بسم الله الرحمن الرحيم

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تم رفع هذه الرسالة بواسطة / سامية زكى يوسف

بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

ملاحظات: لا يوجد

Antidepressant effect of saxagliptin in an experimental model of depression in rats: Role of incretin

Thesis

Presented for the partial fulfillment of

Master Degree in Pharmaceutical Sciences
(Pharmacology & Toxicology)

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2022

ACKNOWLEDGEMENT

All thanks and gratitude is to my lord Allah, who has given me the strength and will to finish this work. Words and thanks will never suffice to praise Allah for his mercy, blessings and guidance that lead me through the tough times.

I would like to express my deepest gratitude and sincere appreciation to ***Dr. Reem Nabil Abou El-Naga,*** Associate professor of Pharmacology and Toxicology, Faculty of Pharmacy, Ain Shams University, for her kind and expert supervision, patience, unlimited support, generous assistance, and for the extensive effort, time and energy. All credit goes to her for participating in choosing the thesis point from the department search line. I am heavily indebted to her tremendous efforts, deep experience, the valuable time, and generous assistance during all stages of this study.

My profound thanks are to ***Dr. Amany Mohammed Ahmed Gad***, Associate professor of Pharmacology and Toxicology, Faculty of Pharmacy, Sinai University, East Kantara Branch, New city, El Esmailia, who was always supporting me with great patience, constructive advice and valuable assistance throughout the whole work and for actively supervising the experimental work steps and solving the daily problems. I will always be indebted to her kindness and continuous encouragement. No words can describe my gratitude to her. It's really an honor to be one of her students. She embraced this thesis with useful comments, and valuable time that she sacrificed for me during this work, without which I would have never been able to produce such a work.

My sincere appreciation to ***Dr. Sara Abdel Moneim Wahdan***, Associate professor of Pharmacology and Toxicology, Faculty of Pharmacy, Ain Shams University, for her supervision, untiring help, valuable assistance, priceless guidance and fruitful opinions throughout the whole practical work which made her a backbone of this research. The supervision and support that she gave me truly helped the progression and smoothness of this work.

I am very grateful to my dear parents, may Allah give them health and wellness, dear brother, dear daughter and especially my dear husband for standing by me in every step, for their praying, their continuous support and encouragement all the way through and giving me all the strength and faith more than I needed.

Finally my sincere appreciation and thanks go to all my colleagues in National Organization for Drug Control & Research (NODCAR), for their friendly cooperation and constant support.

MennatAllah Nazeem Mostafa

"قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ"

سورة البقرة آية (32)

Contents

List of abbreviations

5-HT	Serotonin/5-hydroxytryptamine
p-AKT	phosphorylated-Protein kinase B
ATP	Adenosine triphosphate
AST	Aspartate aminotransferase
ALT	Alanine transaminase
ASC	Apoptosis-associated speck-like protein containing a caspase recruitment domain
ABC-HRP	Avidin-Biotin-Peroxidase Complex
BD	Bipolar Disease
BDNF	Brain-derived neurotrophic factor
BSA	Bovine Serum Albumin
cAMP	Cyclic adenosine monophosphate
CYP	Cytochrome P450
Cu^{+2}	Copper ion
CK	Creatine kinase
CK-MB	Creatine kinase-MB
CUMS	Chronic unpredictable mild stress
DMSO	Dimethyl sulphoxide
DPP-4	Dipeptidyl peptidase-4
DNA	Deoxyribonucleic acid
DOCA	Deoxycorticosterone acetate
DTNB	5`5`dithiobis(2-nitrobenzoic acid)
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
FST	Forced swimming test
FLX	Fluoxetine
Fe^{+3}	Ferric ion
GSH	Glutathione
GIP	Glucose-dependent insulinotropic peptide
GLP-1	Glucagon like peptide-1
GSK-3B	Glycogen synthase kinase-3B
GPCR	G-protein-coupled receptors
GGT	Gamma-glutamyl transferase

List of abbreviations

H&E	Hematoxylin & Eosin
HCl	Hydrochloric acid
HPA	Hypothalamic–pituitary–adrenal
HRP	Horseradish Peroxidase
IL-1β	Interleukin-1β
IL-6	Interleukin-6
iNOS	Inducible nitric oxide synthase
LH	Learned helplessness
LDL	Low-density lipoproteins
MAO	Monoamine oxidase
MAOIs	Monoamine Oxidase Inhibitors
MDA	Malondialdehyde
MDD	Major depressive disorder
mRNA	Messenger ribonucleic acid
MRI	Magnetic resonance imaging
MAPK	Mitogen-activated protein kinase
MnSOD	Manganese superoxide dismutase
MPO	Myeloperoxidase
NaOH	Sodium hydroxide
NE	Norepinephrine
NLRP3	NLR family, pyrin domain-containing 3
NO	Nitric oxide
NF-κB	Nuclear factor kappa B
OD	Optical density
OFT	Open field test
OPT	O-phthalaldehyde
PBS	Phosphate buffered saline
PD	Parkinson disease
p-PI3K	phosphorylated-Phosphatidylinositol3-kinase
PKA	protein kinase A
PKC	protein kinase C
PFC	Prefrontal cortex
P-gp	Permeability glycoprotein
ROS	Reactive oxygen species
RIPA	Radio immunoprecipitation assay

SAXA	Saxagliptin
SAD	Seasonal affective disorder
SDS	The severity of dependence scale
SNRIs	Serotonin Norepinephrine Reuptake Inhibitors
SPT	Sucrose preference test
SSRIs	Selective Serotonin Reuptake Inhibitors
SDS	Sodium dodecyl sulphate
SDS-PAGE	sodium dodecyl sulfate polyacrylamide gel electrophoresis
SGOT	Serum glutamic oxaloacetic transaminase
TBARS	Thiobarbituric acid reactive substances
TCA	Trichloroacetic acid
TCAs	Tricyclic Antidepressants
TMB	Tetramethylbenzidine
TNF-α	Tumor necrosis factor-alpha
TBS	Tris-buffered saline
TrkB	Tyrosine kinase receptor B
WHO	World Health Organization
Zn^{+2}	Zinc ion

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Abstract

Abstract

Depression is recognized to be a worldwide, devastating mental illness, giving rise to poor quality of life and huge economic wastage. It distinguishes by many symptoms; such as persistent depressed mood, loss of pleasure, reduced energy, low self-assuredness, alterations in appetite, and poor concentration. Chronic exposure to stressful life events has been found to be involved in the etiology of neuropsychiatric diseases; such as depression. For that reasons, rats were revealed to an experimental model of chronic unpredictable mild stress (CUMS) model for 14 days. Diverse mild and unpredictable stressors were administered for 14 days in random times with the oral administration of saxagliptin (SAXA) (0.5, 1 and 2 mg/kg) to the treated rat groups.

Saxagliptin which is a member of dipeptidyl peptidase-4 (DPP-4) inhibitors class, has been identified to elevate glucagon-like peptide-1 (GLP-1) level. The emergence of pharmacological agents; such as DPP-4 inhibitors is considered as an important rival in modifying neurodegenerative diseases as Alzheimer's and Parkinson's diseases in the preclinical studies. Accordingly, in the present study, SAXA is utilized to investigate its potential neuroprotective and antidepressant effect in an experimental model of chronic unpredictable mild stress (CUMS) in rats. The effect of SAXA is mostly linked to GLP-1/PI3K/AKT signaling pathway which upon its activation reportedly enhanced cellular survival, reversed neuronal damage and oxidative stress. It also is recognized by its potent anti-oxidant, anti-inflammatory, anti-apoptotic, and neuro-protective activities. SAXA treatment showed a significant elevation in the ambulation frequency, rearing score, grooming time and frequency in open field test (OFT). Additionally, the administration of SAXA displayed a significant increase in struggling time as well as a significant decrease in the immobility time in forced swimming test (FST). Moreover, the sucrose intake in sucrose preference test (SPT) was significantly enhanced in SAXA group. Saxagliptin treatment reversed the CUMS-induced changes in the

histopathological examination. Furthermore, it prohibited the CUMS-induced decrease in the monoamines levels and the brain derived neurotrophic factor (BDNF). Contrarily, it decreased the inflammatory, apoptotic and oxidative stress markers. In addition, SAXA treatment elevated the incretin hormones, glucagon like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), which are associated with the protein kinase B (AKT)/ phosphatidylinositol3-kinase (PI3K) pathway activation. . In conclusion, these findings revealed that SAXA may show antidepressant activity.

Keywords: Saxagliptin; Chronic unpredictable mild stress; Inflammation; Oxidative stress; glucagon like peptide-1; glucose-dependent insulinotropic peptide