethanol-induced motor impairment, hypothermia, and duration of the loss of righting reflex. A group of 3–4-month-old AA rats was included in each test.

Ethanol-induced motor impairment was tested on a tilting plane. In this test the animal was placed on a wire cloth–covered plane, which was tilted at a constant speed from horizontal to vertical in 5 s. The sliding angle (i.e., when the animal looses the grip) was recorded (Arvola *et al.*, 1958; Hellevuo *et al.*, 1987). The rats were given a pre-ethanol test and then injected with 2g/kg of ethanol i.p. (12% wt/vol ethanol in 0.9% saline). Subsequent tilting plane tests were performed at 30 and 60 min after the injection. The results are expressed as the decrease of the tilting angle relative to the value obtained before ethanol administration.

The loss of righting reflex (sleep) was induced by an injection of 3.5 g/kg of ethanol i.p. (15% wt/vol ethanol in 0.9% saline). The time for the onset and the duration of the loss of righting reflex were registered. The duration of the loss of righting reflex ("sleep time") was defined as the time from losing the righting reflex to the regaining of this reflex (Kiianmaa, 1980). A rat was judged to have regained its righting reflex when it was able to right itself three times within 30 s when placed on its back. A blood sample of 0.05 ml was taken from the tip of the tail at the moment of reflex recovery for gas chromatographic determination of the blood ethanol concentration (Eriksson, 1973).

The hypothermic effect of ethanol was determined during the ethanol narcosis. Rectal temperature was recorded at 30-min intervals by inserting the probe into the rectum with care to minimize the disturbance to the rats. The results are expressed as the maximum temperature change relative to the pretreatment value (maximum hypothermia) (Kiianmaa, 1980).

Ethanol elimination rate

The rate of ethanol elimination was estimated on the basis of the decline of ethanol concentration in two blood samples (0.05 ml) collected from the tip of the tail 300 min and 360 min after the administration of ethanol (3.5 g/kg i.p.) during the hypothermia test.

Statistics

The different groups were compared using Student's *t* test or analysis of variance followed by Newman–Keuls test. The standard error (SE) was estimated from the variance between the generations in a manner similar to that used in an analysis of variance for determining the mean square between the groups. If the underlying assumption is valid that the differences between the mean values in each generation (at a particular age) were caused only by chance sampling differences, i.e., that there were no real differences between the generations—and there is no reason to suspect that it is not valid for these measures—then it is possible to obtain estimates of the variability between individual animals (e.g., in food intake), even though the group housing precluded taking individual measurements. Furthermore, it is then possible to use the mean, estimated SE, and number of animals to perform *t* tests comparing the ethanol and water groups on such measures. In survival analysis the chi-square *t* test was used.

When comparing the survival rate of animals on water versus those on a choice of ethanol and water, AA rats of the F_{46}, F_{48}, F_{52}, F_{53}, and F_{55} were used. Additional data concerning body weight and food and liquid consumption were obtained from F_{49} and F_{54} generations, but these animals were euthanized whenever severe signs of illness were observed, thus precluding the use of these animals in the survival data.

TABLE 1. ETHANOL CONSUMPTION AND BODY WEIGHT DURING THE SELF-SELECTION PERIODS

	Age 4 months		*Age 24 months*	
	EtOH + H_2O (n = 60)	*H_2O (n = 55)*	*EtOH + H_2O (n = 62)*	*H_2O (n = 47)*
Ethanol consumption (g/kg/day)	6.45 ± 0.31*	6.33 ± 0.27**	5.37 ± 0.27***	4.14 ± 0.32
Body weight (g)	295 ± 4	299 ± 3	418 ± 9	439 ± 11

Values represent mean ± SE.
*$p < 0.01$, initial vs. final in EtOH + H_2O group.
**$p < 0.001$, inital vs. final in H_2O group.
***$p < 0.01$, compared to H_2O group at the same age.

RESULTS

Ethanol consumption

The ethanol consumption in the ethanol group decreased significantly with age from 6.45 to 5.37 g/kg/day as shown by the individual measurements during the self-selection periods (Table 1). In the control group the level of ethanol intake in the final test (4.14 g/kg/day) was also significantly lower than in the initial test (6.33 g/kg/day), and the final

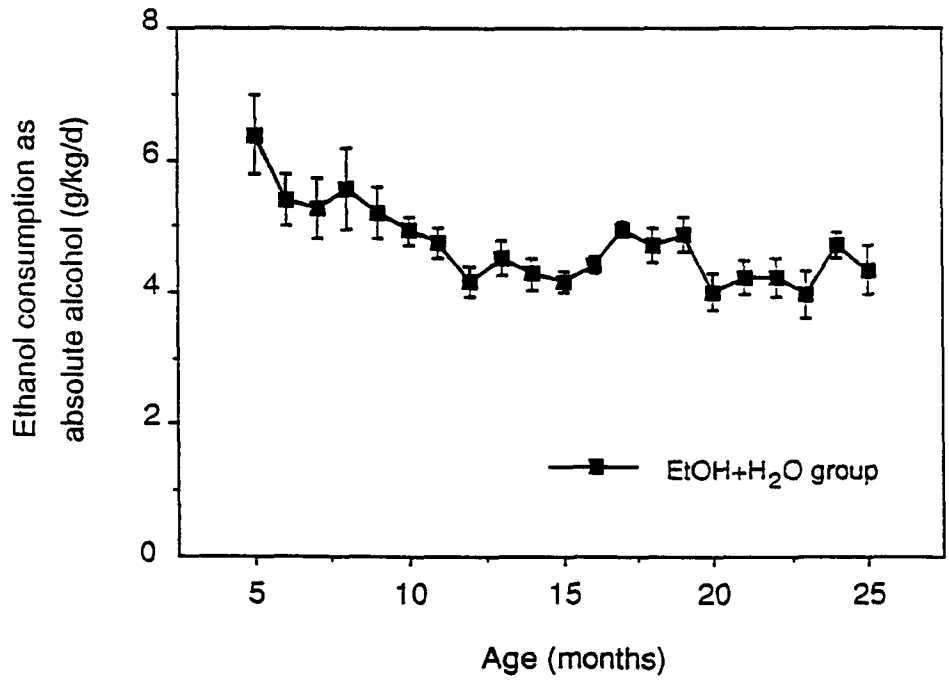

FIG. 1. Intake of ethanol as absolute alcohol (g/kg/day) during 20 months of voluntary ethanol consumption (EtOH + H_2O group). The rats had free access to food, tap water, and 10% (vol/vol) ethanol solution. Means ± SE are given.

level was also significantly lower than the corresponding value in the ethanol group. The follow-up data (Fig. 1) demonstrate that the decrease of ethanol intake in the ethanol group was gradual during the 20-month period.

The consumption of water in the ethanol group was about one-fourth of that in the water group. The difference remained roughly the same with age and was about 60 ml/kg/day (Fig. 2). The difference in the total fluid intake was about 15 ml/kg/day, the ethanol group drinking more than the control group.

As shown in Fig. 3, the intake of food in the ethanol group was lower than in the control group; ethanol constituted about 25% of the total calories consumed in the ethanol group. The rats in both groups gained weight at the same rate and there was no difference in the body weight between the groups at the age of 24 mo (Table 1, Fig. 4).

Survival

Figure 5 sums up the survival of five different cohorts. The first rats in both groups died already during the first few months of the experiment, but the real reduction of the population started after 10 months. As usual under conventional housing conditions, some of the rats suffered from infectious diseases. Judging from the autopsy findings, pulmonary mycoplasma infection was considered the most usual cause of death in all age groups. Tumors in various body organs (e.g., fibromas, testicular and adrenal tumors) were also a

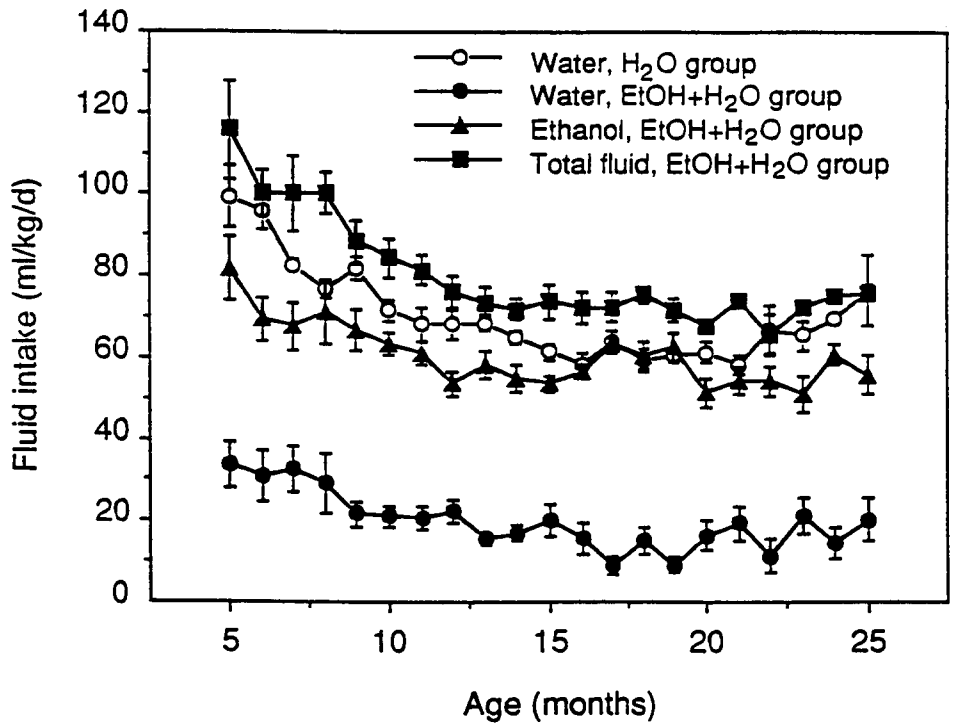

FIG. 2. Intake of fluid (water, ethanol, total fluid) during 20 months of voluntary ethanol consumption (EtOH ± H_2O group). The controls (H_2O group) had only food and water available. Mean ± SE.

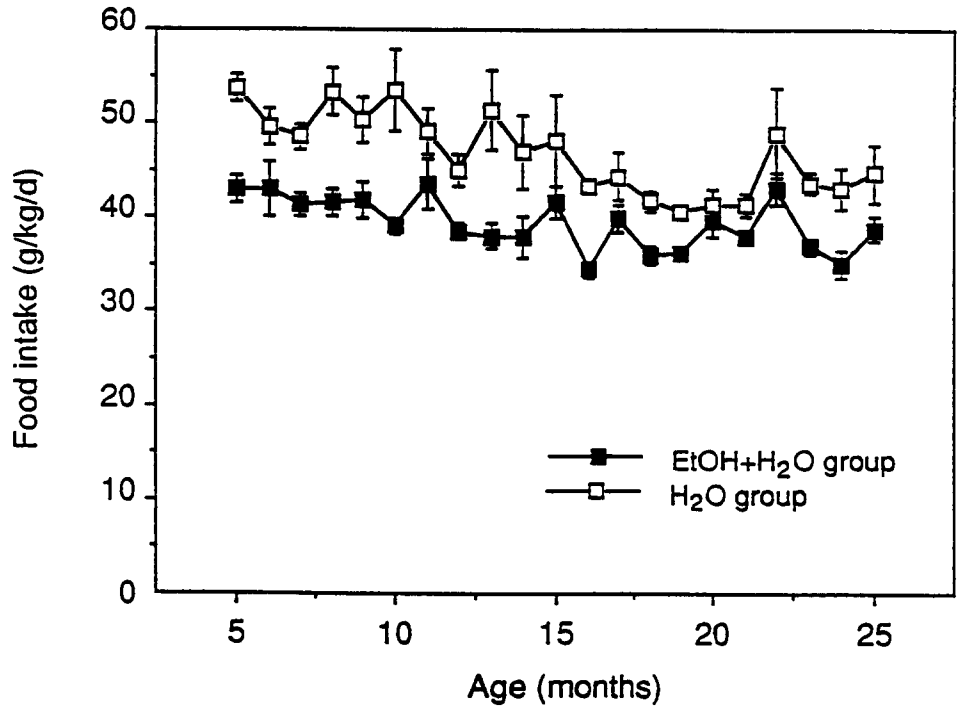

FIG. 3. Intake of food during 20 months of voluntary ethanol ingestion (EtOH + H_2O group). The controls (H_2O group) had only food and water available. Mean ± SE.

rather common finding in the old rats. The comparison of the survival curves did not show any difference in life expectancy between the groups up to 24 months of age. At the age of 24 months 50% of the rats were alive, which is close to the mean life span. One cohort was followed to the age of 28 months. At that point 30% of the animals still survived, and there was no difference between the groups either.

Ethanol sensitivity

Sensitivity to ethanol as revealed by the tilting plane test (Table 2) did not seem to change either with age or ethanol consumption. The hypothermic effect of ethanol was also similar in all groups (Table 3).

The time required for the onset of the loss of righting reflex was significantly shorter in the old controls than in the young rats or in the ethanol group. The duration of ethanol-induced loss of righting reflex was significantly longer in both the ethanol and the control group as compared to the young rats, but there was no difference between the ethanol and the control group (Table 3). There was a tendency for the young rats to have a higher blood ethanol concentration than the old animals at the time of regaining the righting reflex, but the concentrations in the different groups did not differ significantly.

The metabolism of ethanol as reflected by the disappearance of ethanol from the blood flow was essentially similar in all three groups (Table 3).

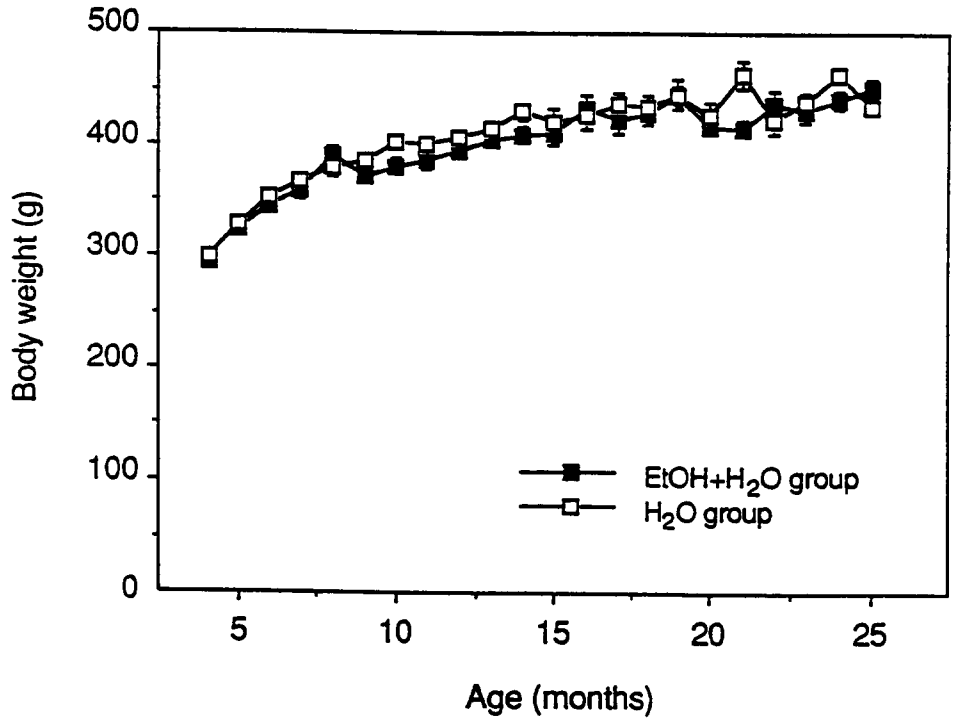

FIG. 4. Lifelong voluntary ethanol consumption did not affect weight gain in the AA (Alko Alcohol) rats. The EtOH + H_2O group had free access to food, tap water, and 10% (vol/vol) ethanol solution at all times. The H_2O group had food and water only. Mean ± SE.

DISCUSSION

The object of this work was to study the interactions of aging and lifelong ethanol consumption on selected well characterized influences of ethanol. In this respect the effect of the designed ethanol feeding regimen proved to be minimal. Tests conducted on the 24-month-old ethanol-treated and control animals did not reveal any differences between the groups in sensitivity to ethanol-induced motor impairment, sleep, or hypothermia, or in the rate of ethanol elimination. The rats in the ethanol group, however, showed a longer onset time of sleep and a higher level of voluntary ethanol consumption, which are the

TABLE 2. ETHANOL-INDUCED MOTOR IMPAIRMENT MEASURED ON A TILTING PLANE

	3–4 month controls (n = *11*)	*H_2O group* (n = *17*)	*EtOH + H_2O group* (n = *11*)
30 min value (%)	29.9 ± 1.7	24.8 ± 1.8	26.0 ± 1.5
60 min value (%)	23.1 ± 2.8	18.6 ± 2.2	19.1 ± 2.3
Blood ethanol concentration (mM)	47.3 ± 1.9	51.7 ± 1.9	50.6 ± 1.5

Values represent impairment as percent of own pre-ethanol value (mean ± SE). Blood ethanol concentrations at 30 min are also given.

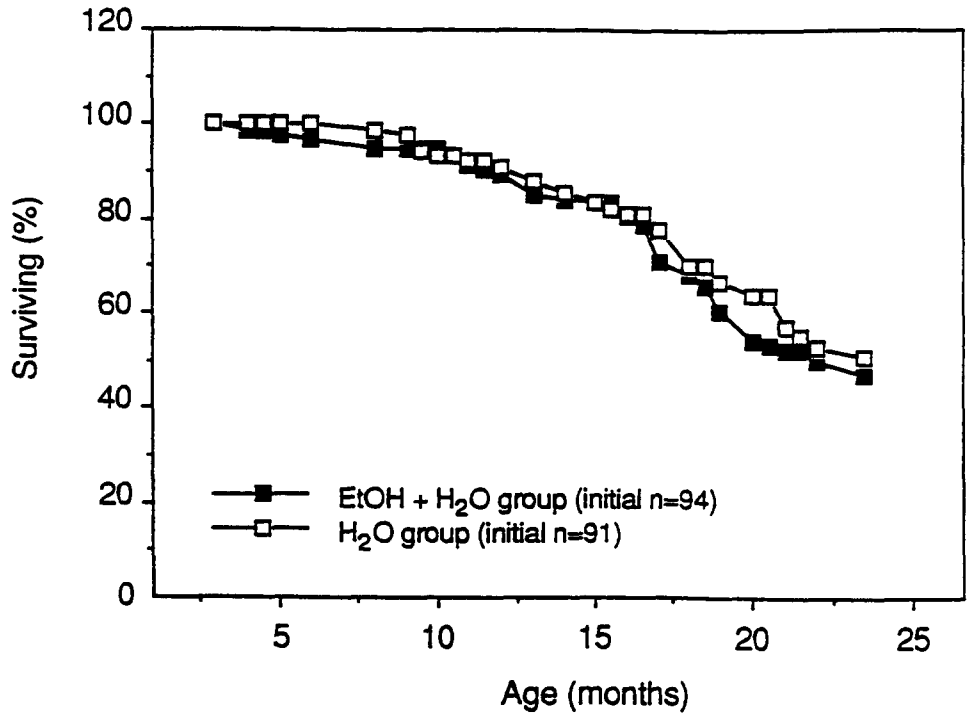

FIG. 5. Survival curves of the ethanol-exposed (EtOH + H_2O) and nonexposed (H_2O) rats. Lifelong voluntary ethanol ingestion had no measurable effect on population longevity. Means of five cohorts are given.

TABLE 3. ETHANOL SENSITIVITY AND ETHANOL ELIMINATION RATE

	3–4 month controls	*H_2O group*	*EtOH + H_2O group*
Onset of sleep (s)	150 ± 8 (26)	109 ± 5* (26)	134 ± 8 (29)
Duration of sleep (min)	195 ± 7** (26)	270 ± 13 (26)	268 ± 12 (25)
Blood ethanol concentration (mM)	70.4 ± 1.0 (26)	66.6 ± 1.5 (26)	68.5 ± 1.3 (25)
Maximum hypothermia (°C)	3.4 ± 0.8 (26)	3.4 ± 1.0 (25)	3.6 ± 1.1 (22)
Ethanol elimination rate (mmol/kg/h)	8.64 ± 0.41 (17)	9.28 ± 0.88 (20)	8.24 ± 0.51 (17)

Ethanol sensitivity determined as the time required for the loss of righting reflex (onset of sleep), duration of the loss of righting reflex (duration of sleep), and ethanol-induced hypothermia (maximum change in body temperature) after an injection of 3.5 g/kg of ethanol i.p. The blood ethanol concentration at the time of regaining the righting reflex and ethanol elimination rate are also given. Values represent mean ± SE. The number of subjects for each measure is stated in parenthesis; the values differ slightly because the study was conducted on several cohorts and not every measure was obtained from each cohort. Some data was also lost for technical reasons independent of the data itself.

*$p < 0.05$, from 3–4 month controls and old EtOH rats, Newman–Keuls test.

**$p < 0.01$, from old water and old EtOH rats, Newman–Keuls test.

only differences found that may suggest a difference in sensitivity to ethanol between the ethanol drinking group and the controls.

It is possible that the level of ethanol consumption was too low to exert deleterious effects. The drinking pattern and blood ethanol concentrations of AA rats (generation F_{46}, which was one of the generations used in the present study as well) have been previously reported (Aalto, 1986). The results showed many of the rats to have blood ethanol levels as high as 25 mM, while the median approached 10 mM, which in both humans and experimental animals is considered to cause inebriation. The only previous study comparable to the present one (Pietrzak *et al.*, 1989) used male Wistar rats that were offered 15% ethanol as their only source of fluid for 24 months. In their study the ethanol-treated rats exhibited increased metabolism of ethanol and a smaller decrease in body temperature after an acute dose of ethanol, as well as mild signs of withdrawal. In our feeding regimen the rats did not show any discernible signs of withdrawal, not even when the exposure was finished a few days before testing the ethanol sensitivity. This suggests that a higher level of daily ethanol intake is needed to produce metabolic and behavioral effects.

The ethanol-exposed and nonexposed rats gained weight at the same rate. The intake of solid food was lower in the ethanol group, but the addition of ethanol increased the total caloric intake over that of the water group. The body weight of the ethanol-fed animals remained slightly lower through the period observed. It is possible that ethanol does not contribute to the energy pool responsible for the weight gain. The caloric restriction of protein has been reported to increase the life expectancy in rodents (Schneider and Reed, 1985). It is possible that the ethanol-induced caloric restriction of other nutrients exerts a positive effect on the life expectancy.

The survival statistics of more than eight cohorts undergoing the same feeding regimen showed no significant difference between the groups. If the exposure to ethanol would have changed the vulnerability of the rats with increasing age, the survival curve would have shifted to the left (Sacher, 1980). If the treatment had accelerated the rate of aging, the slope of the survival curve would have been steeper in the ethanol group. To explore this problem, the population has to be followed close to 3 years because the changes in aging rate have progressively greater effects in more advanced ages (Sacher, 1980). In the present study no difference was found between the groups—not even in the cohort that was followed to the age of 28 months.

It has been previously reported in several studies that old animals are more sensitive to the neurobehavioral effects of ethanol (Wood and Armbrecht, 1982; York, 1983; Ott *et al.*, 1985). In agreement with these findings the onset time of sleep was longer and the duration of the loss of righting reflex was shorter in the young rats than in the old rats, and the blood ethanol concentration when the righting reflex was regained tended to be higher in the young rats than in the older animals. In line with this view the rats reduced their ethanol intake over age. The young and the old rats did not, however, differ in ethanol-induced hypothermia or impairment of motor performance. In agreement with the present findings, York (1983) found that old and young rats did not differ in the hypothermic effect of ethanol, even though a difference was found in the hypnotic effect. Changes in body composition over age may in part contribute to the differences observed in responsiveness to ethanol between young and old animals, as doses of ethanol administered on the basis of total body weight generally produce higher peak blood ethanol concentrations in elderly subjects than in young ones (York, 1982). Respectively, it is possible that in a free choice situation—as in the present study—the rats "adjust" their ethanol consump-

tion according to the ethanol concentration in the body water compartment. If we assume that the lean body mass and the body water content of AA rats decreases during aging, the ethanol consumption calculated per lean body mass seems to remain rather constant over age. No difference between the young and old rats was found here in the rate of ethanol elimination, although a decreased (Hahn *et al.*, 1983) and an accelerated (Ott *et al.*, 1985) rate of ethanol elimination with advancing age have been reported.

The AA rats have been selected for high ethanol intake for more than 50 generations. Even though the ethanol-induced motor impairment, loss of righting reflex, and hypothermia seem to represent different genetic and neuronal mechanisms (Kiianmaa, 1980; Eriksson and Sarviharju, 1984), the AA rats used in the present study are probably selected also for the compensatory reactions efficient enough to mask the possible impacts of ethanol, especially in a life span approach. The "sister" line, the ANA (Alko Non-Alcohol) rats bred along with the AA line (Erikson and Rusi, 1981), was selected for a low level of voluntary consumption of ethanol. These rats might have been selected also for an inadequate defence against the effects of ethanol, which might lead to more pronounced age-related changes in the response. If the expectation was to find support for the "premature aging" hypothesis (Courville, 1955), the rat line used in the present study was probably the wrong one. If the expectation was that "moderate" voluntary intake of ethanol does not accelerate the biological aging processes, at least the results collected from the AA rats support this view.

One further methodological detail may have helped to dissolve the possible impact of ethanol intake. Before the tilting plane test and the ethanol hypnosis the rats were withdrawn from ethanol for 5–7 days. This period of abstinence was necessary for the tests, but it may have further diminished the differences between the groups. The neuronal plasticity in the aged brain may have compensated for the possible impact of ethanol during the long test period but especially when the treatment was finished for a period of time just before killing the animals.

In agreement with our "no change" results, several recent studies have found no clear interaction between aging and chronic ethanol exposure. Studies on, for example, cognitive functions (Becker *et al.*, 1983; Riege *et al.*, 1984), signal transduction mechanisms (Sun *et al.*, 1987), and dendritic morphometrics of Purkinje neurons (Pentney and Quigley, 1987; Pentney and Quackenbush, 1990) have suggested independent or even opposite effects of aging and of long-term ethanol consumption.

In conclusion, the voluntary ethanol feeding regimen used did not show any major interactions between aging and chronic exposure to ethanol in the AA rats. The 24-month-old rats showed higher sensitivity to ethanol in the sleep-time test than the young animals (3–4 months), thus providing some support for the idea of an increased sensitivity to ethanol in old age.

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