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Pharmacology, Biochemistry and Behavior 67 (2000) 719–727

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

Altered behavior and alcohol tolerance in transgenic mice lacking MAO A: a comparison with effects of MAO A inhibitor clorgyline

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Accepted 21 June 2000

Abstract

The influence of deficiency of monoamine oxidase A (MAO A) gene and the lack of enzyme MAO A on the behavior of transgenic mouse strain (Tg8) was studied. It was shown that MAO A-lacking mice differed from mice of the wild-type strain C3H/HeJ (C3H) by an attenuated acoustic startle response, prepulse inhibition (PPI) was unchanged. In Tg 8 mice, the exploratory nose-poking in the holeboard test as well as exploratory line crossing in the "light–dark" test were decreased. No effect of MAO A deficiency on locomotor activity was found. No alcohol preference or difference between Tg8 and C3H in ethanol consumption in the free-choice test has been found, although an increase in alcohol tolerance has been demonstrated. Ethanol-induced (0.3 g/100 g ip) sleep latency was longer, duration of sleep was shorter and ethanol hypothermia was reduced in MAO A-lacking mice. Comparison of effects of MAO A knockout with those of irreversible MAO A inhibitor clorgyline (5 and 10 mg/kg ip) on C3H mice showed a similar reducing effect on ethanol-induced sleep, but potentiated ethanol-induced hypothermia. Clorgyline administration provoked a tendency to decrease of exploratory activity in the nose-poking test and decreased the frequency of exploratory rearings in the light–dark test. Clorgyline (5 and 10 mg/kg) did not affect the acoustic startle response, but a dose of 5 mg/kg diminished PPI. Therefore, Tg8 mice exhibited a decreased startle response and exploratory activity and an increased tolerance to ethanol. A similar increase in tolerance to ethanol-induced sleep and a tendency to decrease exploratory behavior were displayed by clorgyline. Other effects on behavior were different, suggesting the influence of long-lasting action of MAO A knockout and the involvement of a compensatory mechanism in Tg8 mice.

Keywords: MAO A-knockout; Behavior; Startle reflex; Exploratory activity; Alcohol tolerance; Clorgyline; Mice

The recently created transgenic mouse strain Tg8 [4] lacking monoamine oxidase A (MAO A) gene and subsequently deficient in MAO A enzyme is of special interest, since somewhat earlier a hereditary pathology with a point mutation of the gene encoding MAO A was described in man [3].

As is well known, MAO A is one of the basic enzymes of dopamine and noradrenaline degradation and the main enzyme of serotonin catabolism. Genetic deficiency in MAO A in transgenic Tg8 mice was shown to be associated with abolished MAO A activity [4], with an intense activity of the other form of this enzyme, MAO B, in some brain structures [16], and an increased brain level of all the three biogenic amines. In adult brains, noradrenaline and serotonin levels were elevated up to twofold and increase of dopamine only slightly [4].

The behavior of mice deficient in MAO A has been studied rather little [28]. Adult animals exhibited an increase in aggressiveness, enhanced classical fear conditioning avoidance learning, and a decrease of immobility time in forced swimming test, while maternal behavior remained unaffected [4,8,20]. Impulsive aggressiveness was shown also in men of the Dutch kindred with the MAO A gene

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0091-3057/00/$ – see front matter
PII: S0091-3057(00)00417-2

point mutation and completely absent MAO A activity [1]. No considerable changes in motor activity, expression of pinch-induced catalepsy, or behavior in elevated plus maze were found in Tg8 mice [27]. At the same time, it remains obscure whether other forms of behavior in whose regulation brain serotonin and catecholamines participate are affected, and to what degree the behavioral changes occurring in the genetically determined lack of MAO A are commensurable with the effects of acute MAO A inhibition.

The latter question is associated with the fact that the genetic defect is present from the earliest stage of ontogeny throughout the growth of the nervous system. An elevation of serotonin level was detected even in the fetus of MAO A-deficient transgenic mice [22]. Especially pronounced changes in the serotonin level and metabolism were found in newborn animals of this strain, whereas with age the difference between Tg8 and the wild-type mouse strain in serotonin content and metabolism was leveled out [4,26]. In MAO-A-deficient mice, changes in cytoarchitectonics of the somatosensory cortex have also been found [5]. All this gives reasons to hypothesize that at least some of the changes observed in adult mice with genetic knockout may be caused by disturbances of developmental processes, and are not associated with the functional role of the given gene in adult organisms [5,7]. This problem can be elucidated to some extent by comparing the influence of the genetic MAO A knockout on behavior with the effects of an inhibitor of this enzyme.

The goal of the present work was to study the effect of the genetically determined lack of the pivotal enzyme in serotonin and catecholamine metabolism on the behavior of mice with disrupted MAO A gene, and to compare it with the effects of an irreversible MAO A inhibitor, clorgyline [17]. Used as behavioral characteristics were locomotor and exploratory activities, the acoustic startle response and its prepulse inhibition (PPI), alcohol preference, and alcohol tolerance.

1. Materials and methods

Experiments were carried out on transgenic Tg 8 mice with disrupted MAO A encoding gene and on C3H/HeJ (C3H) mice from which the Tg 8 mice had been derived. Tg 8 mice are characterized by a deletion of exons 2 and 3 of the MAO A gene on the X chromosome and the lack of MAO A activity in brain and liver [4]. The mice were obtained from Centre National de la Recherche Scientifique (France) and maintained by inbreeding in the vivarium of the Institute of Cytology and Genetics of the Siberian Branch of Russian Academy of Sciences (Novosibirsk). Tg8 and C3H mice used in the experiments were males at an age of 4 months and weighing about 25 g. The animals were kept in groups of four littermates each together with a female, under natural daylight conditions and with free access to food and water. Two days before the experiments, the mice were put into individual cages to remove the "group effect." All experiments were performed at 2:00–4:00 p.m.

The following kinds of behavior were studied:

(1) Locomotor activity was estimated by placing a mouse for 20 min in a 30×30-cm actometer with two photodiodes and automated recording system.

(2) Exploratory activity was estimated by a somewhat modified holeboard test [11] in special $20 \times 25 \times 15$-cm cages covered with nontransparent covers with three round holes. The number of nose pokes into the holes was recorded for 5 min visually by two observers.

(3) The "light–dark" test is based on the mouse's tendency to avoid illuminated space and on the conflict between exploratory motivation and fear of bright light. The experimental chamber was divided into two sections communicating through a hole of 7×7 cm. The larger section ($40 \times 40 \times 27$ cm) was illuminated by a 60-W white incandescent bulb (900 lx) at 1-m distance; the smaller one ($40 \times 30 \times 27$ cm) was closed on all sides. A mouse was placed in the center of the illuminated section whose surface was lined into 16 squares, and the total time spent in the light section was calculated in percent. Exploratory line crossings and rearings were also recorded.

(4) Acoustic startle reflex and its PPI were measured in the device SR-Pilot (San Diego Instruments, USA). The 115-dB acoustic stimulus (pulse) that provoked fright reaction and startle reflex was switched on for 4 ms simultaneously with automatic recording of the animal's movement on a platform connected to a piezosensor. When studying PPI, an 85-dB 40-ms prepulse was switched on 100 ms before the pulse. A mouse was placed in the device for 3 min for adaptation, and then four consecutive pulses (P) were inflicted, each of which was followed by a prepul-

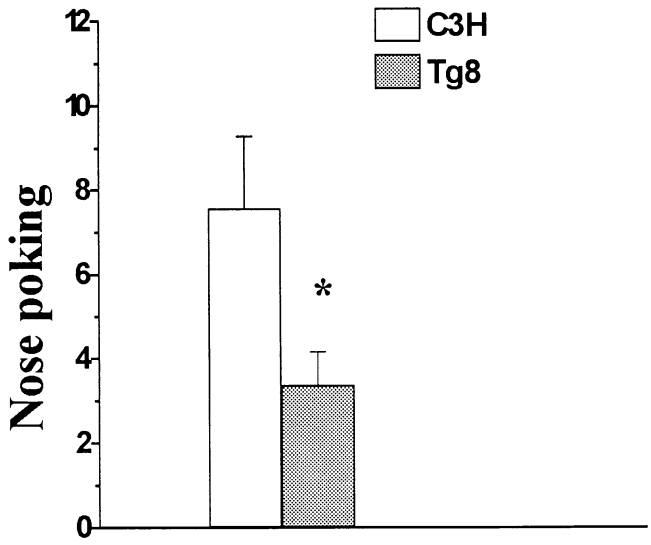


Fig. 1. Exploratory activity of MAO A-deficient Tg8 and wild-type C3H mice in a holeboard. Data are shown as mean values ± S.E.M. from 9 to 11 animals. * $P < .05$.

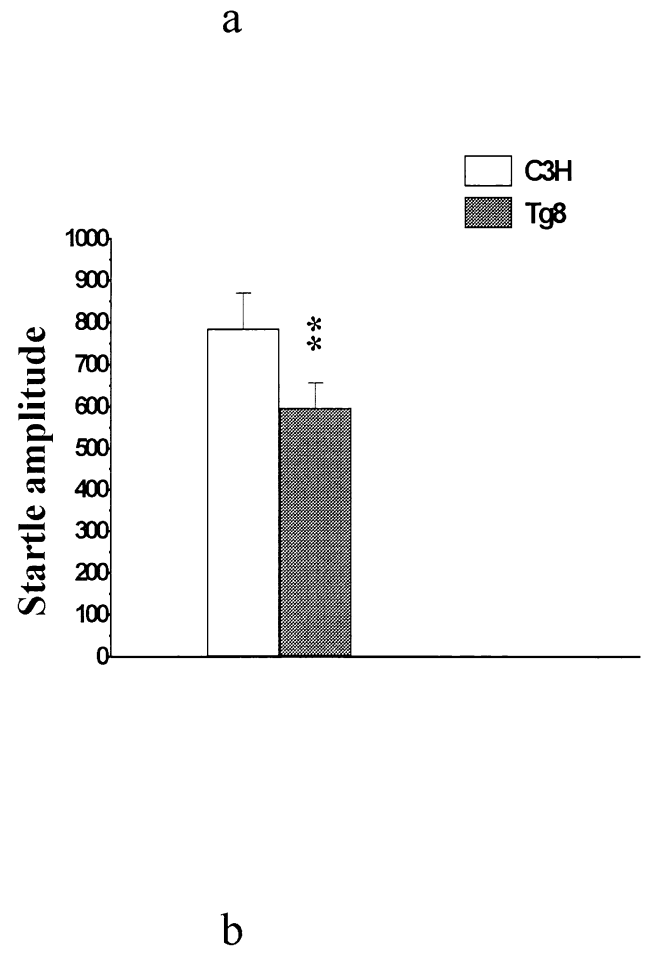


Fig. 2. Acoustic startle reflex in MAO A-deficient Tg8 and wild-type C3H mice: (a) startle amplitude; (b) % of prepulse inhibition. Data are shown as mean values ± S.E.M. from 10 animals. ** $P < .01$.

se + pulse (PP) combination at 15-s intervals. The PPI was calculated in percent: $[(P - PP) \times 100]/P$.

Table 1
Behavior of MAO A-deficient Tg8 and wild-type C3H mice in a light–dark test

Parameters of behavior	C3H ($n = 10$)	Tg8 ($n = 10$)
Time in light (%)	66.0 ± 3.0	68.0 ± 4.0
Exploratory line crossing	54.0 ± 3.5	39.0 ± 5.5*
Rearings	4.0 ± 1.4	3.2 ± 1.2

* $P < .02$ vs. C3H.

(5) In the free choice test for alcohol preference the amount of 10% ethanol and water consumed by mice for 2 and 24 h after a 24-h water deprivation was measured. For

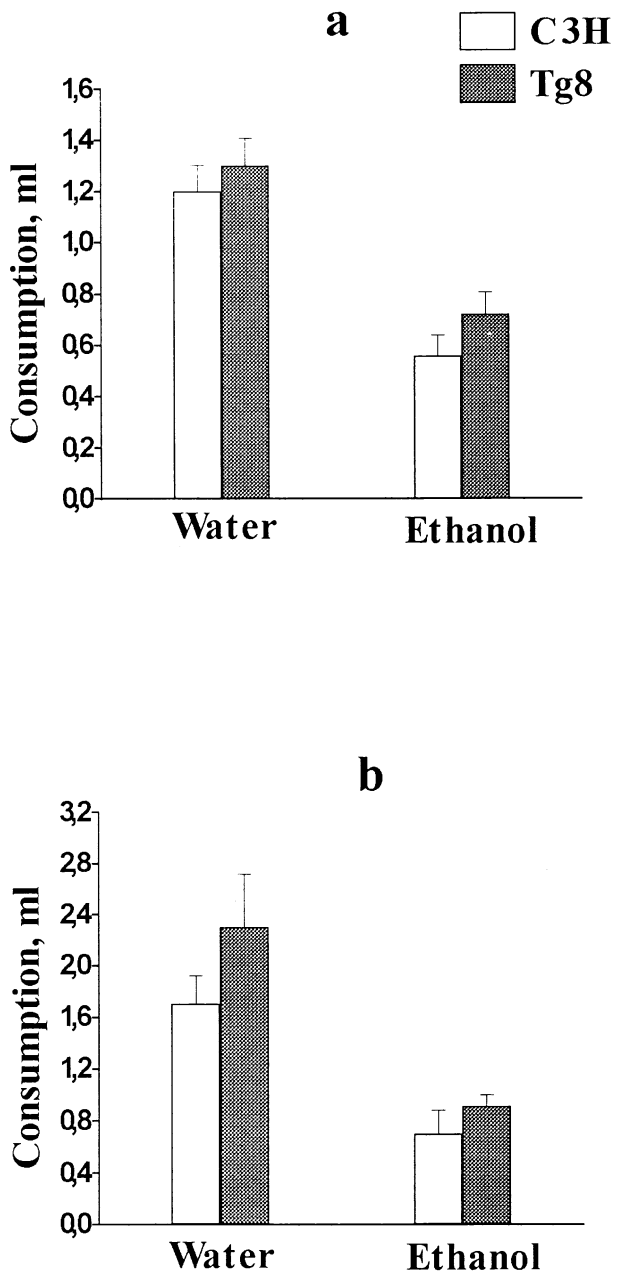
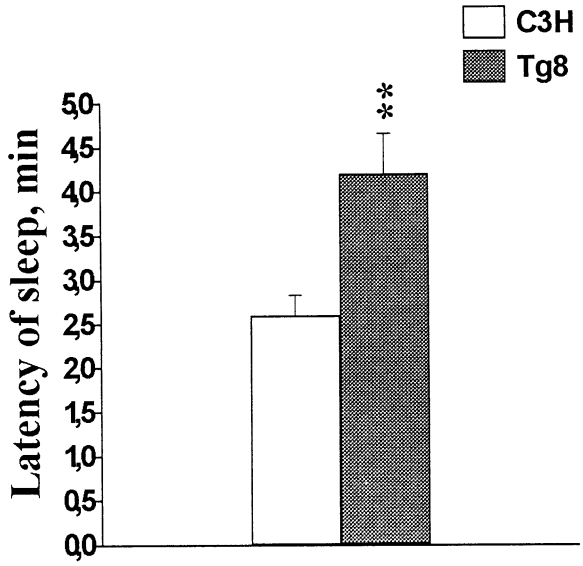


Fig. 3. Water and ethanol consumption in free-choice test in MAO A-deficient Tg8 and wild-type C3H mice: (a) for 2 h after 24-h water deprivation; (b) for 24 h.



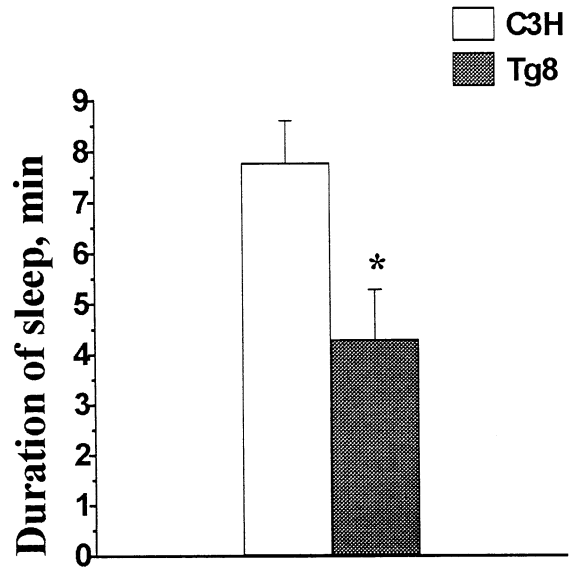


Fig. 4. Ethanol-induced sleep in MAO A-deficient Tg8 ($n=8$) and wild-type C3H mice ($n=10$). Data are shown as mean values ± S.E.M. * $P<.05$; ** $P<.01$ vs. wild-type mice.

estimation of alcohol tolerance, 20% ethanol (0.3 g/100 g) was injected intraperitoneally, and the latency (latency to first immobility), duration of sleep, and the rectal temperature were measured. Temperature measurements were performed every 20 min for 2 h after ethanol injection by means of a KJT thermocouple (Hanna Instrument, Singapore) with a copper–constantan rectal probe for mice (Physitemp Instruments, USA). Ambient temperature was 24°C.

Selective irreversible MAO A inhibitor clorgyline (RBI, USA) was administered intraperitoneally to C3H mice in doses of 5 and 10 mg/kg 30 min prior to testing. Control animals were treated with saline.

All experimental procedures were made in compliance with the European Communities Council Directive of 24 November 1986 (86/609/EEC).

Statistical treatment of data was performed using ANOVA Microcal Origin ver. 5.0. Post hoc multiple comparison was made using Student's t test with Bonferroni correction.

2. Results

2.1. Effect of genetic MAO A deficiency on behavior

It was shown that Tg 8 mice did not differ from the wild-type mice in locomotor activity. The number of radial ray crosses in C3H and Tg 8 was 386 ± 11.5 and 384 ± 7.7 ($P>.05$) subsequently. At the same time, the mice with the genetic MAO A deficiency differed significantly in their exploratory behavior: the number of nose pokings in the holeboard test was more than twice lesser in Tg 8 mice than in wild-type mice (Fig. 1).

Differences have also been found in the expression of acoustic startle response. The magnitude of startle reflex in Tg 8 mice in response to a stimulus of standard intensity and duration was considerably lower than in C3H mice. At the same time, there was no difference in the expression of PPI (Fig. 2).

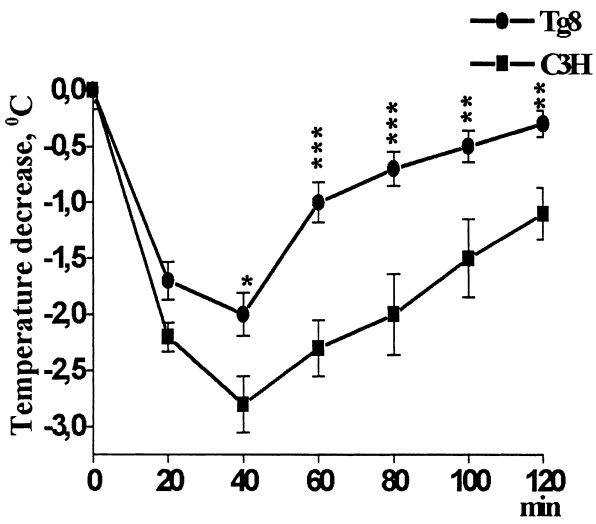


Fig. 5. Ethanol-induced hypothermia in MAO A-deficient Tg8 ($n=18$) and wild-type C3H mice ($n=8$). Data are shown as mean values ± S.E.M. $P<.05$; ** $P<.01$; *** $P<.001$ vs. wild-type mice.

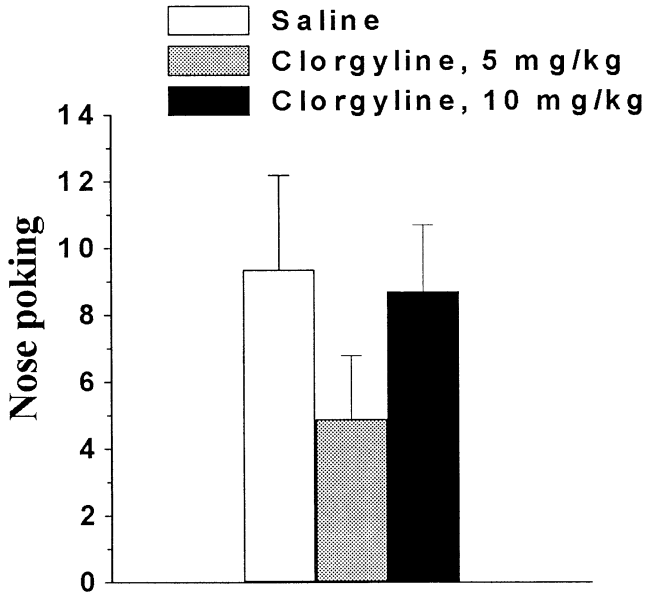


Fig. 6. Effect of clorgyline (5 and 10 mg/kg) on exploratory activity of C3H mice in a holeboard. Data are shown as mean values ± S.E.M. from 10 to 18 animals.

In the light–dark test, mice with genetic MAO A deficiency and C3H mice did not differ either in the time spent in the light and in the dark sections, or in the number of rearings. At the same time, the exploratory line crossing in MAO A-deficient mice was considerably lower than that respective parameter in the wild-type mice (Table 1).

The test for alcohol preference failed to detect any difference between the control C3H and MAO A-deficient Tg8 mice. The two strains under study demonstrated the absence of alcohol preference in the free-choice test both for 2- and 24-h testing (Fig. 3). A statistically insignificant tendency to a higher liquid consumption in Tg 8 than in C3H mice was observed. At the same time, considerable difference in the tolerance of Tg 8 and C3H mice to ethanol was found. While the ethanol in the dose used induced sleep in all the 10 control mice, in two out of Tg 8 mice sleep did not set on. The rest of the Tg 8 mice differed from the wild-type strain by a prolonged latency and shorter duration of ethanol-induced sleep. In MAO A-deficient mice the sleep latency was two times longer [$F(1,18) = 11.29$, $P < .01$] and the duration of sleep was reduced [$F(1,18) = 7.79$, $P < .05$] compared to control C3H mice (Fig. 4).

Table 2
Effect of clorgyline on behavior of C3H mice in a light–dark test

Parameters of behavior	Saline ($n = 11$)	Clorgyline, 10 mg/kg ($n = 9$)
Time in light (%)	60.1 ± 6.0	30.7 ± 8.3**
Exploratory line crossing	58.27 ± 5.4	35.44 ± 14.9
Rearings	15.0 ± 2.4	5.11 ± 2.9*

* $P < .02$.
** $P < .01$ vs. saline.

The difference between strains Tg 8 and wild-type mice was also manifested in the temperature effects of ethanol. The mean rectal temperature at the time of ethanol injection (37.0 ± 0.17° and 37.0 ± 0.11° for C3H and Tg8, respectively) was not different. Intraperitoneal injection of 0.3 g/

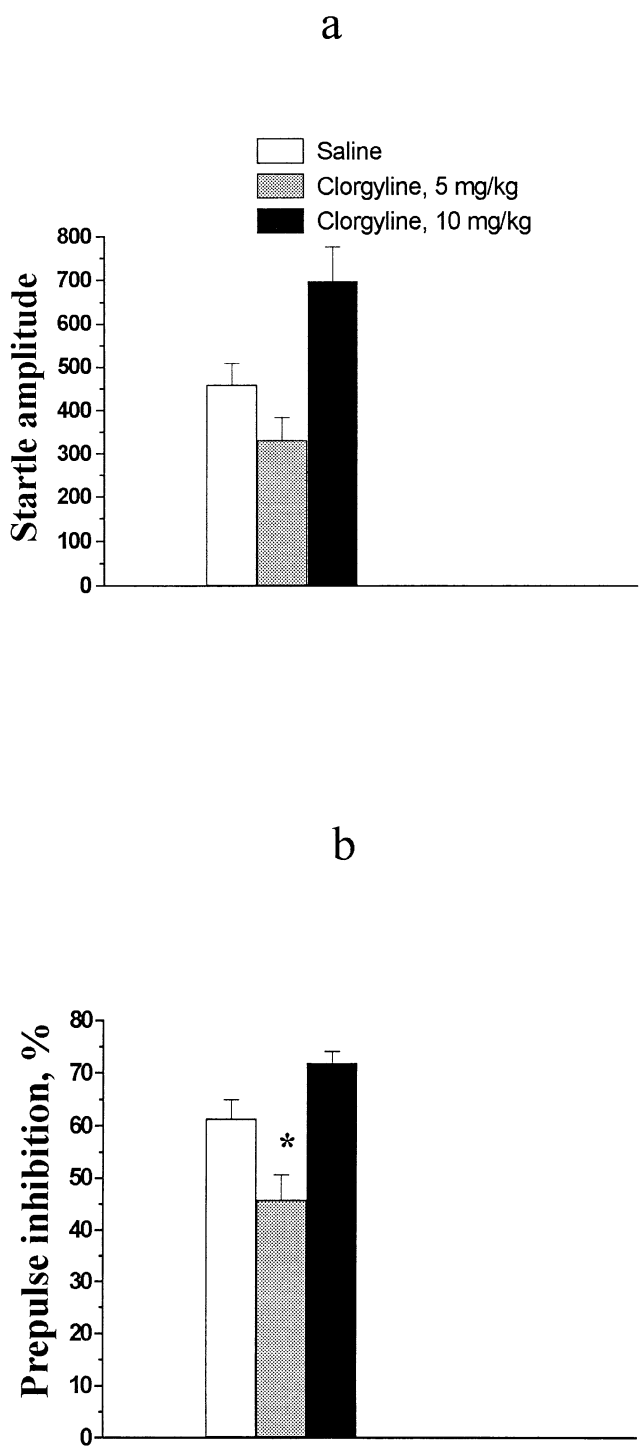


Fig. 7. Effect of clorgyline (5 and 10 mg/kg) on acoustic startle reflex in C3H mice: (a) startle amplitude; (b) % of prepulse inhibition. Data are shown as mean values ± S.E.M. from 10 to 16 animals. * $P < .05$ vs. saline.

100 g of ethanol induced hypothermia in both strains; however, the ethanol-induced hypothermia in MAO A-deprived mice was less deep and less durable than in wild-type animals (Fig. 5).

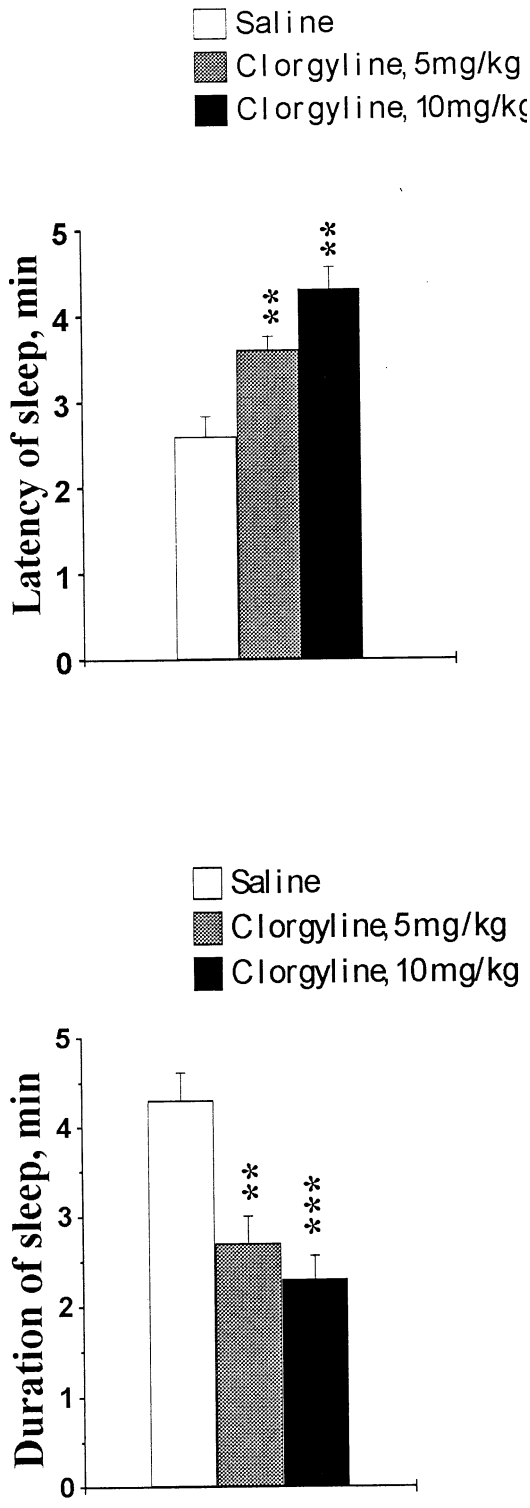


Fig. 8. Effect of clorgyline (5 and 10 mg/kg) on ethanol-induced sleep in C3H mice. Data are shown as mean values ± S.E.M. from 10 animals. ** $P<.01$; *** $P<.001$ vs. saline.

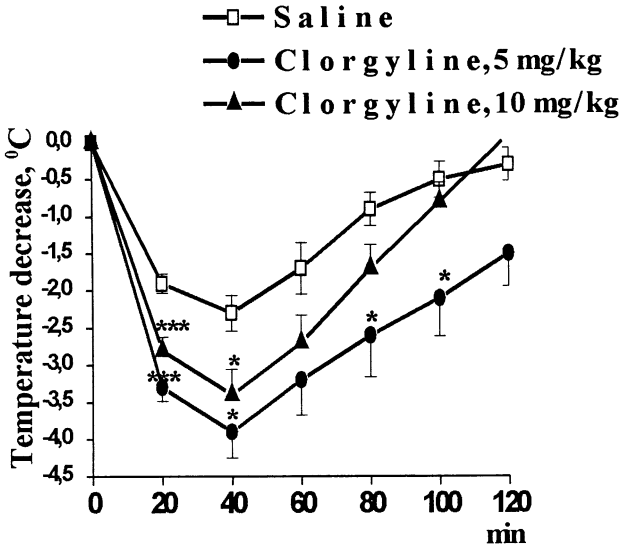


Fig. 9. Effect of clorgyline (5 and 10 mg/kg) on ethanol-induced hypothermia in C3H mice. Data are shown as mean values ± S.E.M. from 10 animals. * $P<.05$; *** $P<.001$ vs. saline.

2.2. Effect of MAO A inhibitor clorgyline on behavior

The effect of clorgyline was studied on C3H mice with respect to those behavior items in which differences between mice with genetic MAO A knockout and control animals were found.

In the nose-poking test, there was a trend for clorgyline (5 mg/kg) to reduce the exploratory activity; however, this effect was not observed at the dose of 10 mg/kg (Fig. 6). A considerable decrease in the time spent in the white section in the light–dark test, a decrease of exploratory rearings, and a tendency to decrease of exploratory line crossing were observed at 10 mg/kg clorgyline (Table 2).

Clorgyline did not affect the magnitude of the acoustic startle response, but decreased PPI at the dose of 5 mg/kg (Fig. 7).

The effect of clorgyline on ethanol-induced sleep was similar to that of genetic loss of MAO A. The two clorgyline doses did not influence voluntary ethanol consumption, but increased latency and decreased the duration of ethanol-induced sleep (Fig. 8). At the same time, unlike the genetic MAO A deficiency, the clorgyline in both doses potentiated the hypothermic effect of ethanol (Fig. 9).

3. Discussion

The deficiency of MAO A gene and the lack of the enzyme affected the behavior of transgenic mice, although the changes were not as considerable as one might expect, taking into account the role of MAO A in catecholamine, and especially serotonin, catabolism [31]. MAO A-lacking mice did not differ essentially from control C3H mice in

the locomotor activity, the time spent in the light area in the light–dark test, and in alcohol preference. Earlier, we failed to find any difference between Tg 8 and the wild-type strain in the expression of anxiety in the elevated plus-maze test, and in predisposition to pinch-induced catalepsy [27]. It is noteworthy that used as control in these experiments were males of the strain C3H from which the transgenic strain with deficient MAO A gene had been derived. This eliminates the problem of control adequacy, which consistently arises in experiments on animals with genetic knockout.

Still another — ontogenetic — aspect of the problem should be noted. All the experiments were carried out on adult, sexually mature mice at an age of about 4 months. Earlier it was demonstrated [4,26] that in the process of late ontogeny a clear-cut normalization of serotonin metabolism, probably associated with the activation of appropriate compensatory mechanisms, took place.

Mice with a genetic MAO A knockout differed from controls by a decreased exploratory activity. This was manifested both in the nose-poking test and in fewer lines crossed in the light–dark test. It is noteworthy that affected men of Dutch kindred in whom the mutation of the structural MAO A gene was found, displayed, besides an increased aggressiveness, a syndrome of borderline mental retardation [1,2].

When studying anxiety in the light–dark test, no difference in the time spent in the light compartment was found between Tg8 and C3H mice. However, one has to bear in mind that the strain C3H and, correspondingly, Tg 8, which is genetically identical to C3H except for MAO A gene deletion, are carriers of a mutation of retina degeneration developing in aging animals [23]. Although the mice in our experiments were not old, the comparison of the time spent in the light section in the light–dark test may be not quite adequate for estimation of anxiety in these strains. However, another index — a decrease of the exploratory line crossing by Tg 8 mice — seems to be more adequate, since in exploratory mouse behavior smell plays a more significant role than vision. In fact, it is considered that the behavior in this test reflects a result of conflict between the exploratory motivation and aversive effect of brightly illuminated space. Decreased exploratory activity in the nose-poking test found in Tg 8 mice probably reflects mainly a decrease of just the exploratory competence rather than an increase of anxiety and fear. A corroboration of this suggestion is the considerable attenuation of the fear-induced acoustic startle reflex in the Tg8 mice.

At the same time, no differences in PPI between MAO A-deficient and control C3H mice were found. Unchanged PPI in Tg 8 mice was in contrast to the reduction in PPI effect of clorgyline. It is known that inhibition of response to an acoustic stimulus by a preceding weak "prepulse" sound is mediated by other brain structures and, most probably, by more complicated mechanisms than the startle response [30]. The expression of PPI is believed to be very important, since it is considered to be associated with processes of sensorimotor gating and selective attention, and PPI deficit has been found in schizophrenia [12]. There is some evidence indicating the involvement of central serotonergic [9,18,29] and dopaminergic [10,33] systems in the modulation of PPI inhibition. However, unchanged PPI expression in genetically MAO A-deficient mice suggests that compensatory mechanisms may be activated during ontogeny, which will correct the damaging effect of MAO A deficiency on the essential mechanisms of sensorimotor gating of the adult animals.

The alcohol preference test failed to show any differences between the control and MAO A-deficient mice. Mice of the two strains did not show any alcohol preference in the free-choice test. At the same time, considerable differences in the tolerance to ethanol-induced sleep and hypothermia were found between Tg 8 and C3H mice. With respect to all the three indices of alcohol tolerance, i.e., ethanol-induced sleep latency, duration of sleep, and temperature response to ethanol [21,24], the MAO A-deficient mice showed an increased tolerance to ethanol as compared to animals of the wild-type strain. Although no peculiarities of alcohol preference were found in Tg 8 mice, the increased alcohol tolerance in animals lacking MAO A is in accordance with the data on the involvement of MAO A in the mechanisms of genetic predisposition to alcoholism in man [13,25,32].

Comparison of the effect of genetic disruption of MAO A with that of the acute pharmacological blockade of this enzyme with clorgyline has detected both similarities and considerable differences. While the exploratory activity of Tg 8 mice was decreased both in the nose-poking and in the light–dark test, the effect of clorgyline was manifested only in a pronounced tendency to decrease of exploratory line crossing and nose-poking, with a simultaneous significant decrease of the exploratory rears. Unlike the inhibitory effect of genetically defined deficiency of MAO A, clorgyline influenced the acoustic startle response only as a tendency to decrease, but decreased PPI.

The greatest similarity was found when comparing the influence of genetic loss with pharmacological inhibition of MAO A on the response of mice to ethanol. No effect of either the former or the latter on the alcohol preference was found, but the two kinds of MAO A blockade increased the tolerance to ethanol-induced sleep. The coincidence of the effect of genetic deficiency of MAO A and of irreversible MAO A inhibitor clorgyline presents another evidence of MAO A being involved in the mechanisms of alcohol tolerance. In a somewhat different test on rats it was demonstrated that clorgyline and a reversible MAO A inhibitor befloxatone reduced ethanol self-administration [6].

Since the genetic deficiencies of MAO A and the pharmacological inhibition of this enzyme result in impairment of brain serotonin, dopamine, and noradrena-

Table 3
Comparative effects of genetic deficiency of MAO A and acute MAO A inhibition by clorgyline

Behavior patterns	MAO A knockout	Clorgyline
Acoustic startle reflex		
Pulse (P)	Decrease	Tendency to decrease
Prepulse inhibition (PPI)	No effect	Decrease
Light–dark test		
Time in light	No effect	Decrease
Exploratory line crossing	Decrease	Tendency to decrease
Rearings	No effect	Decrease
Nose pokes	Decrease	Tendency to decrease
Ethanol consumption	No effect	No effect
Ethanol tolerance		
Latency of sleep	Increase	Increase
Duration of sleep	Decrease	Decrease
Hypothermia	Decrease	Increase

line metabolism, it is rather difficult to attribute the changes in ethanol tolerance found in MAO A-lacking mice to any of them. Nevertheless, the available data give reasons to suppose that alcohol tolerance of MAO A-deficient mice is associated with the decrease of catabolism and increase of the level of brain serotonin. It has been shown that an increase of brain serotonin level brings about an elevation of alcohol tolerance with respect to both its ethanol-induced sleep and hypothermic effect [19].

At the same time, clorgyline displayed an effect opposite to that of genetic MAO A-deficiency, deepening the ethanol-induced hypothermia. One may hypothesize that a long-lasting (throughout the whole ontogeny) lack of MAO A decreases the sensitivity of serotonergic and/or noradrenergic receptors of the preoptic zone of hypothalamus, which, as demonstrated by Huttunen et al. [14,15], are involved in the thermolytic effects of ethanol. However, this problem requires a special study.

Therefore, Tg8 mice exhibited a decrease in startle response and exploratory activity and an increase in tolerance to ethanol. Similar increase in tolerance to ethanol-induced sleep and a tendency to decrease in exploratory behavior and startle response was displayed by clorgyline. Other effects of acute inhibition of MAO A and genetic deficit of enzyme on behavior were different (Table 3). Taking into account the difference between pharmacological blockade of an enzyme and the influence of the lack of the enzyme acting during all ontogeny in genetically deficient animals, the coincidences of some effects of MAO A knockout with clorgyline effects are suggestive. They elucidate the regulatory role of MAO A on these kinds of behavior in adult animals, whereas the changes in behavior, different from those in acute MAO A inhibition seem to reflect a much more complicated effect of genetic MAO A deficiency.

Acknowledgments

The work was supported by the Russian Foundation for Basic Research, grant N99-04-49409.

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