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Hyperglycemia and Hyperlipidemia Induced Inflammation and Oxidative Stress in Human T Lymphocytes and Salutary Effects of ω- 3 Fatty Acid

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1. Abstract

Type 2 Diabetes conditions are associated with hyperglycemia and hyperlipidemia; however, the role of Saturated Fatty Acids (SFA) *vs.* Unsaturated Fatty Acids (UFA) and high glucose on human T lymphocytes (T cells) is not known. We investigated the salutary effect of the UFA ω-3 fatty acid, α-linolenic acid, on glucose and SFA, palmitic acid, induced activation on T cells as a cause of the inflammatory process with high glucose and SFA foods. These cells in the presence of palmitic acid and/or high glucose but not linolenic acid exhibited a concentration and time-dependent emergence of insulin receptors (INSR), expression, generation of ROS, lipid peroxidation, cytokines and NF-kB p65 translocation to the nucleus. Whereas, activation of the cells by elevated levels of glucose and palmitic acid were additive, addition of linolenic acid in a dose-related manner inhibited activation of cells by glucose and palmitic acid and reduced markers of oxidative stress, lipid peroxidation and cytokines. We propose that UFAs such as α-linolenic acid may serve as a protective mechanism against the deleterious effects of hyperglycemia and hyperlipidemia of high sugar and SFA foods as in diabetes.

2. Keywords: Human T lymphocytes; Type 2 Diabetes; Inflammation; α-Linolenic acid; Palmitic acid; Hyperglycemia; Oxidative stress; Lipid peroxidation; Insulin receptors; Cytokines; NF-kB

3. Introduction

Approximately 65% of patients with T2DM die as a result of cardiovascular disease with hyperglycemia and hyperlipidemia being important risk factors for cardiovascular diseases [1]. Both Type 2 diabetes (T2DM) and atherosclerosis are considered to be inflammatory processes [2]. Human T- lymphocytes (T-cells) have been shown to be components of plaque formation in atherosclerosis [2].

T cells are unique in that in their naive state they have no insulin receptors [3] but become activated in presence of phytohemagglutinin (PHA) in vitro [3,4], as well as, in vitro hyperglycemia [5] and in situ hyperglycemic conditions such as diabetic ketoacidosis [6]. These activated T cells can then metabolize glucose in response to insulin with emergence of insulin receptors [7,8] and also develop growth factor receptors such as IGF-1, IL2 [9]. We have previously shown that T-cells in the presence of

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high concentrations of glucose [5] and palmitate [10] become activated as measured by CD69 on the cell surface and express insulin receptors, reactive oxygen species (ROS), cytokine elevation and lipid peroxidation in a time and concentration-dependent manner. Unsaturated fatty acids such as linoleic, oleic, linolenic and arachidonic acids were not able to activate these cells. Studies have shown that dietary SFA can induce insulin resistance [11]. We hypothesized that unsaturated fatty acids (UFA) may provide a protective mechanism against the prooxidant effects of hyperglycemia and high SFA such as palmitate [10].

We, therefore, investigated the in vitro effect of linolenic acid on the glucose and palmitate-induced activation of human T cells by measuring emergence of CD 69, insulin receptors, CD 25 and the production of ROS by dichlorofluorescein (DCF), lipid peroxidation by malondialdehyde (MDA) and cytokines produced. T cells were incubated at baseline, 24 hour and 72 hours with different concentrations of glucose and palmitate alone or in combination in the presence and absence of different concentrations of linolenic acid (5 µM, 100 µM and 300 µM). The inflammatory and proinflammatory effects were detected by the emergence of interleukin (IL) cytokines IL-1B, IL-6, IL-8, IL-2, IL-10 and TNFα. Herein we report on a previously unknown finding that linolenic acid partially inhibits the activation of T cells induced by either glucose or palmitate alone or in combination. Thus, linolenic acid may serve as a protective mechanism against the deleterious effects of high glucose and palmitate in human T-cells and reduce the inflammatory process observed with high blood glucose and high saturated fatty acid foods.

4. Materials and Methods

Subjects

Five non-diabetic subjects with normal glucose tolerance signed the consent form, which was approved by the Institutional Review Board of the University of Tennessee Health Science Center. Subjects were from 22 to 28 years of age and within normal weight (BMI of 21 to 24) and normal lipid and chemistry profiles and on no medications. Blood samples were obtained at sitting position after 12 hours of overnight fast.

T cell Preparation

Blood samples (50 ml) were obtained and collected in EDTA from an antecubital venipuncture and T cells were isolated from the buffy coat. CD4 T cells were isolated using negative selection reagents obtained from Dynal Biotech [5,9,10]. The purity of cells was confirmed by flow cytometry using CD4 fluorescent labeled antibodies. The CD4 T cells were counted by Beckman Coulter AcT diff (Miami, FL) hematology analyzer, viability confirmed by PI and diluted to 10 x 106 cells per ml [5]. A total of 10 x 106 CD4 T cells were used per incubation.

T cell Incubations

CD4 T cells (10 x 106) were placed in 25 cm^2 tissue culture flasks with 20 ml RPMI 1640 containing 5 mM glucose and 10% fetal bovine serum. The cells were incubated in 95% air, 5% CO_2 at 37°C for 0, 24 and 72 hours with 5, 15, or 30 mM glucose and/or 5, 100 and 300 µM of the free fatty acids (FFA) palmitate and/or linolenic acid. Stock solutions of the free fatty acids (FFA) obtained from Sigma (St. Louis, Mo) were prepared as in our previous studies [10], briefly, by dissolving the free fatty acid in ethanol then precipitating the FFA with NaOH, evaporating off the ethanol under nitrogen gas and reconstituting the precipitated fatty acid sodium salt with phosphate buffered saline (PBS) containing 10% fatty acid free bovine serum albumin (BSA) obtained from Sigma. The FFA stock solutions were stored in aliquots in tubes evacuated under nitrogen gas and stored protected from light at –200C. Aliquots of these stock solutions were added for the desired concentrations in the tissue culture media. An equal volume of the PBS solution prepared without the FFA was added to controls.

Flow Cytometry Determination of T Cell Surface Markers and Receptors: Identification of receptors for insulin, CD25, CD69, on the cell membrane were done by flow cytometry using specific fluorescent labeled antibodies from Beckman Coulter [5,10,12-14]. The EPICS Elite EPS Flow Cytometry (Beckman Coulter Inc., Miami, FL) was used for the three-color studies of determination of PBL cell types and expression of cell surface receptor. During analysis, the CD4 T lymphocytes were gated using and the forward scatter-side scatter properties of the cells. The gated cells of interest were recorded using dual color quad stats and single histograms, which records cell number and log fluorescence intensity. The monoclonal antibodies specific for the surface epitopes were CD4 with PC5 labels; CD69 (activation inducing molecule) with PE label and IL-2 receptor (CD25) with FITC label; all obtained from Beckman Coulter Inc. Monoclonal antibodies for the receptors for insulin was PE labeled and obtained from Becton-Dickinson (San Diego, CA) [5,6].

Levels of cytokines (TNF-α, IL-1B, IL-6, IL-8, IL-2 and IL-10), released into the incubation media were determined by immunoassays using a solid phase, two-site sequential chemiluminescent immunometric assays on the Immulite analyzer (Siemens Healthcare Diagnostics Products, Ltd, UK) or ELISA assays from R&D Systems(Minneapolis, MN) as previously described [5,10,12,14,15]. The TBA- reacting materials were measured colorimetrically as malondialdehyde (MDA) as per our earlier described method [5,10,14]. ROS was assayed as % DCF as described previously [5,10,14]. The nuclear extracts from the cells for determination of NF-kB were isolated as previously described [15,16] and NF-kB (p65) Transcription Factor Assay reagents (Cayman Chemical Company, Ann Arbor, MI) were used for determining the cellular levels of NF-kB. The specific NF-kB inhibitor (NF-kBi), 6-amino-4-(phenoxy phenyl ethylamino) quinazoline (Calbiochem, CA) was used at a concentration of 20 nM. Cell viability was determined using Annexin V (Beckman Coulter). Statistical Analysis. The mean and standard error (SE) were calculated for all continuous variables. Baseline (control), concentrations and time-related results were compared using ANOVA and Scheffe's method for continuous variables, with log transformations when necessary. A two-tailed p value of less than 0.05 was considered statistically significant. Stat View version 5.0.1 (SAS Institute, Cary, NC) was the statistical software used for the analysis.

5. Results

T- lymphocytes activation with fatty acids and glucose Table 1 demonstrates the in vitro effects of glucose, palmitic acid and α-linolenic acid in a dose dependent manner alone and in varying combinations on T- cell activation after 72 hours of incubation. The measurement of activation consisted of CD69, CD25 and insulin receptor (INSR) expression determined by flow cytometry and effects on inflammation. The in vitro effects on inflammation was determined by cytokine production (TNFα, IL-1β, IL-6, IL-8, IL-2 and IL- 10) as well as measurements of oxidative stress (DCF) and lipid peroxidation (MDA) and NF-kB inhibitor (NF-kBi). All parameters measured were significantly different at the 15 mM and 30 mM glucose and 100 µM and 300 µM palmitic acid and their combinations than at the baseline of 5 mM glucose and/or 5 µM palmitic acid. Similar results were seen with varying concentrations of stearic acid as with palmitic acid. Both glucose (15 mM) and palmitate (100 µM) caused an increase in production of markers of inflammation as determined by production of the cytokines TNFα, IL-1β, IL-6, IL-8, IL-2 and IL- 10 which was maximum at 72 hours. Alpha-linolenic acid did not cause activation of T cells, INSR, ROS lipid peroxidation (TBA) or production of cytokines, but partially inhibited activation and production of these cytokines when incubated with the T cells with glucose (15 mM), palmitate (100 µM) or in combination of glucose and palmitate.

The inhibitor of NF-kB added to the cells at baseline and incubated for 72 hours inhibited the TNFα-induced expression by the high glucose and palmitate concentrations.

Table 1: Effect of Glucose, SFA (Palmitic Acid) and UFA (α-Linolenic Acid) on Activation of Human T Cells and Inflammation (Proinflammatory Cytokines and IL-10) and Oxidative Stress (DCF & MDA) at 72 hours of Incubation.

	Glucose			Palmitic Acid			Linolenic Acid			Glucose (15 mM) + Palmitic (100 µM)	Glucose (15 mM) + Linolenic (100 µM)	Glucose (15 mM) + Palmitic (100 µM) + Linolenic (100µM)
	5 mM	15 mM	30 mM	5 µM	100 µM	300 µM	5 µM	100 µM	300 µM			
CD69 (%)	<1	11±.7*	26±3*	<1	2±1*	3±.8*	<1	<1	<1	14±2†	4±.6†	6±1.7Δ
INSR (%)	0	5±1*	12±2*	0	8±2*	14±2*	0	0	0	12±2†	2±.6†	5±2Δ
CD25 (%)	0	6±1*	17±3*	0	10±2*	18±3*	0	0	0	15±3†	3±.5†	6.5±.4Δ
DCF (%)	0	7±1.2*	23±2*	1±.3	14±2*	30±3*	0	0	0	21±3†	4±.5†	8±2Δ
TBA (MDA)	0	6±2*	19±4*	.8±.1	10±2*	22±3*	0	0	0	15±2†	3+1†	9±1Δ
TNFα (pg/ml)	7±1	36±2*	185±4*	7±1	71±3*	98±3*	7±2	8±3	7±2	94±4†	15±2†	49±3Δ
IL-1β (pg/ml)	3±1	18±*	51±2*	3±1	21±2*	34±2*	3±1	4±1	3±1	29±3†	11±1†	17±2Δ
IL-6 (pg/ml)	6±1	43±2*	171±3*	6±2	58±3*	87±3*	6±2	7±2	6±2	128±4†	27±3†	71±3Δ

IL-8 (pg/ml)	12±2	184±3*	215±5*	10±2	78±3*	102±4*	9±2	9±2	9±2	235±6†	83±3†	118±3Δ
IL-2 (pg/ml)	23±2	69±3*	172±4*	23±3	87±4*	119±3*	23±2	24±3	23±2	153±4†	36±3†	89±2Δ
IL-10 (pg/ml)	9±1	20±2*	69±3*	9±2	34±3*	58±3*	9±2	9±2	9±2	47±3†	12±1†	29±3Δ
TNF α (+NF kBi)	6±1	6±1	6±2	5±1	5±2	6±2	5±1	5±1	5±1	7±2	7±2	7±3

Values indicate mean ± SE. Measured at 72 hours.

*P < 0.05 from baseline.

†P < 0.05 from glucose (15 mM) or palmitate (100 µM).

ΔP < 0.05 from glucose (15 mM) + palmitate (100 µM).

Figure 1 shows the effect of [A] glucose (15 µM concentration), [B] palmitate (100 µM concentration) and [C] the combination of 15 µM glucose and 100 µM palmitate on the activation of human T- cells, as determined by the emergence of CD 25 and Insulin receptors (INSR) and the production of ROS (DCF) and lipid peroxidation (TBA) in a time dependent manner at baseline, 24 and 72 hours of incubation. There was a time dependent increase over the 72-hour incubation in the activation of the T-cells with both glucose (15 mM) and palmitate (100 µM) and the combination of glucose and palmitate.

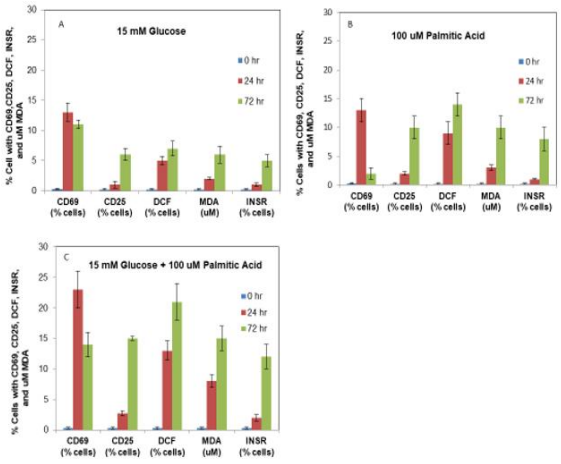

Figure 1: Effects of Glucose and Palmitic Acid on Activation of Human T-Cell, INSR and Markers of Oxidative Stress (DCF & MDA) over time.

As we have previously shown [5,8], CD69 is the earliest marker of activation and is maximal by 24 hours as the other receptors continue to emerge. Linolenic acid did not cause an activation of T cells.

Figure 2 shows the effect of incubation of the T cells with [A] 100 µM linolenic acid alone, [B] 100 µM linolenic plus 15 mM glucose, [C] 100 µM linolenic plus 100 µM palmitic and [D] 100 µM linolenic plus 15 mM glucose and 100 µM palmitate on the activation of human T cells, as determined using the emergence of CD 69, CD 25 and Insulin receptors (INSR) and the production of ROS (DCF) and lipid peroxidation (TBA) in a time dependent manner at baseline, 24 and 72 hours of incubation. No effect on T- cell activation was detected with linolenic (100 µM).

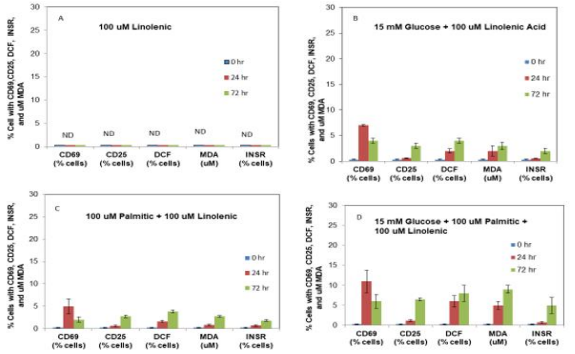

Figure 2: Effects of Linolenic Acid on Glucose and Palmitic Acid

Activation of Human T-Cell, INSR and Markers of Oxidative Stress (DCF & MDA) over time.

There was a time dependent partial inhibition over the 72-hour incubation on the activation of the T-cells when linolenic was added with the glucose (15 mM) or with the palmitate (100 µM), as well as with the combination of glucose and palmitate.

Figure 3 shows the salutary effect of adding 100 µM α- linolenic acid at 24 hours to the T cell incubation after activation of cell at baseline with 15 mM glucose or 100 µM palmitic acid. The demonstrates that the addition of α-linolenic acid after the initiation of activation can suppress further activation of the T cells as shown by CD25 and DCF.

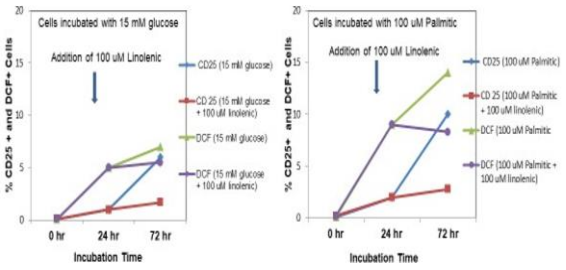

Figure 3: A) Effect of Linolenic (100 µM) added after 24 hours (arrow) of activation of T Cells by 15 mM Glucose

B) Effect of Linolenic (100 µM) added after 24 hours (arrow) of activation of T Cells by 100 µM palmitic acid.

Figure 4 demonstrates the effects of these same concentrations of glucose and palmitate and α-linolenic acid on nuclear translocation of NF-kB as determined by NF-kB p65. Both glucose (15 mM) and palmitate (100 µM) caused an increase in NF-kB p65 nuclear translocation which was maximum at 72 hours. Linolenic acid did not cause an increase in NF-kB p65 nuclear translocation, but partially inhibited the translocation when incubated with the T cells with glucose (15 mM), palmitate (100 µM) or in combination of glucose and palmitate.

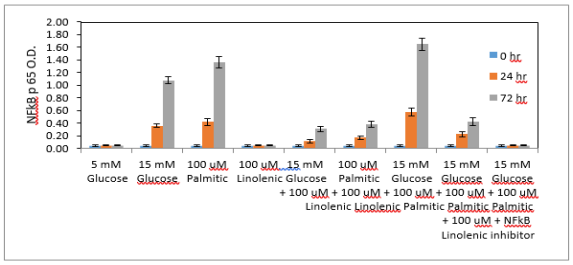

Figure 4: Effects of α Linolenic Acid on Glucose and Palmitic Acid Induced NF-kB p65 in Human T cells.

Thus, as can be seen from Table 1 and 2 and Figures 1, 2 and 3, palmitate at 100 µM and 300 µM as well as glucose at 15 mM and 30 mM alone and in combination induced activation of human T cells in a time and dose- dependent fashion, as compared to controls of 5 mM glucose and 5 µM palmitate. The activation was maximized at 72 hours and act at least in part through the NF-kB inflammatory pathway. Linolenic acid did not exhibit any stimulating effect on the T-cells. Of note, the addition of α-linolenic acid to the T cells exposed to glucose and/or palmitate significantly inhibited T-cell activation induced by the elevated concentration of glucose and/or palmitic acid.

6. Discussion

Previous investigations demonstrated the ability of high glucose concentrations and the saturated fatty acid (SFA) palmitate to induce T cell activation, insulin receptor emergence, cytokine and ROS production and lipid peroxidation. These findings were not seen with T cell exposure to the unsaturated fatty acid (UFA) α-linolenic acid. Studies have shown that high glucose increases expression of insulin receptors and downstream elements of the insulin-signaling pathway in endothelial cells [17]. Studies have shown that the SFA can bind to the Toll-like receptors (TLR) and induce the inflammatory response through NF-kB [18, 19], whereas UFAs do not bind to the TLR. Our study shows that both high levels of palmitic acid and glucose can induce the inflammatory response through NF-kB and linolenic acid can block this effect. Studies have shown that omega-3 fatty acids prevent inflammation and metabolic problems by inhibition of inflammasome activation [20].

The present study demonstrates yet another unique feature of human T cells in that α-linolenic acid has a partial inhibitory effect on the ability of glucose and palmitate to induce T cell activation, insulin receptors, cytokines, ROS production and lipid peroxidation. To

our knowledge, this is the first report of such a phenomenon in these cells.

T2DM is a group of metabolic disorders sharing the common underlying feature of hyperglycemia and hyperlipidemia [1]. It has been suggested that atherosclerotic disease is a proinflammatory state that activates HAEC and T cells [2]. The latter activated cells play pivotal roles in the formation of atherosclerotic plaque and cardiovascular events (CVE). As previously shown, SFA demonstrate toxic effects on the cardiovascular system whereas UFA are shown to protect against cardiovascular disease by lowering serum cholesterol and triglycerides while elevating high-density lipoproteins [21]. Studies have shown that the palmitic and stearic levels in ceramide can predict the incidence of diabetes [22] indicating that higher blood levels of blood levels of SFAs such as palmitic and stearic and can alter sphingolipids and phospholipids in insulin resistance and related metabolic disorders [23]. A prospective, randomized placebo-controlled clinical trial by Marik and Varon [24] evaluated cardiac endpoints, such as cardiovascular death, sudden death and nonfatal cardiovascular events and all- cause mortality in patients randomized to the unsaturated fatty acids eicosopentanoic acid (EPA) and docosahexanoic acid (DHA). They found a significant decrease in cardiovascular deaths and concluded that dietary supplements with omega 3 UFA should be considered in secondary prevention of cardiovascular events. This mode of prevention should apply to diabetic patients as well, based on the significant increase in cardiovascular risk in the diabetic state.

Additional studies by Opara et al. [25] tested the effects of α-linolenic acid on pancreatic islet cells of CD-1 albino mice and found that insulin secretion was increased by greater than 200% in the islets of the adult female mice. This same study aimed to investigate the effect of chain length and the degree of unsaturation on insulin release by using isolated peri fused murine islet cells. Their data demonstrated that increased chain length from 8 carbons to 12 carbons and an increase in the degree of unsaturation, results in an increase in insulin secretion. They concluded that the structural characteristics of FFA, such as chain length and degree of unsaturation, are important determinants in the biological effects of FFA. A mouse model study of NAFLD showed that α-linolenic acid induced apoptosis in CD4 T cells [26]; however, our studies did not show any apoptosis in human CD4 T cells. Studies of the microbiota related metabolites showed that the linoleoyl–GPC decreased the risk of type 2 diabetes [27]. A recent clinical trial utilizing participants of the National Heart, Lung and Blood Institute 1 Family Heart Study investigated the effects of consumption of dietary linolenic acid on plasma levels of fasting insulin and glucose. In this cross- sectional study, they determined that higher consumption of dietary linolenic acid was positively associated with fasting serum insulin in men and women, but had no effect on glucose level [28]. These studies substantiate the vital role that the UFA may have in modifying disease processes.

As indicated by our present study, the addition of α-linolenic acid provides a significant decrease in the levels of T cell activation, insulin receptor emergence, cytokine and ROS production and lipid peroxidation. We hypothesize that UFA have an additional cardiovascular protective feature as it attenuates the harmful effects of high glucose and palmitate.

We propose that the human T cell, a tissue which is normally insulin unresponsive, may become activated and develop insulin responsiveness in the acute stage as a means to protect against the deleterious effects of hyperglycemia and hyperlipidemia [5,6,10]. As the cells become activated, they are able to shield the onslaught of elevated glucose and SFA by the salutary effects of de novo emergence of insulin receptors and GLUT 4 transporters which provide controlled inflow of glucose and palmitate into the cells as an adaptive response to the deleterious effects of high glucose and palmitate. In chronic conditions of hyperglycemia and

hyperlipidemia, however, T cells may become damaged and undergo apoptosis. Damage and destruction of these cells may play a pivotal role in the pathogenesis of cardiovascular events, particularly in chronic hyperglycemia and hyperlipidemia in diabetic states. We propose that this is a maladaptive response of the body that results in a diseased state.

Based on our findings, it is tempting to hypothesize that one beneficial effect of unsaturated fatty acids, especially α-linolenic acid, would be in the prevention of endothelial injury and atherosclerotic plaque formation in those patients suffering from the hyperglycemic and hyperlipidemic state of Type 2 Diabetes.

7. Acknowledgement

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