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Induction Of Non-Cytochrome Mediated Enzymes- Xanthine Oxidase And Glutathione-S-Transferase By 3-Methylcholanthrene In Kidney Tissues Of Male Albino Mice

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Abstract

3-Methycholanthrene, a potent polycyclic aromatic carcinogen, induces the activities of Phase I and Phase II drug metabolism enzymes in the body. Increase in the activities of Cytochrome P-450, a most important Phase I enzyme, by 3-Methylcholanthrene in liver and kidney tissues are well established. However the effect of this aromatic carcinogen on non-cytochrome mediated drug metabolizing enzymes-renal xanthine oxidase and Glutathione-s-transferase in renal tissues is still not clear. In the present investigation it is found that intraperitonal administration of 0.25 ml of 3-Methylcholanthrene significantly elevates the activities of xanthine oxidase ($p< 0.05$) and Glutathione-s-transferase ($p<0.05$) activities in the kidney tissues. From the present study it can be concluded that like liver tissues, kidney tissues are highly modulated by the administration of xenobiotics and carcinogens. This finding can be of significant therapeutic, toxicological and pharmacological importance.

Keywords: 3-Methylcholanthrene (3-MC), Xanthine Oxidase (XO),Glutathione-s-transferase (GST), Kidney tissues, Xenobiotics

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INTRODUCTION

A variety of carcinogenic chemicals of natural or anthropogenic origin are known to exist in human beings based on industrial exposure , epidemiology and migrant population studies, of which chemical agents appear to be of major importance in the induction of neoplasm and other malignancies[1]. Most of these xenobiotics are metabolized in our body through a series of chemical cascade mediated by phase I enzymes lead by cytochrome P-450 isoforms. Similar type of xenobiotic detoxification and metabolism are also carried out by phase II enzymes. Xanthine oxidase (XOD) and glutathione-s-transferase (GSTs) are important phase II xenobiotic enzymes which are reported to produce therapeutically active metabolites and reactive or toxic metabolites and they modulate the efficacy of therapeutically active drugs or contribute to detoxification. Many of them have been shown to be important in endobiotic metabolism[2,3].

Xanthine oxidase (XOD) catalyzes the metabolism of hypoxanthine and xanthine to uric acid, the overproduction and/or under-excretion of which could cause the incidence of hyperuricemia[4]. XOD is a well characterized flavor enzyme containing FAD, molybdenum and iron and is known as the rate limiting enzyme in purine and pyrimidine catabolism[5]. Recent studies have demonstrated its ability in xenobiotics metabolism, drug detoxification[2] and converting number of anti-cancer compounds to their active metabolites[6]. XOD is an important source of oxidant production and plays an essential role in several oxidative stress-related diseases[7]. Unlike XOD, glutathione-s-transferase (GST) family of enzymes comprises a long list of cytosolic, mitochondrial and microsomal proteins that are capable of multiple reactions with a multitude of substrates, both endogenous and xenobiotics[8]. GST supergene family is considered as an important part of cellular enzymic defense against endogenous and exogenous chemicals, many of which reported to have a carcinogenic potential[9, 10]. GST are said to take part in cellular defense detoxification system, and, perhaps evolved to protect cell against reactive oxygen metabolites[11,12]. GSTs are considered, among several others, to contribute to the phase II biotransformation of xenobiotics and carcinogens[13].Thus it can be said that both XOD and GST play an important role in detoxification and metabolism of xenobiotics.

Induction of cytochrome P-450 enzymes by polycyclic aromatic hydrocarbons such as beta-naphthoflavone or 3-methylcholanthrene (3-MC) in the hepatic and renal tissues is a well-established fact[14,15]. Methylcholanthrene is a major carcinogenic compound of polycyclic aromatic hydrocarbon groups the target organs of which are the lung, breast, oropharynx, genitourinary and gastro intestinal tracts[16].However induction of two very important xenobiotic metabolizing enzymes –XOD and GST isoforms by the 3-MC in the kidney tissues is not very clear and it is important to find out the fact whether like liver, kidney enzymes are also modulated by xenobiotics, anabolic steroids, polycyclic aromatic hydrocarbons such as 3-MC and others. Previous studies concluded no XOD activity in chicken kidney tissues[17] .Similarly most of the GST activities upon induction by 3-MC is reported from liver tissues only [11, 18, 19] .However, it is concluded that both liver and kidney tissues are effected by xenobiotics including drugs[20]. So, in the present investigation, an attempt has been undertaken to study the effect of administration of 3-methylcholanthrene on xanthine oxidase and glutathione-s-transferase activities in the kidney tissues of male albino mice.

MATERIAL AND METHODS

The experimental set up for the present investigation is started after clearance from the Ethical committee of animal welfare, department of zoology, Gauhati University, Guwahati, Assam (India). Healthy mice weighing 25 to 30 grams were collected to carry out the study. Before the experimental procedure is started, all the animals are acclimatized in the animal room for four weeks and fed on standard animal diet. Adequate measures were taken to minimize pain or discomfort to the mice and the experiments were conducted in accordance with international standards on animal welfare and were also compliant with local and national regulations. As per plan of the study the targeted number of animals are randomly divided as follows-

Group I (Normal Control Group)

10 healthy male albino mice of approximately similar weight without any sign of deficiencies are randomly selected for normal control group and maintained throughout the whole period of experiment in the same condition. During the whole period of experiment these group received normal standard diet and received no doses.

Experimental Groups

Animals selected for the experimental groups are further sub-divided into two sub-groups as-

Group II (Castor Oil Control Group)

10 healthy animals are randomly selected for the group and each animal of the group is exposed to single dose of 0.25 ml of castor oil by intraperitoneal injection. Castor oil is used as vehicle for 3-methylcholanthrene administration.

Group III (3-Methylcholanthrene [3-MC] Treated Group)

This group consists of randomly selected 30 animals weighing 27 grams (± 1gms) from the general normally healthy pool of already acclimatized animal for the study. A single dose of 0.25 mg of 3-MC dissolved in 0.25 ml of castor oil is administered intraperitoneally to each animal of these group. Prior importance is given in dose selection taking account the weight of each animal.

In the present study, an attempt is taken to investigate the effect of GST and XOD activities in kidney tissues upon administration of 0.25 mg 3-Methylcholanthrene as there is no such reported study. The study focuses to investigate the induction of GST activity by 3-MC in kidney tissues, so only the activity of GST is investigated as a general, no investigation on specific GST isoform is conducted.

3-MC is a potent carcinogen and it can induce tumour formation in the target tissues. Keeping this in mind, day selection i.e 15th, 30th, 45th, 60th, 75th and 90th for accessing enzymatic alterations and histopathogy of renal tissues has been done.

Renal tissues (10 mg) are collected from all the experimental groups of animals at selected different day interval for the estimation of GST and XOD activities. The mice were anaesthetized by diethyl ether and dissected to collect the kidney tissues. The tissues are dried over a filter paper and immediately weighted and recorded. The tissue homogenate is prepared in deionised water with the help of homogenizer and standard procedures for enzyme estimations were followed.

The method for estimation of glutathione-s-transferase (GST) and xanthine oxidase (XOD) is followed by Griffith[21] and Fried and Fried[22].

Statistical calculations were done by following Croxton methodologies[23].

RESULTS

Xanthine oxidase in kidney tissue

The mean ,SD,SEM and CV% values of XOD (unit/mg) in kidney tissue of different experimental animals are presented in Table 1 and the percentage deviation of different experimental groups from the normal control mean values are presented in Table 1.1 and the comparison of mean values with significance of variance are presented in Table 1.2.The mean xanthine oxidase activities in the normal control group of animals are found to be 0.210± 0.024 on 15th day, 0.207 ± 0.028 on 30th day, 0.198 ± 0.027 on 45th day, 0.200 ± 0.028 on 60th day, 0.204 ± 0.025 on 75th day and 0.203 ± 0.025 unit/mg on 90th day of treatment. In castor oil control group the xanthine oxidase activities are within the range of 0.201 ± 0.026 to 0.209 ± 0.027 unit/mg.

In the group of animals treated with 3-MC alone, the mean xanthine oxidase activities are 0.354 ± 0.014 on 15th day ,0.324 ± 0.055 on 30th day and 0.320 ± 0.047 unit/mg on 45th day of treatment. The enzyme activity is found to be decreased to 0.355 ± 0.010 on 75th day of treatment and 0.268 ± 0.011 unit/mg on 90th day of treatment.

Groups		Days of treatment					
		15th	30th	45th	60th	75th	90th
Normal Control Group (n=10)	Mean	0.210	0.207	0.198	0.200	0.204	0.203
	SD±	0.024	0.028	0.027	0.028	0.025	0.025
	SEM±	0.008	0.009	0.009	0.009	0.008	0.008
	CV%	11.42	13.52	13.63	14.00	12.25	12.31
Castor Oil Control Group (n=10)	Mean	0.207	0.209	0.204	0.203	0.202	0.201
	SD±	0.026	0.027	0.023	0.021	0.028	0.026
	SEM±	0.008	0.008	0.007	0.006	0.008	0.008
	CV%	12.56	12.91	11.27	10.34	13.86	12.93
3-MC treated Group (n=10)	Mean	0.354	0.324	0.320	0.393	0.355	0.268
	SD±	0.014	0.055	0.047	0.029	0.010	0.011
	SEM±	0.004	0.017	0.015	0.009	0.003	0.003
	CV%	3.95	16.97	14.69	7.38	2.81	4.10

Table 1: Presenting the mean values of xanthine oxidase (Unit/mg) in kidney tissue of different experimental groups at different days of interval

Groups	Mean % deviation	Days of treatment					
		15th day	30th day	45th day	60th day	75th day	90th day
Normal control group	Mean	0.21	0.207	0.198	0.2	0.204	0.203
Castor oil control group	% deviation	-1.42	0.966	3.03	1.5	0.98	-0.985
3-MC treated group	% deviation	68.57	56.52	61.61	96.5	74.01	32.01

Table 1.1: Presenting percentage deviation of xanthine oxidase (Unit/mg) in kidney tissue of different experimental groups from the mean values of normal control group

Glutathione-s-transferase in kidney tissues

The mean, SD ,SEM and CV% values of glutathione-s-transferase (Unit/mg) in liver tissue of different experimental animals are presented in Table 2 and the percentage deviation of different experimental groups from the normal control mean values are presented in Table 2.1 and the comparison of mean values with significance of variance are presented in Table1.2.

Enzymes	Groups		Days of treatment					
			15th day	30th day	45th day	60th day	75th day	90th day
GST	Between normal control and 3-MC	t	-2.49	-5.75	-3.03	-3.71	-3.18	-3.57
		p	>0.01	<0.01	<0.01	<0.01	<0.01	<0.01
		df	18	18	18	18	18	18
XOD	Between normal control and 3-MC	t	-5.18	-1.89	-2.25	-4.79	-5.61	-2.38
		p	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
		df	18	18	18	18	18	18

Table 1.2: Presenting significance of difference in the mean values of xanthine oxidase (Unit/mg) in kidney tissue between different experimental groups at different days interval

Groups		Days of treatment					
		15th day	30th day	45th day	60th day	75th day	90th day
Normal Control Group (n=10)	Mean	0.348	0.345	0.347	0.349	0.351	0.353
	SD±	0.046	0.031	0.038	0.033	0.041	0.039
	SEM±	0.014	0.009	0.012	0.01	0.013	0.012
	CV%	13.21	8.98	10.95	9.45	11.68	11.05
Castor Oil Control Group (n=10)	Mean	0.350	0.348	0.35	0.351	0.353	0.357
	SD±	0.041	0.046	0.031	0.026	0.021	0.032
	SEM±	0.113	0.014	0.009	0.008	0.006	0.01
	CV%	11.71	13.21	8.85	7.4	5.95	8.96
3-MC treated Group (n=10)	Mean	0.675	0.835	0.923	1.01	0.795	0.667
	SD±	0.066	0.053	0.048	0.082	0.081	0.073
	SEM±	0.02	0.016	0.015	0.025	0.025	0.023
	CV%	9.78	6.35	5.2	8.12	10.91	10.94

Table 2: Presenting the values of mean glutathione-s-transferase (Unit/mg) in kidney tissue of different experimental group in different days interval

Groups	Mean % deviation	Days of treatment					
		15th day	30th day	45th day	60th day	75th day	90th day
Normal control group	Mean	0.348	0.345	0.347	0.349	0.351	0.353
Castor oil control group	% deviation	0.574	0.869	0.864	0.573	0.569	1.13
3-MC treated group	% deviation	93.96	142.02	165.99	189.4	126.5	88.95

Table 2.1: Presenting significance of difference in the mean values of glutathione-s-transferase (Unit/mg) in kidney tissue between different experimental groups at different days interval

The mean glutathione-s-transferase activities in the normal control group of animals are 0.348 ± 0.046 on 15th day, 0.345 ± 0.031 on 30th day, 0.347 ± 0.038 on 45th day, 0.349 ± 0.053 on 60th day, 0.351 ± 0.041 on 75th day and 0.353 ± 0.039 unit/mg on 90th day of treatment. In castor oil control group the glutathione-s-transferase activities are within the range of 0.348 ± 0.046 to 0.357 ± 0.032. In the group of animals treated with 3-MC alone, increasing trend of the mean glutathione-s-transferases activities is observed with terminal decline after 60th day of treatment. The values recorded are 0.675 ± 0.066 on 15th day,0.835 ± 0.053 on 30th day,0.923 ± 0.048 on 45th day, 1.01 ± 0.082 on 60th day, 0.795 ± 0.081 on 75th day and 0.667 ± 0.073 unit/mg on 90th day of treatment. The highest activity of enzyme is observed on 60th day of treatment 0.357 ± 0.032 unit/mg.

DISCUSSION

Drug-induced liver injury has been a growing concern in the fields of drug development and clinical drug therapy because numerous drugs have been linked to hepatotoxicity[24] .However it is also stressed that like liver tissues, renal or kidney tissues are also under tremendous xenobiotic stress. Phase I enzymes mediated by Cytochrome P-450s and Phase II xenobiotic-metabolizing enzyme mediated by non - Cytochrome P-450s are involved in the metabolic activation and detoxification of various classes of environmental carcinogens and xenobiotics [13, 25]. Glutathione S-transferases (GSTs) are Phase II drug-metabolizing enzymes that catalyze the conjugation of electrophilic compounds to glutathione. This reaction generally detoxifies reactive metabolites of xenobiotics, such as drugs and environmental chemicals, and therefore, GSTs are considered toxicologically important enzymes[26].Whereas, Xanthine oxidase (XOD) plays an important role in the metabolism of drugs[27] and production of oxidative stress[28], however its role in carcinogen metabolism is still unclear.

The administration of polycyclic aromatic compounds such as beta-naphthoflavone or 3-methylcholanthrene (3-MC) is known to cause the induction of many liver microsomal monoxygenase or mixed function oxygenase activities[29] .However, activation of such enzymes in the kidney tissues by aromatic hydrocarbons is still doubtful. Polycyclic aromatic hydrocarbons (PAHs) have the potential to induce GST activity in human liver tissue and that species and tissue difference exist in the induction of this enzyme system in rats[30]. Among the inducers of mammalian drug metabolizing enzymes 3-MC, benzo(a)pyrene and polychlorinated biphenyl enhanced the microsomal GST activity quite considerably. Study also contradicts that treatment with MC had no effect on the levels of GST enzyme activity in either the fetal lung or liver tissue of mice[31]. Either increased or decreased XOD activities have been noticed after drug administration in liver and kidney tissues [28, 32, 33]. The treatment of mice with 3-MC is reported to induce XOD activities in

liver tissues[32] the effect of carcinogens on XOD activity in kidney tissues are still fragmentary.

In the present study a significant XOD activities have been observed in selected days intervals upon the administration of 3-MC. Under 3-methylcholanthrene exposure the xanthine oxidase activity initially responded by about 75 percent increase above base line with a secondary peak by the 60th day of administration subsequently declining to the terminal part of study. It may be due to the production of oxygen free radicals by XOD occurred due to metabolism of carcinogen, xenobiotics and drugs[32]. Study indicates involvement of the oxygen radicals probably formed by the enzyme xanthine oxidase during reperfusion injury to the kidney and skin that help in organ preservation and transplantation[34]. Augmentation of XOD activities on free radical production is also documented[35].

Declining XOD expression may also indicate altered histo-pathological conditions. Patients with breast cancer showed a decreased xanthine oxido-reductase expression. Decreased Xanthine oxido-reductase (XOR) is reported with advanced stage deep tumour penetration, large tumour size, cellular aneuploidy and high cycloxygenase-2 expression[36].Marked alteration of XOD, in present study, thus can be said significant. XOD expression in carcinogen metabolism thus needed much more elaborate study as there is an significant correlation between XOD activity and carcinogenesis process.

GSTs are considered, among several others, to contribute to the phase II biotransformation of xenobiotics and carcinogens[13] .Drugs, poison and other compounds are usually somewhat modified by the phase I and/or phase II mechanisms, and finally found to excrete from the body. GSTs are thought to contribute to this type of metabolism by conjugating these compounds with reduced glutathione to facilitate dissolution in the aqueous cellular and extracellular media, and, from there, out of the body. Glutathione conjugation is considered to be an innate protective mechanism, developed to protect the body from potentially damaging electrophilic compounds.

In the present study, increasing trend of the mean GST activities are observed with terminal decline after 60th day of 3-MC treatment. A number of studies showed the effect of 3-MC on GST isoform activities in liver tissues but the present study showed the possible alternation of GST isoforms in renal tissues upon 3-MC administration from the normal baseline. GSTs are critical enzymes for detoxification of endogenous and environmental carcinogens and in a study increased GST activities were observed in liver and kidney tissues upon Adriamycin administration[37].

It is interesting to notice that the activities of both XOD and GST enzymes accelerated till 60th days of 3-MC treatment after that both showed declining trends. This is a remarkable trend which shows a positive correlation between the modes of action of both enzymes. It can be said that oxidative stress marker – GST may have played a protective during free radical production by XOD.As in one of the study it is observed that there is a concrete relationship between GST isoforms and oxidative stress in hepatocellular carcinoma[38]. It is also reported that reduced GST expression might contribute to oxidative stress in the development of hepatocelluar carcinoma and it is concluded that GST isoform (GST P1) is an important phase II enzyme that can protect cells from oxidative stress in various human cancers[38].

From the above investigation it can be concluded that kidney tissues, like the hepatic tissues, are also modulated by the exposure to the carcinogens and xenobiotics. It is also suggested that the contribution of specific isoform of GST that showed the enzymic variation is to be investigated which can help in deeper view of the histo-pathological conditions. The altered GST and XOD enzyme activities found in renal tissues is a significant finding and this result can be of great toxicological and pharmacological importance.

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