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Both inorganic and organic selenium supplements can decrease brain monoamine oxidase B enzyme activity in adult rats

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It has been observed that the levels of brain monoamine oxidase B (MAO-B) increase during ageing. MAO catalyses the oxidative deamination of neurotransmitters, in which the by-product H_2O_2 is subsequently generated. Se exists naturally in inorganic and organic forms and is considered to play a key role in antioxidation functioning. The objective of the present study was to investigate two chemical forms of Se compounds for their inhibition effect on rat brain MAO-B. The total antioxidant capacity and lipid peroxidation of rats were also examined. The rats (age 7 weeks) were divided into four groups: the control group, tocopherol group (T group, positive control), selenite group (SE group, representing the inorganic Se group) and seleno-yeast group (SY group, representing the organic Se group). The rats were fed for 11 weeks with normal diets and 12 weeks with test diets. The serum total antioxidant capacity of the SE and SY groups was significantly higher than that in the control and T groups. In rat brains and livers, the lipid peroxidation levels were significantly decreased in the T, SE and SY groups. MAO-B activity showed a significant decrease in the T, SE and SY groups in rat brains but no significant change could be noted in the rat livers. In conclusion, the present study indicates that inorganic or organic Se supplementation can decrease the brain MAO-B enzyme activity in adult rats and can be accomplished by the effect of the Se antioxidation capability.

Selenium: Seleno-yeast: Monoamine oxidase B: Brain: Antioxidation

Monoamine oxidase (MAO; *E.C.* 1.4.3.4) is an enzyme that has two isoenzymes: type A and B. It is widely distributed in tissues including the nerves, kidneys, liver and gastrointestinal tract. The enzyme catalyses the metabolism of biologically active amine compounds and participates in the oxidative deamination reaction of a variety of amine neurotransmitters, such as dopamine, adrenaline, serotonin, etc[1]. Because of the observation that MAO-B levels are increased during ageing[2,3], the relationship between MAO-B and ageing-related diseases has been extensively discussed. Several neurodegenerative diseases, such as Parkinson's and Alzheimer's, reveal high MAO-B in the brain, but have no difference in MAO-A[1,2,4,5]. In addition, inhibitors of MAO-B have been applied to Alzheimer's patients, in whom improvements have been observed[6–8].

Se is a dietary essential trace element for humans. Se can be incorporated into selenoproteins in the form of selenocysteine and selenomethionine. It is also necessary for Se-containing enzymes, such as glutathione peroxidase. Glutathione peroxidase can take part in the catalysing of H_2O_2 to water and, consequently, it contributes to antioxidation. Therefore, Se plays a key role in antioxidation functioning. It is well known that Se possesses many benefits including protection against oxidative damage, reduction of cancer risk and regulation of immune function[9–11]. Se exists naturally in inorganic (for example, selenite and selenate) and organic (for example, seleno-yeast, selenomethionine and selenocysteine) forms. These two forms vary in bioavailability and protective effects[12–14]. As determined by the glutathione peroxidase activity and Se concentrations in tissue, organic Se sources are absorbed and retained more efficiently than the inorganic Se sources[15,16]. In mammals, dramatic differences are found in the uptake and binding of selenite and selenomethionine by brush-border membrane vesicles[17]. For the purpose of Se supplementation, selenite, selenomethionine and seleno-yeast are usually administered as commercial products in diets. Yeast (*Saccharomyces cerevisiae*) can uptake Se and most of the total Se is converted to the form of selenomethionine[14]. For this reason, selenomethionine is the major Se compound in seleno-yeast.

The relationship between Se and brain function is also another interesting topic. It becomes more and more apparent that Se plays a critical role in the maintenance and modulation of brain functions[18]. Se is involved in the conservation of functional brain activity and protects against the oxidative

Abbreviations: MAO, monoamine oxidase; ppm, parts per million; SE group, selenite group; SY group, seleno-yeast group; T group, tocopherol group; TBARS, thiobarbituric acid-reactive substances.

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stress-related brain disorders, such as Parkinson's disease and brain damage[19,20]. It is widely accepted that oxidative stress is involved in the degeneration of dopaminergic cells, possibly because of the formation of H_2O_2 from dopamine by MAO-B or by the auto-oxidation of dopamine[21,22]. H_2O_2 can be eliminated by glutathione peroxidase, an Se-containing enzyme. Se chemical compounds have also been suggested for use in Alzheimer's disease prevention trials[23].

It has been observed that there was an increase of dopamine turnover in rats that were fed on an Se-deficient diet[24]. However, there are few publications that have proposed the relationship between MAO-B enzyme activity and supplementing with different types of Se compounds in adult rats. In summary for the correlation among Se, MAO-B, ageing and other oxidative brain damage we would like to propose the possibility of Se influence on the MAO-B reaction. Because of the different chemical forms and distinct bioavailability, we selected two chemical forms of Se compounds for their inhibition effect on MAO-B. The present study was undertaken in order to discuss the possibility of the prevention capability of Se on MAO-B enzyme activity in adult rats.

Materials and methods

Materials

AIN-76-based diets were purchased from ICN Biomedicals (Los Angeles, CA, USA). The α-tocopherol, sodium selenite, 2,2-azobis (2-amidinopropane) dihydrochloride, β-phycoerythrin, Trolox, TCA, thiobarbituric acid, 2,6-ditertbutyl-4-methylphenol and benzylamine were all purchased from Sigma Chemical Co. (St Louis, MO, USA). Seleno-yeast was supplied by the product VIVA Selenium Yeast (Westar Nutrition Corp., Costa Mesa, CA, USA).

Animals and diets

The experimental design was approved by the Animal Experiment Committee of Chung Hwa University of Medical Technology. Twenty-four male Long–Evans rats (age 7 weeks) were purchased from the National Laboratory Animal Center. Rats were housed individually in stainless-steel wire-bottomed cages in a room with a controlled temperature and 12 h light and dark cycles. Food and distilled water were provided *ad libitum*. The animals were fed on chow diets for 10 weeks and then were fed on diets based on AIN-76 for 1 week. Then, the rats were divided into four groups: control group, tocopherol group (T group, positive control), selenite group (SE group, representing the inorganic sodium selenite supplement group) and seleno-yeast group (SY group, representing the organic seleno-yeast supplement group). The assigned procedure was randomly by body weight in order to equalise the mean body weight of the rats in each group. The compositions of the experimental diets for the four groups are shown in Table 1. The concentration of Se in the fortified test diets was adjusted to 2 mg Se equivalent per kg diet in the SE and SY groups. Food intake and body weight were recorded every 3 d.

After 12 weeks, adult rats were fasted for 12 h and then were killed by carbon dioxide inhalation. Their blood was collected into tubes followed by centrifugation (3000 ***g***; 20 min; 4°C) to separate the serum. The rat brains and livers were removed and stored at −80°C for the experiments as described below.

Table 1. Composition of test diets

Diet	Control	α-Tocopherol	Selenite	Seleno-yeast
Diet ingredients (g/kg diet)				
Casein	200	200	200	200
d,l-Methionine	3	3	3	3
Sucrose	325	325	325	325
Maize starch	325	325	325	325
Soyabean oil	50	50	50	50
Cellulose	50	50	50	50
AIN-76 vitamin premix	10	10	10	10
AIN-76 mineral mixture	35	35	35	35
Choline	2	2	2	2
α-Tocopheryl acetate (mg)	–	450	–	–
Sodium selenite (mg)	–	–	4·243	–
Seleno-yeast (g)	–	–	–	7·125
Se equivalent (mg)	0·1	0·1	2	2

Serum oxygen-radical absorbance capacity assay

The total antioxidant capacity in the serum of rats was estimated by an oxygen-radical absorbance capacity assay[25]. The 0·01 ml diluted rat serum contained 2,2-azobis (2-amidinopropane) dihydrochloride (75 mM; 0·01 ml), β-phycoerythrin (0·4 μM; 0·015 ml) and sodium phosphate buffer to 0·25 ml final volume. The assay mixture was incubated at 37°C and the fluorescence was measured at an excitation wavelength of 492 nm and an emission wavelength of 565 nm for 200 min. Trolox was used for the standard curve and antioxidant equivalent calculations. The final results were calculated using the differences of the areas under the fluorescence curves during 200 min, in which they were expressed as μmol Trolox equivalents/l serum.

Lipid peroxidation assay

Lipid peroxidation in rat brains and livers was estimated fluorescently by the modified thiobarbituric acid-reactive substances (TBARS) method[26]. In brief, 0·5 ml of tissue homogenate (in potassium phosphate buffer, pH 7·4) was treated with 0·5 ml of TCA solution (10 %) and centrifuged at 1500 ***g*** for 10 min. The clear supernatant fraction was collected and treated with thiobarbituric acid solution (0·4 % in 0·2 M-HCl) and 2,6-ditertbutyl-4-methylphenol (0·2 % in 95 % ethanol), and then placed in a 50°C water-bath for 1 h. *n*-Butanol was added to the cooled solution and centrifuged at 1500 ***g*** for 10 min. The clear supernatant fraction was collected and used for the measurement of fluorescence at an excitation wavelength of 515 nm and an emission wavelength of 550 nm (Hitachi F-4500 Fluorescence Spectrophotometer; Hitachi, Tokyo, Japan).

Monoamine oxidase B activity assay

MAO-B enzyme activity in rat tissue was measured by a modification of a standard assay procedure[27]. Tissues were

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homogenised in 0·2 M-phosphate buffer (pH 7·4) and centrifuged at 1000 *g* for 10 min (4°C). The supernatant fraction was collected and further centrifuged at 17 000 *g* for 30 min (4°C). The pellet was collected and re-suspended in 1 ml phosphate buffer (0·2 M; pH 7·4). Benzylamine solution (0·3 ml; 8 mM) was added to 0·125 ml re-suspended pellet solution, and then adjusted to the final volume of 3 ml by phosphate buffer. The mixture was shaken at 37°C for 3 h. The reaction was stopped by the addition of 0·3 ml of 60 % perchloric acid. The reaction product benzylaldehyde was extracted with 3 ml cyclohexane. The organic phase was separated by centrifugation at 3000 *g* for 10 min, and read for absorbance at 242 nm (Hitachi U-2001 spectrophotometer). The protein concentration assay method was used as described by Lowry *et al.* [28]. For verifying purposes, pargyline (MAO-B inhibitor) was used to confirm the type of MAO isoforms.

Statistical analysis

Values are presented as means and standard deviations from all the sets of independent experiments. Differences between the groups were studied by using one-way ANOVA, followed by Duncan's multiple-range test. Differences between the control and experimental groups for all the parameters were analysed by using Student's *t* test. The difference was considered significant when *P* was 0·05 or less. The correlation among the serum oxygen-radical absorbance capacity, brain TBARS, liver TBARS, brain MAO and liver MAO was analysed by using the Pearson correlation. Statistical analysis was furthered by using a SAS statistical computer program (version 13.0.161; SAS Institute Inc., Cary, NC, USA).

Results

The data for the rats that were fed on test diets through the experimental period are shown in Table 2. At the end of 12 weeks of Se supplementation, there were no significant differences in the rats' body weight, body-weight gain, food intake or feed efficiency between the four groups. This shows that the fortified constituents have no influence on rat growth and food intake. However, after the rats were fed on test diets for 12 weeks, the SE and SY groups' serum total antioxidant capacity was significantly higher than that in the control and T groups ($P<0·05$) (Fig. 1). In addition, the T group had no marked differences from the control group. The SE and SY groups were shown to have an equal effect of the total antioxidant capacity compared with the other groups.

The lipid peroxidation status in the brains and livers of the control, T, SE and SY groups of rats was tested by the TBARS method. The brain and liver relative TBARS levels of the rats that were fed on four test diets for 12 weeks are shown in Fig. 2. In the rat brains, the TBARS levels were significantly decreased in the T, SE and SY groups ($P<0·05$) (Fig. 2 (a)). A significant decrease in the rat liver TBARS levels of the T, SE and SY groups were also shown ($P<0·05$) (Fig. 2 (b)). It was demonstrated that the inorganic Se (selenite) and organic Se (seleno-yeast) supplements exhibit a similar lipid peroxidation-preventive effect on α-tocopherol in rats, which is caused by ageing.

The MAO-B enzyme activities in rat brains and livers are shown in Fig. 3. In the rat brains, MAO-B activity showed a significant decrease in the T, SE and SY groups ($P<0·05$). However, no significant change could be noted with respect to MAO-B activities in the rat livers between each group. For confirming the type of MAO isoforms, we also tested the MAO type by treating pargyline (MAO-B inhibitor) in partial tissue samples and demonstrated a decrease in MAO-B enzyme activity.

The correlation statistical analyses among the total antioxidant capacity, lipid peroxidation and MAO activity are shown in Table 3. Brain MAO activity has a positive correlation with brain and liver lipid peroxidation. Nevertheless, liver MAO has a negative correlation with serum total antioxidant capacity. In addition, there is a negative correlation between serum total antioxidant capacity and brain lipid peroxidation, and a positive correlation between brain and liver lipid peroxidation.

Discussion

Se is an essential micronutrient at levels of about 0·1 parts per million (ppm) in the animal diet, but it is toxic at levels of 8 or 10 ppm[12,29]. Moreover, Se possesses advanced effects, such as anticarcinogenesis, usually at levels above dietary requirement in the range of 1–5 ppm[12]. In this experiment, control and T group diets provided 0·1 mg Se/kg. It is the standard diet recommended by the American Institute of Nutrition for growth and maintenance of rodents. Similarly, previous studies indicated that 0·1 mg Se/kg diet provides an Se-adequate intake for rats[30]. The Se doses used in the SE and SY groups were high for rats. To realise the advanced effect of Se supplementation, the Se administration level in the SE and SY groups should be increased more than adequate dietary content. Se (as sodium selenite) dietary formulas of 0·2 and 2 mg/kg have been used to ascertain chemopreventive

Table 2. Body-weight gain, food intake and feed efficiency of the rats fed on test diets (eight rats per group)*
(Mean values and standard deviations)

	Final body weight (g)		Body-weight gain (g/d)		Feed intake (g/d)		Feed efficiency (body-weight gain/feed intake)	
Group	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Control	618·7	48·9	1·00	0·38	22·1	1·4	0·045	0·016
α-Tocopherol	612·3	50·2	0·80	0·44	21·4	1·5	0·036	0·019
Selenite	603·4	40·5	0·72	0·23	21·1	1·0	0·033	0·010
Seleno-yeast	611·3	25·4	0·81	0·41	21·4	0·8	0·038	0·020

* There are no significant differences between the groups (Duncan's multiple-range test; $P<0·05$).

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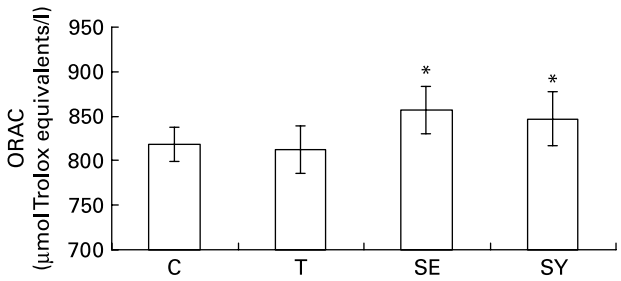

Fig. 1. The effect of total antioxidant capacity in the serum of rats fed control (c), tocopherol supplement (T), sodium selenite supplement (SE) and seleno-yeast supplement (SY) diets for 12 weeks. Values are means for seven or eight rats, with standard deviations represented by vertical bars. * Mean value is significantly different from that of the control group ($P<0{\cdot}05$; Student's *t* test). ORAC, oxygen-radical absorbance capacity.

mechanisms of Se in rats and mice[31]. It has previously also been demonstrated that when fed in a diet supplemented with 3 ppm Se (as either sodium selenite and Se-garlic), Se exerts its cancer-preventive activity[32]. In addition, diets containing either 0·225 or 4·2 mg Se/kg (as sodium selenite) were fed as part of the design in rat heart function research[33]. Considering these dietary supplementations, 2 mg Se/kg may be appropriate to apply in the SE and SY groups.

There have been mounting discussions about MAO-B, focusing on neurotransmitter regulations, ageing-concerned diseases, molecular mechanisms, enzyme inhibitors, and so on. However, only a few reports have been discussed regarding the relationship between supplementation and MAO-B enzyme regulation. In the present study, we investigated the antioxidation regulation and MAO-B activity moderation effect of inorganic and organic Se supplements in adult rats.

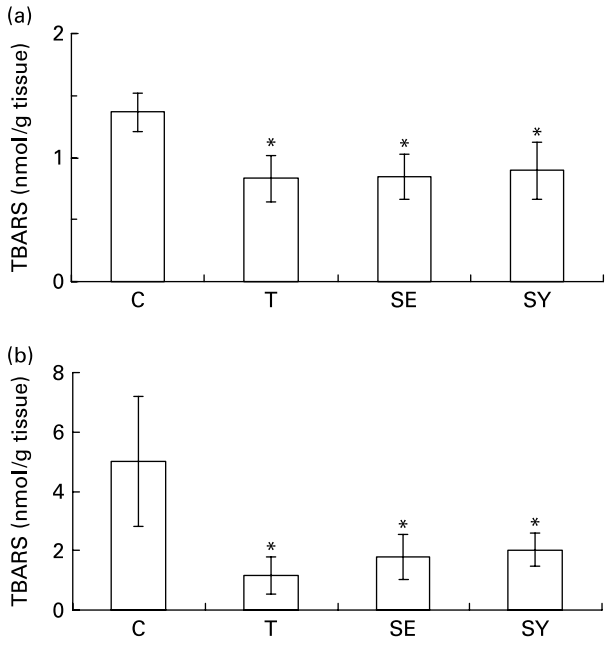

Fig. 2. The brain (a) and liver (b) relative thiobarbituric acid reactive substances (TBARS) fluorescence of rats fed control(c), tocopherol supplement (T), sodium selenite supplement (SE) and seleno-yeast supplement (SY) diets for 12 weeks. Values are means for seven or eight rats, with standard deviations represented by vertical bars. * Mean value is significantly different from that of the control group ($P<0{\cdot}05$; Student's *t* test).

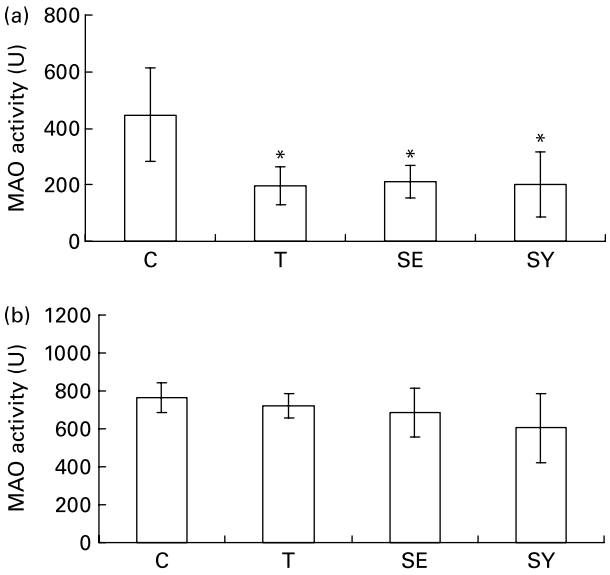

Fig. 3. Brain (a) and liver (b) monoamine oxidase (MAO) activity of rats fed control (c), tocopherol supplement (T), sodium selenite supplement (SE) and seleno-yeast supplement (SY) diets for 12 weeks. Activity is given in units (U) of nmol/h per mg protein. Values are means for seven or eight rats, with standard deviations represented by vertical bars. * Mean value is significantly different from that of the control group ($P<0{\cdot}05$; Student's *t* test).

We found that selenite or seleno-yeast supplements can increase the total antioxidant capacity in the serum of rats (Fig. 1). In contrast to this finding, in earlier work about long-term Se deficiency rat arterial walls, a significant decrease was observed in the total antioxidant capacity, and an increase was observed after 1 month of Se (sodium selenite) supplementation[34]. In addition, moderate Se supplementation (as sodium selenite or as Se-rich food) caused an increase in the total antioxidant activity in rat hearts[35]. Nevertheless, there are fewer studies noted about seleno-yeast supplementation for the effect of total antioxidant capacity. The T (α-tocopherol supplement) group showed no significant difference from the control group (see Fig. 1). The total antioxidant capacity assay of rat serum in our research was evaluated according to the oxygen-radical absorbance capacity method which is based on the absorbance capacity of oxygen radicals by antioxidants. However, the

Table 3. Correlation among total antioxidant capacity, lipid peroxidation and monoamine oxidase (MAO) activity

	TBARS (brain)	TBARS (liver)	MAO (brain)	MAO (liver)
Serum ORAC (μmol Trolox equivalents/l)				
r	−0·36	−0·19	−0·22	−0·43
P	0·04	0·36	0·28	0·03
Brain TBARS (nmol/g brain)				
r		0·61	0·42	0·24
P		0·002	0·04	0·24
Liver TBARS (nmol/g liver)				
r			0·70	0·28
P			0·004	0·25
Brain MAO (nmol/h per mg protein)				
r				0·51
P				0·02

TBARS, thiobarbituric acid reactive substances; ORAC, oxygen-radical absorbance capacity.

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reaction of α-tocopherol is not a reaction with oxygen, but with fatty acid peroxyl radicals, and intercepts the chain reaction. Thus the antioxidant reaction is not the removal of oxygen but the interception of the auto-oxidation radical chain process which is perpetuated by fatty acids[36]. It may be due to this that T groups showed no significant difference from the control group. Because of the reaction features, tocopherol would protect lipid peroxidation and cause a decrease in the TBARS assay level. It also explains the result that a significant decrease was observed in the T group of the rat TBARS levels.

Previous studies proposed that selegiline, a selective irreversible MAO-B inhibitor, is able to reduce the TBARS levels in rat brain tissue[37,38]. In the present study, it was demonstrated that there is a positive correlation between brain MAO activity and lipid peroxidation of brain and liver (Table 3). A possible link between MAO activity and lipid peroxidation can be assumed, at least in part, which remains for further investigation. However, since the similar protective action to lipid peroxidation of the T, SE and SY groups was shown in both rat brains and livers (Fig. 2), this shows that these antioxidants may affect the rat physiological function and in turn lead to a lipid peroxidative protection effect. These results can be explained by the important role of Se in preventing lipid peroxidation[39–41].

MAO-B levels are increased during ageing[2,3]. Nevertheless, the T, SE and SY groups demonstrated a significant decrease in MAO-B activity compared with the control group in rat brains. Brain MAO catalyses the oxidative deamination of a variety of amine neurotransmitters, and then the by-product H_2O_2 will be generated. H_2O_2 is widely believed to be one of the sources of oxidative stress and induces physiological peroxidation. To summarise the results of the increased serum total antioxidant capacity and decreased organ lipid peroxidation, it can be claimed that both the inorganic and organic Se supplements can positively affect the improvement of the physiological antioxidative status. By preventing physiological peroxidation, brain MAO-B activity was kept from increasing during the study period. In addition, it is interesting to note that rat brain MAO-B activity exhibited a decrease in the T group. There are few studies that indicate the effect of tocopherol supplementation in MAO-B activity. In our opinion, this is the first demonstration that tocopherol supplementation is effective in decreasing MAO-B activity in rat brain. α-Tocopherol is an isoform of lipid-soluble vitamin E, and is well known as an antioxidant. It seems therefore reasonable to assume that tocopherol conducts these effects via protecting tissue peroxidation. The further mechanisms remain to be investigated. However, rat liver MAO-B activity exhibited a non-significant difference among the groups. In Table 3, brain MAO activity has a positive correlation with brain and liver lipid peroxidation, but there is no correlation between liver MAO activity and brain or liver lipid peroxidation. This may be due to the reason of different functions between brain MAO (for amine neurotransmitters transformation) and liver MAO (for foreign amine compounds detoxification)[42].

We also investigated the influence of lipid peroxidation and total antioxidant capacity on brain MAO activity (Table 3). Table 3 shows that physiological lipid peroxidation has a positive correlation with brain MAO activity, but serum total antioxidant capacity has not the same correlation with brain MAO activity. We propose that lipid peroxidation should play an important role in brain MAO activity. There are reverse results of these correlations among liver MAO activity, serum total antioxidant capacity, and brain and liver lipid peroxidation. The results can at least partly explain the diverse inhibition effect of Se supplements on brain and liver MAO activity in rats.

It is well known that MAO inhibitors, such as pargyline and L-deprenyl, have been shown to protect against central nervous system oxygen toxicity in rats by decreasing intracellular H_2O^+ production from the oxidation of catecholamine in the brain[43,44]. In addition, MAO inhibitors possess the therapeutic value of MAO inhibition effect in the treatment of Parkinson's disease and depressive illness, although some side effects are still unavoidable[44,45]. Some MAO inhibitors showed further advances of tissue selectivity in that they inhibited MAO enzymes in the brain, but caused little inhibition of the enzymes in the liver[46,47]. Nevertheless, supplementation may be the better pathway for neuroprotection, which can be applied daily. In the present study, we suggest that inorganic or organic Se supplementation can decrease brain MAO-B enzyme activity in adult rats. Furthermore, our research proposes the possible application of Se supplements for the tissue-selective effect of dietary MAO-B inhibitors.

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