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NEW PERSPECTIVES ON THE RESEARCH AND TREATMENT OF TYPE 2 DIABETES MELLITUS AND ITS COMPLICATIONS. THE ROLE OF L-ARGININE AND POLYAMINES

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ABSTRACT

In this paper, evidence on the beneficial actions of L-arginine and polyamines obtained in experimental diabetes and from *in vitro* studies carried out under hyperglycemia conditions are presented. Several decades ago L-arginine was shown to be one of the most potent insulin secretagogue. Subsequently, polyamines, arginine-derived molecules, were shown to increase in pancreatic islets when the proliferation of cells is induced by glucose and other substances with hormonal action. L-Arginine and polyamines have shown beneficial effects not only in the regulation of hyperglycemia and dyslipidemia in experimental diabetes, but also in the prevention of glycation of proteins, lipid peroxidation, and embryotoxicity, in addition to the antiaggregant effect on platelets from different sources including human platelets. Inhibition of low density lipoprotein oxidation of type 2 diabetics was also demonstrated, being spermine the polyamine with the most potent inhibitory effect than α-tocopherol. Recently, was informed that fragmentation of sperm DNA in hyperglycemia conditions is inhibited by polyamines, specially by spermine. Other studies are being conducted to evaluate the possible use of these substances in humans as a therapeutic treatment.

KEYWORDS: Diabetes mellitus, Hyperglycemia, Glycation, Lipid peroxidation, L-Arginine, Polyamines, Spermine, Spermidine, Putrescine, Cadaverine.

INTRODUCTION

Human tissues and fluids contain significant amounts of the polyamines putrescine, spermidine and spermine, which play a major role in modulating metabolic processes. The physiology of polyamines has been studied in health and disease. Polyamine synthesis is described elsewhere.[1] In mammals ornithine decarboxylase (E C 4. 1. 1. 17) catalyzes the formation of putrescine from ornithine. On the other hand, arginase (E C 3. 5. 3. 1), an enzyme that catalyzes the hydrolysis of L-arginine to form L-ornithine and urea, is one of the polyamine biosynthesis enzymes in extrahepatic tissues.[2] L-Arginine provides ornithine for subsequent formation of putrescine. There is evidence that extrahepatic arginase provides ornithine for other metabolic purposes. After the prostate gland, high polyamine concentrations are formed in the pancreas. The presence of polyamines in pancreatic islets is restricted to the insulin-producing beta cells and it has been found that polyamines are associated with the secretory granules.[3] Putrescine and spermidine are necessary for *in vitro* insulin and protein biosynthesis, whereas spermine depletion affects several processes involved in insulin metabolism. Since we observed that L-arginine causes an increase in putrescine concentration in the pancreas of diabetic rats, [4] we stated the hypothesis that polyamines or L-arginine may be utilized in regeneration processes or for recovering the pancreatic function, later it was demonstrated. From these initial observations on the effect of both L-arginine and polyamines, several studies on diabetes have been conducted in our Laboratory using experimental models with chemically-induced diabetes and cells and body fluids of type 2 diabetic patients. In this paper some successful results are presented.

EXPERIMENTAL STUDIES AND RESULTS

1. Regulation of hyperglycemia and dyslipidemia by L-arginine

The effect of 10 mM L-arginine on the pattern of lipids and lipoproteins in normal and diabetic rats (alloxan 120 mg/Kg, *i. m.)* was studied.[5] Three groups of 48 rats were studied during 12 days and compared with a control group. Glucose, triglycerides (TG), cholesterol, total lipids, and low (LDL) and high density lipoproteins (HDL) and their corresponding apoproteins (Apo A-1 and Apo B-100) were determined in blood. Hyperglycemia (132.5 ± 7.6 to 544 ± 16.9 mg/dL) was produced in 96 h. As a consequence, the levels of TG, cholesterol, total lipids, and LDL and its apoprotein ApoB-100 were increased, whereas HDL and its apoprotein A-1 were diminished. The L-arginine injection tends to normalize the glycemia from 24 h; similarly, hyperlipidemia (TG from 924.7 ± 220.1 to 68.5 ± 8.4 mg/dL, cholesterol from 107.7 ± 0.6 to 64.5 ± 4.2 mg/dL, LDL from 24.2 ± 2.5 to 8.0 ± 2.9 mg/dL)

was also diminished. These results suggest that the beneficial effect of L-arginine administration on serum glucose values and lipid levels in diabetic rats can be mediated by polyamine formation. Since L-arginine is an insulin secretagogue, insulin release also has been observed.

2. Inhibition by L-arginine and spermidine of haemoglobin glycation and lipid peroxidation

Five groups of 40 rats were studied during 20 days and compared with a control group. Rats were diabetized as described above. Experimental groups received 10 mM L-arginine and 10 µM spermidine. In addition to the parameters listed in part 1 except Apo A-1 and Apo B-100, determination of glycated haemoglobin (HbA_{1c}; 2.85 ± 0.18 to 7.67 ± 0.76%) and thiobarbituric acid- reactive substances (TBARS; 0.88 ± 2.11 to 2.183 ± 0.021 M, P <0.005) were made in this study. L-arginine and spermidine injection tends to normalize the glycemia from 24 hours, similarly, hyperlipidemia, TBARS and HbA_{1c} concentrations. From these results, we concluded that L-arginine and spermidine exerted an inhibitory effect of hemoglobin glycation and lipid peroxidation *in vivo* which may be relevant in preventing diabetic complications.[6] Lipid peroxidation *in vivo* has been identified as a basic deteriorative reaction in cellular mechanisms of the ageing. Intracellular *de novo* synthesis and concentrations of polyamines in cells and tissues, especially those of spermine and spermidine, decrease with ageing. In uncontrolled type 2 diabetics a premature ageing is presented.

3. Inhibition of platelet aggregation

L-Arginine and polyamines have also shown beneficial effects not only in the regulation of hyperglycemia and dyslipidemia in experimental diabetes, but also in the prevention of glycation of hemoglobin and lipoperoxidation. In addition to this, an excellent antiaggregant effect has been observed in rat platelets, in platelets of rabbit with induced atherosclerosis,[7] and in human platelets.

4. Inhibition by polyamines of the uptake of oxidized-LDL by macrophages from type 2 diabetics

The effect of polyamines on human LDL oxidation and the ability of macrophages derived from type 2 diabetic patients to uptake oxidized-LDL were evaluated. Polyamine effect was compared with α-tocopherol. Healthy subjects and type 2 diabetic patients were included. Glucose, HbA1c, TG, LDL, HDL and serum lipid peroxidation were measured in blood. The

study was performed in three stages. For each stage, ten experimental conditions comparing the effect of polyamines with α-tocopherol (10 µM solutions) on LDL and the uptake of oxidized-LDL by macrophages were analyzed. Malondialdehyde concentration was found to be significantly higher in type 2 diabetic patients compared to healthy subjects (5.6 ± 0.58 vs. 2.66 ± 0.31 µM malondialdehyde, respectively, (P <0.05)). Percent of macrophages containing oxidized lipoprotein was determined by means of red oil staining. The uptake of oxidized-LDL by macrophages derived from diabetic patients was clear. The uptake of oxidized lipoprotein was inhibited when the oxidation was prevented by polyamines or α-tocopherol (Figure 1). Spermine showed high antioxidant capacity (96.67 ± 1.53% vs.25.67 ± 2.30%) compared to α-tocopherol (96.67 ± 1.53% vs. 47.00 ± 7.20%) at the concentration tested.[8]

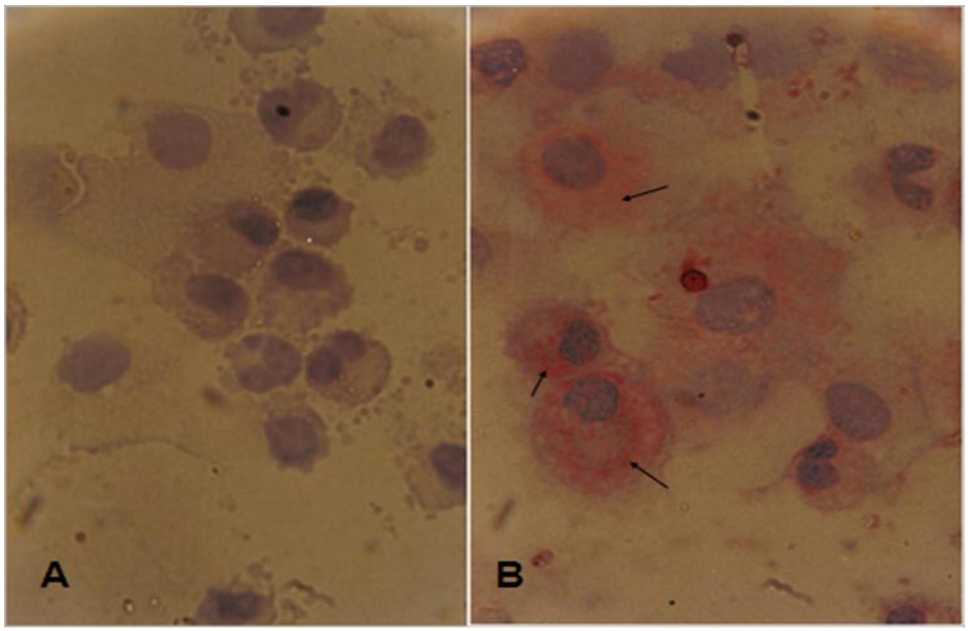

Figure 1. Macrophage derived monocytes from healthy subjects after the incubation with non-oxLDL and oxLDL in the presence of 100 µM Cu^{2+} and 40 µM H_2O_2. A. The presence of lipids revealed by red oil staining is almost undetectable into the macrophages (Control). B. The uptake of oxLDL by macrophages is clear, an intense positive reaction to lipid fraction can be seen into the cells (arrow). (Immersion technique 100X).[8]

5. Protection of pancreatic β-cells by L-arginine and polyamines against alloxan diabetogenic effect

In the searching for new substances with the capacity to protect β-cells from the toxic effects of alloxan, we evaluated the effect of L-arginine and the polyamines putrescine, spermidine

and spermine in rats.[9] Diabetes was induced by the i. p. injection of either 200 mg/Kg (24 hours experiments or 120 mg/Kg (12 days experiments) body weight. L-arginine and polyamines were administered 10 min after alloxan administration. The results show a clear protective role of L-arginine and polyamines over the pancreatic β-cell, in addition to the induction of neogenesis from ductal and acinar cells that leads to the recovery of endocrine pancreatic function in rats with experimental diabetes.[10]

6. Inhibition by L-arginine and polyamines of *in vitro* glycation of bovine serum albumin

It is known that under hyperglycemia conditions amino groups of biological molecules react with glucose to form unstable Schiff bases that can then undergo the Amadori rearrangement to form irreversible advanced glycation end products (AGE´s).[11] Several years ago we tested the *in vitro* inhibition of pyrraline formation on bovine serum albumin and L-lysine by L-arginine and the polyamines spermine, spermidine, putrescine and cadaverine (synthesized from lysine by lysine decarboxylase; EC 4.1.1.18). Among the inhibitors, L-arginine and spermine potently inhibited pyrraline formation.[12] This effect was be related to the presence of the guanidinio group in L-arginine and four amino groups in spermine, but this inhibitory effect was also shown by spermidine, putrescine and cadaverine.

7. Other beneficial actions of polyamines in hyperglycemia conditions

7.1. Role of polyamines in reproductive processes

The physiology of polyamines has been widely studied in reproductive processes in both animals and humans. Using experimental models we showed that delayed fetal development and embryotoxicity caused by induced diabetes can be prevented by L-arginine and polyamines.[13] In woman polyamine metabolism has been studied in different physiological conditions including pregnancy and abortion and it is known that they are required for multiple processes.[14] In man polyamine metabolism in reproductive system has also been studied in health and disease.[14] Several years ago we showed that L-arginine and polyamines increase the progressive motility in spermatozoa of patients with idiopathic and diabetic asthenozoospermia.[15] Although polyamine metabolism in sperm cell has been extensively studied, some aspects remain unknown.[16,17] Recently, we informed that glycation and fragmentation of sperm DNA in hyperglycemia conditions is inhibited by polyamines, which has important implications not only in normal reproductive processes but also in assisted

reproduction.[18] Due to the relevance of the effects of hyperglycemia on reproductive processes, particularly on human reproduction, this topic will be analyzed separately.

CONCLUSIONS AND PERSPECTIVES

L-Arginine is a versatile amino acid in animal and human cells, serving as a precursor for the synthesis not only of protein but also of nitric oxide, urea, proline, glutamate, creatine, polyamines and other molecules involved in regulating cellular homeostasis. Even though it is clear that more studies should be conducted in order to know the precise mechanisms involved, these results provide information concerning the beneficial effects of L-arginine and their metabolic products, the polyamines on hyperglycemia, dyslipidemia and in the preventing of AGEs formation. The relevant role in the protection of the β-cell on its neogenesis and on the recovering of the endocrine pancreatic function suggest that the polyamines and their precursor L-arginine may have a novel therapeutic potential in preventing and treatment of diabetic complications in humans.

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