Characterization of Insulin Secretion In Valproate-treated Children and Adolescents with Epilepsy

Thesis

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By

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List of Abbreviations

AD	Autosomal dominant
ADH	Antidiuretic hormone
ADP	Adenosine -ᵒ-diphosphate
AEDs	Antiepileptic drugs
AIDS	Acquired immunodeficiency disease
ATP	Adenosine triphosphate
ATP	Adenosine-ᵒ-triphosphate
ATRA	All-trans retinoic acid
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca^{++}	Calcium ions
CAD	Coronary artery disease
CAE	Childhood absence epilepsy
CBC	Complete blood count
CBZ	Carbamazepine
CLB	Clobasma
Cl	Chloride ion

CLL	Chronic lymphocytic leukemia
CNS	Central nervous system
CPS	Simple partial seizure
CPS	Complex partial seizures
CREB	(ca) responsive element binding protein

List of Abbreviations (Cont.)

CSF	Cerebrospinal fluid
DAP	Dihydroxyacetone phosphate
EEG	Electroencephalogram
EPSPs and IPSPs	Excitatory and inhibitory postsynaptic potentials
ERK ½	Extracellular signal-regulated kinases ١/٢
ESM	Ethosuximide
F.T.G	Fasting triglyceride
FBM	Felbamate
FFA	Free fatty acid
FGIR	Fasting glucose/ insulin ratio
FPIA	Fluorescence polarization immunoassay
GABA	γ-Aminobutyric Acid
GABA	Gamma amino butyric acid
GBP	Gabapentin
GIP	Gastro intestinal inhibitory peptide
GK	Glycerol kinase

GLUT٢	Glucose transporter
GLUT-٤	Glucose transporter ٤
GP-١	Glucagon-like peptide ١
GPO	Glycerylphosphate oxidaze
GTC	Generalized tonic-colonic seizures

List of Abbreviations (Cont.)

HAART	Highly active antiretroviral therapy
HCO٣	Bicarbonates
HDAC	Histone deacetylases
HDAC١	Histone deacetylase١
HDL	Heigh density lipoprotein
HIV	Human immunodeficiency virus
HOMA	Homeostatic model assessment
ICU	Intensive care unit
IDF	International Diabetes Federation
IFG	Impaired fasting glucose
IGF-١	Insulin like growth factor ١
IgG	Immunoglobulin G
IGT	Impaired glucose tolerance
ILAE	International League Against Epilepsy
IRS-١	Insulin- receptor substrate١
ISI	Insulin sensitivity index
JAE	Juvenile absence epilepsy

JME	Juvenile myoclonic epilepsy
K^+	Potassium ion
LDL	Low density lipoprotein
LTG	Lamotrigine
MAbs	Monoclonal antibody

List of Abbreviations (Cont.)

mEH	microsomal epoxide hydrolase
MRI	Magnetic resonance imaging
Na^+	Sodium ion
NEAD	Non- Epileptic Attack Disorder
NIDDM	Non insulin dependent diabetes mellitus
NMDA receptor	N-methyl-D- aspirated receptors
OCBZ	Oxcarbamazepine
OGTT	Oral glucose tolerance test
PAI-١	Plasminogen activator inhibitor ١
PCI and PC٢	Prohormone convertases (١ and ٢)
PCOD	Polycystic ovary disease
PERR	Polarization Error
PET	Positron emission tomography
PHB	Phenobarbitone
PHT	Phenytoin
Pl٣ – kinase	Phospholatidy١ inositol ٣kinase
POD	Peroxidase

QUIKI	Quantitative insulin sensitivity check index
rCBF	regional cerebral blood flow
rCGM	regular cerebral glucose metabolism
RMSE	Root Mean Squared Error
SH٢domains	Specific domains

List of Abbreviations(Cont.)

SJS	Stevens-Johnson syndrome
SPECT	Single photon computerized tomography
SPSS	Standard computer program
TG	Triglycerides
TNF	Tumor necrosis factor
TPM	Topiramate
TRAIL	Tumor necrosis factor-related apoptosis-inducing ligand
TSH	Thyroid stimulating hormone
VGB	Vigabatrin
VLDL	Very low density lipoprotiens
VPA	Valproic acid
ZNS	Zonisamide

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INTRODUCTION

Valproate (VPA) is extensively used broad spectrum antiepileptic drug ***(Davis et al., ١٩٩٤)***. In many cases of epilepsy ,the duration of treatment may be long which emphasize the importance of long term safety of the drug. it is as well established that VPA treatment is associated with significant weight gain and increase in serum leptin level ***(Luef et al., ٢٠٠٣)*** respect to the long treatment period, these side effect may increase insulin resistant and metabolic risk factors ***(Luef et al., ٢٠٠٣).*** Furthermore, other mechanisms have been suggested for the pathophysiology of weight gain, of these, impairment of beta-oxidation of fatty acids and increased insulin secretion ***(Deimer and Aysun, ٢٠٠٠).***

VPA is a fatty acids derivative, which competes with free fatty acids for albumin binding, and acts as a gamma aminobutyric acid (GABA)-ergic agonist, mechanisms which are known to be involved in pancreatic, beta cell regulation and insulin secretion. Therefore, it might be suspected that VPA therapy is associated with increased glucose stimulated pancreatic secretion and thus a higher body weight in VPA treated patients ***(Luef et al., ٢٠٠٣).***

AIM OF THE WORK

The aim of this work is:

١- To evaluate the possible changes in insulin secretion, and metabolism during VPA treatment.

٢- The role of triglycerides in those changes.

٣- The role of insulin in VPA related weight gain.

Epilepsy

Definition:

Epilepsy is a chronic disorder or group of chronic disorders, in which the indispensable feature is recurrence of seizures that are typically unprovoked and usually unpredictable ***(Carl et al., ٢٠٠٥).***

A seizure is a transient event, a symptom of disturbed brain function. Although seizures are the cardinal manifestation of epilepsy, not all seizures imply epilepsy ***(Johnston, ٢٠٠٤).***

An epileptic seizure is the result of temporary physiologic dysfunction of the brain caused by a self limited, abnormal, hypersynchromous electrical discharge of cortical neurons ***(Carl et al., ٢٠٠٥).***

Convulsion is a paroxysmal; time limited changes in motor activity and\or behavior that result from abnormal electrical activity in the brain**,** ***(Johnston ٢٠٠٤).***

Intractable seizure is defined as inadequate control of seizure despite treatment with conventional medications ***(Francois et al., ٢٠٠٣).***

Intractable seizures in children less than ٢ year of age are often associated with later on mental retardation ***(Hutterlocher and Hapke, ١٩٩٠).***

Epidemiology:

Epilepsy is a common medical condition affecting ٠.٥-١ percent of all children in industrial countries ***(Hauser, ١٩٩٥).***

Commission on Epidemiology and prognosis International league against Epilepsy "ILAE" (١٩٩٧) found that the incidence of epilepsy in developing countries is more than ١٠٠ per ١٠٠.٠٠٠ of normal population. This high rate in developing countries is mainly due to acute infections, parasitic infestations and poor postnatal care ***(Jallon, ٢٠٠٢).***

In Egypt, ***EL- Khayat et al., (١٩٩٤),*** studied the prevalence of epilepsy in primary school children and reported a prevalence rate of ٣.٥/١٠٠٠ while ***Massoud (١٩٩٧),*** reported even a lower overall prevalence of ١.٩/١٠٠٠.

Age specific incidence:

Regarding the incidence of epilepsy, which refers to the number of new cases occurring within a given period, ***Hauser et al., (١٩٩٣)*** who studied the incidence rate in the first year of life reported an incidence reaching as high as ٨٠ per ١٠٠.٠٠٠ infant. The rates then decline through childhood and adolescence reaching plateau of ٤٠ /١٠٠.٠٠٠ person/year in the middle age.