Modulation of DMBA-induced biochemical changes by organoselenium compounds in blood of rats

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The protective role of two synthetic organoselenium compounds 1-iso-propyl-3-methylbenzimidazole-2-selenone (SeI) and 1, 3-di-p-methoxybenzylpyrimidine-2-selenone (SeII) was examined against the 7,12-dimethylbenz[a]anthracene (DMBA)-induced changes in biochemical parameters in blood of rats. Albino Winstar rats (150-200 g body wt) were treated with single dose of DMBA (50 mg/kg body wt) and organoselenium compounds (25 µmol/kg) for 4 weeks at two days internal. Blood was taken from the anaeasthetized rats ventricle from their hearts for biochemical analysis. Administration of DMBA resulted in elevation of urea, uric acid and creatinine levels as well as AST, ALT and LDH activities and decrease in levels of total proteins, albumin and globulin. SeI and SeII caused a significant (p<0.05) decrease in urea, uric acid and creatinine levels and alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) activities and significantly increased the levels of total protein and albumin (p<0.05). These organoselenium compounds are likely to be beneficial in human health.

Keywords: Biochemical parameters, 7,12-Dimethylbenz[a]anthracene or DMBA, Oxidative stress, Organoselenium compounds

DMBA (7,12-dimethylbenz[a]anthracene) is a polycyclic aromatic hydrocarbon (PAH) that causes tumors in rats1. PAHs, such as petroleum and petroleum derivatives are widespread organic pollutants enter the environment through oil spills and incomplete combustion of fossil fuels and their bioaccumulation is detrimental to life2. Selenium (Se), an essential micronutrient is associated with antioxidant functions and physiological defense mechanisms against different diseases. Several inorganic and organic compounds of Se have been tested for their protective effects3. Additionally, organoselenium compounds such as ebselen (2-phenyl-1,2-benziselenazol-3[2H]-one) and simple diorganyl chalcogenides have shown anti-inflammatory property4. Moreover, clinical trials in humans have shown beneficial effects of organoselenium compounds such as ebselen in pathological situations5. The concept that selenium-containing molecules may be better nucleophiles (and therefore antioxidants) than classical antioxidants have led to the design of synthetic organoselenium compounds6. Such compounds have been found to inhibit or delay carcinogenesis induced by chemical carcinogen (DMBA), which is one of the important environmental pollutants7,8.

In the present study, we have investigated the protective effect of organoselenium compounds 1-iso-propyl-3-methylbenzimidazole-2-selenone (SeI) and 1, 3-di-p-methoxybenzylpyrimidine-2-selenone (SeII) (Fig. 1) against the DMBA-induced changes by determining levels of urea, uric acid, creatinine, total protein, albumin, globulin and the activities of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH) activities in blood of rats.

Materials and Methods

Selenium compounds

The novel synthetic organoselenium compounds 1-iso-propyl-3-methylbenzimidazole-2-selenone (SeI) and 1, 3-di-p-methoxybenzylpyrimidine-2-selenone (SeII) were synthesized in our laboratory (Fig. 1a and b) and identified by 1H-NMR (300 MHz), 13C-NMR (75.5 MHz), FT-IR spectroscopic techniques and microanalysis9-11.

Fig. 1—Structure of (a) 1-iso-propyl-3-methylbenzimidazole-2-selenone (SeI); and (b) 1, 3-di-p-methoxybenzylpyrimidine-2-selenone (SeII)
**Animals and treatment**

Albino Winstar rats (150-200 g body wt) were used in the study. The animals were maintained in a controlled temperature (20±2°C) room and consistent light conditions on a daily basis (12 h light-12 h dark cycle). Food and water were provided ad libitum. Rats were divided into five groups each consisting of 5-8 animals. Group I used as a control; Group II received only the vehicle solution (corn oil) for 4 weeks at 2 days interval; Group III were given a single dose of 50 mg/kg DMBA and sacrificed 4 weeks later; Group IV also received DMBA as in group III, but after 6 h of DMBA application, SeI at 25 µmol/kg was administered for 4 weeks at 2 days interval; and Group V animals were treated exactly as group IV, except that the SeII was used, instead of SeI. Animals were sacrificed after anaesthetizing with 75 mg/kg of sodium pentobarbital.

**Biochemical analysis**

After treatments, 2 mL blood was taken from the anesthetized rats from right ventricle of their hearts and centrifuged at 3000 g, 4°C for 5 min. AST, ALT and LDH activities and urea, uric acid, creatinine, total protein, albumin and globulin levels in the plasma were assayed by Olympus AU 600 autoanalyser (Olympus Optical Corp, Shizuoka-ken, Japan) by using commercially available kits.

**Statistical analysis**

Data were analyzed with SPSS 9.0 for Windows using ANOVA. Differences between means were determined using Duncan’s multiple range tests in which the significance level defined as P<0.05.

**Results and Discussion**

Administration of DMBA resulted in elevation of urea, uric acid and creatinine levels (Table 1). The elevation in their levels in DMBA-treated rats is considered as one of the markers of renal dysfunction. SeI and SeII caused a significant (P<0.05) decrease in their levels (Table 1), therefore appeared to have potential to maintain renal function and avoid hypercatabolism in the DMBA-treated rats.

Administration of DMBA caused decrease in levels of total proteins, albumin and globulin (Table 1). The decrease in their levels in plasma was reported in nephritic syndrome, inflammation, and chronic diseases etc and ascribed to change in proteins synthesis and/or their metabolism. Thus, DMBA might have adversely affected the proteins synthesis and their metabolism in the present study. SeI and SeII significantly increased the levels of total protein and albumin (P<0.05) (Table 1).

DMBA administration also resulted in elevation of AST, ALT and LDH activities (Table 1). Pathological changes in liver, kidney, heart and skeleton muscle and erythrocytes were found to increase these activities in plasma. DMBA might have induced pathological alteratations in these organs, particularly liver, resulting in elevation of these activities. SeI and SeII caused a significant (P<0.05) decrease in these activities (Table 1). These results were consistent with earlier study. DMBA is known to generate free radicals. As selenium compounds possess antioxidant properties, SeI and SeII are also likely to behave as an antioxidant.

In conclusion, the present study demonstrated that SeI and SeII could protect animals against detrimental

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Table 1—Changes in biochemical parameters with SeI and SeII in DMBA-administered rats

<table>
<thead>
<tr>
<th></th>
<th>Control (Group I)</th>
<th>Corn oil (Group II)</th>
<th>DMBA (Group III)</th>
<th>DMBA + SeI (Group IV)</th>
<th>DMBA + SeII (Group V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total protein (g/dL)</td>
<td>6.52 ± 0.22ab</td>
<td>6.60 ± 0.17a</td>
<td>5.93 ± 0.07b</td>
<td>6.20 ± 0.11ab</td>
<td>6.20 ± 0.15ab</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>2.72 ± 0.08a</td>
<td>2.73 ± 0.21a</td>
<td>2.23 ± 0.06b</td>
<td>2.63 ± 0.06a</td>
<td>2.56 ± 0.12a</td>
</tr>
<tr>
<td>Globulin (g/dL)</td>
<td>4.14 ± 0.17ab</td>
<td>3.63 ± 0.03ab</td>
<td>3.36 ± 0.04b</td>
<td>3.56 ± 0.06b</td>
<td>3.40 ± 0.11b</td>
</tr>
<tr>
<td>Urea (mg/dL)</td>
<td>20.80 ± 0.73b</td>
<td>20.0 ± 2.08b</td>
<td>24.0 ± 0.44a</td>
<td>21.66 ± 1.20ab</td>
<td>22.33 ± 0.33ab</td>
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<tr>
<td>Creatinine (mg/dL)</td>
<td>0.36 ± 0.02b</td>
<td>0.36 ± 0.03b</td>
<td>0.45 ± 0.02a</td>
<td>0.40 ± 0.01b</td>
<td>0.40 ± 0.05b</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>0.64 ± 0.21c</td>
<td>0.70 ± 0.15c</td>
<td>1.63 ± 0.08a</td>
<td>1.26 ± 0.26b</td>
<td>1.33 ± 0.08b</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>111.60 ± 5.87c</td>
<td>138.33±5.60c</td>
<td>230.50±40.26c</td>
<td>159.0 ± 9.50b</td>
<td>147.33±18.26b</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>59.6 ± 5.04c</td>
<td>69.33±0.66c</td>
<td>103.5 ± 4.41a</td>
<td>80.66 ± 0.66b</td>
<td>86.66 ± 4.91b</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>1232.2±88.56c</td>
<td>1282±160.0c</td>
<td>2072.5±108.3a</td>
<td>1813.0±168.0b</td>
<td>1502.0±166.0b</td>
</tr>
</tbody>
</table>

abcStatistically significant (P<0.05)
effects induced by DMBA, probably due to their free radical scavenging ability.

Acknowledgement
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References
17 Yu-Tong He, Dian-Wu Liu, Li-Yu Ding, Qing Li & Yong-Hong Xiao (2004) World J Gastroenterol 10, 703-706