Effect of Lacosamide on cognitive dysfunction in streptozotocin-induced Alzheimer rat model

Thesis

Submitted for partial fulfillment of the master degree of **Pharmacology**

By: Fatma Sobhy Ibrahim

M.B.B.Ch.

Demonstrator in Clinical Pharmacology Department Faculty of Medicine, Kafr-Elsheikh University

Supervised by

Dr. Lobna Fouad Abdel-Aziz

Professor and Head of Clinical Pharmacology Department Faculty of Medicine, Ain Shams University

Dr. Wesam Mostafa Soliman Elbakly

Assistant professor in Clinical Pharmacology Department Faculty of Medicine, Ain shams University

Dr. Nesreen Hamdy El Gayar

Lecturer in Clinical Pharmacology Department Faculty of Medicine, Ain shams University

> Faculty of Medicine Ain Shams University 2019

Acknowledgement

First of all, all gratitude is due to God almighty for blessing this work, until it has reached its end, as a part of His generous help, throughout my life.

Really I can hardly find the words to express my gratitude to **Dr. Lobna Fouad Abdel-Aziz** Head of Clinical Pharmacology Department, Faculty of Medicine, Ain Shams University, for her supervision, continuous help and encouragement throughout this work. It is a great honour to work under her guidance and supervision.

Really I can hardly find the words to express my gratitude to **Dr. Wesam Mostafa Elbakly** Assistant Professor in Clinical Pharmacology Department, Faculty of Medicine, Ain Shams University, for her encouragement throughout this work and tremendous effort she has done in the meticulous revision of the whole work. It is a great honour to work under her guidance and supervision.

I would like also to express my sincere appreciation and gratitude to **Dr.** Nesreen Hamdy El Gayar Lecturer in Clinical Pharmacology Department, Faculty of Medicine, Ain Shams University, for her continuous directions and support throughout the whole work.

Sincere appreciation to **Dr. Shrein Ismail** Assistant professor in Clinical Pharmacology Department, Faculty of Medicine, Alexandria University for her valuable help in Experimental model induction.

Last but not least, I dedicate this work to my family, whom without their sincere emotional support, pushing me forward this work would not have ever been completed.

Contents

List of Abbreviations	I
List of Tables	II
List of Figures	III
Literature review	1
Aim of the study	32
Material and Methods	33
Results	54
Discussion	83
Summary	92
Reference	98
Arabic Summary	

List of Abbreviations

AD	Alzheimer's disease
AEDs	Antiepileptic drugs
App	Amyloid precursor protein
Αβ	Amyloid beta
BBB	Blood Brain Barrier
CRMP2	Collapsin response mediator protein 2
Cdk5	Cyclin Dependent Kinase 5
EEG	Electroencephalogram
ELT	Escape Latency Time
FAD	Familial Alzheimer's disease
FDA	Food and Drug Agency
GLUT2	Glucose Transporter 2
GSK-3β	Glycogen Synthase kinase 3 β
HATs	Histone Acetyl Transferase
HDAC	Histone deacetylase
ICV	Intracerebroventricular
IRs	Insulin receptors
IRS1	Insulin receptor substrate1
LCM	Lacosamide
LEV	Leviteracetam
LTG	Lamotrigine
MAP	Microtubule Associated protein
MAPT	Microtubule Associated protein tau
MTs	Microtubule
MWM	Morris Water Maze
NFT	Neurofibrillary tangles
NMDAR	N methyl D aspartate receptor
NSAIDs	Non - Steroidal Anti- inflammatory drugs
PCR	Polymerase Chain Reaction
SAD	Sporadic Alzheimer disease
STZ	Streptozotocin
VPA	Valporate
WHO	World Health Organization

List of tables

Table	Title	Page
1	Alzheimer's disease categories according to biomarkers profile	18
2	Forward and reverse primers sequence used in qPCR.	50
3	The thermal cycler condition used during RT- PCR.	51
4	Effect of chronic treatment with Lacosamide (3mg, 10mg, 30mg orally) for 3 weeks on Locomotor activity in open field test in STZ induced AD rat model	55
5	Effect of chronic treatment with Lacosamide (3mg, 10mg, 30mg orally) for 3 weeks on learning and memory in Morris Water Maze test in STZ induced AD rat model	58
6	Effect of chronic treatment with Lacosamide (3mg, 10mg, 30mg orally) for 3 weeks on learning and memory in Morris Water Maze test in STZ induced AD rat model (probe trial)	60
7	Effect of chronic treatment with Lacosamide (3mg, 10mg, 30mg orally) for 3 weeks on spatial memory deficit in Y Maze test in STZ induced AD rat model	63
8	Effect of chronic treatment with Lacosamide (3mg, 10mg, 30mg orally) for 3 weeks on the relative expression of mRNA of APP in hippocampus of and frontal cortex of STZ induced AD rat model	67
9	Effect of chronic treatment with Lacosamide (3mg, 10mg, 30mg orally) for 3 weeks on the relative expression of mRNA of MAPT in hippocampus and frontal cortex of STZ induced AD rat model	71
10	Effect of chronic treatment with Lacosamide (3mg, 10mg, 30mg orally) for 3 weeks on the relative expression of mRNA of IRS1 gene in hippocampus and frontal cortex of STZ induced AD rat model	75
11	Effect of chronic treatment with Lacosamide (3mg, 10mg, 30mg orally) for 3 weeks the HDACs activity in hippocampus of STZ-induced AD rat model	79

List of Figures

3	Demonsrate Key neuropathological features of AD Illustrate the role of insulin and insulin receptor signaling mechanism in synaptic function and neurotransmission which disrupted with STZ leading to Amyloid AB and tau proteins deposition Demonstrate different STZ pathological effects in	3 10
	signaling mechanism in synaptic function and neurotransmission which disrupted with STZ leading to Amyloid AB and tau proteins deposition	10
3	Demonstrate different STZ pathological effects in	
	AD	14
4	Clinical and neuropathological AD stages And different diagnostic tools	19
5	Demonstrate different mechanisms of HDAC inhibitors to improve cognitive deficit and memory impairment	31
6	stereotaxic instrument	38
7	stereotaxic surgery (Intracerebro-ventricular administration of streptozotocin)	39
8	Effect of chronic treatment with Lacosamide (3mg, 10mg, 30mg orally) for 3 weeks on Locomotor activity in open field test in STZ induced AD rat model	56
9	Effect of chronic treatment with Lacosamide (3mg, 10mg, 30mg orally) for 3 weeks on on learning and memory in Morris Water Maze test in STZ induced AD rat model escape latency time among different group during acquisition phase and probe trail	59
10	Effect of chronic treatment with Lacosamide (3mg, 10mg, 30mg orally) for 3 weeks on learning and memory in Morris Water Maze test in STZ induced AD rat model (probe trial)	61
11	Effect of chronic treatment with Lacosamide (3mg, 10mg, 30mg orally) for 3 weeks on spatial memory deficit in Y Maze test in STZ induced AD rat model.	64
12	Nanodrop curve showing concentration and purity of extracted RNA from a representative sample which is 2020 ng/µl	65

figure	Title	Page
13	Effect of chronic treatment with Lacosamide (3mg, 10mg, 30mg orally) for 3 weeks on the relative expression of mRNA of APP in hippocampus of and frontal cortex of STZ induced AD rat model	68
14	The linear (upper) and log (lower) amplification curves representing the Ct values of APP gene	69
15	Effect of chronic treatment with Lacosamide (3mg, 10mg, 30mg orally) for 3 weeks on the relative expression of mRNA of MAPT in hippocampus and frontal cortex of STZ induced AD rat model.	72
16	The linear (upper) and log (lower) amplification curves representing the Ct values of MAPT gene	73
17	Effect of chronic treatment with Lacosamide (3mg, 10mg, 30mg orally) for 3 weeks on the relative expression of mRNA of IRS1 gene in hippocampus and frontal cortex of STZ induced AD rat model	76
18	The linear (upper) and log (lower) amplification curves representing the Ct values of IRS1 gene	77
19	Effect of chronic treatment with Lacosamide (3mg, 10mg, 30mg orally) for 3 weeks on the HDACs activity in hippocampus of STZ-induced AD rat model	80
20	Effect of chronic treatment with Lacosamide (3mg, 10mg, 30mg orally) for 3 weeks on hippocampal histopathological changes of STZ-induced AD rat model	82

تأثير عقار اللاكوساميد على الخلل المعرفي في نموذج الجرذان المصابه بالزهايمر المسبب بالستربتوزتوسين

مقدمة توطئة للحصول على درجة الماجستير بالأدويه

من الطبيبة فاطمه صبحي ابراهيم اللبيشي معيد بقسم الادويه الاكلينيكيه كلية الطب- جامعة كفر الشيخ

تحت اشراف
د/ لبنى فؤاد عبدالعزيزبسيوني
أستاذ ورئيس قسم الأدويه الاكلينيكيه
كلية الطب- جامعة عين شمس
د/ وسام مصطفى البقلي
أستاذ مساعد بقسم الأدويه الاكلينيكيه
كلية الطب- جامعة عين شمس
كلية الطب- جامعة عين شمس
مدرس بقسم الأدويه الاكلينيكيه
مدرس بقسم الأدويه الاكلينيكيه

كلية الطب جامعة عين شمس

Literature Review

Aim of the study

Material and Methods

Results

Discussion

Summary

References