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Plasma Insulin and Working Dynamics of Calcium Channel Blockers on Thyroid Hormone Impaired Glucose Metabolism

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Authors' contributions

This work was carried out in collaboration between both authors. Author EEB designed the study, wrote the protocol and wrote the first draft of the manuscript. Author ISE managed the literature searches, analyses of the study performed the spectroscopy analysis and the experimental process. Both authors read and approved the final manuscript.

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ABSTRACT

The use of calcium channel blocker as supplementary in thyroid hormone treatment had been strongly proposed but gradually became unpopular after observations that clinical outcomes for angina, or myocardial infarct were not improved by the use of these agents. This study therefore examined the influence of calcium channel blockers on thyroid hormone impaired glucose metabolism. Twenty (20) male albino Wistar rats were randomized into four groups (n= 5 per group). Two groups were respectively pre-treated with verapamil (20 mg/Kg body weight) or nifedipine (20 mg/Kg body weight) 20 mins before oral administration of L- Thyroxine (L-T4) 20 ug/kg body weight twice daily for six (6) days. One group received only L- Thyroxine (L-T4)

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20 ug/kg body weight twice daily for six (6) days while the control group received no drug. Glucose concentrations were measured in blood obtained from the tip of tail with one- Touch Basic glucometer on 1st, 4th and 7th days and fasting plasma insulin was measured on the 7th day using ELISA. The results showed raised plasma glucose levels on days 4 that were not significantly different from those of day 1 in all the groups. However, plasma glucose concentrations on day 7 in groups treated with L-T4 and after verapamil or nifedipine pre-treatment were significantly higher than those on day 1 and also significantly higher than those of the control group on day 7. Highest concentration of plasma glucose was observed in the nifedipine pre-treatment group on day 7. Plasma insulin level was not significantly changed. Insulin resistance indices for the levothyroxine group were not significantly higher ($p>0.05$) than that of the control. However, HOMA- IR values were significantly higher and the QUICKI values lower when levothyroxine was administered to calcium channel blockers pre-treated animals. This suggests that the thyroid hormone induced hyperglycemia was neither due to alterations in insulin concentrations by thyroxine nor can be ameliorated by the blockage of the opening of the L-voltage gated calcium channels but may be associated with increased insulin resistance.

Keywords: L-thyroxine; hyperglycaemia; calcium channel blockers; insulin resistance.

1. INTRODUCTION

The use of thyroid hormone, thyroxine (T_4) in the replacement therapy for hypothyroidism, may induce myocardial ischemia and lead to angina pectoris [1]. More recently, it has been shown that elevation of serum T3 at hospital admission is associated with the development and progression of acute myocardial ischemia [2]. This effect may in part be secondary to the profound influence of thyroid hormone on Ca^{2+} handling by the heart [3]. In the cardiomyocytes, uptake of Ca^{2+} by L-type voltage gated channels in the plasma membrane is enhanced [4,5], accelerated in the sarcoplasmic reticulum [5,6] and Ca^{2+} storage capacity is increased by thyroid hormone [6]. Therefore, Ca^{2+} channel blockers are widely used in the treatment of angina pectoris and hypertension [7]. Besides these conventional applications, Ca^{2+} channel blockers have also been proposed as supplement to T4 treatment to control cardiac thyrotoxic symptoms [1,8]. Ca^{2+} channel blockers acts by inhibiting the Ca^{2+} influx via the slow voltage gated channels in the plasma membrane thus reducing contractility of vascular smooth muscle and heart [7].

The crucial role of calcium in the control of the secretary mechanism of several endocrine glands has received a great deal of experimental and clinical supports [9]. Calcium plays an essential role in the stimulus – secretion coupling for insulin release [10,11,12]. The cytosolic accumulation and intracellular distribution of Ca2+ are important for growing number of events in the secretary process which is affected by not only the major secretagogue, glucose, but also by a variety of cholinergic, adrenergic and peptidergic influences [10,13,14,15,16]. The organic calcium blockers of both dihydropyridine (verapamil) and phenylalkylamine (nifedipine) families have been employed in the supplementary treatment with T4 [17]. The effects of the channel blockers on the blood glucose concentrations had earlier been reported [18], it was conceived that the observed thyroid hormone and verapamil potentiated hyperglycemia might be associated with changes in plasma insulin level. Therefore, this research aims to investigate the plasma insulin level following treatment with thyroid hormone in the presence and absence of verapamil pretreatment. A physiological mechanism for the possible role of thyroid hormone on insulin secretion has not been clearly established [19]. Thus, the difference in the working dynamics of the organic calcium channel blockers was considered necessary for investigation in this study.

2. MATERIALS AND METHODS

2.1 Animals

The studies were performed on twenty albino wistar rats weighing between 75 g to 123 g body weight (average of 96 g). The animals were randomly assigned to groups and were allowed seven (7) days for acclimatization before the commencement of the experiment. They were kept in the animal house under normal room temperature and a 12-12 hour dark and light cycle. The animals were fed with normal rats feed (top feed) and they had free access to drinking water.

2.2 Experiments

Experiment 1: Levothyroxine effect on blood glucose and insulin. This experiment involves treatment of five rats randomly selected with levothyroxine (L-T4) at a dose of 20 ug/Kg body weight (Forley Generic NLA; UK). Levothyroxine was administered twice daily by oral gavage for a period of six days. The body weight of the animals was taken with electronic weighing balance at intervals of two days. Samples of blood for measurement of glucose and insulin were respectively obtained from the tip of the tail and through cardiac puncture at the end of the end experiment.

Experiments 2: Effect of verapamil and nifedipine pretreatment on blood glucose and insulin levels.

In order to study the possible changes in the levothyroxine influenced blood glucose level and serum insulin in the presence of a calcium channel blocker, tens rats were treated with thyroid hormone and calcium channel blocker. A non-selective calcium channel blocker verapamil (Actavis Barinstaple, U.K) and nifedipine (dihydropyridine derivative) were used for pretreatment of these animals. In five rats, 20 mg/kg of verapamil was administered by oral gavage 20 minutes before the levothyroxine administration, and a separate set of five rats 20 mg/kg of nifedipine was used for the pretreatment. Blood sample for glucose determination was also collected from the tip of the tail while sample for insulin assay was obtained by cardiac picture.

2.3 Placebo Group

A set of five rats was equally used which received neither levothyroxine nor calcium channel blockers. Distilled water was given to ensure that they served as a control group.

2.4 Estimation of Blood Glucose and Insulin Levels

The procedures for estimation of blood glucose and serum insulin levels were as described below.

Blood glucose: The fasting blood glucose concentration was obtained using one touch glucometer (lifeScan one touch Basic, Johnson and Johnson Company, USA). The procedures were as described by the manufacturer. Determination of blood glucose was done on the day one after which the administration commences (blood glucose before treatment – BGBT) subsequent determination of blood glucose (blood glucose after treatment – BGAT) followed at intervals of two days (day 4 and day 7). The glucose levels were read off after 45 seconds from the glucometer

Serum insulin: At the end of the treatment with levothyroxine and the last glucose measurement on the seventh day, the animals were sedated with chloroform and dissected to expose the heart from which blood was collected by cardiac puncture for the insulin estimation. The blood samples centrifuged at 3000 rpm for 5 minutes the serum was carefully decanted as supernatant and stored in plain sample bottles in the freezer for the analysis. Determination of serum insulin level was done using Enzyme – linked immunosorbent Assay (ELISA) (DRS insulin ELISA kit) method. The estimation of insulin by ELISA methods follows the prescribed protocol as seen in the user's manual and reading was taken at 450 + 10 nm wavelength with a microtitre plate reader within 10 minutes after adding the stop solution.

Insulin resistance indices were calculated as follows: The HOMA index and QUICKI were derived as estimates of insulin resistance. The HOMA index was calculated as fasting insulin concentration (uU/mL) x fasting glucose concentration (mmol/L)/ 22.5. The QUICKI was calculated as 1/[log fasting insulin concentration (uU/mL) + log glucose concentration (mg/dL)].

The protocols of the research were approved by the University of Uyo Postgraduate School Research and Ethical Committee.

2.5 Statistical Analysis

Data are presented as Mean ± standard deviation. Differences between means were compared employing student's t-test and ANOVA post hoc, a probability of $p < 0.05$ was considered significant.

3. RESULTS

3.1 Changes in Blood Glucose Level within the Levothyroxine Treated Group

The blood glucose level of the L – T4 treated group is represented in Table 1. The level of blood glucose before treatment (BGBT) in levothyroxine treated group was 76.6 ± 8.73 mg/dl on day 1 of the experiment. After three

days of L - T4 administration, the level of blood glucose after treatment (BGAT) on the 4th day showed some increase up to 83.2 ± 9.34 mgdl. This increase was not significant (p>0.050) when compared to day 1 glucose level. But the BGAT on the 7th day (after six days of treatment), increased to 135.8 ± 15.44 mg/dl, indicating a percentage rise of 77.28% which was very significant (p<0.001) when compared to the value for day 1.

3.2 Blood Glucose Level in Levothyroxine Treated Group Compared to Placebo Group

Comparison between blood glucose concentrations of the L – T4 treated group and placebo group showed that the glucose levels in the L – T4 treated group on the 4th and 7th days increased significantly (p<0.05) from mean value of 97.5 + 13.9 mg/dl to 135.8 + 15.44 mg/dl representing 39.28% rise on day 7 while the increase on day 4 from mean value of 81.75 + 8.0 mg/dl to 83.2 + 9.3 mg/dl which was only 1.77% rise was not significant.

3.3 Changes in Blood Glucose Level in Levothyroxine and Verapamil Group

The result showing the comparison of blood glucose level of L – T4 + verapamil group and the placebo group was presented in the table. The results showed that the level of blood glucose after treatment (BGAT) increase from the mean value of 74.6 + 10.2 mg/dl on the first day (BGAT) to 85.4 + 9.9 mg/dl and 150.2 + 16.6 on the 4th and 7th day representing 14.48% and 101.34% increase respectively and the increase in day 7 was highly significant at p<0.001. Comparing these changes in L – T4 + verapamil treated group with the placebo, the glucose level of the treated group also showed significantly higher values on the 7th day (p<0.001) than that of the control, The percentage rise represented were 4.46% on day 4 and 54.05% for day 7.

3.4 Changes in Blood Glucose Level in Levothyroxine and Nifedipine

The result of nifedipine pretreatment and then levothyroxine showed that blood glucose increased from mean basal value of 65 + 12.0 mg/dl to 66.6 + 11.3 mg/dl (2.46%) and 172.6 + 17.41 mg/dl (165.54%) on days 4 and 7 respectively. The increase was not statistically significant on comparing between day 4 and day 1 but was highly significant (p<0.001) when glucose level on day 7 was compared to the glucose level on the 1st day. A comparison with the placebo on the other hand showed 23.31% decrease in blood glucose on the 4th day followed by a significant (p<0-001) increase of 97.3% on the 7th day.

3.5 Changes in Serum Insulin Level and Insulin Sensitivity Indices

The result at the end of the experiment shows that insulin level for the levothyroxine treated group was 8.40 + 0.43 uU/ml. and this was slightly lower than the placebo treated group which 8.68 + 0.45 mg/dl. The decrease was not statistically significant. The mean value of insulin level for levothyroxine and verapamil group was 9.0 ± 0.51 uU/ml, while the group with nifedipine was 9.28 ± 0.41 uU/ml. These values were not significantly different from those of the control group. Similarly, insulin resistance indices for the levothyroxine group were not significantly higher (p>0.05) than that of the control. However, homeostasis model assessment for insulin resistance indices (HOMA- IR) values were significantly higher and the quantitative insulin sensitivity check index (QUICKI) values lower when levothyroxine was administered to calcium channel blockers pre-treated animals.

Table 1. Blood glucose concentration (mg/dl) according to days of treatment of animals in control and experimental groups

Day	Control N = 4	L-T4 N = 5	L-T4 + Verapamil N = 5	L-T4 + Nifedipine N = 5
Day 1	71.5 ± 11.79	76.6 ± 8.73	74.6 ± 10.2	65 ± 12 .0
Day 4	81.75 ± 8.0	83.2 ± 9.34	85.4 ± 9.9	66.6 ± 11 .3
Day 7	87.5 ± 9.7	135.8 ± 15.44*[a]	150.2 ± 16.6*[a]	172.6 ± 17.4*[a]

*Mean ± standard deviation. * Significantly different from day 1 at p<0.05. [a] significantly different from control at day 7 at p<0.05*

Table 2. Plasma insulin levels and insulin resistance indices of animals in control and experimental groups

Group	Insulin µU/ml	HOMA1 – IR	QUICKI
Control	8.68 ± 0.45	2.09 ± 0.76	0.342 ± 0.018
L-T4	8.40 ± 0.43	2.82 ± 0.68	0.327 ± 0.014
L-T4 + Verapamil	9.0 ± 0.51	3.36 ± 0.58*	0.319 ± 0. 016*
L-T4 + Nifedipine	9.28 ± 0.41	3.95 ± 0.64*	0.312 ± 0.017*

*Mean ± standard deviation. * Significantly different from control at day 7 at p<0.05. N = 5 for all groups*

4. DISCUSSION

Previous studies in our laboratory reported that T4-induced blood glucose increase was potentiated by calcium channel blocker, verapamil [18]. It had been shown in the literature that insulin release depends on increase in cytosolic calcium in vitro [20] and therefore calcium channel blockers have been advocated in the treatment of hyperinsulinaemia [21]. The changes in the plasma levels of insulin were observed to be insignificant. However, there was slight decrease and slight increase in the insulin levels in the thyroid hormone and T4+ verapamil pretreated groups respectively. Nifedipine pretreatment presented with result similar to that of the verapamil pretreated group. Although this in general suggests that the insulin level was not significantly affected by the calcium channel blockers and that the observed hyperglycemia was not dependent on the effect of thyroid hormone on the plasma level of insulin, the slight decrease might be a pointer to certain events not possibly elucidated in this studies following thyroid hormone treatment.

The working dynamics of calcium channel blockers are different thus it was viewed necessary to use nifedipine since our earlier report showed that the thyroid hormone induced hyperglycemia was neither ameliorated nor abolished by verapamil [18]. It's been reported that the verapamil influences the kinetics of opening of the L-voltage channel while nifedipine influences the translocation dynamics by reducing the number of the calcium channels to the cell membrane without altering the kinetics [22]. Why the blood glucose was unaltered is not well understood and the investigated calcium channel dynamics does not show involvement of the number of calcium channel at the membrane or the opening dynamics in the thyroid hormone induced hyperglycemia. One of the nongenomic action of thyroid hormone [23,24,25] is its effect in intracellular calcium mobilization by cooperatively stimulating the endoplasmic reticulum and the mitochondria. Therefore, it might not be out of place to suggest that a different mechanism involving intracellular calcium mobilization may be activated by thyroid hormone rather than just an influx of extracellular calcium. Blood glucose in itself is a known secretagogue of insulin. Therefore, the high level of plasma glucose might rather be the reason for the slight increase in the pretreated groups insulin levels showing an indirect (permissive) influence of these calcium blockers on the T4-induced hyperglycemia.

Cellular actions of thyroid hormone have been shown to be initiated within the cell nucleus, at the plasma membrane, in cytoplasm, and at the mitochondrion [24]. Thyroid hormone nuclear receptors (TRs) mediate the biological activities of T_3 via transcriptional regulation. The transcriptional activity of TRs is regulated at multiple levels. Actions of thyroid hormone that are not initiated by liganding of the hormone to intranuclear TR are said to be nongenomic. They may begin at the plasma membrane or in cytoplasm. Plasma membrane-initiated actions begin at a receptor on integrin αvβ3 that activates ERK1/2 and culminate in local membrane actions on ion transport systems, such as the Na^+/H^+ exchanger, or complex cellular events including cell proliferation. T_3 can activate phosphatidylinositol 3-kinase by a mechanism that may be cytoplasmic in origin or may begin at integrin αvβ3 [26]. Downstream consequences of phosphatidylinositol 3-kinase activation by T_3 include specific gene transcription and insertion of Na/K-ATPase in the plasma membrane and modulation of the activity of the ATPase [27]. Systemic glucose tolerance is orchestrated by the regulated release of insulin and glucagon from the β and α cells of the pancreatic islets of Langerhans. The α and β cells are electrically excitable and use electrical signals to couple changes in blood glucose concentration to stimulation or inhibition of hormone release. In both cell types, influx of extracellular Ca^{2+} through voltage-gated Ca^{2+} channels with resultant elevation of intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) triggers exocytosis of

the hormone-containing secretory granules. Like other electrically excitable cells, both α and β cells contain several types of voltage-gated Ca^{2+} channel [27]. Pretreatment with calcium channel blocking agents, verapamil and nifedipine, in this study significantly increased the concentration of glucose compared to group without calcium blockers and also caused minimal increase in insulin levels. This slight increase in insulin may be a normal islet cell response to increased plasma glucose through mechanisms which are not necessarily related to the intracellular calcium – dependent first phase insulin release involving the L-type voltage gated channels that are sensitive to the used calcium channel blockers. Other non L-type voltage gated channels, the R-type (Cav2.3) which are not sensitive to dihydropyridines have also been identified to be responsible for the less prominent but sustained second-phase insulin secretion that can maintain the basal insulin concentration for several hours [28].

Stimulus-secretion coupling (SSC) of pancreatic islet cells resulting in insulin release involves electrical activities. The changes of the membrane potential (V(m)) are regulated by metabolism-dependent alterations in ion channel activity which in beta-cells are the effects of glucose as linked directly to mitochondrial metabolism. Cellular ATP/ADP ratio determines the opening probability of ATP-sensitive K(+) channels (K(ATP) channels) and nucleotide concentrations in the direct vicinity of the channels are controlled by several factors including phospholipids, fatty acids, and adenylate kinase. Closure of K(ATP) channels leads to depolarization of beta-cells via a yet unknown depolarizing current and Ca(2+) influx during the action potentials (APs) results in an increase of the cytosolic Ca(2+) concentration that triggers exocytosis of insulin containing granules [26].

Our results of the calcium channel blocker effects does not support the earlier reports by Fehmann et al. [29] who suggested that calcium channel blockers may reduce insulin secretion to induce hyperglycemia in isolated perfused rat pancreas. The presentation of close resemblance in the pattern of effect of the channel blockers suggest a possible different mechanism involved by thyroid hormone in its hyperglycemic action. The results of our assessment of insulin sensitivity indices were suggestive of insulin resistance as a mechanism of thyroxine-induced hyperglycaemia in the experimental animals. The insulin resistance indices (HOMA-IR) of groups pretreated with verapamil or nifedipine before levothyroxine administration were significantly higher than the group without pretreatment. The findings in this study corroborate those of Bhatnagar and colleagues [30] who reported the case of deteriorating diabetic condition following nifedipine treatment in hypertensive diabetic. This patient however, was said to recover after withdrawal of the nifedipine treatment. Thyroid hormone induced insulin resistance and hyperglycaemia may be due to thyroid hormone receptor crosstalk with other receptors that regulate glucose metabolism. Heterodimerization of thyroxine receptors with other members of the receptor superfamily, such as RXRs, vitamin D receptor, and all subtypes of the retinoic acid receptors have been shown to dramatically increase the binding of TRs to TREs, the responsiveness of TR to T_3, and the transcriptional activation [31]. Due to ubiquitous distribution of RXR and its promiscuity in heterodimerization with many members of the receptor superfamily, heterodimerization with RXR provides a means for TR to crosstalk with other receptors. Crosstalk with peroxisome proliferator-activated receptor (PPAR) signaling via heterodimerization with RXR by TR had been reported [32,33]. PPARγ regulates the expression of its target genes by binding to the PPAR response element (direct repeat+1; DR1) as a heterodimer with RXR. It has also been shown that TRβ competes with PPARγ for binding to DR1 as a heterodimer with RXR *in vitro* and *in vivo* to repress the transcriptional activity of PPARγ. Because PPARγ plays a key role in lipid metabolism and cardiovascular diseases, repression of PPARγ results in impaired fatty acid oxidation and its accumulation has been linked with increased insulin resistance, hyperglycaemia and type 2 diabetes mellitus. Repression of PPARγ activity had also been shown to activate the nuclear factor κB and JNK downstream signaling, thereby promoting chronic inflammatory activities, increased cytokines and adipokines release, impaired insulin sensitivity and hyperglycaemia [34]. The blood glucose concentrations of all the groups receiving L- thyroxine treatment were not significantly raised in day 4 of the experiment, but in day 7 the levels became dramatically increased. This observation suggest that the hyperglycemic action of thyroxine may not be related to its immediate effect of cell membrane action potential but may be the result of interactions of the cytoplasmic thyroid hormone receptors with transcription factors leading to

expression of genes whose products are diabetogenic in action. These events require longer period than cell membrane depolarization associated with intracellular calcium dynamics. Crosstalk of thyroid hormone receptors with transcription factors recognizing steroid hormone response elements can also lead to thyroxine related hyperglycemia and insulin resistance.

5. CONCLUSION

In conclusion, there is no statistically significant change in the plasma insulin levels in T4, T4+verapamil and T4+nifedipine treated rats. But the marginal increase might be secondary to the high glycemic status which was potentiated by both verapamil and nifedipine. This suggests that the thyroid hormone induced hyperglycemia was neither due to alterations in insulin concentrations by thyroxine nor can be ameliorated by the blockage of the opening of the L-voltage gated calcium channels but may be associated with increased insulin resistance.

CONSENT

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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