Acetyl-L-carnitine supplementation restores decreased tissue carnitine levels and impaired lipid metabolism in aged rats

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Abstract The effects of long-term carnitine supplementation on age-related changes in tissue carnitine levels and in lipid metabolism were investigated. The total carnitine levels in heart, skeletal muscle, cerebral cortex, and hippocampus were ~20% less in aged rats (22 months old) than in young rats (6 months old). On the contrary, plasma carnitine levels were not affected by aging. Supplementation of acetyl-L-carnitine (ALCAR; 100 mg/kg body weight/day for 3 months) significantly increased tissue carnitine levels in aged rats but had little effect on tissue carnitine levels in young rats. Plasma lipoprotein analyses revealed that triacylglycerol levels in VLDL and cholesterol levels in LDL and in HDL were all significantly higher in aged rats than in young rats. ALCAR treatment decreased all lipoprotein fractions and consequently the levels of triacylglycerol and cholesterol. The reduction in plasma cholesterol contents in ALCAR-treated aged rats was attributable mainly to a decrease of cholesteryl esters rather than to a decrease of free cholesterol. Another remarkable effect of ALCAR was that it decreased the cholesterol content and cholesterol-phospholipid ratio in the brain tissues of aged rats. These results indicate that chronic ALCAR supplementation reverses the age-associated changes in lipid metabolism.—Tanaka, Y., R. Sasaki, F. Fukui, H. Waki, T. Kawabata, M. Okazaki, K. Hasegawa, and S. Ando. Acetyl-L-carnitine supplementation restores decreased tissue carnitine levels and impaired lipid metabolism in aged rats. J. Lipid Res. 2004. 45: 729–735.

Supplementary key words triacylglycerol • cholesterol • lipoproteins • ketone bodies • synaptic membranes

Aging causes quantitative and compositional changes in body lipids. Analyses of plasma samples from humans and experimental animals indicate that cholesterol and triacylglycerol levels increase with aging (1–3). Aging increases total cholesterol and decreases phospholipids, leading to increased cholesterol-phospholipid molar ratios in hepatic mitochondria (4), brain (5), and cerebral synaptic membranes (6). These age-related changes in lipid composition in various tissues and organs are thought to account not only for the age-related accumulation of body fat, which is a risk factor for diabetes and atherosclerotic diseases, but also for age-related cellular hypofunction. Therefore, reversing age-related changes in lipid metabolism would help to maintain normal cellular function and prevent common diseases.

Carnitine plays an essential role in transporting fatty acids into mitochondria, where they are oxidized to produce energy in tissues (7). Carnitine levels in cardiac and skeletal muscles, both of which are major storage sites of carnitine, appear to decrease with age (8–11). In plasma, however, it is unclear whether carnitine levels decrease with age. Some studies have shown an increase in plasma carnitine levels with aging (12, 13), whereas others have found significant decreases in human (14) and rat (10). This inconsistency is a problem because plasma carnitine levels are often used as an index of body carnitine status. Concerning the age-related changes in carnitine levels in tissues and organs, cardiac and skeletal muscles have frequently been investigated (8–11), but other organs have not attracted much attention. One study reported a decrement of carnitine contents in the brain and a drastic increment in the liver of aged rats (10).

Carnitine supplementation has long been known to ameliorate lipid metabolism in patients with type IV hy-
perilipoproteinemia (15), hemodialysis complications (16, 17), and primary hyperlipoproteinemia (18). Similar beneficial effects of carnitine on lipid metabolism have been reported in studies using hyperlipidemic animal models (19–25). Several studies reported beneficial effects of carni-
tinite supplementation on age-related changes in lipid metabolism. Treatment of aged rats with acetyl-l-carnitine (ALCAR) reversed age-associated increases in the levels of free and esterified cholesterol in plasma (26) and re-
stored age-associated decreases in cardiolipin levels in heart mitochondria (27). Long-term feeding with ALCAR was reported to reduce age-related increments of sphingo-
myelin and cholesterol in rat brains (28). Thus, more de-
tailed studies are needed to clarify age-related changes in the carnitine levels and lipidic parameters in plasma and tissues. In the present study, carnitine levels and lipidic pa-
rameters were determined in young and aged rats, and the effect of ALCAR supplementation on these values was examined. We report that beneficial effects of ALCAR on lipid metabolism are not seen in young rats but are ob-
erved in aged rats that have low tissue carnitine levels.

MATERIALS AND METHODS

Animals and carnitine administration

Two age groups of male Fischer 344 rats were used. At the start of the experiments, they were aged 3 and 19 months, with average body weights of 273 and 439 g, respectively. The rats were ob-
tained from an aging farm at our institute and divided into two subgroups, a control group and an ALCAR group. ALCAR group rats were given ALCAR in drinking water at a daily dose of 100 mg/kg body weight for 3 months, whereas control group rats were given tap water. All rats were given standard laboratory chow ad libitum. After an overnight fast of 16 h, rats were decap-
titated, and the heart, muscle, liver, plasma, and brain were rap-
idly removed and frozen. The present study was approved by the Animal Care and Use Committee of the Tokyo Metropolitan In-
stitute of Gerontology.

Determination of carnitine

L-Carnitine and its short chain acyl esters were quantitatively determined using high-performance liquid chromatography by a modification of the method of Longo et al. (29). Briefly, 25 μl of plasma was diluted with 0.01 M NaH₂PO₄ (pH 3.5) after adding a known amount of n-valeryl-l-carnitine as an internal standard. The sample was reacted with 1-aminonanthrene in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydro-
chloride for 20 min at room temperature. The reaction was stopped by washing the mixture with diethyl ether. The reaction mixture was adjusted to 7 pH with 0.01 M Na₂HPO₄ (pH 9) and washed with chloroform. An aliquot of the washed aqueous phase was diluted with 0.01 M NaH₂PO₄ (pH 3.5) and injected into the HPLC system (LC-10A: Shimadzu Co. Ltd., Kyoto, Ja-
pan) using an ODS column (YMC-Pack Pro C18, 75 mm × 1.5

mm inner diameter; YMC Co., Kyoto, Japan) and spectrofluoro-
metric detection. The spectrophuorometer (SPD-10A; Shimadzu) was operated at excitation and emission wavelengths of 248 and 418 nm, respectively. The flow rate of the mobile phase was 0.7

ml/min. During a run, the mobile phase was changed from 0.1 M ammonium acetate-acetonitrile (75:25) to pure aceto-
nitrile in 45 min. For samples other than plasma, free carnitine and acyl carnitines were extracted from 100 mg (wet weight) of tissue with methanol and analyzed in the same way.

Determination of lipids and plasma ketone bodies

Total lipids of plasma, liver, and brain were extracted by the method of Bligh and Dyer (30). Total phospholipid contents in the total lipids of plasma, liver, and brain were determined by the method of Bartlett (31). Concentrations of triacylglycerol and cholesterol in the total lipid samples were determined enzymati-
cally using commercial kits (Wako Pure Chemical Co.). Plasma ketone body levels were determined using a commercial kit (Sanwa Kagaku Kenkyusyo Co. Ltd.).

Determination of plasma lipoprotein profiles

Lipoproteins were analyzed with high-performance gel permeation chromatography followed by enzymatic reactions using postcolumn reactors (32, 33). Plasma samples, which were di-
luted with 0.15 M NaCl containing 20 mM HEPES, were injected into an HPLC system equipped with two connected gel permea-
tion columns (TSK gel, Lipopropak XL, 300 mm × 7.8 mm inner diameter; Toyo Soda). Separation was performed with 0.3 M sodium acetate solution containing 0.005% Brij-35 and 0.05%

Na₃ at a flow rate of 0.7 ml/min. Triacylglycerol or cholesterol in the effluents from the columns was monitored by measuring the absorbance at 550 nm of the mixed eluate and enzyme solution (Determiner TG or Determiner TC kit) after passage through postcolumn reactors.

Determination of protein concentrations

Protein concentrations in tissue samples were determined by the method of Lowry et al. (34) using bovine plasma albumin as a standard.

Statistical analyses

Data in this paper are reported as means ± SD. Statistical signi-
ficance was evaluated using one-way ANOVA with Schefl e’s method for multiple comparisons. Differences were considered statistically significant at $P < 0.05$.

RESULTS

Food and water consumption and body weight changes

Three-month administration of ALCAR to aged rats (initially 19 months old) decreased the mean body weight from 439 ± 19 g to 417 ± 16 g ($P < 0.05$ by Schefl e’s method), whereas the weights of aged control rats did not change significantly (Table 1). Young rats in the control and ALCAR groups gained weight at almost the same rate throughout the administration period. Food intake and water consumption were not significantly different among the four groups of rats (Table 1).

Age-related changes in carnitine levels

Carnitine levels in different tissues of the control rats (Fig. 1, dotted bars) were variously affected by aging. Ag-
ing did not affect carnitine levels in plasma, but it caused a significant increase in carnitine levels in liver. The car-

nitate levels in cardiac and skeletal muscles in the aged control rats were 24% and 17% lower, respectively, than the levels in young rats. Carnitine levels in the cerebral cortex and hippocampus in the aged control rats were sig-

nificantly lower than those in the young rats. However, ag-
Changes in body weight (g) 10.2 27.7 439.3 ± 16.6 b 439.4 ± 21.0 b
Final body weight (g) 352.0 ± 15.8 361.5 ± 15.5 447.3 ± 18.2 b 447.1 ± 15.8 b
Food consumption (g/day/rat) 14.2 ± 0.4 14.5 ± 0.4 14.9 ± 0.4 14.6 ± 0.6
Water consumption (ml/day/rat) 17.4 ± 0.8 18.8 ± 1.1 18.5 ± 0.5 17.2 ± 0.4

Values shown are means ± SD (n = 6). ALCAR, acetyl-l-carnitine. P values were determined by one-way ANOVA and Scheffe’s method.

Effects of aging and ALCAR supplementation on plasma lipids

Plasma lipid levels were higher in aged rats than in young rats (Table 2). Total lipids were 40% higher, total phospholipids were 30% higher, triacylglycerols were 20% higher, and cholesterol, including free and esterified cholesterol, was 71% higher. Plasma total lipid contents were significantly lower in ALCAR-supplemented aged rats than in aged control rats. The levels of triacylglycerol and total cholesterol in aged rats were reduced to the levels of young rats with ALCAR treatment. The reduction of total cholesterol was largely attributable to the decrease of esterified cholesterol. ALCAR supplementation increased plasma ketone body levels in aged rats but not in young rats.

In the control rats, aging resulted in a significant increase in triacylglycerol in the VLDL fraction (Fig. 2A) and significant increases in cholesterol in the LDL and HDL fractions (2.4-fold and 1.4-fold, respectively) (Fig. 2B). ALCAR treatment decreased triacylglycerol in the VLDL fraction in aged rats to the level in young rats. The levels of cholesterol in LDL and HDL in aged rats were reduced by ALCAR supplementation. ALCAR supplementation did not have any effects on the lipoprotein profiles in young rats.

Effects of aging and ALCAR supplementation on liver and brain lipids

Aging did not affect the levels of total lipids, triacylglycerol, total cholesterol, or phospholipids in the liver of control rats. ALCAR treatment slightly increased triacylglycerol levels in aged rats but did not affect other lipids (Table 3). Cholesterol contents in the cerebral cortex increased in aged rats and were reduced by ALCAR administration (Table 4). The amounts and composition of phospholipids in the brain were not affected by aging. The molar ratio of cholesterol to phospholipids in the synaptic plasma membranes from the brain cortex was higher in aged rats and was restored to the level of young rats by ALCAR treatment (Table 5).

DISCUSSION

Carnitine levels in rats were found to change with aging in a tissue-specific manner. Total carnitine contents in the
liver were increased in aged rats. In the extrahepatic tissues, such as heart, skeletal muscle, and cerebral cortex, carnitine levels in aged rats were significantly decreased compared with those in young rats. These changes, except for the changes in plasma, are comparable to those reported by Maccari et al. (10). l-Carnitine is synthesized mainly in the liver from lysine and methionine in rats and delivered to other tissues via the blood stream (35). The increase of carnitine in the liver of aged rats may be caused by impaired transport of carnitine from the liver as a result of decreased activity of the transfer protein that transports carnitine from the liver (36). Maccari et al. (10) concluded that the reductions of extrahepatic tissue carnitines in aged rats were caused by a decrease in plasma carnitines. However, this is not likely because no age-related decline of plasma carnitine levels was observed in the present study. The absence of an age-related decline of plasma carnitine levels suggests that the decreases of carnitine contents in extrahepatic tissues in aged rats are caused not simply by the decreased plasma carnitine levels but by other mechanisms. Carnitine has been shown to be transported from blood plasma to extrahepatic tissues by Organic Cation Transport Protein 2 (37, 38). The reduced tissue carnitine levels in aged rats may be caused by a decrease in the activity of this transporter. Although long-term treatment with ALCAR increased plasma carnitine levels in both young and aged rats, the recovery of the carnitine levels in heart, skeletal muscle, cerebral cortex, and hippocampus occurred in aged rats but not in young rats. This suggests that that the carnitine levels in tissues of young rats are strictly regulated.

The levels of triacylglycerol and cholesterol in plasma were found to increase with aging. This is consistent with the results obtained for rodents (26, 39) and humans (40, 41). As shown by the present lipoprotein analysis, the increase of plasma triacylglycerol level in aged rats was caused by an increase of VLDL. The age-related increase in the concentration of plasma VLDL-triaclyglycerol has been shown to be attributable to enhanced secretion of triacylglycerol from the liver and to decreased removal of triacylglycerol from plasma (42, 43). Aging was found to decrease lipo-protein lipase activity in adipose tissue, which explains the higher plasma triacylglycerol levels in aged animals (44). ALCAR supplementation significantly reduced the increased plasma triacylglycerol levels in aged rats, and this

### Fig. 2
The effects of aging and ALCAR supplementation on the levels of plasma triacylglycerol (A) and cholesterol (B) among lipoprotein classes. Black bars represent the levels in ALCAR-supplemented rats, and dotted bars represent the levels in control rats. Values shown are means ± SD (n = 6). Statistically significant differences are indicated as follows: *P < 0.05 versus young control rats; **P < 0.05 versus aged control rats (one-way ANOVA and Scheffe’s method).

### Table 2
Plasma lipids in Fischer 344 rats with or without ALCAR supplementation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Young (6 Months)</th>
<th>Aged (22 Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>ALCAR</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>ALCAR</td>
</tr>
<tr>
<td>Total lipids (mg/dl)</td>
<td>359.4 ± 32.9</td>
<td>358.2 ± 43.3</td>
</tr>
<tr>
<td>Total phospholipids (mg/dl)</td>
<td>160.7 ± 24.0</td>
<td>163.0 ± 28.0</td>
</tr>
<tr>
<td>Triacylglycerol (mg/dl)</td>
<td>77.6 ± 19.8</td>
<td>72.7 ± 15.2</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>102.5 ± 6.2</td>
<td>100.4 ± 5.2</td>
</tr>
<tr>
<td>Free cholesterol (mg/dl)</td>
<td>32.9 ± 3.3</td>
<td>34.0 ± 5.3</td>
</tr>
<tr>
<td>Esterified cholesterol (mg/dl)</td>
<td>69.8 ± 3.9</td>
<td>66.4 ± 6.9</td>
</tr>
<tr>
<td>Ketone bodies (µmol/l)</td>
<td>144.5 ± 14.1</td>
<td>132.1 ± 22.7</td>
</tr>
<tr>
<td>3-Hydroxybutyrate (µmol/l)</td>
<td>104.1 ± 12.7</td>
<td>89.0 ± 29.4</td>
</tr>
<tr>
<td>Acetoacetate (µmol/l)</td>
<td>40.1 ± 6.7</td>
<td>48.6 ± 9.0</td>
</tr>
</tbody>
</table>

Values shown are means ± SD (n = 6). P values were determined by one-way ANOVA and Scheffe’s method.

- *P < 0.001, young rats versus aged rats.
- †P < 0.005, young rats versus aged rats.
- ‡P < 0.01, young rats versus aged rats.
- ‡‡P < 0.01, control group versus ALCAR-supplemented group.
- ‡‡‡P < 0.05, young rats versus aged rats.
- ‡‡‡‡P < 0.001, control group versus ALCAR-supplemented group.
reduction was achieved by a decrement of VLDL-triaclylglycerol (Fig. 1, Table 2). Richter et al. (45) reported that administration of L-carnitine reduced the sucrase-induced hypertriglyceridemia and the increase of free fatty acid levels in rat plasma. Carnitine supplementation of semistarved rats was recently found to significantly increase the activity of preheparin plasma lipoprotein lipase and to restore plasma triacylglycerol secretion rate to the normal level (46).

If carnitine supplementation enhances the oxidation of fatty acids, there should be a concurrent increase in the production of ketone bodies. In this study, a remarkable increase of 3-hydroxybutyrate was observed in aged rats given ALCAR. Stimulation of ketogenesis by ALCAR was reported in vivo in perfused livers (47). The amount of ketone bodies changed inversely with the change in triacylglycerol levels. In addition, liver triacylglycerol levels of ALCAR-treated aged rats were 11–13% higher than those in the aged control rats. These observations suggest that ALCAR supplementation prevents the age-related increase in plasma triacylglycerol levels by increasing the removal of VLDL-triacylglycerol through the activation of lipoprotein lipase and fatty acid oxidation.

The increase of plasma cholesterol levels in aged rats was attributable mainly to an increase in cholesterol in the LDL fraction (Fig. 2). This observation is consistent with the finding that age-related hypercholesterolemia was caused by LDL plus HDL1 fractions (48). Plasma LDL-cholesterol levels are known to be regulated by receptor-mediated clearance of the lipoprotein (49), so the increase of plasma LDL-cholesterol in aged rats is thought to be caused by the reduction of catabolic pathways. Among lipoprotein classes, ALCAR treatment exclusively decreased the levels of cholesterol in the LDL fraction (Fig. 2). This indicates that ALCAR treatment enhances LDL catabolic activity. Interestingly, the reduction of total cholesterol contents in plasma of aged rats with ALCAR treatment was attained mostly by a decrease of cholesteryl esters rather than by a decrease of free cholesterol (Table 2). This result suggests that the hypocholesterolemic effect of ALCAR is attributable to an enhanced breakdown of cholesteryl esters. Diaz et al. (50) reported a similar effect of L-carnitine on cholesterol metabolism in the plasma of rabbits fed a high-cholesterol diet. Although how ALCAR treatment enhances the breakdown of cholesteryl esters in aged rats is not known, it may be through an increase in carnitine-induced fatty acid catabolism. These observations suggest that ALCAR supplementation can reduce the risk factors for atherosclerosis induced by hypercholesterolemia.

ALCAR supplementation reduced the body weight in aged rats but not in young rats. The reduction of body weight in aged rats occurred at ~1 month after the start of supplementation. Why did ALCAR treatment decrease body weight only in aged rats? In aged rats, a significant reduction of carnitine levels in extrahepatic tissues would lead to a decrement of fatty acid oxidation and consequently an accumulation of body fat, resulting in a tendency to overweight compared with young rats. ALCAR supplementation restored tissue carnitine levels in aged rats. The fact that chronic supplementation with ALCAR reduced plasma triacylglycerol and cholesteryl ester levels and increased ketone bodies in aged rats suggests that fatty acid oxidation and lipid metabolism are activated with increasing tissue carnitine contents. The recovery of tissue carnitine levels with its supplementation is considered one of the causes of body weight loss in aged ALCAR-treated rats. Brandsch and Eder (51) reported that L-carnitine did not show a positive effect on body weight reduction and body composition among rats fed an energy-deficient diet.

### Table 3. Effects of aging and ALCAR supplementation on liver lipids

<table>
<thead>
<tr>
<th>Variable</th>
<th>Young (6 Months)</th>
<th>Aged (22 Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>ALCAR</td>
</tr>
<tr>
<td>Total lipids (mg/g wet weight)</td>
<td>42.0 ± 2.1</td>
<td>42.5 ± 2.7</td>
</tr>
<tr>
<td>Total phospholipids (mg/g wet weight)</td>
<td>24.8 ± 1.6</td>
<td>25.4 ± 1.6</td>
</tr>
<tr>
<td>Triacylglycerol (mg/dl)</td>
<td>5.2 ± 0.1</td>
<td>5.7 ± 0.4</td>
</tr>
<tr>
<td>Total cholesterol (mg/g wet weight)</td>
<td>2.1 ± 0.2</td>
<td>2.4 ± 0.2</td>
</tr>
</tbody>
</table>

Values shown are means ± SD (n = 6). P values were determined by one-way ANOVA and Scheffe’s method.

*P < 0.01, control group versus ALCAR-supplemented group.

### Table 4. Effects of aging and ALCAR supplementation on lipid levels in the cerebral cortex

<table>
<thead>
<tr>
<th>Variable</th>
<th>Young (6 Months)</th>
<th>Aged (22 Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>ALCAR</td>
</tr>
<tr>
<td>Total lipids (mg/g wet weight)</td>
<td>77.7 ± 2.8</td>
<td>84.7 ± 2.5</td>
</tr>
<tr>
<td>Total phospholipids (mg/g wet weight)</td>
<td>43.9 ± 2.0</td>
<td>45.1 ± 2.8</td>
</tr>
<tr>
<td>Cholesterol (mg/g wet weight)</td>
<td>6.7 ± 0.6</td>
<td>6.4 ± 0.2</td>
</tr>
</tbody>
</table>

Values shown are means ± SD (n = 6). P values were determined by one-way ANOVA and Scheffe’s method.

*P < 0.05, young rats versus aged rats.

*P < 0.05, control group versus ALCAR-supplemented group.
Eight weeks of L-carnitine supplementation to moderately overweight premenopausal women did not alter the body weight or fat mass (52). The subjects in these studies were in adult stage and not in senescent stage, so they would have sufficient capacities for carnitine synthesis and transport to ensure competent fatty acid oxidation and lipid metabolism. Under these conditions, carnitine supplementation is thought to be ineffective. Our data suggest that ALCAR supplementation is beneficial to elderly individuals who show decreased tissue carnitine levels.

Cholesterol levels in brain tissues were found to increase with aging. ALCAR supplementation reduced cholesterol levels to the levels in young rats. In synaptic plasma membranes, ALCAR was found to decrease cholesterol levels without affecting phospholipid levels, resulting in a reduced ratio of cholesterol to phospholipid. This change may affect the physicochemical properties of the membranes. Aureli et al. (28) found that ALCAR reduced both cholesterol and sphingomyelin in the brains of aged rats and proposed that the decrease in sphingomyelin was responsible for the decrease in cholesterol. However, the decrease in brain cholesterol level might be attributable to other mechanisms, because no age-related changes in the composition of brain phospholipid, including sphingomyelin, were observed in the present study.

The results of the present study indicate that chronic supplementation with ALCAR enhances the carnitine levels in extrahepatic tissues and reverses the age-related changes in plasma and tissue lipid levels.}

### Table 5. Effects of aging and ALCAR supplementation on lipid levels in the synaptic plasma membranes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Young (6 Months)</th>
<th>Aged (22 Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total phospholipids (µg/mg protein)</td>
<td>480.8 ± 10.6</td>
<td>512.0 ± 35.1</td>
</tr>
<tr>
<td>Cholesterol (µg/mg protein)</td>
<td>183.8 ± 3.3</td>
<td>188.9 ± 14.8</td>
</tr>
<tr>
<td>Cholesterol-phospholipid molar ratio</td>
<td>0.79 ± 0.02</td>
<td>0.76 ± 0.01</td>
</tr>
<tr>
<td>Control</td>
<td>491.7 ± 12.1</td>
<td>489.0 ± 7.7</td>
</tr>
<tr>
<td>ALCAR</td>
<td>195.4 ± 4.7</td>
<td>181.1 ± 7.1</td>
</tr>
<tr>
<td>Control</td>
<td>0.82 ± 0.01*</td>
<td>0.77 ± 0.03*</td>
</tr>
</tbody>
</table>

Values shown are means ± SD (n = 6). *P values were determined by one-way ANOVA and Scheffe’s method.

* P < 0.05, young rats versus aged rats.

* P < 0.05, control group versus ALCAR-supplemented group.

### References


