Influence of diallyl disulphide on temporal patterns of liver marker enzymes in experimetal hepatocarcinogenesis in rats

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Abstract: The present study aims to investigate the effects of diallyl disulphide (DADS) on the temporal patterns of tumor marker enzymes, such as serum alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate transaminase (AST), and γ-glutamyl transpeptidase (GGT) during *N*-nitrosodiethylamine (NDEA) induced hepatocarcinogenesis in rats. The acrophase of all marker enzymes was found to be delayed in NDEA-treated rats. The increased mesor, altered amplitude and acrophase of these markers indicated the index of liver damage. Oral treatment of DADS results in normalization of the altered rhythms of these tumor markers (compared with controls) by its anticarcinogenic and antiproliferative effects. Furthermore, this study indicates the necessity of detailed investigation to reveal the temporal interplay between the central biological clock (suprachiasmatic nucleus), peripheral tissue (liver) based oscillators and cancer processes.

Key words: circadian rhythms, *N*-nitrosodiethylamine, diallyl disulphide, tumor marker enzymes.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; DADS, diallyl disulphide; GGT, γ-glutamyl transpeptidase; GST, glutathione *S*-transferase; NDEA, *N*-nitrosodiethylamine.

Introduction

Experimental models that mimic human tumors are needed to understand malignant processes and to guide subsequent patient investigations. These malignant tumors can be induced by chemical carcinogens or radiations. *N*-nitrosodiethylamine (NDEA), a potent hepatocarcinogen has been reported to cause carcinogenesis in different animal species including rats, mouse, guinea pigs, rabbits, dogs and monkeys (Verna et al., 1996).

Diallyl disulphide (DADS) is not present in garlic cloves, but it is present (60%) in garlic oil. It is produced when the enzyme allinase acts on its substrate allin during garlic cutting or crushing and has been found in human breath after garlic consumption, which shows that this compound is garlic metabolite *in vivo* (Block, 1996). It is the major oil soluble organosulfur compound in garlic and appears to be the most effective in growth inhibition of human cancer cells. It is an effective inhibitor in the growth of neoplastic CMT-13 cells (Sundaram & Milner, 1996) and in the promotion phase of DMBA induced skin tumors in mice (Lu et al., 2004).

Interest in rhythms of experimental tumors and different kinds of human cancers began more than 20 years ago. Knowledge of the circadian rhythms in normal and pathological conditions can be used to improve the understanding of pathophysiological processes and the therapeutic approach to the illness. The connection between circadian rhythmicity and cancer extends well beyond chronotheraphy (Sephton & Spiegel, 2001). Among patients with breast, ovarian, prostate, stomach and colon cancer, disruption of circadian function has been noted in endocrine (cortisol, melatonin, TSH, GH, LH and FSH), metabolic (proteins and enzymes) and immunological (e.g. peripheral lymphocyte) rhythms. All these may serve as markers of tumor status (Mormont & Levi, 1997).

Liver marker enzymes such as γ-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), asparate transaminase (AST), and alanine transaminase (ALT) have been found to be useful in detection and monitoring of the induction and progression of NDEA-induced hepatocarcinogenesis (Sunderasen & Subramanian, 2002). The present experiments, however, aim to study the effect of DADS in the temporal patterns of these marker enzymes in NDEA-induced hepatocarcinogenesis, which can be involved in early diagnosis and prognosis of cancer and its treatment.

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