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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July 2023

Thesis No: D-173

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 .

از پدر، مادر و خواهران عزیزم که همواره با تشویق بی‌پایان، درک، و اعتمادشان به توانایی‌های من، مرا در این مسیر همراهی کردند، از صمیم قلب سپاس‌گزارم. دستاوردهای من در این مسیر، بدون فداکاری‌های شما هرگز میسر نبود . حضور همیشگی شما به همراه عشق بی قید و شرط و سخنان گهربارتان، مرا به چیزی که امروز هستم رساند.

و به دوست عزیزم شقایق؛ ثابت قدمی تو در شب‌های تاریک زندگی ، همچون چراغ راه در این مسیر پرتلاطم بوده است. مهربانی و سخنان الهام‌بخش تو، سفر من را لبریز از امید و انگیزه، مرا عاری از شک و تردید و اراده من را پولادین ساخت.

حال که اندک مجالی برای نوشتن سخنان دل خود یافته‌ام، واضح است که این کلمات، از بیان دقیق اینکه چقدر قدردان شما هستم عاجزند. شما عزیزان در آسمان زندگی من تا ابد جاودانه بوده و الگوی همیشگی من در ادامه راه آن

Letter of Thanks

I extend my deepest gratitude to my extraordinary thesis advisors, Dr. Masoomeh Dadkhah and Dr. Leila Rezaie. Your wisdom, expertise, and unwavering support have sculpted me into a capable researcher. Every step, you led me through uncharted territories, shaping the very essence of my academic voyage.

I am incredibly grateful to my loving parents and sisters for their endless encouragement, understanding, and faith in my abilities. Your sacrifices have been the foundation upon which I have built my academic pursuits. Without your constant presence, words of wisdom, and unconditional love I would not have become the person I am today.

And to my dear friend Shghayegh; your steadfast companionship has been a beacon in the darkest of nights. Your kind heart and uplifting words have infused my journey with hope and inspiration, casting away doubts and fueling my determination.

As I pen these words of gratitude, they can only begin to convey the depth of my appreciation. To my professors, family, and

Dr. Tara Samizadegan kindly provided the nanoparticles utilized in this study.

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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Figures and charts

Abbreviations

PNS: peripheral nervous system

CNS: central nervous system

MS: multiple sclerosis

PML: Progressive multifocal leukoencephalopathy

CIS: clinically isolated syndrome

RRMS: relapsing-remitting multiple sclerosis

SPMS: secondary progressive multiple sclerosis

PPMS: primary progressive multiple sclerosis

MHC: major histocompatibility complex

CI: cognitive impairment

OPC: oligodendrocyte precursor cells

MSC: Mesenchymal Stem Cell,

HSCT: hematopoietic stem cell transplantation

HRQOL: health-related quality of life

FBF: fibroblast growth factor

IGF-1: Insulin-like growth factor 1

BDNF: brain-derived neurotrophic factor

NT-3: neurotrophin-3

EAE: experimental autoimmune encephalomyelitis

SSRI: selective serotonin reuptake inhibitor

TMEV: Theiler's murine encephalomyelitis virus

FLX: fluoxetine

CYP 450: cytochrome P450

OCTs: organic cation transporters

NPs: nanoparticles

BBB: the blood-brain barrier

Ip: intraparietal

OFM: open filed maze

DS: discrimination ratio

LFB: Luxol fast blue

NORM: novel object recognition maze

EPML elevated Plus Maze

NK cell: natural killer cell

SS: serotoninergic system

SERT: serotonin reuptake transporter

HPA: hypothalamic-pituitary-adrenal

CRH: corticotropin releasing hormone

GABA: Gamma-aminobutyric acid

TrkB: tropomyosin-related kinase B

CREB: C-AMP regulatory element-binding protein