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OXIDATIVE STRESS AND ANTIOXIDANTS STATUS IN PEPTIC ULCER AND GASTRIC CARCINOMA

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Abstract : Oxidative stress is believed to initiate and aggravate many diseases including peptic ulcers and gastric carcinoma. We observed an increase in rat gastric mucosal lipid peroxidation (LPO) and superoxide dismutase (SOD) and a decrease in catalase (CAT) levels in cold restraint stress-induced gastric ulceration while, in clinical peptic ulceration and gastric carcinoma patients, an increase in serum LPO and a tendency to decrease in SOD and CAT levels were observed. The result thus, indicated a positive correlation between free radical-induced oxidative stress both in gastric and duodenal ulcers and gastric carcinoma.

Key words : oxidative stress, free radicals, antioxidants, rat, gastric carcinoma, peptic ulcer

INTRODUCTION

Peptic ulcers and carcinomas are two pathological conditions affecting the gastrointestinal tract. Malignancies of the G.I. tract are relatively resistant to radiation therapy and chemotherapy has also had modest benefit, whereas an effective therapy still remains elusive in the treatment of gastroduodenal ulceration (1). One of the common denominators for the genesis of these diseases is the involvement of free radicals. Reactive oxygen species (ROS) are generated through numerous normal metabolic processes and are needed for normal functioning of the organism. Various antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT) and gluthathione peroxidase (GPX) control their accumulation (2). Any imbalance in the activity of these enzymes normally leads to faulty disposal of free radicals and its accumulation. These ROS are responsible for oxidation of tissues leading to lipid peroxidation and tissue damage. They are also responsible for oxidation of bases in cellular DNA making them mutagenic, cytotoxic and crosslinking agents, which in turn causes uncontrolled expression of certain genes causing increased multiplication of cells leading to cancer (2). Antioxidants seemed to have protective role in gastric ulcers and carcinomas (3). The present

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study includes the status of free radicals in both experimental gastric and clinical peptic ulcers and gastric carcinoma patients and their role in these diseases.

METHODS

Animals– Inbred Charles-Foster (CF) albino rats (130–180 g), of either sex, obtained from the Central animal house of our Institute were used for the study. Animals were provided with standard rodent pellet diet (Hindustan lever Ltd.) and the food was withdrawn 18–24 h before the experiment though water was allowed *ad libitum*. 'Principles of laboratory animal care' (NIH publication no. 82–23, revised 1985) guidelines were followed.

Anti-ulcer study: Cold-restraint stress (CRS) gastric ulcers were induced in rats by strapping the rats on a wooden plank and keeping them for 2 h at 4°–6° C. Eight animals were taken each in control (unstressed) and CRS groups. Ulcer index was calculated following the method as reported earlier (4). Statistical analysis was done by using Wilcoxon Sum Rank test.

Estimation of free radical generation, enzymatic antioxidants and proteins: These were estimated following methods as reported earlier (4). Briefly the fundic part of the stomach of treated animals was homogenized (5%) in ice cold 0.9% saline and the mitochondrial fraction obtained by differential centrifugation was used the estimation of lipid peroxidation (LPO) and enzymatic antioxidants like superoxide dismutase (SOD) and catalase (CAT). Protein was estimated in mucasal homogenate for expressing the activities of LPO, SOD and CAT per mg of protein (4, 5).

Clinical study

Endoscopically proved cases of gastric and duodenal ulcers patients and histologically proved cases of gastric carcinoma and normal subjects as control, were selected from the outpatient departments of Medicine and Gastroenterology, University hospital, Banaras Hindu University, Varanasi. The ethical committee of the Institute approved the selection of patients and a written consent of the patients was also obtained.

The serum was separated and used for the estimation of LPO, SOD and CAT as mentioned above. Statistical analysis was done using Student's *t* test.

RESULTS AND DISCUSSION

The result is summarized in Table I. Stress causes both sympathetic (causes direct arteriolar vasoconstriction) and parasympathetic (induces an increased motility and muscular contraction) stimulation of stomach leading to local hypoxia and near or actual "ischemia". The ischemic condition caused an increase in the level of H2O2 (by the action of SOD), which, in conjugation with O2 generates OH via the methyl catalyzed Haber-Weiss reaction (6). Hydroxyl radicals thus generated, oxidizes important cellular constituents such

TABLE I: Status of Lipid peroxidation (LPO, MDA nmoles/mg of protein), Superoxide dismutase (SOD) and Catalase (CAT) (units/mg of protein) in cold restraint stress-induced gastric ulcers (CRS-GU) in rats and in patients of gastric (GU), duodenal ulcers (DU) and Gastric carcinoma (GC).

Groups	*N*	*LPO*	*SOD*	*CAT*
Rat study (Gastric mucosal homogenate)				
Control	8	0.40±0.02	101.2±10.7	31.5±2.0
CRS-GU	8	0.58±0.03[C]	247.6±6.4[C]	19.2±1.2[C]
Human study (Serum)				
Control	15	0.32±0.01	25.6±2.7	9.13±1.53
GU	10	0.66±0.01[C]	20.2±2.7	6.18±1.27
DU	20	0.68±0.02[C]	22.8±3.1	6.71±1.01
GC	30	0.92±0.02[C]	19.1±1.9	5.80±1.68

Data are mean ± SEM, P value: [C]<0.001 when compared to respective control groups.
N-Number of animals or patients in respective studies.

as structural and functional proteins, membrane lipids and depletes glutathione. Lipid peroxidation causes loss of membrane fluidity, impaired ion transport and membrane integrity and finally loss of cellular functions. Stress also causes inactivation of prostaglandin synthetase leading to decreased biosynthesis of prostaglandin-the master molecule for gastroprotection against all forms of insults to the mucosa.

Cold restraint stress (CRS) in rats significantly increased the ulceration with concomitant increase in LPO and SOD but decrease in CAT levels in comparison to the control group in gastric mucosal homogenate which, the patients of peptic ulcers and gastric carcinoma showed a significant increase in serum LPO and a tendency to decrease in SOD and CAT levels (Table 1). The increase in LPO may suggest a possible mechanism of tissue injury by reactive oxygen intermediates (7). This may result in ulcers or lead to permanent alteration to genetic material, which may serve as an initial step in the process of carcinogenesis. Cancer development is presently recognized as a micro-evolutionary process that requires cumulative action of multiple events. In recent years there is convincing evidence that free radicals can stimulate cancer development at all the three stages of cancer development directly or through lipid peroxidation (8). The patients are further prone to oxidative damage as observed from the decrease in anti-oxidant enzymes SOD and CAT although these were insignificant, but may be enough to cause lipid peroxidation (9). This shows that these patients are susceptible to free radical damage and necessitates the use of antioxidants as adjuvants in treatment of cancers. There are some limited clinical trial on the beneficial effects of antioxidant supplements in treatment of gastric ulcers and carcinoma. Antioxidant enzymes which were significantly changed in experimentally induced stress may be due to the fact that the experimental stress is of acute nature, where the system tends to defend itself from the oxidative damage. The

insignificant decrease in antioxidant enzymes observed in case of clinical study was of chronic nature and could lead to adaptation to oxidative damage. However there was an increase in lipid peroxidation in both the conditions, indicating extensive oxidative damage which may be either the cause or the effect of stress.

The present study thus, indicates an important role played by free radicals in peptic ulcers and gastric carcinomas.

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