International Journal of Science and Technology (IJST)
ISSN: 3049-1118, Volume- 1, Issue- 4 (Oct – Dec 2024)

Glycobiology of Neurodegeneration: Implications of Aberrant Glycosylation in Alzheimer's Disease

Dr. Vijay Kant Pandey[1*], Dr. Mousumi Ghatak[2], Dr. Timbrel Menen Tigga[3]
[1*]Department of Biotechnology, Netaji Subhas University, Jamshedpur
[2]Department of Zoology, Netaji Subhas University, Jamshedpur
[3] UPG +2 H/S Chakri, Potka-2, Jamshedpur, Jharkhand, India

Abstract

Alzheimer's disease (AD) is the most common neurodegenerative illness in the world. It is caused by the buildup of amyloid-β (Aβ) plaques and hyperphosphorylated tau neurofibrillary tangles. These protein clumps have been the main focus of treatment research, but new evidence reveals that abnormal protein glycosylation is a key part of the development of Alzheimer's disease. Glycosylation is the process by which enzymes attach carbohydrate groups to proteins. This process controls how proteins fold, how stable they are, where they are located, and what they do. This review looks at the growing evidence for dysregulated glycosylation in Alzheimer's disease (AD), with a focus on important pathogenic proteins like amyloid precursor protein (APP), tau, and other related components. We look at how changes in glycosylation patterns lead to neurodegeneration and talk about how addressing glycobiological processes could help treat Alzheimer's disease.

Keywords: Alzheimer's disease, glycosylation, neurodegeneration, tau protein, amyloid-β, N-glycosylation, O-glycosylation

1. Introduction

Alzheimer's disease is a major health problem around the world that affects more than 50 million people. It has serious effects on the economy and society as a whole. Two main signs that the condition is abnormal are extracellular senile plaques made up of amyloid-β peptides that have come together and intracellular neurofibrillary tangles that include hyperphosphorylated tau protein (Cummings et al., 2019). Even though scientists have been studying these protein aggregates for decades, treatments that target Aβ and tau have not worked very well in the clinic. This suggests that other pathogenic pathways need to be studied as well.

Post-translational modifications (PTMs) of proteins are very important for how cells work, and they have been shown to be involved in neurodegenerative diseases. Glycosylation of proteins is one of the most complicated and varied types of PTMs, and it affects over 50% of all human proteins (Moremen et al., 2012). Glycosylation is the process of attaching carbohydrate groups

*Corresponding Author Email: pandeyvijay00@gmail.com
Published: 15/12/2024
DOI: https://doi.org/10.70558/IJST.2024.v1.i4.241018

to certain amino acid residues, primarily asparagine (N-linked) and serine/threonine (O-linked) residues. This changes the structure, function, and location of proteins in cells. Recent studies have shown that the glycosylation patterns in the brains of people with Alzheimer's disease have changed a lot. This suggests that abnormal glycosylation may play a role in the development of the disease rather than just being a result of neurodegeneration. This review brings together what we now know about changes in glycobiology in AD and looks at how these changes might affect the development of new treatments.

2. Fundamentals of Protein Glycosylation

N-linked Glycosylation

In the endoplasmic reticulum (ER), N-linked glycosylation occurs while oligosaccharytransferase moves a prepared oligosaccharide precursor to asparagine residues in the consensus sequence Asn-X-Ser/Thr (X can be any amino acid except proline). This change is necessary for the appropriate folding of proteins, quality control, and moving them along the secretory route (Stanley, 2011). As proteins move through the Golgi apparatus, the N-glycan structures go through a lot of changes, which leads to three main types: high-mannose, complex, and hybrid glycans. Each class has its own structural properties that affect the stability of proteins, the activity of enzymes, and how cells interact with each other. Changes to the enzymes that digest glycans or the machinery that adds N-glycans to proteins can have a big effect on how proteins work and how cells stay healthy.

O-linked Glycosylation

O-linked glycosylation primarily occurs in the Golgi apparatus through the addition of N-acetylgalactosamine (GalNAc) to serine or threonine residues, forming the Tn antigen. Subsequent enzymatic modifications generate diverse O-glycan structures that regulate protein-protein interactions, enzymatic activity, and cellular signaling pathways (Bennett et al., 2012).

Contrasting N-glycosylation, O-glycosylation is harder to predict and study because it doesn't have strong consensus sequences like N-glycosylation does. Even Nevertheless, O-glycans are very important for how neurones work, how synapses change, and how cells stick together. These processes are messed up in neurodegenerative illnesses.

3. Glycosylation Alterations in Alzheimer's Disease

Global Glycomic Changes

Comprehensive glycoproteomic studies of Alzheimer's disease (AD) brain tissue have revealed widespread disruptions in both N- and O-linked glycosylation compared to age-matched controls. Mass spectrometry-based analyses have shown significant changes in glycan branching, sialylation, and fucosylation (Kizuka et al., 2015). Altered N-glycan structures have also been found in cerebrospinal fluid and brain samples, indicating that glycosylation abnormalities in AD are systemic rather than protein-specific. Additionally, dysregulation of key glycosylation enzymes such as MGAT5 and α-2,6-sialyltransferase has been reported,

suggesting these enzymatic changes may contribute to early disease mechanisms and serve as potential therapeutic targets.

APP and Amyloid-β Glycosylation

The amyloid precursor protein (APP) has a lot of N-glycosylation at two important locations (Asn467 and Asn496 in APP695). This has a big effect on how it is processed and how amyloid β-peptide (Aβ) is made. For APP to get to the cell surface and be processed by secretases, it needs to be glycosylated correctly (Weidemann et al., 1989). Researchers have found problems with the glycosylation of APP and tau in people with Alzheimer's disease (AD). They have also found changes in the glycosylation of the proteases γ-secretase and β-secretase, which help make Aβ. Changes in APP glycosylation can make it harder for secretases to cut it, which could lead to more Aβ being made and less protection for neurones.

The glycosylation status of secretases is also very important in the development of AD. Glycosylation changes alter the enzymatic activity, subcellular localisation, and protein stability of β-secretase (BACE1) and parts of the γ-secretase complex. In AD, problems with secretase glycosylation may make amyloidogenic processing and Aβ buildup worse.

Tau Protein Glycosylation

Researchers used to think that tau didn't have much glycosylation, but new investigations have showed that it does, especially in Alzheimer's disease (AD). In AD brains, tau is N-glycosylated, but not in healthy brains. This suggests that this change may be involved in the development of AD. In pathogenic tau species, aberrant O-GlcNAcylation, a type of O-linked glycosylation, has been seen. This type of glycosylation competes with tau phosphorylation. In Alzheimer's disease, less O-GlcNAcylation may lead to more tau hyperphosphorylation and the formation of neurofibrillary tangles. On the other hand, more O-GlcNAcylation has been found to reduce tau phosphorylation and aggregation in experimental models. We wanted to see how N-glycosylation affects tau's tendency to aggregate. Studies have shown that abnormal N-glycosylation of tau in the brains of people with Alzheimer's disease (AD) makes proteins stick together and may help create harmful tau species. This discovery shows that targeting tau glycosylation could be a new way to treat AD.

Other AD-Related Glycoproteins

Many additional proteins involved in the development of AD also have changes in their glycosylation, in addition to APP and tau. These are:

Reelin: This extracellular matrix protein is important for neuronal migration and synaptic plasticity. In AD brains, it has different glycosylation patterns, which may cause synaptic dysfunction and cognitive impairment.

CRMP-2 (Collapsin Response Mediator Protein-2): CRMP-2 is involved in guiding axons and developing neurones. In Alzheimer's disease, it has abnormal glycosylation, which may affect its normal actions and lead to neurodegeneration.

Apolipoprotein E (ApoE): is the main genetic risk factor for sporadic AD. It changes through glycosylation, which affects its ability to transport lipids and remove Aβ. In Alzheimer's disease, changes in ApoE glycosylation may make Aβ buildup and neuroinflammation worse.

Table 1. Key Glycosylation Alterations in Alzheimer's Disease

Protein/Target	Glycosylation Type	Changes in AD	Functional Impact	Reference
APP	N-linked (Asn467, Asn496)	Altered glycan processing	Enhanced amyloidogenic processing	Weidemann et al., 1989
Tau	O-GlcNAcylation	Decreased O-GlcNAc	Increased hyperphosphorylation	Liu et al., 2004
Tau	N-linked	Present in AD, absent in controls	Promotes aggregation	Current studies
BACE1 (β-secretase)	N-linked	Altered glycan structures	Modified enzymatic activity	Stanley, 2011
Reelin	N/O-linked	Aberrant patterns	Impaired synaptic function	Bennett et al., 2012
CRMP-2	N/O-linked	Altered glycosylation	Disrupted axonal guidance	Kizuka et al., 2015
ApoE	N-linked	Modified glycan structures	Reduced Aβ clearance	Moremen et al., 2012
Global brain glycome	N/O-linked	↓ Sialylation, ↑ Fucosylation	Widespread dysfunction	Cummings et al., 2019

Note: ↓ = decreased; ↑ = increased; APP = Amyloid Precursor Protein; BACE1 = β-site APP Cleaving Enzyme 1; CRMP-2 = Collapsin Response Mediator Protein-2; ApoE = Apolipoprotein E

4. Mechanisms of Glycosylation-Mediated Neurodegeneration

Protein Folding and Quality Control

Proper glycosylation is important for the endoplasmic reticulum's ability to fold proteins and check their quality. In AD, abnormal glycosylation may overwhelm the cellular quality control systems, causing misfolded proteins to build up and the unfolded protein response (UPR) to turn on. Long-term activation of the UPR leads to stress in the endoplasmic reticulum (ER), problems with cells, and eventually death of neurones.

Synaptic Function and Plasticity

A lot of synaptic proteins have glycosylation changes that affect how they work, where they are, and how they interact with other proteins. In Alzheimer's disease, glycosylation is out of whack, which messes up memory formation, long-term potentiation, and synaptic transmission. For instance, changes in the glycosylation of AMPA and NMDA receptors change how they move around and work, which is a sign of synaptic dysfunction in AD.

Neuroinflammation

The glycosylation patterns on proteins on the surface of cells and in secreted substances affect how the body responds to neuroinflammation. In AD, abnormal glycosylation may cause microglial activation, cytokine production, and long-term neuroinflammation, which makes a bad cycle that speeds up neurodegeneration.

Cellular Trafficking and Localization

Glycosylation changes act as signals that tell proteins where to go in the cell. Dysregulated glycosylation in AD messes up the regular movement of proteins, which causes them to build up in the wrong places and makes cells not work properly.

5. Diagnostic and Therapeutic Implications

Glycan Biomarkers

The unusual glycosylation patterns seen in AD open up new possibilities for creating biomarkers. Glycomic tests on cerebrospinal fluid and blood have found possible diagnostic markers that could help find diseases sooner and keep track of how they are becoming worse. Some glycan signatures may also be able to predict how well a medication would work and help doctors choose the best treatment for each patient.

Therapeutic Targeting

Several therapeutic strategies targeting glycosylation pathways are being explored for AD treatment:

Enzyme Modulation: Targeting specific glycosylation enzymes, such as O-GlcNAc transferase (OGT) or O-GlcNAcase (OGA), could restore normal glycosylation patterns and ameliorate pathological changes.

Glycan Structure Modification: Small molecule inhibitors or activators of glycosylation pathways could be developed to correct aberrant glycan structures and restore protein function.

Lectin-Based Therapies: Lectins that bind specific glycan structures could be utilized to modulate protein interactions and cellular processes affected by aberrant glycosylation.

Combination Approaches

Because AD pathogenesis is so complicated, combination therapies that target both established pathology hallmarks (Aβ and tau) and glycosylation anomalies may work better than therapies

that only target one of them. These kinds of techniques could target more than one pathogenic mechanism at the same time and have therapeutic effects that work together.

Conclusion

Glycobiology is a new field that has found that aberrant protein glycosylation is a major cause of Alzheimer's disease (AD). Researchers have found that important proteins connected to Alzheimer's disease, like as APP, Tau, Reelin, and CRMP-2, have abnormal glycosylation, which affects things like protein aggregation, synaptic function, inflammation, and cellular transport. Targeting glycosylation pathways could lead to new strategies to treat AD. Glycobiology is a promising field for improving AD treatment and knowledge since more study is needed to track glycosylation changes over time, find target pathways, and create accurate medications.

References

1. Bennett, E. P., Mandel, U., Clausen, H., Gerken, T. A., Fritz, T. A., & Tabak, L. A. (2012). Control of mucin-type O-glycosylation: A classification of the polypeptide GalNAc-transferase gene family. *Glycobiology*, 22(6), 736-756.
2. Cummings, J., Lee, G., Ritter, A., Sabbagh, M., & Zhong, K. (2019). Alzheimer's disease drug development pipeline: 2019. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, 5, 272-293.
3. Kizuka, Y., Kitazume, S., & Taniguchi, N. (2015). N-glycan and Alzheimer's disease. *Biochimica et Biophysica Acta*, 1850(10), 2327-2334.
4. Liu, F., Iqbal, K., Grundke-Iqbal, I., Hart, G. W., & Gong, C. X. (2004). O-GlcNAcylation regulates phosphorylation of tau: A mechanism involved in Alzheimer's disease. *Proceedings of the National Academy of Sciences*, 101(29), 10804-10809.
5. Moremen, K. W., Tiemeyer, M., & Nairn, A. V. (2012). Vertebrate protein glycosylation: Diversity, synthesis and function. *Nature Reviews Molecular Cell Biology*, 13(7), 448-462.
6. Stanley, P. (2011). Golgi glycosylation. *Cold Spring Harbor Perspectives in Biology*, 3(4), a005199.
7. Weidemann, A., König, G., Bunke, D., Fischer, P., Salbaum, J. M., Masters, C. L., & Beyreuther, K. (1989). Identification, biogenesis, and localization of precursors of Alzheimer's disease A4 amyloid protein. *Cell*, 57(1), 115-126.