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RESEARCH ARTICLE

CHANGES IN SERUM GLUCOSE, CHOLESTEROL AND PROTEIN AS METABOLIC MARKERS DURING 3MC INDUCED CARCINOGENESIS SUPPLEMENTED WITH THYROXINE

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ABSTRACT

There are convincing evidences from animal model system that thyroid hormone exhibits strong link with carcinogenesis through its profound impact on metabolism.However, the relationship between thyroxine and different metabolic markers to denote the stage of progression or regression of carcinogenesis is still not clear. The present study was therefore conducted to highlight the effect of thyroxine on some metabolic markers- glucose**,** cholesterol and total protein during 3-methylcholanthrene (3MC) induced carcinogenesis in male albino mice. In the animal group treated with single dose of 0.5mg 3-methylcholanthrene and daily dose of thyroxine, the fluctuation trend of serum glucose level was similar and which was decreased than the normal control group. The serum cholesterol level also revealed a declining trend from the normal control base line on exposure to thyroxine-3-methylcholanthrene combination and solitary 3- methylcholanthrene treated group. The total protein level showed a steady increase throughout the period of experiment which begin with 48.80% elevation and finally reached 118.86% increase on maintenance of an adequate thyroxine level in presence of 3-methylcholanthrene. The catabolic parameters represented by glucose and cholesterol were not drastically influenced but the anabolic parameter protein was considerably stabilized and augmented.

INTRODUCTION

Thyroid hormone stimulates almost all aspects of carbohydrate metabolism, including rapid uptake of glucose by adipose tissue and muscles enhanced glycolysis,enhanced gluconeogenesis, increased rate of absorption from the gastrointestinal tract and even increased insulin secretion with its resultant secondary effects on carbohydrate metabolism. T3 and T4 stimulate enzymes concerned with glucose oxidation which in turn increase metabolic rate, oxygen consumption and body heat production (Rall *et al.*,1964).The reported data suggested that impaired glucose tolerance is an independent predictor for cancer mortality(Oh *et al.*,,2004; Khaw *et al.*,2004;Short *et al.*,2007). Breast cancer is characterized by elevated glucose consumption (Avril et al, 2001). Neoplastic cells have been shown to extensively use glucose for proliferation(Warburg,1956) .Abnormal glucose metabolism is associated with pancreatic cancer mortality (Dimitriadis et al**,** 2008 ; Gapstur et al , 2001). Plasma glucose might influence circulating hormone, such as insulin,which might themselves be involved in cancer.

Alteration of thyroid function affect the level of lipid in serum. The lipid most usually examined is cholesterol and most animal studies have showed that cholesterol synthesis is augmented in hyperthyroidism and depressed in hypothyroidism(Kritchevsky , 1960).The conversion of cholesterol to bile acid is accelerated by the presence of the circulating thyroid hormone(E.rikosson, 1957).The mildly hyperthyroid state has an accelerated rate of cholesterol turnover which suggests increased rate degradation of the plasma cholesterol (Rall *et al.*,1964).The low serum cholesterol has been associated with an increased rise of cancer mortality (Hughes *et al.*,2001; Homma *et al.*,2004).Findings of various experimental works suggested a positive association between serum total cholesterol levels and the rise of colorectal cancer (Oh *et al.*,2004 ;Corpet,2003; Giovannucci *et al.*,2004; Hauret *et al.*,2004; Higginbotham et al, 2004; Slattery *et al.*,2004).The available data on serum cholesterol level and cancer suggested that preclinical cancer causes a lowering of blood cholesterol(McMichael *et al.*,1984).Thyroid hormone increases the production of enzymes which promote protein synthesis. According to various investigators T4 plays a major role in the synthesis of protein and stimulates microsomal protein synthesis (Lewallen *et al.*,, 1959; Sokoloff *et al.*, 1968)

Though various investigators reported the role of thyroid hormone on metabolism but the interconnecting mess among the metabolism, thyroid hormone and cancer is not clear.Therefore the present investigation was aimed to evaluate further the changes in serum glucose,cholesterol and total protein as metabolic markers during 3-methylcholanthrene induced carcinogenesis supplemented with thyroxine.

MATERIALS AND METHODS

20 healthy male albino mice weighing between 55gm-60gm were taken as the experimental animals. Animals were randomly divided into five groups - Group I - Normal control group, Group II- Castor oil control,Group III -Thyroxine treated, Group IV- 3-methylcholanthrene treated(3MC),

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GroupV- 3-methylcholanthrene + Thyroxine combination treated.Each animal of the castor oil group was exposed to single dose of 0.25ml(250µl)of castor oil by intraperitoneal injection. Thyroxine treated group consist of male albino mice each of which was fed daily with 10µg of thyroxine solution till the end of the experiment. In the 3- methylcholanthrene treated group each animal was administered intraperitonially a single dose of 0.5 mg of 3-methylcholanthrene in 0.25ml of castor oil.On the onset of the experiment in the thyroxine supplemented 3-methylcholanthrene treated group all animals were intraperitoneally administered with a single dose of 0.5mg 3-methylcholanthrene with simultaneous daily oral administration of 10 µg of thyroxine.All animals were kept under the same environmental conditions and were fed with the same standard diet.

All chemicals were used of highest grades available.Serum glucose was estimated by following Trinder's (1969) method of glucose oxidase peroxidase using 4-amino antipyrine and phenol as the chromogenic reagent- producing maximum absorbance at 546 nm .Serum cholesterol was estimated by reagent kit of Dr.Reddy's dependent on enzymatic method with end point suitable colorimetric estimation. Total protein blood serum was estimated by following the method of Lowry *et al.*, 1951.

The data obtained during the period of investigation were statistically analysed after Croxton (1953).The mean,the standard error of mean,coefficient of variation (%)and the percentage deviation for each set of data were calculated and compared with different set of data by applying standard statistical procedure to evaluate the changes among different groups in the study. The levels of significance between two sets of data were calculated according to student "t" test.Probability i.e p value <0.01 for two sets of data were taken as significant.

Blood collection

Before initiation of the experimental part blood samples were collected from the whole general pool of acclimatized animals to get a normal baseline on the day "zero"of the experimental period. Subsequently,blood samples were collected from each of the individual group along with the normal group on 10^{th},15^{th},20^{th},25^{th},30^{th},45^{th},60^{th},75^{th},90^{th} and 120^{th} days of treatment.

RESULTS

The results obtained in the investigation were summarized in the table 1, 2 and 3. In the animal group receiving daily dose of thyroxine, there was depression of serum glucose between -10 to -30% below the baseline represented by normal control group.However, no significant difference in mean values was observed between normal control and castor oil treatment group. The blood glucose values exhibited a similar depressing trend with fluctuation between -10 to -30% in both the solitary 3MC treated group and the 3MC - thyroxine combined group (Table- 1).

The serum cholesterol level of both the normal and experimental control group revealed no significant ($p>0.05$) variation throughout the period of experiment. On exposure to the daily dose of thyroxine the serum cholesterol level gradually declines from the normal control base line and the maximum value of -40% from the reference base line was attained on the 90^{th} day (Table- 2).On single dose administration of 3MC followed by daily dose of thyroxine,cholesterol level exhibited a fluctuating trend signified by decline initiated with -22% on 10^{th} day which recovered to a level of -9.78% on 25^{th} day followed by a second phase of augmented decline reaching its peak of about -36.29% on 45^{th} day which subsequently recovered and attained the normal base line at the end of the experiment on 120^{th} day (Table-2).On administration of 3-methylcholanthrene the serum cholesterol level exhibited a trend similar to the group receiving both thyroxine and 3MC but they were in opposite phase. In the fluctuating trend line of percent deviation of these two groups the values of one group corresponded with the peaks of the other (Table-2).

In contrast to the absence of any significant variation ($p>0.05$)in the serum total protein of the normal and castor oil control groups there was elevation between 20% to 80% in the thyroxine treated group throughout the period of experiment. In the group treated with single dose of 3MC serum protein level exhibited a rhythmic fluctuation with amplitudes of 0 - 25% elevation within the initial period up to the 30^{th} day which was followed by 12 to 52% elevation towards the later part up to the 90^{th} day ultimately leveling with the baseline with 0% deviation on 120^{th} day (Table-3).On simultaneous administration of 3MC followed by daily thyroxine administration serum total protein values exhibited a increasing trend line throughout the period of experiment which began with a 48.80% elevation on 10^{th} day finally reaching a 118.86 % increase on 120^{th} day (Table- 3)

DISCUSSION

The thyroid metabolic hormone has profound impact on metabolism and specific bodily mechanism (Rall et al ,1964).Increased thyroid hormone decreases the quantity of cholesterol,phospholipids and triglycerides in the plasma,even though it increase the free fatty acids (Jones *et al.*,1955).T4 plays a important role in synthesis of protein. Thyroid hormone increases synthesis of serum albumin (Lewallen *et al.*,1959).Hyperthyroidism is typically associated with worsening glycemic control and increased insulin requirement which might themselves be involved in cancer development (Larson *et al.*,2007; Hartman *et al.*,2010; George *et al.*,2009).

In the present study it was observed that the effect of thyroxine on the three metabolic parameters represented by glucose, cholesterol and total protein basically catabolic for glucose and cholesterol and anabolic for protein metabolism. On exposure to 3MC the equilibrium of these metabolic indexes were altered and the tendency for attaining re-equilibrium was observed as the fluctuating trends in the investigation.On maintenance of an adequate thyroxine level in presence of 3MC the catabolic parameters represented by glucose and cholesterol were not drastically influenced but the anabolic parameter protein is considerably stabilized and augmented. The coupled effect of 3MC and thyroxine on protein metabolism may be explained in terms of the common nuclear target of both the agents whereas the relatively

Table 1 Mean values of serum glucose (mg/dl)in different groups with percent deviation from the normal control group.

Groups		DAYS OF TREATMENT 10th	15th	20th	25th	30th	45th	60th	75th	90th	120th
Normal control GroupI	Mean	130.60	131.02	130.75	30.25	132.20	130.85	131.92	132.66	131.94	130.65
	±SEM	1.83	1.80	1.81	1.89	1.92	1.64	1.77	1.81	1.87	1.84
	CV%	6.27	6.11	6.19	6.48	6.51	5.62	5.99	6.12	6.33	6.31
Castor oil control GroupII		ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	Mean	132.01	128.90	130.56	134.06	131.02	132.78	129.21	135.44	132.79	134.13
	±SEM	1.86	1.80	1.88	2.03	1.80	1.82	1.94	0.06	2.05	2.02
	CV%	6.29	6.24	6.43	6.76	6.11	6.13	6.71	5.97	6.89	6.75
	%Dev	1.08	-1.62	-0.15	2.93	-0.89	1.47	-2.05	2.10	0.64	2.66
Thyroxine control GroupIII		▲	*▲Φ	*▲Φ	* Φ	*▲Φ	*	*▲Φ	* Φ	*▲Φ	*
	Mean	135.65	93.28	109.03	105.40	101.95	111.35	100.35	102.11	94.01	113.25
	±SEM	1.73	1.90	1.98	1.80	1.79	2.27	1.90	1.76	2.33	2.06
	CV%	5.72	9.14	8.10	7.67	7.88	9.14	7.85	7.75	11.08	8.15
	%Dev	3.87	-28.80	-16.41	-19.08	-22.88	-14.90	-23.93	-23.03	-28.75	-13.32
3MC GroupIV		*◙Φ	◙	*◙ Φ	*Φ	*◙ Φ	*	*◙	*	*◙ Φ	*
	Mean	116.40	131.45	91.80	107.05	93.25	10.45	116.08	101.01	144.80	110.70
	±SEM	2.18	1.11	1.45	2.05	2.36	1.10	1.77	1.88	2.05	2.26
	CV%	8.37	3.80	7.10	8.59	11.32	4.15	6.80	8.35	6.34	9.16
	%Dev	-10.87	0.33	-29.79	-17.81	-29.46	-15.59	-11.46	-23.79	9.75	-15.27
3MC + Thyroxine GroupV		▲	◙	*◙▲	*◙▲	*◙▲	*	*◙	*◙	*◙▲	*
	Mean	134.50	128.60	100.40	145.05	112.05	108.00	115.40	99.60	125.05	112.65
	±SEM	1.26	1.60	2.45	1.86	1.85	1.76	1.39	2.01	1.65	1.80
	CV%	4.19	5.59	10.95	5.76	7.37	7.32	5.39	9.05	5.91	7.16
	%Dev	2.99	-1.85	-23.21	11.36	-15.24	-17.46	-12.52	-24.92	-4.88	-13.78

ND =Not detectable,* p =<0.01as compared with GrI, ◙ P =<0.01as compared with GrIII, ▲ P =<0.01as compared with GrIV,Φ P =<0.01as compared with GrV.

Table 2 Mean values of cholesterol (mg/dl) in different groups with percent deviation from the normal control group.

Groups		DAYS OF TREATMENT 10th	15th	20th	25th	30th	45th	60th	75th	90th	120th
Normal control GroupI	Mean	80.05	80.47	81.10	80.91	80.76	82.41	81.72	82.02	81.35	80.67
	±SEM	2.38	2.26	2.33	2.17	2.22	2.18	2.24	2.26	2.18	2.36
	CV%	13.31	12.55	12.84	12.01	12.28	11.81	12.24	12.31	11.97	13.08
Castor oil control GroupII		ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	Mean	82.51	81.75	78.46	84.46	82.97	8.94	82.69	81.82	79.77	82.98
	±SEM	2.29	2.25	2.17	2.23	2.36	2.20	2.23	2.35	2.27	2.27
	CV%	12.39	12.29	12.39	11.85	12.72	12.47	10.12	12.83	12.71	12.15
	%Dev	3.07	1.59	-3.26	4.39	2.74	-4.21	1.19	-0.24	-1.94	0.02
Thyroxine control GroupIII		▲ Φ	▲ Φ	* Φ	*▲	▲ Φ	* Φ	*	*▲ Φ	*▲ Φ	*▲ Φ
	Mean	74.00	80.60	70.50	70.45	79.55	68.70	65.40	66.28	50.25	61.45
	±SEM	1.95	1.79	1.83	1.83	2.04	2.16	1.86	2.16	1.70	1.95
	CV%	11.80	9..96	11.64	11.66	11.48	14.07	12.73	14.62	15.20	14.26
	%Dev	-7.56	0.16	-13.07	-12.93	-1.50	-16.64	-19.97	-19.19	-38.23	-23.83
3MC GroupIV		*◙ Φ	*◙ Φ	* Φ	*◙ Φ	Φ◙	* Φ	*	◙ Φ	*◙	*◙ Φ
	Mean	54.80	57.05	68.57	56.05	76.10	69.30	66.00	81.20	62.60	54.30
	±SEM	1.48	1.77	1.36	1..50	1.84	2.00	1.79	1.77	1.40	1.42
	CV%	12.15	12.56	8.88	12.02	10.81	12.95	12.19	9.79	10.06	11.72
	%Dev	-31.54	-29.10	-15.45	-30.73	-5.77	-15..91	-19.24	-1.00	-23.05	-32.69
3MC + Thyroxine GroupV		*◙▲	*◙▲	*◙▲	*	*◙▲	*◙▲	*	*◙▲	*◙▲	◙▲
	Mean	63.20	67.75	61.55	73.00	69.50	52.50	66.70	60.10	64.35	79.30
	±SEM	1.19	1.40	1.30	1.73	1.67	1.16	1..29	1.31	1.09	1.47
	CV%	8.46	9..29	9.45	10.65	10.79	9.89	8.68	9.79	7.58	8.34
	%Dev	-21.05	-15.81	-24.11	-9.78	-13..94	-36.29	-18.38	-26.73	-20.73	-1.70

ND =Not detectable,* p =<0.01as compared with GrI, ◙ P =<0.01as compared with GrIII, ▲ P =<0.01as compared with GrIV,Φ P =<0.01as compared with GrV.

inconsistent effects observed on the carbohydrate and lipid metabolism may be the decentralized influence of these agents through fractional sharing of some metabolic loops. With thyroxine administration the total protein is elevated with a sinusoidal trend which is also the character of total protein elevation under the influence of solitary 3MC exposure but the trends are totally phase reversed. The phenomenon of observed phase reversal may be due to coincidence of the periods of maximal metabolic degradation of 3MC with minimal circulating thyroid hormone level due to feedback control mechanism coinciding around ninety days of treatment. The observed phenomenon of phase reversal in the fluctuating serum cholesterol levels with solitary and thyroxine coupled 3MC

The overall trends of changes in carbohydrate and lipid metabolism under influences of thyroxine and 3-methylcholanthrene is basically similar to the changes in protein levels in the reverse direction with lowering of circulating values below the normal control base line and with a diminished scale. administration suggest an interactive mechanism between thyroxine and 3-methylcholanthrene which is basically synergistic but controlled by a feedback loop,a part of which is common to the metabolic locus of both the agents. The overall trend of changes in carbohydrate and lipid metabolism under influence of thyroxine and 3-methylcholanthrene is basically similar to the changes in protein levels in the reverse direction with lowering of

circulating values below the normal control base line and with a diminished scale.The stabilizing and augmenting effect of the 3-methylcholanthrene and thyroxine combination on total protein have two components. One of the component may act through the 3MC induced changes in the nuclear level which may augment the thyroxine induced effects on protein synthesis. The other component may act through the thyroxine mediated control of gene expression ,some products of which may dampen the fluctuation in protein synthesis induced by 3MC.

Table 3 Mean values of serum total protein (gm/dl) in different groups with percent deviation from the normal control group.

DAYS OF TREATMENT

Groups		10th	15th	20th	25th	30th	45th	60th	75th	90th	120th
Normal	Mean	4.57	4.80	4.10	4.92	4.74	4.25	4.91	4.50	4.74	4.93
control	±SEM	0.08	0.17	0.09	0.11	0.08	0.09	0.10	0.09	0.08	0.07
GroupI	CV%	7.66	15.42	10.73	9.96	7.59	9.65	9.37	9.33	7.38	6.49
		ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Castor oil	Mean	4.74	5.10	4.27	4.93	4.91	4.44	4.88	4.57	5.02	4.84
control	±SEM	0.09	0.11	0.16	0.02	0.14	0.04	0.04	0.03	0.17	0.09
GroupII	CV%	9.28	9.80	16.63	2.23	12.63	3.60	3.89	2.63	15.53	9.09
	%Dev	3.72	6.25	4.15	0.20	3.59	4.47	-0.61	1.53	5.91	-1.83
		*▲	*▲	*▲Φ	* ▲Φ	*▲Φ	*▲Φ	*▲Φ	* Φ	*▲Φ	*▲Φ
Thyroxine	Mean	6.71	7.48	7.33	6.73	7.64	7.08	7.23	6.26	5.86	6.96
control	±SEM	0.15	0.15	0.73	0.13	0.15	0.16	0.15	0.18	0.15	0.17
GroupIII	CV%	10.05	9.29	9.99	9.28	9.18	10.50	9.45	13.41	11.72	11.06
	%Dev	46.83	55.83	78.78	36.79	61.18	66.59	47.25	39.11	23.63	41.18
		◙Φ	◙Φ	*◙Φ	◙Φ	◙Φ	*◙Φ	*◙Φ	* Φ	*◙Φ	◙Φ
3MC	Mean	5.58	4.88	5.17	4.69	4.62	6.43	5.51	6.50	6.74	4.91
GroupIV	±SEM	0.20	0.16	0.16	0.18	0.19	0.14	0.14	0.17	0.19	0.18
	CV%	16.80	15.32	14.46	17.36	18.74	9.96	11.73	11.87	13.08	16.94
	%Dev	22.10	1.67	26.10	-4.67	-2.53	51.29	12.21	44.44	42.19	-0.41
		*▲	*▲	*◙▲	*◙▲	*◙▲	*◙▲	*◙▲	*◙▲	*◙▲	*◙▲
3MC +	Mean	6.80	7.48	8.27	7.53	9.39	7.97	9.74	9.41	10.97	10.79
Thyroxine	±SEM	0.18	0.20	0.12	0.20	0.15	0.12	0.18	0.12	0.14	0.11
GroupV	CV%	12..14	12.45	6.97	12.30	7.30	7.19	8.39	5.82	6.09	4.58
	%Dev	48.80	55.83	101.71	53.05	98.10	87.53	98.37	109.11	131.43	118.86

ND=Not detectable, * P=<0.01as compared with GrI, ◙ P=<0.01as compared with GrIII, ▲ P=<0.01as compared with GrIV,Φ P=<0.01as compared with GrV .

CONCLUSION

The metabolic response is basically augmentive with protein metabolism and repressive with carbohydrate and lipid metabolism.Under a steady but minimal hyperthyroid state maintained under the experimental condition a marginally hypermetabolic state easily explained the observed depression of glucose and cholesterol under the influence of the thyroid hormone. From the observation presented in tables-1,2and 3 it may be suggested that 3-methylcholanthrene does not exert much interference in the metabolism of carbohydrates and lipid but significantly alter the protein homeostasis which is augmented in presence of thyroxine.

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