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Review Article

The Effects of Mesenchymal Stem Cell on Calpains, Glycogen Synthase Kinase-3*β*, and Ryanodine Receptor 3 in Animal Models of Alzheimer's Disease: A Systematic Review

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ABSTRACT

Alzheimer's disease (AD) is a major common neurodegenerative disease characterized by progressive memory loss and decline in cognitive function, leading to dementia. Unlike pharmacological therapies, which are targeted toward symptoms, cell-based therapies target the underlying causes of AD. Therapies using mesenchymal stem cells (MSC) that target several important proteins such as calpains, glycogen synthase kinase 3-beta (GSK3*β*), and ryanodine receptor 3 (RYR3) related to amyloid-beta (A*β*) which contribute to AD pathophysiology need further investigation. This systematic review explored studies that examined the effects of MSC on the expression of calpains, *GSK3β*, and *RYR3* in mouse models of AD. A literature search of Medline/PubMed electronic database identified seven studies that met the inclusion criteria. These studies suggested that MSC may be associated with reduced GSK3*β* activity in AD mice by activating its inhibitory pathway and suppressing its activation pathway. MSC could also suppress *RYR3* expression in AD mice, reducing calcium (Ca^{2+}) levels in the cytosol. The beneficial effects of reduced GSK3*β* and RYR3 activity after MSC treatment include improved cognitive function, and reduced tau phosphorylation and A*β* plaques in AD mice. This systematic review emphasizes the need for further research on which MSC types, doses, and administration routes are most effective, as well as the immune response and effects in humans.

***Keywords*:** Alzheimer's Disease, Mesenchymal Stem Cells, Glycogen Synthase Kinase-3*β*, Ryanodine Receptor 3, Calpains, Stem Cells.

Introduction

Alzheimer's disease (AD) is a major form of neurodegenerative disease that is characterized by progressive memory loss and decline in cognitive function, leading to dementia.[1] One in ten individuals aged >65 years suffers from AD. The prevalence of AD increases with age, with 85% of patients with AD currently aged ≥75 years.[1] AD causes significant disability, including a decline in quality of life. It is the eighth most common cause of death in the United States with an estimated total treatment cost of approximately 305 billion dollars in the year 2020.[2]The basic feature of AD is the progressive accumulation of amyloid-beta (A*β*) plaques and neurofibrillary tangles (NFT), although its precise pathophysiology remains unknown. Extracellular A*β* plaques and intracellular NFT result in dystrophic neurites, microgliosis, synapse dysfunction, and cell death, collectively causing brain dystrophy and exacerbating AD.[3] Pharmacological treatment for patients with AD generally uses psychotropic drugs that aim to relieve symptoms, including improving cognitive function. Current US Food and Drug Administration-approved drugs cannot halt AD progression; they only reduce its symptoms.

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Therefore, new anti-AD drugs that directly target its root cause urgently need to be developed.[1,4] Unlike pharmacological therapies, which are targeted at symptomatic relief, cell-based therapies focus more on targeting the underlying causes of AD, such as replacing damaged neuron cells, cleaning toxin aggregate, stimulating neuron precursors, and neuroprotection.[5] Stem cells are particularly used for therapies because of their ability to differentiate and regenerate. Mesenchymal stem cells (MSC) are a popular cell therapy. Studies on MSC therapies for AD have been widely conducted *in vitro* and *in vivo*.[5,6] MSC can protect neurons by secreting various neuroprotective and growth factors,[7-9] accelerate microglia accumulation around A*β* deposits, and promoting microglia phagocytosis activity to encourage A*β* clearance.[10,11]

Studies on MSC therapies have mainly focused on several important proteins related to A*β* that contribute to AD pathophysiology: calpains, glycogen synthase kinase 3-beta (GSK3*β*), and ryanodine receptor 3 (RYR3). Calpains are a family of cytoplasmic nonlysosomal cysteine proteases widely expressed in human cells and other organisms. Calpains play several roles in cellular functions regulated by calcium (Ca^{2+}).[12] Also related to Calpains, is RYR3 an intracellular Ca^{2+} release channel in the sarcoplasmic and endoplasmic reticulum (ER), releasing Ca^{2+} from intracellular stores to activate important functions. Increasing calpains and RYR3 levels accelerates synaptic dysfunction and neurodegeneration by elevating A*β* and P-Tau levels.[12,13] Activating GSK3*β* also causes A*β* aggregation and tau phosphorylation.[14] Therefore, targeting these three proteins would be a new, promising approach in AD therapy.

Many researches have examined the relationships between MSC and RYR3, GSK3*β*, and calpains. But, to the best of our knowledge, the review on the effects of MSC on the expression of calpains, GSK3β, and RYR3 as candidate for AD treatment have not been comprehensively done. This systematic review examines how several findings have advanced the understanding of the relationships between

MSC and RYR3, GSK3*β*, and calpains, and explores in much more detail their prospects for AD treatment.

Materials and Methods

Search Strategy

This systematic review was conducted from August 2023 to October 2023. Articles were identified from the Medline/PubMed database using medical subject headings (MeSH) and various topic-related keywords (Table 1). The Medline/PubMed database was used due to its accessibility and completeness. Literature searches were not limited by language. The articles included in this systematic review were published between 2016 and 2023. The inclusion criteria were primary (original) journal articles with accessible full text that reported research on relevant topics in animal models (*in vivo*) and had a control group. Human or *in vitro* studies, review articles, and editorials were excluded.

Table 1: The keywords and Medical Subject Headings (MeSH)

Topic	Keyword and MeSH
Mesenchymal Stem Cells	"Mesenchymal Stem Cells"[Mesh] OR "Stem Cells"[Mesh] OR "Mesenchymal Stem Cells"[tw] OR "Stem Cells"[tw] OR "Adult Stem Cells"[tw]
Alzheimer's Disease	"Alzheimer Disease"[Mesh] OR Alzheimer[tw] OR "Alzheimer's Disease"[tw]
Calpain	"Calpain"[Mesh] OR Calpain[tw] OR "Calcium-activated neutral proteinase"[tw]
Glycogen synthase kinase-3*β*	"Glycogen Synthase Kinase 3 beta"[Mesh] OR "Glycogen Synthase Kinase 3"[Mesh] OR "glycogen synthase kinase-3β"[tw] OR "GSK3-β"[tw] OR "Glycogen Synthase Kinase 3" [tw] OR "Glycogen Synthase Kinase 3 beta"[tw]
Ryanodine Receptor 3	"Ryanodine Receptor Calcium Release Channel"[Mesh] OR "Ryanodine Receptor 3"[tw] OR "RyR 3" [tw]

Note: MeSH: Medical Subject Headings; tw: text word; GSK3-β: Glycogen synthase kinase-3β; RyR 3: Ryanodine Receptor 3

Study Selection and Data Extraction

Two authors independently selected the articles from Pubmed/Medline database. Potential articles underwent a two-stage evaluation: assessment of their titles and abstracts followed by their full text based on topic relevance and the eligibility criteria.

Data from the selected literature were extracted into a matrix table, including reference information (name, title, publication year, and publisher), the animal model, the administered intervention (MSC source, dose, and administration route), the study indicators, and the main results.

Data from all the articles were reviewed to assess similarities, differences, strengths, and weaknesses. These data were synthesized with existing theoretical bases for a systematic study. The methods and results of this systematic review were presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist. The PRISMA statement provides updated reporting guidance for systematic reviews that reflects advances in methods to identify, select, appraise, and synthesis studies.[15]

Results and Discussion

The screening process and database search results are presented in a PRISMA flow diagram (Figure 1). From 53 records, seven studies were identified, of which six (85.7%) examined GSK3*β*,[16-21] and one (14.3%) examined RYR3 (Figure 2).[22] No studies discussed calpains, so they will not be discussed further. Each article is summarized in the matrix table (Table 2). Bone marrow was the most widely used MSC source (42.9%), followed by human umbilical cord (28.8%), adipose tissue (14.3%), and others (14.3%) (Figure 3). Meanwhile, four studies used intravenous as route of MSC administration (57.1%) and three studies used intracerebral route (42.9%) (Figure 4).

AD is a multifactorial disease. Various pathological disorders cause cognitive impairments in patients with AD. Current pharmacological therapies for AD focus on treating its early symptoms without addressing the underlying pathology. Since AD pathogenesis is multifactorial, searching for interventional therapies with a multi-pronged approach to slow its progression has been considered an efficient strategy. Therefore, identifying treatment strategies seems urgent and challenging.[23,24] MSC have generally been recognized as a popular therapeutic cells. Studies on MSC therapies in neurodegenerative diseases, including AD, have been widely conducted.[5] Several studies have examined the relationships of MSC with GSK3β, and RYR3 expression, which is considered an important target in AD therapy.[16-21]

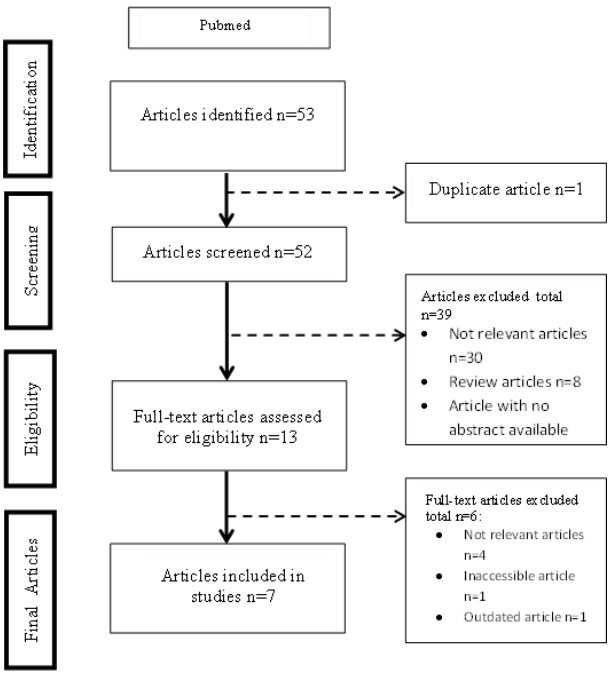

Figure 1: PRISMA Flow Diagram*MSCs Reduce GSK3β Activity*

Table 2: Matrix Table of Summary Article Included

Reference	Animal Model	MSC Type	Administration Route	Main Targets	Results
16	APP/PS1 mice	Mice BM-MSCs	Lateral Ventricle	Activity PI3K/Akt and GSK-3 β	• Reduces neuroinflammation • Reduces worsening of cognitive function via MWM test • Increases neurogenesis in the hippocampus • Inhibition of GSK3 β via PI3K/ Akt signaling pathway
17	Aβ 41-42 injected mice	Mice NTF-SCs from AD-MSC	Hippocampus	Wnt/ β-catenin signaling pathway gene expression	• Improve memory performance via MWM test • Increases hippocampal neurogenesis • Decreases GSK-3β levels and increases PI3K, Akt, MAPK, and β-catenin.
18	5xFAD mice	hUCB-MSCs	lateral ventricle	Tau hyperphosphorylation and GSK 3β	• Reduces worsening of cognitive function via T-Maze test • Decreases Tau phosphorylation and inhibits the formation of Tau deposits • Clears tau deposits by reducing tau hyperphosphorylation through decreasing GSK-3β
19	Mice were given $AlCl_3$ orally	Mice BM-MSCs	IV	SIRT1/MiR-134/ GSK3β signaling pathway	• Decreases Aβ-42 protein aggregates and tau protein • Reduces neuroinflammation (IL-1β) in the brain • Suppresses *STAT3* expression due to decreased proinflammatory cytokine • Ameliorates the decrease in p-PI3K and inhibits the activation of GSK-3β by increasing the expression of *p-GSK-3β* • Inhibits mTOR and increases autophagy and lysosomal clearance of Aβ • Increases *SIRT1* gene and protein and decreases *MiR-134* gene expression
20	Aβ 25-35 injected mice	Mice BM-MSC	IV	Aβ, APP, p-tau, and GSK-3β, neuroinflammation and, neuroprotective factor	• Corrects pathological changes • Normalizes the levels of proinflammatory cytokines (IL-1β TNF 1), prodegenerative and neuroprotective • Reduces tau hyperphosphorylation by decreasing GSK-3 β activity and improving BDNF levels
21	Mice SCO	Mice BM-EPCs	IV	Aβ, APP, p-tau, and GSK-3β, neuroinflammation and, neuroprotective factor	• Improve memory deficits and cognitive function via MWM and Y Maze tests • Prevents amyloid plaque deposition and histopathological changes in the hippocampus • Suppresses the increase in Aβ, APP, p-tau, and GSK-3β in the hippocampus • Increases neuroprotective expression (*VEGF*, *BDNF*, and *NGF*) in the Hippocampus
22	Mice were given $AlCl_3$ intraperitoneally	Wharton's jelly-derived mesenchymal stem cells	IV	*RYR3* Expression	• Reduces amyloid accumulation in the cortex and hippocampus • Decreases *RYR3* expression

GSK3*β* is a constitutively active and widely expressed serine-threonine kinase. It is involved in regulating numerous important cell biology pathways, some of which are also associated with neurodegeneration. There are two glycogen synthase kinase 3 isoforms: GSK3*α* and GSK3*β*.[25] GSK3*β* is highly expressed in different areas of the brain and has been implicated in Alzheimer's disease.[23] GSK3*β* was found to be hyperactive in the brains of patients with AD, and numerous compelling arguments indicate that dysregulation of this kinase contributes to AD pathogenesis via various processes by influencing all the major hallmarks of the disease including: tau phosphorylation, amyloid-*β* production, memory, neurogenesis and synaptic function.[14]

Two distinct processes are involved in promoting A*β* production by increasing GSK3*β* activity. First, GSK3*β* increases the regulation of nuclear factor kappa beta (NF-κ*β*) signaling and modifies *γ*-secretase activity to induce beta-secretase 1 (*BACE1*) expression.[14] Elevated BACE1 levels mediate A*β* synthesis via amyloid beta precursor protein (APP) processing.[1] Secondly, GSK3*β* directly interacts with and controls presenilin 1 (PSEN1/PS1) activity and cellular localization, thereby affecting *γ*-secretase activity. These processes promote A*β* production.[14]

Furthermore, GSK3*β* is one of the primary kinases implicated in tau protein phosphorylation. A phosphate group is added to a particular tau protein residue (threonine 231), resulting in microtubule disintegration and encouraging the formation of tau oligomers and NFT, which are involved in neuronal malfunction and degeneration.[14]

Some types of MSC, such as those from bone marrow (BM-MSC), adipose tissue (AD-MSC), and human umbilical cord blood (hUCB-MSC), reduced GSK3*β* activity, A*β* plaques, and NFT formation, simultaneously improving cognitive function in mouse models of AD.[16-21] The mechanisms involved in reducing GSK3*β* are quite diverse. The administration of MSC is known to activate the GSK3*β* inhibitory pathway. GSK3*β* inhibition is mediated by its phosphorylation at serine 9 by several kinases, including protein kinase B (AKT).[14] Various studies have reported that administering BM-MSC to mouse models of AD increased AKT levels, leading to decreased GSK3*β* activity.[16,17,19-21] Another GSK3*β* inhibitory pathway is the mitogen-activated protein kinase (MAPK) pathway. Phosphorylation at serine 389 by the p38 MAPK was shown to inhibit GSK3*β* activity.[14] AD-MSC were shown to increase MAPK after intracerebral administration in mice.[17]

Besides activating the GSK3*β* inhibitory pathway, MSC administration can inhibit the GSK3*β* activation pathway. GSK3*β* is structurally activated via autophosphorylation at tyrosine 216 (Tyr216).[14] hUCB-MSC administered to AD mice reduced Tyr216 phosphorylation of activated GSK3*β* by secreting galectin 3 (LGALS3).[18]

These studies have demonstrated the beneficial effects of reducing GSK3*β* activity by administering MSC to AD mice in improving cognitive function and memory and reducing tau phosphorylation and A*β* plaques.[16-22]

MSC Inhibit RYR3 Expression

Dysregulation of Ca^{2+} is hypothesized to disrupt synaptic networks in AD.[26,27] Synapse dysfunction, A*β* production and accumulation, as well as tau hyperphosphorylation are associated with increased ER Ca^{2+} release and Ca^{2+} hyperactivity.[28-30] RYR3 is an ER Ca^{2+} channel sensitive to Ca^{2+} changes in the cytosol. Changes in Ca^{2+} levels in the cytosol activate RYR3 channels and inositol 1,4,5-triphosphate receptors (IP3R) as one of the synaptic processes to maintain Ca^{2+} homeostasis in various neural functions.[27,31,32] Previous studies have shown that *RYR* expression was elevated as well as increased intracellular calcium concentrations in the AD mice model.[31,33] RYR3 has been reported to promote AD and mediate changes in ER Ca^{2+} levels.[31,34]

This systematic review demonstrated the role of MSC in inhibiting *RYR3* expression. Administering Wharton's jelly-MSCs reduced *RYR3* expression and the accumulation of A*β* deposits in the cortex and hippocampus of AD mice model.[22] However, the specific mechanism linking Wharton's jelly-MSC and *RYR3* expression remains unknown.

Future Prospects of MSC Therapy for AD

Variables affecting the therapeutic success of MSC-based therapies include the optimal dose of transplanted cells, the MSC source, transplant timing, a homogeneous cell population, and an appropriate transplantation route. The ideal procedure for MSC expansion, characterization, and isolation is still poorly standardized.[23]

In this review, the predominant MSC source was mice, and the question remains whether MSC originating from humans will show the same effects. Regardless of the source, bone marrow was the most widely used MSC source (42.9%), followed by human umbilical cord (28.8%), adipose tissue (14.3%), and others (14.3%) (Figure 3). This was in line with a previous study where the major sources of MSC were reported to be the bone marrow, adipose tissue, muscle, peripheral blood, umbilical cord, placenta, fetal tissue, and amniotic fluid.[35] Among them, BM-MSC has been applied as the most common source for the last two decades, however, umbilical cord-derived MSC (UC-MSC) and adipose tissue-derived MSC (AT-MSC) have also been widely explored.[36] Even though BM-MSC are the most commonly used in clinical setting, harvesting of these cells requires invasive procedures.[35] The process of isolating MSC from adult sources entails invasive and frequently painful procedures that may cause morbidity at the donor site.[35] Donor age, genetics, and exposure to environmental stressors all significantly impact the regeneration and differentiation capabilities of MSC.[37] More promising alternative sources of MSC include perinatal sources, such as umbilical cord blood, placenta, and fetal sources, such as fetal tissue and amniotic fluid.[35]

It was possible to determine the dose, MSC type, and administration route that is optimal for MSC because no animal studies have directly compared these variables. Four studies used intravenous route for MSC administration (57.1%) and three studies used intracerebral route (42.9%) (Figure 4). Even though it is easier, very few intravenously injected cells successfully migrate to the target site, and the majority end up entrapped in the lung microvasculature instead of the brain.[38] The blood-brain barrier (BBB) is another major limiting factor that compromises the delivery of therapeutics, including MSC, into the brain for treatment of neurodegenerative diseases.[39] As a result, several studies have attempted to bypass the BBB by delivering MSC via intraparenchymal or intracerebroventricular routes.[16-18] In addition, the body's immune response to MSC must be studied in greater depth, including the ability of MSC to cross the BBB.

It should be noted that this systematic review examined researches on the use of MSC in mice. Randomized controlled trials on the administeration of MSC to patients with AD remain scarce. Further studies on the use of MSC in humans are required and crucial. Questions that needs to be addressed with respect to the use of MSC in humans include; How safe is it for humans? What is the optimal dose and time needed? What is the best type and route of administration of MSC in humans? Which forms of AD can be optimally treated with MSC?

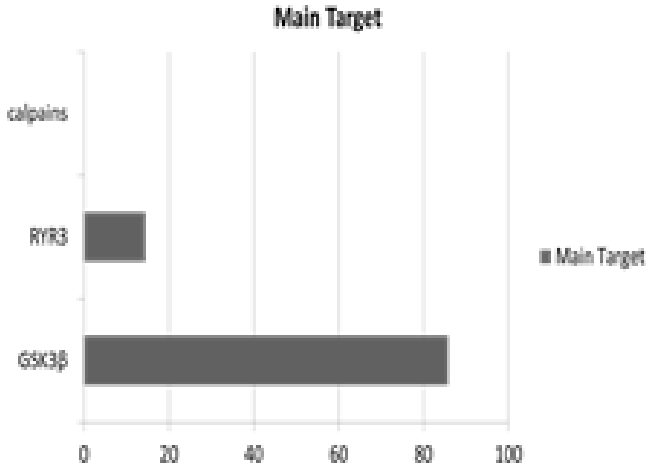

Figure 2: Percentage of Main Target

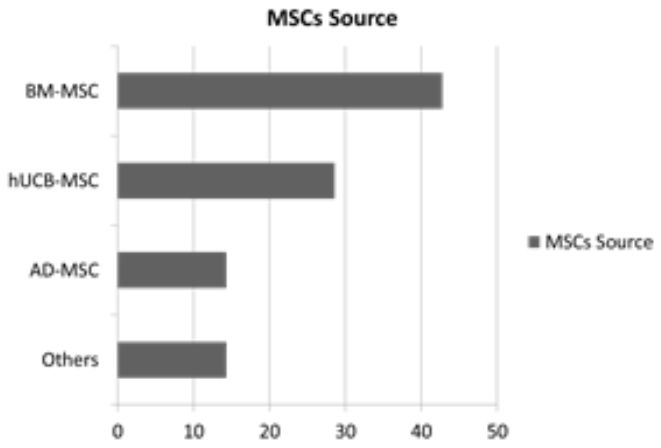

Figure 3: Percentage of MSC Source

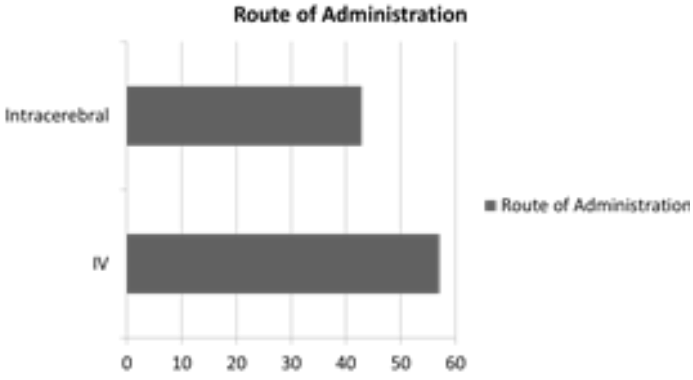

Figure 4: Percentage of Route of Administration

Conclusion

MSC have great potential as an AD therapy option. Several mechanisms can explain the effects of MSC on *GSK3β* and *RYR3* expression. Several types of MSC are known to suppress GSK3*β* activity by activating its inhibitory pathway and suppressing its activation pathway. MSC can also suppress *RYR3* expression, reducing Ca^{2+} levels in the cytosol. The beneficial effects of reducing GSK3*β* and RYR3 activity by administering MSC to AD mice include improved cognitive function, and reduced tau phosphorylation and A*β* plaques. Further studies are needed to determine which MSC types, dose, and administration routes are most effective, as well as to assess the immune response and effects in humans.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by authors.

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