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Protective Effects of Gramine on Cell Surface Integrity and Status of Lipid Profile during DMBA induced Oral Carcinogenesis

Ramu Arun Kumar, Kathiresan Suresh*, Ramadoss Hemavardhini and Nallu Anandhi

Department of Biochemistry and Biotechnology, Faculty of Science, Annamalai University, Annamalainagar- 608002, Tamilnadu, India

*Corresponding author

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A B S T R A C T

Gramine is a pungent alkaloid significantly found in barley (*Hordeum vulgare*), that have antioxidant and chemopreventive properties owing their indoles nature. The present study aimed to examine the protective effect of gramine on cell surface glycoconjugates and lipid profile status against 7,12-dimethylbenz[a]anthracene (DMBA) induced hamster buccal pouch carcinogenesis. Oral squamous cell carcinoma was induced in male Syrian golden hamster's buccal pouch by painting with 0.5% DMBA in liquid paraffin at three times a week of 16 weeks. We observed malignancy with marked abnormalities of glycoconjugates (protein bound hexose, hexosamine, sialic acid and fucose), lipid (Total cholesterol, Phospholipids, Free fatty acid and C/P ratio) status in tumor bearing hamsters. Oral administration of gramine (80 mg/kg b.wt), to DMBA painted cancer animals significantly modulate the levels of cell surface glycoconjugates and lipid profiles activity to near normal range. Present study suggested that gramine has potent chemopreventive efficacy on protected the abnormalities on cell surface glycoconjugates and lipid status against oral cancer.

Introduction

Oral squamous cell carcinoma is the fifth most major neoplasm in the worldwide and is the leading cancer among males in Indian subcontinent accounting for 40-50% of all cancers (Gaur *et al.*, 2011). Utilization tobacco, betel quid and liquor are major risk factor associated with development of oral SCCs (Attolini and Michor, 2009). DMBA are potent poly aromatic hydrocarbon found

40-100ng per cigarette, which recognized as a causal agent of oral cancer (Lee *et al.*, 2002). Glycoproteins are well suited as primary factor for intermediating cell surface functions like cellular bond, cell to cell recognition (Casper *et al.*, 1999). Samples of oral cancer patients and DMBA painted tumor bearing laboratory animals were identified when aberrant expression of

hexosamine, protein-bound hexoses, lipid-bound sialic acid, total sialic acid, and fucose which demonstrating their helpfulness in judgment or screening treatment (Bose *et al.*, 2013).

The hexose and hexosamines are an essential role in the body being present in the ground substance of every single connective tissue as parts of mucopolysaccharides and mucoproteins (Blumenkrantz and Asboe-Hansen, 1976). Strangely, increased hexosamine exhibits the dynamic development and proliferation of tumor cells (West *et al.*, 1985). Therefore, hexosamine is a target for chemoprevention of different tumors including oral squamous cell carcinomas. Fucose is a typical monosaccharide residues those are present in the terminal chains of oligosaccharides of membrane bound or secreted molecules as it can slow down the growth of cancer cells (Walz *et al.*, 1990; Patel *et al.*, 1994). Sialic acid is a strong electronegative charge acidic sugar at physiological conditions that is observed at the external ends of cell surface glycan chain (Varki and Varki, 2007). Abnormally increased sialic acid content was correlated with cell attachment and migration thus contributing to the migratory and invasive phenotype of the cells (Seales *et al.*, 2005). However, the high expression of sialic acids can shield tumor cells from apoptosis and has been suggested to confer resistance to tumor therapy (Bull *et al.*, 2014).

Lipids play an important role in several cellular processes and altered levels of lipids affect the structure and function of the cell. Free radical induced lipid peroxidation is regarded as one of the basic mechanisms for cellular damage and therefore, the extent of tissue damage can be monitored by measuring the concentration of plasma lipid peroxides (Hail *et al.*, 2008). Abnormalities in cholesterol phospholipid ratio lead to affects

the physio-chemical properties of the cell, contributing to malignant transformation (Fliesler *et al.*, 1995). Several studies also reveal lipid alterations in certain human pathogenesis. It is a conceivable that molecules capable of interacting with membrane lipids may induce modifications in membrane composition, protein function or gene expression and reversion of the pathological state (Bartsch and Nair, 2000).

The indole alkaloid, gramine (3-[Dimethylaminomethyl]indole) is an active constituent of several cereals and it significantly occurs in *Hordeum vulgare*. Numerous studies showed diverse pharmacological and biochemical impacts of gramine, such as, vasorelaxation, blood pressure elevation, bronchial asthma and antioxidant properties (Iwata *et al.*, 2001). It additionally assumes important roles for the metabolite action of amino acid in living organism (Ke *et al.*, 2012). Present study was designed to focus the protective effect of gramine on cell surface glycoproteins integrity and status of lipid profile during DMBA induced oral carcinogenesis in golden Syrian hamsters.

Materials and Methods

Chemicals

DMBA and gramine were bought from Sigma-Aldrich Chemical Pvt. Ltd., Bangalore, India. All other chemicals used were of analytical grade, obtained from Hi-media Laboratories, Mumbai, India.

Animals

Male golden Syrian hamsters, 8-10 weeks and weighing 80-120 g, were obtained from the National Institute of Nutrition, Hyderabad, India and were maintained in the Central Animal House, Rajah Muthaiah

Medical College and Hospital, Annamalai University. The animals were housed in polypropylene cages at proper temperatures ($27\pm 2^{\circ}\text{C}$) with relative humidity $55\pm 5\%$, light: dark cycle is almost 12:12h and provided standard pellet diet and water ad libitum. Hamsters were maintained in accordance (Proposal No. 946) with the guidelines of ethical committee for animal care of Annamalai University (Register number 160/1999/CPCSEA) in accordance with Indian National law on animal care and use.

Experimental design

A total number of 40 hamsters were randomized into four groups and each group contained 10 hamsters. Group I animals served as the control and were treated with liquid paraffin alone. Group II hamsters were painted with 0.5% DMBA in liquid paraffin three times a week on their left buccal pouches. Group III animals were treated with DMBA and received in addition oral administration of gramine at a dose of 80 mg/kg b.wt alternate days to DMBA painting. Group IV animals received oral administration of gramine only. The experiment was terminated at the end of 16th week and all animals were sacrificed and blood samples were collected into heparinized tubes. The plasma was separated by centrifugation at 3000 rpm for 15 mins. After plasma separation, the erythrocyte membrane was prepared by the method of Dodge *et al.*, (1963) modified by Quist (1980).

Preparation of Tissue Homogenate

Tissue samples from animals were washed with ice cold saline and dried between folds of filter paper, weighed and homogenized using appropriate buffer (appropriate buffer of concerned parameter [TBARS-0.025M Tris-Hcl buffer, pH 7.5; GSH and GPx- 0.4

M phosphate buffer, pH - 7.0; SOD - 0.025 M sodium pyrophosphate buffer, pH 8.3; CAT - 0.01 M phosphate buffer, pH 7.0]) in an all-glass homogenizer with teflon pestle. The homogenate was centrifuged at 1500 rpm for 5 minutes and the supernatant was then used for the biochemical estimations.

Biochemical studies

Protein bound hexose in plasma were estimated by method of Niebes (1972). Plasma protein bound hexosamine were determined by method of Wagner (2008). The total sialic acid in plasma and defatted buccal mucosa tissues were estimated by the method of Warren (1959). Plasma lipid bound sialic acid concentration was determined by the procedure of Katopodis and Stock (1980). Fucose in plasma and buccal mucosa tissue were determined by the method of Dische and Shettles (1948). Total cholesterol was estimated by the method of Parekh and Jung (1970). Phospholipids were estimated in plasma and erythrocyte membrane by the method of Zilversmit and Davis (1950). Free Fatty Acids were estimated by the method of Falholf *et al.*, (1973). Triglycerides were estimated by the method of Foster and Dunn (1973).

Statistical analysis

The data were expressed as mean \pm S.D with six animals in each group. Values were analysed using SPSS/15.0 software. Hypothesis testing methods were included with analysis of variance [ANOVA] followed by least significance difference [LSD]. P values of > 0.05 were considered statistically significant.

Results and Discussion

Table 1 Shows the levels of glycoconjugates (Protein bound hexose, Protein bound hexosamine, Total sialic acid, Lipid bound

sialic acid and Fucose,) in the plasma of control and experimental animals in each group. The levels of glycoconjugates in the plasma were significantly increased in DMBA alone painted animals as compared to control animals. Oral administration of gramine (80 mg/kg bw) on DMBA painted animals brought back the levels of above mentioned abnormal glycoconjugates to near normal range. No significant differences were noticed in the levels of plasma glycoconjugates in gramine alone treated animals as compared to control animals.

Table 2 Shows the levels of glycoconjugates (Protein bound hexose, Protein bound hexosamine, Total sialic acid and Fucose) in the erythrocyte membrane and buccal mucosa of control and experimental animals in each group. The levels of glycoconjugates in erythrocyte membrane were significantly decreased and buccal mucosa was significantly increased in DMBA alone painted animals as compared to control animals. Oral administration of gramine (80 mg/kg b.wt) against DMBA painted animals restored the levels of above mentioned glycoconjugates to near normal range. No significant differences were noticed in the levels of erythrocyte membrane and buccal mucosa glycoconjugates in gramine alone treated animals as compared to control animals.

Table 3 Shows the levels of lipid profile (Total cholesterol, Phospholipids, Free fatty acid, Triglyceride and C/P ratio) in the plasma and buccal mucosa of control and experimental animals in each group. The total cholesterol, free fatty acid and C/P ratio levels were increased whereas phospholipids and triglyceride levels were decreased in plasma and buccal mucosa of DMBA alone painted animals as compared to control animals. Oral administration of gramine (80 mg/kg b.wt) restored the status of cholesterol,

phospholipids, free fatty acid, triglyceride and C/P ratio to near normal. No significant differences were noticed in gramine alone treated animals as compared to control animals.

Table 4 shows the levels of lipid profiles (Total cholesterol, Phospholipids, Free fatty acid and C/P ratio) in the erythrocyte membrane of control and experimental animals in each group. The levels of total cholesterol, free fatty acid and C/P ratio were increased in erythrocyte membrane of DMBA alone painted animals as compared to control animals. Oral administration of gramine (80 mg/kg b.wt) treatment against DMBA painted animals brought back the levels of total cholesterol, phospholipids, free fatty acid and C/P ratio to near normal range. No significant differences were observed in gramine alone treated animals as compared to control animals.

Extracellular matrix plays an essential role in the surface properties of the cells such as regulating cell proliferation, adhesion and migration to induce cell differentiation and death (Hynes, 2009). Experimental studies shows that oral cancer alters the hexosamine, hexoses, sialic acid, fucose, phospholipids, glycolipids and cholesterol in extracellular matrix, which causes up-regulates proliferation, evades apoptosis, angiogenesis and metastasis (Kumar *et al.*, 2015; Taqi, 2015; Isozaki *et al.*, 2014; Bayer *et al.*, 2013). Therefore, novel agent that capable to down-regulate the aberrant expressions of glycoconjugates and lipids of oral cancer would be great benefit for patients. Now-a-days, phytochemicals from edible plants received much attention as chemopreventive agents for defending cells and tissues against various carcinogens. Present study, we examined the anticancer efficacy of gramine, a natural indole alkaloid and its mechanism of action on

modulates glycoconjugates, lipids profiles in 7,12-dimethylbenz[a]anthracene (DMBA) induced hamster buccal pouch (HBP) cancer model.

The malignant transformation is usually associated with molecular changes such glycosylation of glycoproteins and glycolipids. Aberrant glycosylation can have an effect on macromolecule function such as modulates protein stability and solubility thereby induces malignant transformation in oral epithelial tissue (Stowell *et al.*, 2015). Fernandez *et al.*, (1997) noted that increased fucose content in tumor tissue and plasma is probably due to increased turnover of malignant cells with subsequent shedding into circulation. Goodarzi *et al.*, (2005) reported that marked elevation of total sialic acid and lipid bound sialic acid in plasma are found to reflect tumor burden. It is clear from this study that, DMBA induced tumor bearing animals that exhibits elevated levels of hexose, hexoseamine and sialic acid expression in plasma, whereas decreased in erythrocyte membrane (Suresh *et al.*, 2007). Hence,

aberrant activations of these glycoproteins represent an effective target for treatment of oral cancer. Present study, oral administration of gramine (80mg/kg bw) restores the altered status of hexose, hexose amine and sialic acid expression in the DMBA induced hamster buccal pouch carcinoma. Similar with our study, Sindhu and Manoharan (2010) reported that alkaloid berberine reduces plasma and tissue glycoprotein levels in DMBA induced oral carcinogenesis. Therefore, reduction within the status of glycoprotein expression indicates gramine has the ability to suppress malignant transformation.

The abnormalities of lipids have been implicated proliferation and progression of cancer cells. In particular, changed level of phospholipid and cholesterol malformed the fluidity of lipid membranes thereby upregulated progression of cancer (Swierczynski *et al.*, 2014). Raised plasma fatty acid concentration elevates the liver in the transformation of some unsaturated fats into phospholipids and cholesterol.

Table.1 The levels of glycoconjugates in the plasma of control and experimental animals in each group

Parameters/ Groups	Control	DMBA	DMBA + Gramine (80 mg/kg bw)	Gramine alone
Protein bound hexose [mg/dl]	88.36±8.91 ^a	131.62±13.09 ^b	99.44±10.39 ^c	90.13±9.05 ^a
Protein bound hexosamine [mg/dl]	72.61±7.32 ^a	117.45±11.53 ^b	84.11±8.72 ^c	73.18±7.56 ^a
Total Sialic acid [mg/dl]	45.73±4.67 ^a	74.82±7.53 ^b	57.94±5.77 ^c	46.43±4.66 ^a
Lipid bound sialic acid [mg/dl]	11.46±1.17 ^a	30.95±3.03 ^b	19.63±1.94 ^c	12.86±1.29 ^a
Fucose [mg/dl]	7.98±0.9281 ^a	19.73±1.96 ^b	10.62±1.13 ^c	8.05±0.79 ^a

Values are expressed as the mean ± SD for 10 hamsters in each group. Values that are not sharing a common superscript letter in the same column differ significantly at p<0.05[DMRT].

Table.2 The levels of glycoconjugates in the erythrocyte membrane and buccal mucosa of control and experimental animals in each group

Parameters/ Groups	Control	DMBA	DMBA + Gramine (80 mg/kg bw)	Gramine alone
Erythrocyte Membrane				
Protein bound hexose [µg/mg protein]	126.15±12.63 ^a	87.52±8.81 ^b	113.21±11.97 ^c	125.63±12.57 ^a
Protein bound hexosamine [µg/mg protein]	87.50±8.71 ^a	55.40±5.62 ^b	74.27±7.50 ^c	85.29±8.49 ^a
Total sialic acid [µg/mg protein]	35.43±3.57 ^a	19.14±2.02 ^b	30.96±3.11 ^c	34.90±3.61 ^a
Buccal Mucosa				
Protein bound hexose [mg/g tissue]	109.74±10.98 ^a	156.15±15.71 ^b	121.49±12.11 ^c	111.19±11.27 ^a
Total sialic acid [mg/g tissue]	17.13±1.80 ^a	34.55±3.67 ^b	22.12±2.30 ^c	17.95±2.03 ^a
Fucose [mg/g tissue]	12.64±1.27 ^a	25.36±2.61 ^b	18.73±1.88 ^c	13.74±1.40 ^a

Values are expressed as the mean ± SD for 10 hamsters in each group. Values that are not sharing a common superscript letter in the same column differ significantly at p<0.05[DMRT].

Table.3 The levels of lipid profile in the plasma and buccal mucosa of control and experimental animals in each group

Parameters/ Groups	Control	DMBA	DMBA + Gramine (80 mg/kg bw)	Gramine alone
Plasma				
Total cholesterol [mg/dl]	97.10±9.69 ^a	131.69±13.17 ^b	108.82±10.81 ^c	96.13±9.61 ^a
Phospholipids [mg/dl]	130.49±13.05 ^a	93.62±9.41 ^b	119.18±12.10 ^c	129.56±13.07 ^a
Free fatty acid [mg/dl]	8.96±0.97 ^a	16.71±1.68 ^b	10.96±1.03 ^c	9.21±0.93 ^a
Triglyceride [mg/dl]	85.29±8.64 ^a	51.89±5.20 ^b	76.13±7.70 ^c	84.53±8.49 ^a
C/P Ratio	0.87±0.09 ^a	1.45±0.16 ^b	1.03±0.10 ^c	0.89±0.09 ^a
Buccal Mucosa				
Total cholesterol [µg/mg tissue]	4.21±0.44 ^a	7.95±0.80 ^b	5.17±0.52 ^c	4.36±0.42 ^a
Phospholipid [µg/mg tissue]	14.71±1.50 ^a	8.45±0.91 ^b	11.85±1.12 ^c	15.62±1.60 ^a
Free fatty acid [µg/mg tissue]	15.29±1.56 ^a	7.94±0.83 ^b	13.07±1.40 ^c	15.93±1.60 ^a
C/P Ratio	0.37±0.04 ^a	0.89±0.09 ^b	0.43±0.05 ^c	0.38±0.04 ^a

Values are expressed as the mean ± SD for 6 hamsters in each group. Values that are not sharing a common superscript letter in the same column differ significantly at p<0.05[DMRT].

Table.4 The levels of lipid profile in the erythrocyte membrane of control and experimental animals in each group

Parameters/ Groups	Control	DMBA	DMBA + Gramine (80 mg/kg bw)	Gramine alone
Total cholesterol [$\mu\text{g}/\text{mg}$ protein]	118.63 \pm 11.92 ^a	159.74 \pm 16.27 ^b	127.13 \pm 12.60 ^c	119.62 \pm 12.07 ^a
Phospholipids [$\mu\text{g}/\text{mg}$ protein]	245.63 \pm 24.67 ^a	193.27 \pm 19.40 ^b	232.19 \pm 23.15 ^c	244.87 \pm 24.51 ^a
Free fatty acid [$\mu\text{g}/\text{mg}$ protein]	13.95 \pm 1.41 ^a	27.65 \pm 2.81 ^b	18.94 \pm 2.02 ^c	14.20 \pm 1.47 ^a
C/P ratio	0.53 \pm 0.05 ^a	1.08 \pm 0.11 ^b	0.64 \pm 0.07 ^c	0.54 \pm 0.05 ^a

Values are expressed as the mean \pm SD for 10 hamsters in each group. Values that are not sharing a common superscript letter in the same column differ significantly at $p < 0.05$ [DMRT].

However, decrease in plasma triglycerides indicates an increase in lipolysis during carcinogenesis (Rajkamal *et al.*, 2010). Increase in C/P ratio in plasma and tumor tissue has been well documented in several types of cancerous conditions. Hence agents that recover these abnormal lipid statuses in the cell membrane have been successfully used in treating of oral cancer. In the present study it was observed the aberrant levels of total cholesterol, triglycerides, phospholipids, free fatty acids and C/P ratio in DMBA induced tumor bearing hamsters. Oral administration of gramine (80 mg/kg bw) significantly normalized the levels of lipid profile and improved the integrity of cell structure and function.

A similar finding were obtained from anticancer agent taxol that modulate these lipid abnormalities on 7, 12-dimethylbenz[a]anthracene induced mammary gland carcinogenesis in Sprague Dawley rats (Gokul Raj *et al.*, 2015). Thus, gramine significantly normalized the levels of lipid profile leads to improve the integrity of cell structure and function against DMBA induced HBP carcinomas.

Taken together, these data indicate that gramine regulate altered membrane glycoprotein and lipid profiles and structure in tumor bearing animals. Further studies are warranted to elucidate the mechanistic pathway on effect of gramine in DMBA affected hamster buccal pouch carcinogenesis by molecular signalling pathway. These finding may clarified that gramine has ability to suppress malignancy through modulating cell membrane abnormalities thereby suppressing oral cancer.

Conflict of interests: This research has no conflict of interest

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