SERUM APELIN IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DM: RELATION TO GLUCOSE METABOLISM AND INSULIN SENSITIVITY

Thesis
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List of Abbreviations

AA	Aminoacids
ACE2	Angiotensin converting enzyme 2
ACTH	Adrenocorticotrophic hormone
ADA	American Diabetes Association
Ang II	Angiotensin II
APJ	Apelin recpeotr
AT-1	Angiotensin II type 1 receptor
AUC	Areas under the curve
BMI	Body mass index
cGMP	Cyclic guanosine monophosphate
CNS	Central nervous system
CVD	Cardiovascular disease
DAG	Diacylglycerol
DIAMOND	Diabetes mondiale
DM	Diabetes mellitus
eNOS	Endotheial nitric oxide Synthase
ERKs	Extracellular regulated kinases
EURODIAB	European diabetes
FSH	Follicle stimulating hormone
GPCRs	G protein-coupled membrane receptors
h	Hour
HO	Null hypothesis

HbAlc	Glycosylated Hemoglobin
HF	heart failure
HLA	Human Leucocytic Antigen
HOMA-IR	Homeostatic model assessment- insulin resistance
IDDM	insulin-dependent diabetes mellitus
IL	interleukin
kg	kilogram
LADA	latent auto-immune diabetes of adult
LH	luteinizing hormone
MCP	monocyte chemo-attractant protein
MHC	major histocompatibility complex
ml	milliliter
NCX	Na+-Ca2+ exchanger
ng	nanogram
NHE	Na+-H+ exchanger
NO	nitric oxide
PCR	polymerase chain reaction
PI3K	Phosphoinositide 3-kinase
PKC	Protein Kinase C
PLC	phospholipase C
P_{max}	Maximum pressure
pmol	pico mole
PTX	pertussis toxin

SNPs	Single nucleotide polymorphisms
T1D	Type 1 diabetes
T2D	Diabetes mellitus type 2
Th	T helper cell
TNFa	Tumor necrosis factor -α

Introduction

Diabetes Mellitus (DM) is group of metabolic diseases characterized by hyperglycemia resulting from defect in insulin secrtion, insulin action, or both ***(American Diabetes Association, 2007).***

Apelin, a recently described adipocytokine, is abundantly expressed in adipose tissue and produced in the endothelial cells in various parts of the body ***(Kleinz et al., 2004).***

Plasma apelin levels were reported to increase in obesity in association with hyperinsulinemia ***(Boucher et al., 2005).***

The first evidence of an involvement of apelin on insulin secretion came from the study of Sorhede Winzell et al. showing that apelin inhibits insulin secretion stimulated by glucose in vivo in mice and in vitro in isolated islets of Langerhans ***(Sorhede Winzell et al., 2005).***

Apelin was also shown to stimulate glucose transport in an AMPK-dependent manner in human adipose tissue **(*Attane et al., 2011).*** Moreover, in insulin-resistant 3T3-L1 adipocytes (due to TNFa treatment for 24 h), insulin-stimulated glucose uptake was reduced by 47%, whereas apelin treatment resulted in an increased glucose uptake through the PI3K/Akt pathway and improved insulin-stimulated glucose uptake ***(Zhu et al., 2011).***

Intravenous apelin administration at low concentration (200 pmol/kg) decreased blood glucose in mice and improved glucose ***(Dray et al., 2008).***

Furthermore during an hyperinsulinemic-euglycemic clamp, when the hepatic glucose production is totally inhibited, apelin increases glucose utilization throughout the entire organism mainly due to a rise in glucose uptake by skeletal muscles and adipose tissues. In isolated skeletal muscle (soleus), apelin stimulates glucose transport and its effect is additive to that of insulin ***(Dray et al., 2008).***

The role of central apelin on glucose metabolism has been recently studied in our group. Acute intracerebroventricular. apelin has differential effect depending of the injected dose and the nutritional status. Acute low-dose of intracerebroventricular. apelin injection decreased peripheral fed glycemia, increased glucose and insulin tolerance in mice via a NO signaling pathway. All these beneficial actions of i.c.v. apelin on glucose homeostasis were blunted in HFD obese/diabetic mice. As the opposite, acute high-dose of intracerebroventricular. apelin injection provoked fasted hyperglycemia/ hyperinsulinemia and decreased insulin sensitivity in normal mice ***(Duparc et al., 2011).***

Aim of the work

To evaluate Serum apelin level in children and adolescent with type 1 diabetes mellitus and its relation to glycemic control, lipid metabolism and markers of insulin sensitivity.

Diabetes Mellitus

Definition

Diabetes mellitus (DM) is a group of metabolic disorders characterized by hyperglycemia resulting from defect in insulin secretion, action, or both ***(ADA, 2007)***.

DM is not a simple disease but it is a heterogeneous group of disorders in which there are distinct genetic pattern of inheritance as well as separate etiologic and physiologic mechanisms all leading to impairment of glucose metabolism ***(Gabir et al., 2000)***.

Systemic vascular dysfunction is a central part of the pathophysiology of both type I insulin dependent and type II non insulin dependent coronary heart disease is the leading cause of morbidity and mortality in diabetes and account for 60% of death in this group peripheral vascular disease, retinopathy and nephropathy are all more common in diabetes and lead to significant morbidity ***(Schallcwijlc et al., 2005)***.

The development and progression of diabetic complications are strongly related to the degree of glycemic control ***(Ozmen and Boyuada, 2003)***.

Classification

Etiologic classification of diabetes mellitus ***American diabetes Association (ADA, 2007)***

I. Type 1

β-cell destruction, usually leading to absolute insulin deficiency

a. Autoimmune

b. Idiopathic

II. Type 2

May range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance

III. Other specific types

A. Mongenic defects of β-cell function

1. HNF-1α MODY (MODY 3),
2. Glucokinase MODY (MODY 2)
3. HNF-4 α MODY (MODY 1),
4. HNF-1β MODY (MODY 4)
5. WFS1 Wolfram syndrome
6. Neonatal diabetes
7. Other MODY

B. Mitochondrial diabetes

C. Genetic defects in insulin action

1. Type A insulin resistance
2. Leprechaunism
3. Rabson-Mendenhall syndrome
4. Lipoatrophic diabetes
5. Others

F. Drug- or chemical-induced

1. Glucocorticoids
2. Vacor
3. Pentamidine
4. Nicotinic acid
5. Thyroid hormone
6. Diazoxide
7. β-adrenergic agonists
8. Thiazides
9. Dilantin
10. α-Interferon
11. Others

G. Infections

1. Congenital rubella
2. Cytomegalovirus
3. Others