



Ardabil University of Medical Sciences

School of Pharmacy

Title of Dissertation

Investigating the Comparative Effects of Fluoxetine and Nano-Encapsulated Fluoxetine
on Cognitive Impairment Induced by Lysophosphatidylcholine: Behavioral and
Molecular Studies in Male Wistar Rats

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نامه ی سپاس

در ابتدا، بر خود می‌بینم تا از خانم دکتر معصومه دادخواه و خانم دکتر لیلا رضائی، اساتید راهنمای خود، کمال تشکر و قدردانی را به جا آورم، زیرا حمایت‌های بی‌بدیل و دانش ژرف ایشان، راه رسیدن به یک پژوهشگر موفق را برای من هموار ساخت. مسیر پژوهشی که تا به امروز پیموده‌ام، در هر مرحله خود، مرهون راهنمایی‌های بی‌شائبه و دلسوزانه ایشان بوده است .

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All the artwork featured in this thesis is the original creation of the author.

Abstract

Introduction: Destruction of myelin sheaths while preserving the underlying axons can lead to disruptions in information transmission, a crucial factor in various neurodegenerative diseases such as Multiple Sclerosis (MS). This study investigates the potential of enhancing the positive effects of fluoxetine, a neuroprotective agent known for its ability to increase neurotrophins levels, on remyelination by utilizing pegylated chitosan nanoparticles loaded with fluoxetine.

Methods and material: Local demyelination was induced in the CA1 region of the hippocampus using lysolecithin injection, and anxiety-like behavior was assessed through open field maze (OFM) and elevated plus maze (EPM) tests. The novel object recognition memory test (NORMT) was employed to evaluate recognition memory. ELISA was used to measure insulin like growth factor 1 (IGF-1) and brain derived neurotrophic factors (BDNF) levels in the hippocampus, while Luxol fast blue staining was utilized to quantify the extent of remyelination.

Results: The nanoparticle (NP)-treated groups exhibited reduced anxiety-like behavior in the OFM and EPM tests. NORMT results showed a better performance in NP-treated groups. Moreover, the NP-treated groups demonstrated significantly higher levels of BDNF ($P < 0.01$), no significant change in IGF-1 levels ($P > 0.05$), along with a reduced extent of demyelination ($P < 0.001$).

Conclusion and discussion: Treatment with nanoparticles of fluoxetine resulted in better cognitive performance, enhanced levels of BDNF, and decreased extent of demyelination lesion compared to fluoxetine. These findings support the argument for further research into innovative drug delivery systems for repurposed drugs, as they have the potential to yield improved and sometimes unexpected outcomes.

Keywords: *Nanoparticles, Multiple Sclerosis, Novel drug delivery, Fluoxetine, Nano-encapsulated fluoxetine*

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Abbreviations

PNS: peripheral nervous system	SSRI: selective serotonin reuptake inhibitor
CNS: central nervous system	TMEV: Theiler's murine encephalomyelitis virus
MS: multiple sclerosis	FLX: fluoxetine
PML: Progressive multifocal leukoencephalopathy	CYP 450: cytochrome P450
CIS: clinically isolated syndrome	OCTs: organic cation transporters
RRMS: relapsing-remitting multiple sclerosis	NPs: nanoparticles
SPMS: secondary progressive multiple sclerosis	BBB: the blood-brain barrier
PPMS: primary progressive multiple sclerosis	Ip: intraparietal
MHC: major histocompatibility complex	OFM: open field maze
CI: cognitive impairment	DS: discrimination ratio
OPC: oligodendrocyte precursor cells	LFB: Luxol fast blue
MSC: Mesenchymal Stem Cell,	NORM: novel object recognition maze
HSCT: hematopoietic stem cell transplantation	EPML elevated Plus Maze
HRQOL: health-related quality of life	NK cell: natural killer cell
FBF: fibroblast growth factor	SS: serotonergic system
IGF-1: Insulin-like growth factor 1	SERT: serotonin reuptake transporter
BDNF: brain-derived neurotrophic factor	HPA: hypothalamic-pituitary-adrenal
NT-3: neurotrophin-3	CRH: corticotropin releasing hormone
EAE: experimental autoimmune encephalomyelitis	GABA: Gamma-aminobutyric acid

TrkB: tropomyosin-related kinase B

CREB: C-AMP regulatory element-binding protein