Effect of selenium-enriched malt on hepatocarcinogenesis, paraneoplastic syndrome and the hormones regulating blood glucose in rats treated by diethylnitrosamine

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Abstract

233 SD rats weighing 100~120 g were divided randomly into 6 groups. The animals in group I and group II received 0.1 mg/kg selenium in the form of sodium selenite only and served as the negative control and positive control, respectively. Animals in groups III, IV and V were fed with selenium as Se-enriched malt supplemented diets (0.3, 1 and 3 mg/kg), and group VI with selenium by using sodium selenite supplemented diets (3 mg/kg). Animals of groups II~VI were induced hepatoma by diethylnitrosamine (100 mg/l) for 16 weeks, then drunk with sterilized water for 2 more weeks. Subsequently, the effects of Se-enriched malt and sodium selenite on hepatoma nodules, relative liver weight, the liver function indices including alanine aminotransferase (ALT), alkaline phosphatase (ALP), albumin (ALB), total bilirubin (TBIL), and the tumor markers, named as gamma-glutamyltranspeptidase (GGT), α-fetoprotein (AFP), insulin-like growth factor-II (IGF-II) were recorded. The calcium concentration, glucose content in plasma and values of the hormones regulating blood glucose, such as insulin, glucagons and thyroid hormones (3,5,3′-tetraiodothyronine, T₃; 3,5,3′,5′-tetraiodothyronine, T₄) were observed as well. At the same time, the correlations between the concentration of plasma glucose and related hormones were also analyzed. The results indicated that Se-enriched malt showed a better chemopreventive efficiency in decreasing the number of hepatoma nodules, relative liver weight and the contents of AFP, GGT, IGF-II, ALT, ALP and TBIL in the plasma, and delaying the descent of hormones in the serum, names as insulin, glucagons, T₃ and T₄ than those feeding with sodium selenite. Effect of Se-enriched malt excelled sodium selenite in the aspects of deadening the descent of glucose concentration in the plasma and the rise of calcium concentration in the serum of the rats with hepatoma induced by diethylnitrosamine. The values of glucose and calcium were significantly related to those items forenamed. In conclusion, the function of Se-enriched malt in deadening the lesion and delaying the development of hepatoma of rats induced by diethylnitrosamine was better than that of sodium selenite. Hypoglycemia and hypercalcemia were significantly correlated with the multifactors mentioned above.

Keywords: Selenium-enriched malt; Rats; Plasma glucose; Serum calcium; Tumor markers; Hormone; Paraneoplastic syndrome

Introduction

Cancer is one of the leading causes of death in the world, resulting in more than 10 million new patients and 6 million deaths per year (Greenlee et al., 2001; Parkin et al., 2001). Burner estimated in 1992 (Burner et al., 1992) that the total annual cost of cancer care in the United States only in the year 2001 would reach $200 billion. Selenium (Se), an essential trace element and normal constituent of diets, has been shown to have chemopreventive potential by a converging body of evidence from epidemiological, experimental, and clinical studies (Combs et al., 2001; Raich et al., 2001; Lü and Cheng, 2001). Many papers have demonstrated that the protective
effects of Se on cancer were strongly influenced by Se form (Ip et al., 2000; Davis et al., 1999). Some authors suggest that organic Se is an ideal additive for being absorbed and retained more than inorganic Se by animals and humans (Ortman and Pehrson, 1997). In contrast to selenite, the organoselenium compounds can be tailored to achieve greater chemopreventive efficacy with minimal toxic side effects by structural modifications (Howard and Ganther, 1999). Food is the major source of selenium intake but limited efforts in common foods have been made (Bird et al., 1997a,b). Supplementation of dietary selenium intake has been the aim of few clinical trials in cancer prevention. With the rapid rise of cancerous morbidity, more and more attention has been paid to the strong protective properties of Se (Popova, 2002). The selenium-enriched malt (SM), as a possible ideal organic Se supplement, which has a greater bioactivity than sodium selenite in animals and humans (Xu et al., 2000; Li and Wang, 2004), showed an ideal preventive function on the aflatoxin B1-induced hepatocarcinogenesis in rats by enhancing the antioxidative function (Liu et al., 2005). But the effect of SM on diethylnitrosamine (DEN)-induced chronic hepatocarcinogenesis has not been investigated yet. It was well known that paraneoplastic syndromes, such as hypoglycemia and hypercalcemia are the obvious and primary symptoms in human hepatocarcinoma besides typical liver injury (Liu and Wang, 2000). The result was that though the tumor remained small, patients have probably suffered severe damage for a long time. Moreover, paraneoplastic syndrome has been considered as an important reference in the early diagnosis of tumor (Darnell and Posner, 2003; Albert and Darnell, 2004; Lalita and Arthur, 2004; Jerome and Josep, 1997). The effect of Se on the paraneoplastic syndrome and the relative endocrine has not been investigated yet. Therefore, the present study was designed to compare the possible effect of SM and sodium selenite in preventing DEN-induced hepatocarcinogenesis and paraneoplastic syndrome in rats and the hormones regulating their metabolism of blood glucose.

Materials and methods

Se-malt

Selenium-enriched malt was provided by the Institute of Nutritional and Metabolic Disorder in Domestic Animals and Fowls, Nanjing Agricultural University, China and manufactured according to the method reported by Li and Wang (2004) and Zhu (1999). The Se concentration of malt was 60.5 mg/kg dry matter. Se existed mostly in organic form (Li and Wang, 2004; Xu and Xiao, 1989).

Animals and treatments

This experiment was carried out on 233 Sprague–Dawley male rats weighing 100–120 g and supplied by the Shanghai Research Center of Experimental Animal Academy in China and kept at standardized room conditions. Animals were caged in groups of five and given food and sterilized water. The animal room was maintained at 21–24 °C and 40–60% relative humidity with 12 h light–dark cycles, the light cycle coinciding with the day light hours. After 1 week of acclimation, the groups were assigned at random to the following treatments: animals in group I and group II received 0.1 mg/kg selenium as sodium selenite only and served as the negative control and positive control, respectively. Animals in groups III, IV and V were fed with selenium as Se-enriched malt supplemented diets (0.3, 1 and 3 mg/kg, respectively). While animals in group VI received selenium as sodium selenite supplemented diets (3 mg/kg). To balance the nutrition content among each group, normal malt which was not treated with selenium was added into the diets of the relative groups. The nutrition contents except the selenium of the diet in each group were similar and in accordance with the standard of NCR. Animals of groups II–VI were induced hepatoma by diethylnitrosamine diluted with sterilized water at the dose of 10 mg/kg body weight every day for 16 weeks, and then drunk with sterilized water for 2 more weeks. Rats of group I were drunk normal water during the whole experimental time. Subsequently, all the rats were denied diet for 12 h, weighed and humanely sacrificed by cervical decapitation.

Sampling and samples analysis

Eyeground blood samples were collected before the animals were sacrificed. Livers were immediately excised from the animals and weighed respectively, and hepatoma nodules subsequently calculated. Half of heparinized whole blood samples were subsequently centrifuged at 1500 g for 15 min and their plasma was removed into disposable pipettes. In plasma samples, the values of alanine aminotransferase (ALT), alkaline phosphatase (ALP), albumin (ALB), total bilirubin

<table>
<thead>
<tr>
<th>Items</th>
<th>Group I (10)</th>
<th>Group II (10)</th>
<th>Group III (11)</th>
<th>Group IV (9)</th>
<th>Group V (10)</th>
<th>Group VI (12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatoma nodules</td>
<td>0</td>
<td>44.6±1.4a</td>
<td>27.2±1.6b</td>
<td>25.4±1.7b</td>
<td>13.1±0.8c</td>
<td>42.9±2.9a</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>661.3±18.2*</td>
<td>458.1±27.0b</td>
<td>461.0±17.1b</td>
<td>474.1±13.0b</td>
<td>421.3±25.7b</td>
<td>421.0±22.7b</td>
</tr>
<tr>
<td>Liver weight (g)</td>
<td>14.68±0.18c</td>
<td>28.48±1.97bc</td>
<td>26.51±1.11b</td>
<td>35.14±2.18a</td>
<td>24.80±2.40a</td>
<td>25.06±1.36b</td>
</tr>
<tr>
<td>Relative liver weight (%)</td>
<td>2.23±0.07b</td>
<td>6.56±0.79a</td>
<td>5.73±0.34b</td>
<td>7.40±0.37a</td>
<td>5.78±0.27a</td>
<td>6.21±0.57a</td>
</tr>
</tbody>
</table>

Rats of groups II–VI were treated with DEN resolved in sterilized water at a dose of 10 mg/kg body weight every day for 16 weeks to induce hepatocarcinogenesis. Rats of groups I, II and VI were fed with sodium selenite supplemented diet at the contents of 0.1, 0.1 and 3.0 mg/kg, respectively. Rats of groups III, IV and V were fed with Se-enriched malt supplemented diets at the contents of 0.3, 1.0 and 3.0 mg/kg, respectively. The aforesaid treatments lasted for 16 weeks. Values are mean±SE. Relative liver weight was calculated from the percent of liver weight to body weight. Means in the same row without common superscript letters are significantly different at p<0.05 by Duncan’s multiple range test. The number of each group is printed in its respective parentheses.
The intra and inter-assay coefficient of variation for IGF-II were 10% and 15%, respectively. The minimum detectable concentration of IGF-II was 0.1 ng/ml. Recovery of human IGF-II ranged between 96% and 108%. The intra and inter-assay coefficient of variation for AFP were 6% and 11%, respectively. The minimum detectable concentration of AFP was 2.0 ng/ml.

The insulin (pmol/l)/glucose (mmol/l) ratios (IGR1), insulin (pmol/l) × 100/glucagon (ng/l) ratios (IGR2), glucagon (ng/l)/glucose (mmol/l) ratios (GGR) and T3 (nmol/l) × 100/T4 (nmol/l) ratios (TTR) for each sampling time were also calculated respectively.

Statistical analysis

Data are expressed as means ± SE. Statistical analysis was performed with variance for repeated measures (Excel 2000). When the appropriate main effect or interaction was significant, Duncan’s Multiple Range Test and SAS (Berron, 1986) were used to separate means. A Spearman rank nonparametric correlation analysis was used to test for associations between measured parameters. Significance was determined as p < 0.05 or p < 0.01.

Results

The body weight gain, liver weight, relative liver weight to body weight and hepatoma nodules of liver in rats are shown in Table 1. Although the liver weight, relative liver weight to body weight of the negative control group (I) were significantly lower than that of the DEN treated groups, there was no difference among the DEN treated groups. Compared with the positive control group (II) and the sodium selenite (3 mg/kg) treated group (VI), the numbers of hepatoma nodules in the groups treated with SM significantly decreased.

The levels of AFP, GGT, IGF-II, ALT, ALP, TBIL and ALB are shown in Table 2. In general, the levels of the above indexes except ALB in negative group were significantly lower than those of treated with DEN. Among the DEN treated

Table 3

| Plasma glucose and serum calcium contents in different groups (mmol/l) |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Items           | Group I (10)    | Group II (10)   | Group III (11)  | Group IV (9)    | Group V (10)    | Group VI (12)   |
| Plasma glucose  | 7.704±0.249a    | 5.571±0.324a    | 6.063±0.267b    | 5.031±0.441c    | 5.553±0.304bc   | 3.915±0.144d   |
| Serum calcium   | 2.874±0.049b    | 3.404±0.181a    | 2.826±0.151b    | 3.309±0.192a    | 3.209±0.263ab   | 3.022±0.118ab   |

Rats of Groups II–VI were treated with DEN resolved in sterilized water at a dose of 10 mg/kg body weight every day for 16 weeks to induce hepatocarcinogenesis. Rats of groups I, II and VI were fed with sodium selenite supplemented diet at the contents of 0.1, 0.1 and 3.0 mg/kg, respectively. The aforesaid treatments lasted for 16 weeks. Values are mean ± SE. Means in the same row without common superscript letters are significantly different at p < 0.05. The number of each group is printed in its respective parentheses.
groups, the aforesaid indexes except ALT and ALP in the positive control group were significantly higher than those of Se treated group (III – VI). Compared with those groups treated with SM supplemented diets (except group IV), the levels of AFP, GGT, TBIL, and ALT in sodium selenite (3 mg/kg) treated group (VI) were significantly higher. While the activities of ALP among these Se treated groups did not show significant difference, the levels of IGF-II in positive control group, sodium selenite (3 mg/kg) treated group and 1 mg/kg SM treated group (IV) were significantly higher than that of the negative control group and SM treated group (III, V). There was, however, no significant difference among the positive control group, sodium selenite (3 mg/kg) treated group and 1 mg/kg SM treated group (IV) or among the negative control group and SM treated group (III, V).

The contents of plasma glucose and serum calcium in rats are shown in Table 3. The plasma glucose contents in DEN-treated groups were significantly lower than that of the negative control group. The plasma glucose value in sodium selenite (3 mg/kg) treated group was lower significantly than that of any other groups. The plasma glucose contents in SM treated group (III, V) were higher than that of the positive control group. The serum calcium content in positive control group was raised significantly than that of the negative control group. As compared with that of the negative control group, the serum calcium values of Se treated groups except group IV had no statistical difference.

Values of hormones regulating blood glucose concentration, including insulin, glucagon, T3, T4, IGR1, IGR2, GGR and TTR are shown in Table 4. Values of insulin, glucagon, T3 and T4 in the DEN treated groups, except the T3 value in group V decreased sharply as compared with that of the negative group (I). Content of insulin in sodium selenite (3 mg/kg) treated group (VI) was significantly lower than that of in SM treated groups and the positive control group (II). While there were no statistical differences in insulin values among the SM treated groups and the positive control group, values of glucagon in groups III and V were significantly higher than that of the positive control group and sodium selenite (3 mg/kg) treated group (VI). Values of T3 and T4 in Se treated groups increased compared to the positive control group. In addition, T4 contents in SM treated groups were elevated significantly as compared with the sodium selenite (3 mg/kg) treated group (VI). There was no significant difference in T4 and T3 contents respectively between the positive control group and the sodium selenite (3 mg/kg) treated group (VI).

IGR1 did not show significant differences among the six groups. IGR2 in DEN treated groups increased significantly compared to the negative group (I). While IGR2 of Se treated groups were lower than that of the positive control group, especially in that of Se treated groups (III, IV), GGR in negative control group was significantly higher than that of in DEN treated groups. While GGR in DEN treated groups did not show significant difference compared with the negative control group, TTR in DEN treated groups increased sharply. In addition, TTR in Se treated groups were significantly decreased as compared with the positive control group, especially in that of SM treated groups.

Correlation coefficients of the plasma glucose related to the aforesaid indexes are shown in Table 5. The plasma glucose concentration showed a significant correlation to the aforesaid indexes except ALB (P<0.05). The items, named as the tumor markers, liver function indexes, liver weight and relative liver weight respectively showed a highly significant negative correlation to the plasma glucose concentration. In addition, the serum calcium showed highly negative correlation to the plasma glucose (r=−0.443, P<0.01). The plasma glucose showed a significantly positive correlation to the level of

| Table 5 | Correlation coefficient of the plasma glucose concentration related to the tumor markers, liver function indexes and hormones regulating blood glucose |
|---|---|---|---|
| Tumor markers and liver function indexes | Correlation coefficients | Relative hormones and the ratios | Correlation coefficients |
| AFP | -0.834*** | Insulin | 0.969** |
| GGT | -0.721** | Glucagon | 0.932** |
| IGR-II | -0.729** | IGR1 | 0.322* |
| ALT | -0.590** | IGR2 | -0.713** |
| ALP | -0.694*** | GGR | 0.781*** |
| TBIL | -0.441*** | T3 | 0.709*** |
| ALB | -0.210 | T4 | 0.842** |
| Liver weight | -0.666*** | TTR | -0.594** |
| Relative liver weight | -0.833** |

*p<0.05; **p<0.01.

Rats of groups II – VI were treated with DEN resolved in sterilized water at a dose of 10 mg/kg body weight every day for 16 weeks to induce hepatocarcinogenesis. Rats of groups I, II and VI were fed with sodium selenite supplemented diet at the contents of 0.1, 0.1 and 3.0 mg/kg, respectively. Rats of groups III, IV and V were fed with Se-enriched malt supplemented diets at the contents of 0.3, 1.0 and 3.0 mg/kg, respectively. The aforesaid treatments lasted for 16 weeks. Values are mean±SE. Means in the same row without common superscript letters are different (p<0.05). The number of each group is five.

| Table 4 | Values of hormones regulating blood glucose of rats in different groups |
|---|---|---|---|---|---|
| Items | Group I | Group II | Group III | Group IV | Group V | Group VI |
| Insulin (pmol/l) | 221.892±11.608a | 142.547±10.597b | 156.170±2.801b | 142.415±5.664b | 138.198±2.991b | 110.534±3.348b |
| Glucagon (ng/l) | 140.569±4.758a | 54.131±4.770a | 75.274±5.612a | 55.096±2.451a | 70.400±2.234a | 47.632±3.097a |
| IGR1 | 29.08±2.19a | 26.48±2.83a | 26.64±1.94a | 28.44±2.11a | 24.89±1.19a | 28.73±1.85a |
| IGR2 | 159.42±13.12a | 276.57±4.14a | 211.16±12.85a | 260.93±17.73a | 196.68±4.40a | 235.70±14.97a |
| GGR | 18.41±0.92a | 10.07±0.71a | 13.07±1.72b | 11.01±0.68b | 12.71±0.68b | 12.41±1.00b |
| T3 (nmol/l) | 2.202±0.05a | 1.239±0.086b | 1.598±0.101b | 1.383±0.147b | 2.075±0.083b | 1.415±0.071b |
| T4 (nmol/l) | 47.253±0.746a | 14.293±1.265a | 32.220±2.847b | 25.935±2.743a | 31.469±1.928b | 19.663±1.065b |
| TTR | 4.66±0.10a | 8.75±0.42b | 5.05±0.37c | 5.37±0.30c | 6.65±0.25b | 7.35±0.06b |

Rats of groups II – VI were treated with DEN resolved in sterilized water at a dose of 10 mg/kg body weight every day for 16 weeks to induce hepatocarcinogenesis. Rats of groups I, II and VI were fed with sodium selenite supplemented diet at the contents of 0.1, 0.1 and 3.0 mg/kg, respectively. Rats of groups III, IV and V were fed with Se-enriched malt supplemented diets at the contents of 0.3, 1.0 and 3.0 mg/kg, respectively. The aforesaid treatments lasted for 16 weeks. Values are mean±SE. Means in the same row without common superscript letters are different (p<0.05). The number of each group is five.
insulin, glucagon, IGR₁, GGR, T₃ and T₄, respectively, while a significantly negative correlation was found between the plasma glucose and level of IGR₂ and TTR, respectively.

Discussion

It is well known that hepatocarcinoma is one of the most important cancers in the world, resulting in more than 1 million patients and over 260,000 deaths per year. Hepatocarcinoma is the third leading cause of death in China, resulting in more than 110,000 deaths per year, occupying over 40% of the total deaths caused by hepatocarcinoma (Liu and Wang, 2000). Therefore, the prevention and treatment of hepatocarcinoma in China looks very important. All these undermentioned items, named as AFP, GGT, IGF-II, ALT, ALP, TBIL, ALB, relative liver weight to body weight and hepatoma nodules of liver are the valuable references to diagnose and observe the development of hepatocarcinoma, and these references have been widely used in the studies on hepatocarcinoma (Kweon et al., 2003; Ozardali et al., 2004; Lii et al., 2000). In the present study, values of AFP, GGT, IGF-II, ALT, ALP, TBIL, ALT (except that of group IV) and the number of hepatoma nodules in Se treated groups decreased significantly compared to that of the positive control group, and increased sharply as compared with that of the negative control group. In addition, these parameters in SM treated groups were lower than that of sodium selenite (3 mg/kg) treated group (Tables 1, 2). The results suggested that Se might validly deaden the lesion of liver and delay the development of DEN-induced hepatocarcinoma. Moreover, the effect of SM was better than that of sodium selenite. The difference between SM and sodium selenite is probably thought to be due, in part, to the difference in metabolic pathways. Organic Se can be absorbed easily and retained more than inorganic Se, and achieve greater efficacy (Ortman and Pehrson, 1997; Shigeyuki et al., 2000). In contrast to sodium selenite, the organoselenium compounds can be tailored to achieve greater chemopreventive efficacy with minimal toxic side effects by structural modifications (Howard and Ganther, 1999; Ganther, 2001). In addition, it has to be reminded that the values of the foressed parameters in Se treated groups were still significantly higher than those of the negative control group, which was suggested that both SM and sodium selenite could not fundamentally prevent DEN-induced hepatocarcinogenesis.

Paraneoplastic syndromes are disorders of organs or tissues that occur at a site distant from a primary cancer or its metastases (Yarbro et al., 1997). Hypoglycemia and hypercalcemia are the most important paraneoplastic syndromes in hepatocarcinoma with a morbidity of 30~100% and 4.26~10%, respectively (Liu and Wang, 2000). In the present study, the plasma glucose concentrations in SM treated groups were higher than that of positive control group (except that of group IV) and significantly higher as compared with that of sodium selenite (3 mg/kg) treated group (VI). In addition, the serum calcium concentrations in SM treated groups were lower than that of the positive control group (except that of group IV). The results suggested that SM could delay the development of hypoglycemia and hypercalcemia in DEN-induced hepatocarcinoma rats to some extent. Moreover, the effect of SM was better than that of sodium selenite. Hypoglycemia in DEN-induced hepatocarcinoma rats resulted much earlier and more significantly than that of hypercalcemia. The significant correlation between plasma glucose concentration and tumor markers, liver function indexes (Table 5) respectively suggested that the generation and development of hypoglycemia in DEN-induced hepatocarcinoma rats were significantly correlated to multifactorial changes in hepatocarcinoma and influenced by each other, while the mechanism requires further investigation. One of the important reasons for hypoglycemia in DEN-induced hepatocarcinoma rats was probably due in part to the enhanced bioactivity of IGF-II, which increases glucose availability. In the course of the hepatocarcinogenesis, the tumor would secrete quantities of IGF-II, which would have several-fold higher serum concentrations than the normal subject. This elevation may already elicit insulin-like effects and thus hypoglycemia (Zapf, 1995). Our data showing the value of IGF-II in the positive control group was significantly higher than that of the negative control group in the present study support this result.

Hormones, such as insulin, glucagon, T₃ and T₄ play an important role in plasma glucose regulation. In the present experiment, hypoglycemia in DEN-induced hepatocarcinoma rats resulted much earlier and more significantly up to the 18th week than that of hypercalcemia. Consequently, the aforesaid hormones were investigated to discover the endocrine regulating status of SM delaying the development of hypoglycemia in DEN-induced hepatocarcinoma. The significant correlation between plasma glucose concentration and the aforesaid hormones suggested that the formation and development of hypoglycemia in DEN-induced hepatocarcinoma were due in part to the co-regulation of these hormones. The failure of administrated growth hormones glucocorticoid and glucagon to revert the changes of plasma glucose (Liu and Wang, 2000) was consequently due in part to the co-regulation. Any of the above single hormone could not be responsible for the thorough regulation of glycometabolism. The less significant changes of these hormones in SM treated groups as compared with that of the positive control group and sodium selenite (3 mg/kg) treated group suggested that SM could effectively delay the development of hypoglycemia by regulating the status and relation among the forenamed hormones. In general, selenomethionine is the major seleno-compound in cereal grains (Finley, 2005). The difference between SM and sodium selenite is probably thought to be due in part to the difference in metabolic pathways between organic Se and inorganic Se. Organic Se mostly existing in SM (Li and Wang, 2004; Xu and Xiao, 1989) can therefore achieve greater efficacy (Ortman and Pehrson, 1997; Shigeyuki et al., 2000).

All the forenamed hormones decreased significantly as compared with that of the negative control group. However, different hormones showed different descents during DEN-induced hepatocarcinogenesis. In the present study, the results that the similar IGR₁, the marked increase in IGR₂ and the sharp decrease of GGR in DEN treated groups compared to that of the negative control group (Table 4) suggested that serum glucagon is severely destitute, whereas insulin activity
looks relatively superabundant. Lower determined serum insulin levels accompanied by relatively higher insulin activity seems partially that basal sensitivity of the body reacting to the hormone of insulin was upraised. However, the direct evidence remains undefined (Moller et al., 1991). Another reason for the state of insulin in the rats seems in part due to the decrease of insulin receptor. However, Mourelle et al. (1980) found that though the plasma levels of insulin in the tumor bearing animals were approximately half of those in control, the binding capacity of hepatoma cell membrane for insulin was the same as that of the control livers. The significantly raised TTR, the relative excess of insulin and the scarce glucagon suggested that there was a relatively high metabolic reaction in the hepatocarcinoma rats. The significant correlation between plasma glucose concentration and the glucose regulation-related hormones (Table 5) suggested that the generation and development of hypoglycemia in DEN-induced hepatocarcinoma rats were also significantly correlated to multi-glandular secretions in hepatocarcinogenesis.

Mechanism of SM regulating the hormones of T3 and T4 may be due to an increase in the biological half-life of T4. T3 deiodination was reciprocally decreased, thereby compensating for the impaired conversion of T4 to T3 and resulting in only relatively minor changes in plasma T3 concentrations (Chang et al., 2005; Chanoine et al., 1992). However, which is secondary, the hypoglycemia or the changes of hormones requires further investigation.

Supplementation of Se to populations and animals with adequate intakes may reduce the risk of cancer. Se-enhanced plants may be one of the best means of accomplishing this (Finley, 2005). A better understanding of the compounds and mechanisms through which Se exerts anticancer activity of selenium-enriched malt will be important for helping to develop safer and more effective Se agents for cancer prevention, especially in organ site-specific manners. Sensitive and robust new analytical methods are needed for this purpose.

**Conclusion**

In the present study, the function of Se-enriched malt in deadenizing the lesion and delaying the development of hepatoma of rats induced by diethylnitrosamine was better than that of sodium selenite. Hypoglycemia and hypercalcemia were significantly correlated with the multifactors mentioned above.

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**References**


