Promotion of Liver Lesion Development in the Syrian Hamster by Dietary fat Following Multi-organ Initiation is Inhibited by DHEA-S Administration

Cheol Beom Park1,2, Dae Joong Kim1,3, Malcolm A Moore1,4, Nobuo Takasuka1, Hiroyuki Tsuda1

Abstract

The influence of dietary supplementation with dehydroepiandrosterone-sulphate (DHEA-S) at 0.6% was investigated in male Syrian golden hamsters initiated by treatments with azoxymethane (AOM), and dihydroxy-di-n-propyl nitrosamine (DHPN), timed after transfer from a choline-deficient to a normal diet. These carcinogens respectively target the colon, and the respiratory tract, the liver and pancreas. A total of 75 animals were divided into 6 groups, 1-3 (20 animals each) receiving the initiation protocol of during the first 8 weeks, and 4-6 (5 animals each) given the vehicles alone. The hamsters in groups 2, 3 and 5, 6 then received a high fat diet (20% corn oil) while DHEA-S was given in addition for 20 weeks to groups 3 and 6. Groups 1 and 4 served as controls on the basal diet. Assessment of development of preneoplastic and neoplastic lesions, after sacrifice at week 28, revealed increase in hepatocellular liver nodules and the index of BrdU incorporation in the hepatocellular cells of the liver in the initiated animals given the high fat diet. This was significantly reduced by the DHEA-S supplementation. Non-significant tendencies for high fat enhancement and hormone protection were also observed for lung and colon tumors.

Key words: hamster hepatocarcinogenesis - fat promotion - DHEA chemoprevention - wide spectrum inititiation

Asian Pacific J Cancer Prev, 1, 329-332

Introduction

There is now a great deal of interest in chemoprevention of cancer development. One agent which has received attention in this respect is dehydroepiandrosterone, the adrenal steroid. Dietary administration has been found to exert inhibitory potential in a large number of animal models (Gordon et al., 1987; Schwartz et al., 1990) and there are also data pointing to protective effects in humans (Gordon et al., 1987). However, it may also cause adverse effects, including liver neoplasms when given long-term to the rat (Rao et al., 1992). In assessing influence of potential chemopreventors it is clearly important that account be taken of organ or tissue-dependence. For this purpose, models using combinations of carcinogens targeting different organs can be employed.

In the present study, Syrian hamsters were initiated with DHPN and AOM to induce lesions in the hepatobiliary axis and the pancreas, as well as the lung and colorectum. A modification of the rapid induction model of Konishi and co-workers (Mizumoto et al., 1989; 1990) was selected as the inducing regimen.

Since fat consumption is reported to be associated with adenocarcinoma development in many organs (World Cancer Research Fund, 1997) , a 20% corn oil diet was administered to appropriate groups. This was followed by DHEA-Sulphate at 0.6% in the diet as a test agent.

Materials and Methods

Male Syrian hamsters were purchased at six weeks of age and maintained under constant conditions. After one week for acclimation, the experimental protocol was performed (see Figure 1). The carcinogens were commercially purchased and the DHEA-S was kindly supplied by Kanebo, Osaka. A number of animals died during the experiment,
Table 1. Body, Organ and Serum Insulin Data

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of animals</th>
<th>Body weight (g)</th>
<th>Relative liver weight (%)</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>3</td>
<td>165.0±13.4</td>
<td>4.1±0.3</td>
<td>2.96±0.39</td>
</tr>
<tr>
<td>High Fat</td>
<td>3</td>
<td>197.2±12.8</td>
<td>4.1±0.2</td>
<td>54.9±32.8</td>
</tr>
<tr>
<td>DHEA-S</td>
<td>4</td>
<td>223.2±28.6</td>
<td>3.8±0.4</td>
<td>35.5±17.9</td>
</tr>
<tr>
<td>Carc</td>
<td>13</td>
<td>164.0±25.8</td>
<td>4.3±0.5</td>
<td>4.43±4.63</td>
</tr>
<tr>
<td>C+HF</td>
<td>13</td>
<td>183.3±14.2</td>
<td>3.8±0.6</td>
<td>2.95±2.54</td>
</tr>
<tr>
<td>C+DHEA-S</td>
<td>17</td>
<td>171.5±18.7</td>
<td>4.0±0.3</td>
<td>14.8±14.3</td>
</tr>
</tbody>
</table>

Table 2. Incidence and Multiplicity Data

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of animals</th>
<th>Liver Nodules</th>
<th>Lung Nodules</th>
<th>Pancreatic Lesions</th>
<th>Colon Polyps</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>%Inc No/Hamster</td>
<td>%Inc No/Hamster</td>
<td>%Inc No/Hamster</td>
<td>%Inc No/Hamster</td>
</tr>
<tr>
<td>Carc</td>
<td>13</td>
<td>7.7 0.08*</td>
<td>54 0.62*</td>
<td>15 0.15</td>
<td>69 0.9</td>
</tr>
<tr>
<td>C+HF</td>
<td>13</td>
<td>39 0.61</td>
<td>77 1.15</td>
<td>38 0.38</td>
<td>85 1.6</td>
</tr>
<tr>
<td>C+DHEA-S</td>
<td>17</td>
<td>29 0.29*</td>
<td>71 0.94</td>
<td>35 0.59</td>
<td>69 1.1</td>
</tr>
</tbody>
</table>

Results

The results for body and liver weights, as well as insulin, are given in Table 1 and for incidence data in Table 2. There were no significant differences regarding weights. The insulin level appeared to be increased by high fat in the controls without carcinogen exposure but not in animals bearing lesions.

Development of liver nodules was significantly increased by the high fat diet, this being inhibited by DHEA-S. Similar non-significant tendencies were observed for the lung and colon, but not the pancreas. Percentages of hepatocytes incorporating BrdU were 2.1±1.3, 6.3±1.7 and 3.1±1.3 for the C+Basal diet, HF and HF + DHEA-S groups, the increase with HF and the reduction by the hormone both being significant (p<0.05).

Discussion

The present study provided evidence that DHEA-S can inhibit the development of liver nodules after DHPN and AOM initiation, associated with a decrease in the cell turnover. Links to proliferation and its suppression have been reported earlier (Pashko et al., 1981; Garcea et al., 1988;
DHEA-S inhibits enhancement of hepatocarcinogenesis by dietary fat

Shulz and Nyce, 1994).

DHEA and now its sulphate, DHEA-S, have been shown to exert modifying effects on tumorigenesis in very many organs (see the Table). Other hypolipidemic agents have also been shown to have protective actions (Maruyama et al., 1994; Mizumoto et al., 1988).

Clearly the adrenal steroid DHEA itself is not an agent that promises universal benefit for all aillments (Pugh et al., 1999). However, the interplay between this hormone and others in the body, including insulin, has yet to be elucidated in detail, although a great deal is known, for example, about effects in the liver (Belli, et al., 1992). In the present study the data for serum insulin were very difficult to interpret, since there was no consistency. The fact that the expected rise in insulin could be confirmed in a parallel experiment looking at starvation-refeeding (data not shown) might suggest that the high fat diet did induce an increase, but that this was masked by other influences in animals bearing neoplastic lesions.

The present findings offer some support for beneficial actions of DHEA, generally in line with the literature. The question now is whether more interest should be placed in this and similar compounds acting in concert with other chemopreventors. Suitable markers for assessment of different possibilities are now required.

Acknowledgements

The authors would like to express their appreciation to Dr Norio Awata of Kanebo Ltd, Japan, for the kind gift of DHEA-S and DHEA for the present work. During the performance of this study, Cheol Beom Park and Malcolm Moore were recipients of Research Fellowships from the Foundation for Promotion of Cancer Research Program for Invitation of Foreign Researchers, Japan. This work was supported in part by a Grant-in-Aid for Cancer Research from the Ministry of Health and Welfare, by a Grant-in-Aid for Cancer Research from the Ministry of Health and Welfare.

References


Asian Pacific Journal of Cancer Prevention, Vol 1, 2000 331


**Personal Profile: Cheom Beol Park**

Dr Park obtained his Ph.D in the Veterinary Medicine Faculty, Seoul National University in 1999.

His major work experience has been in the Korean National Institute for Toxicological Research, as well as the Korean Environmental Management Research Office. For a two year period in the late 1990s he visited the Japanese National Cancer Center, conducting research in chemoprevention of cancer under Dr Hiroyuki Tsuda in the Experimental Pathology and Chemotherapy Division

Dr Park presently has a position at the Catholic Medical University in Seoul, where he is engaged in toxicological research related to NOS.