RESEARCH COMMUNICATION

Inhibition by Vitamin E of Cholangiocarcinoma Induction due to Combined Nitrite and Aminopyrine

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Abstract

The present experiment was conducted to assess the influence of vitamin E, given in the diet at 0.5 or 1%, on induction of lesions in the Syrian hamster liver by long term combined administration of sodium nitrite and aminopyrine in the drinking water. Inhibition of both cholangiofibrosis and cholangiocarcinoma development, as well as a reduction in hepatocellular nodules was the result. The underlying mechanisms presumably involve alteration of endogenous dimethylnitrosamine formation by the vitamin, with clear implications for prevention in the human environment.

Key Words: vitamin - endogenous nitrosation - inhibition - hamster liver - neoplasia

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Introduction

Liver cancer is a major problem in Thailand in terms of both hepatocellular and cholangiocellular carcinomas (Deerasamee et al.,1999) with a major impact of the environment in causing geographic differences (Srivatakul et al., 1988). Therefore prevention is very important and dietary improvement is one area of importance in this respect. The Thai diet may contain nitrates and nitrites (Migasena et al., 1980), precursors for endogenous formation of carcinogens targeting the liver (Lijinsky and Greenblatt, 1972; Bergman and Wahlin, 1981, Lijinsky, 1984). Protection may be offered by vitamin supplementation, however, as reported for ascorbic acid and α-tocopherol (Garland et al., 1988; Knekt et al., 1991). Here, the influence of vitamin E on induction of lesions in both ductular and hepatocellular compartemnts of the liver was examined using a hamster model (Thamavit et al., 1988).

Materials and Methods

Syrian golden hamsters, bred in our laboratory from pairs originally obtained from the Armed Force Research Institute of Medical Science, were used at the age of 7-8 weeks. The animals were kept five to a cage in air-conditioned room at 25-27°C with 12 hours light and dark control. They were fed a basal pellet diet and tap water ad libitum and cages were changed twice weekly.

The experimental regimen is shown in the Figure. At the end of the treatment period the surviving animals were sacrificed under ether anesthesia and their livers were excised and routinely processed for production of H&E stained slides and histopathological diagnosis.Incidence data were compared using the $\chi 2$ test.

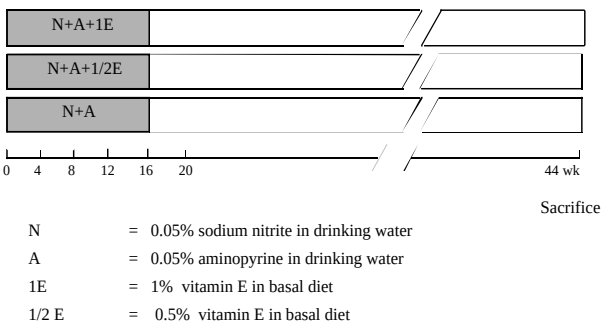

Figure. Experimental Protocol

Results

The results are summarized in the Table. Significant reduction in quantitative data for both cholangiofibrosis and cholangiocellular carcinomas, as well as hepatocellular nodules, was evident with 1% vitamin E. This was reflected in decrease in liver weights, without overt t oxicity.

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Table 1. Quantitative Data for Body and Liver Weights and Incidence Data for Histopathological Finding of Liver Hamsters treated with 0.05% nitrite plus 0.05% Aminopyrine Combined with 0.5% or 1% Vitamin E.

Group[a]	Effective No (Total No)	Body Weight (g)	Liver % Body Weight	Cholangiofibrosis Incidence (%)	Degree[b]	Incidence of Cholangio carcinoma	Hepatocellular nodules Incidence (%)	No animal
.05N + .05A+1E	23 (25)	152.9±27.6	4.8±0.7**	3** (13.0)	1+	3** (13.0)	0** (0)	0
.05N + .05A+.5E	24 (25)	147.9±18.3	6.8±5.1	9 (37.5)	1+	5 (20.8)	5 (20.8)	0.3±0.6
.05N + .05A	19 (25)	150.5±24.0	6.9±2.6	10 (52.6)	1+	8 (42.1)	6 (31.6)	0.4±0.7

Discussion

The present study revealed clear preventive inluence of a 1% supplement with vitamin E on induction of hepatocellular and cholangiocellular lesions in Syrian hamsters given nitrite and aminopyrine in combination.While no such effects were evident with the 0.5% supplement this might only be a reflection of the dose dependent generation of nitrosamines by the precursors (Lijinsky and Greenblatt, 1972).

Since it has been found in experimental animals that both proliferative stimuli and carcinogen exposure are necessary for effective induction of tumors of hepatocellules (Bannasch et al.,1995) and cholangioles (Thamavit et al., 1990), the results offer hope that increase in dietary intake of vitamin E might be associated with reduced risk in human populations. This possibility now needs to be assessed by appropriate epidemiological studies.

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Personal Profile: Witaya Thamavit

Professor Witaya Thamavit studied at Mahidol University, Faculty of Science, where he is now head of a section for chemical carcinogenesis research in the Department of Pathobiology. Witaya Thamavit is a veterinary surgeon and his main research interest in the past has been the association

between opisthorchiasis and cholangiocarcinoma development, for which he developed the first animal model, utilising the Syrian hamster. Keen on jogging, he also has an enormous appetite for all types of fruit - including durian!