Faculty of Pharmacy
Department of Pharmacology and Toxicology

كلية الصيدلة
قسم الأدوية والسموم

"Pharmacological Study on the Neuroprotective Effect of Selegiline in 3-Nitropropionic Acid-Induced Experimental Animal Model of Huntington's Disease Phenotype"

A thesis submitted in partial fulfillment of the requirements
for the master degree in Pharmaceutical Sciences
(Pharmacology and Toxicology)

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Faculty of Pharmacy, Ain Shams University

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" دراسة تأثير دواء سيليجيلين الواقي للخلايا العصبية في مرض هنتجتون المحدث تجريبيا بواسطة حمض ٣– نيتروبروبيونيك "

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Pre-requestic Post-Graduate Courses

Besides the work presented in this thesis, the candidate has attented the following courses:

General courses:

1-Instrumental analysis

2-Physical pharmacy

3-Statistics

4-Computer skills

Special courses:

1- Pharmacology

2- Clinical pharmacology and therapeutics

3- Neuropharmacology

4- Molecular pharmacology

5- Selected topics in pharmacology and toxicology

She successfully passed examination in these courses with general grade **Excellent.**

Head of pharmacology and Toxicology Department

Prof. Ebtehal El Demerdash

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Abstract:

3-Nitropropionic acid (3-NP), a mitochondrial toxin, is considered a reliable agent for inducing HD-like phenotype in experimental animals. Reduction of prepulse inhibition (PPI) of acoustic startle response, locomotor hypoactivity, increased oxidative stress, activation of apoptotic cascade and bilateral striatal lesions are the major manifestations of 3-NP-induced neurotoxicity. Selegiline is a non-competitive monoamine oxidase-B (MAO-B) inhibitor with previously reported antioxidant and antiapoptotic effects. The present study was designed to investigate neuroprotective effect of selegiline on 3-NP induced neurotoxicity. Rats administered 3-NP (20 mg/kg, i.p.) for four consecutive days exhibited PPI deficits, locomotor hypoactivity, increased striatal and cortical malondialdehyde (MDA) and reduced respective glutathione (GSH) level, catalase and superoxide dismutase (SOD) activities. Changes in the level of apoptotic regulatory gene expressions were demonstrated as increased striatal and cortical caspase-3 and Bax expression and decreased respective Bcl2 expression. Selegiline was given by i.p. injection at doses 2.5, 5 and10 mg/kg, 3 days prior to- and continued daily, 30 minutes before 3-NP administration. The high dose levels of selegiline (5 and 10 mg/kg), significantly increased locomotor activity, improved PPI, reduced striatal and cortical MDA, caspase-3 and Bax and increased respective GSH level, catalase and superoxide dismutase activities and Bcl2 expression. Selegiline at dose 2.5 mg/kg could only reverse some of the manifestations of 3-NP-induced neurotoxicity. It could significantly improve PPI, reduce striatal MDA level and Bax expression, and increase striatal GSH level, catalase and superoxide dismutase activities. It could also significantly increase cortical superoxide dismutase level and decreased cortical Bax expression. Histological examination further affirmed the neuroprotective effect of high dose levels of selegiline against 3-NP toxicity. Taken together, these results suggest that selegiline attenuate 3-NP-induced neurotoxicity. This neuroprotective effect may be related to antioxidant properties and antiapoptotic effects.

Key words: 3-nitropropionic acid; Selegiline; Prepulse inhibition; Glutathione; Caspase-3

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List of Abbreviations

3-NP	3-Nitropropionic acid
A	Absorbance
AD	Alzheimer's disease
AIF	Apoptosis inducing factor
ANOVA	Analysis of variance
ANT	adenine nucleotide translocator
ARE	Antioxidant response elements
ASR	Acute startle response
ATP	Adenosine triphosphate
Bax	Bcl2-associated X protein
Bcl2	B-cell-lymphoma 2
Bcl xl	B-cell-lymphoma-extra large
BDNF	Brain derived neurotrophic factor
Bp	Base pairs
BSA	Bovine serum albumin
CAG	Cytosine-Adenine-Guanine
CDDO	2-cyano-3,12-dioxooleana 1,9-dien-28-oic acid
cDNA	Complementary DNA
c-fos	Cellular oncogene-fos
CNTF1	Ciliary neurotrophic factor 1
CYP 450	Cytochrome P 450
DA	Dopamine
Da	Daltons
dB	Decibel
DHBS	3,5-Dichloro-2-hydroxybenzene sulfonic acid
DNA	Deoxyribonucleic acid
DTNB	5,5' dithiobis 2-nitrobenzoic acid
ETC	Electron transport chain
FAD	Flavine adenine dinucleotide
GABA	Gamma amino buteric acid
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase
GDNF	Glial call derived neurotrophic factors
GSH	Reduced glutathione
GPx1	glutathione peroxidase-1
H & E	Hematoxylin and eosin
H2O2	Hydrogen peroxide
HD	Huntington's disease
HDACIs	Histone deacetylase inhibitors
HIV	Human immunodeficiency virus
HO-1	Heme-oxygenase-1
Htt	Huntingtin
Hsps	Heat shock proteins

IA	Ibotenic acid
i.p.	Intraperitoneal
IR	Infrared
IT 15	Interesting transcript 15
i.v.	Intravenous
KDa	Kilo Dalton
KA	Kianic acid
LD50	Median Lethal Dose
MAO-B	Monoamine oxidase B
MDA	Malondialdehyde
mPTP	Mitochondrial permeability transition pore
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
mRNA	Messenger RNA
MSNs	Medium-sized spiny neurons
NADPH	Nicotinamide adenine dinucleotide phosphate, reduced form
NBQX	6-nitro-7-sulfonylbenzo (f)quinoxaline-2,3-dione
NGF	Nuclear growth factor
NRF-1	Neuclear respiratory factor-1
Nrf2	Nuclear factor-erythroid 2-related factor-2
NMDA	N-methyl-D-aspartate
NO2	Nitric oxide
$O2^-$	Superoxide radical
OH^-	Hydroxyl radical
OD	Optical Density
PD	Parkinson's disease
PGC-1α	Peroxisome proliferator-activated receptor gamma coactivator 1- alpha
PPAR-γ	Peroxisome proliferator-activated receptor-gamma
PPI	Prepulse inhibition
QA	Quinolinic acid
s.c.	Subcutaneous
ROS	Reactive oxygen species
RNS	Reactive nitrogen species
Rpm	Round per minute
SDH	Succinate dehydrogenase
SEM	Standard error of mean
SOD	Superoxide dismutase
SSRIs	Selective serotonin reuptake inhibitors
TBA	Thiobarbituric acid
TCA	Tricarboxylic acid
TBARS	Thiobarbituric acid reactive substances
TBS	Tris buffered saline
TUDCA	Tauroursodeoxycholic acid
U	Units

UV	Ultraviolet
VDAC	Voltage-dependent anion channel
YAC	Yeast artificial chromosome

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