RESEARCH ARTICLE

Exploring the molecular interactions between cadmium and glycogen synthase kinase-3β in Alzheimer's disease and their implications for neurodegeneration and therapeutic strategies

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ABSTRACT

Background: Alzheimer's disease (AD) is a leading cause of dementia, characterized by neurodegeneration associated with the accumulation of amyloid-beta plaques and hyperphosphorylated tau proteins. Glycogen synthase kinase-3β (GSK3β) plays a critical role in these processes. *Hypothesis:* This study explores cadmium's interaction with GSK3β, positing that cadmium-induced activation of GSK3β exacerbates neurodegeneration in AD. *Materials and Methods:* We employed bioinformatics tools for molecular docking analyses of cadmium acetate and GSK3β, utilizing structures from the Protein Data Bank. Binding affinities were assessed across multiple binding modes, with interactions analyzed using Discovery Studio and PyRx software. *Results:* Cadmium exhibited strong binding affinities to GSK3β, with the most favorable binding observed in Mode 1 (-3.4 kcal/mol). Interaction analysis revealed significant involvement of key residues (e.g., Arg223, Ser215), highlighting various bonding interactions, including hydrogen bonds and van der Waals forces. *Conclusion:* The findings indicate that cadmium binding may disrupt normal GSK3β function, potentially enhancing tau hyperphosphorylation and amyloid-beta accumulation, contributing to AD pathophysiology. This research underscores cadmium's role as a neurotoxin in AD and suggests targeted therapeutic strategies to mitigate its effects on GSK3β, offering avenues for novel interventions in neurodegenerative diseases.

Keywords: Alzheimer's disease, Glycogen synthase kinase-3β, Cadmium, Neurodegeneration, Molecular docking

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INTRODUCTION

Alzheimer's disease (AD), the foremost cause of dementia, affects over 55 million people worldwide, with its prevalence rising with age, and it is characterized by progressive memory loss, cognitive decline, and behavioral changes, AD significantly burdens patients, caregivers, and healthcare systems.[1] Pathologically, it involves the accumulation of amyloid-beta plaques and neurofibrillary tangles from hyperphosphorylated tau proteins, leading to synaptic dysfunction, neuronal death, and brain atrophy.[2] Key mechanisms of neurodegeneration in AD include oxidative stress, mitochondrial dysfunction, inflammation, and calcium homeostasis dysregulation.[3] Glycogen Synthase kinase-3β (GSK3β) plays a crucial role in AD by driving tau-related and amyloid-beta-related neurodegeneration. It promotes tau hyperphosphorylation, leading to neurofibrillary tangles, and increases amyloid-beta production, exacerbating synaptic dysfunction and neuronal loss.[4] Dysregulated GSK3β activity is closely linked to cognitive decline, making it a vital therapeutic target in AD. While GSK3β normally regulates glycogen metabolism, cell cycle progression, and signaling pathways, its hyperactivation in AD accelerates neurodegeneration through excessive tau phosphorylation and amyloid-beta accumulation.[5]

Cadmium (Cd) is a heavy metal and environmental neurotoxin found in industrial waste, tobacco smoke, and contaminated food or water. Upon absorption, it accumulates in the brain, causing oxidative stress, inflammation, and neuronal apoptosis. Chronic cadmium exposure is linked to neurodegenerative disorders like AD, as it disrupts calcium signaling and exacerbates neuroinflammation. This exposure impairs brain function by promoting oxidative stress, accelerating protein aggregation, and increasing neuronal damage.[6] Cadmium's neurotoxic effects are strongly associated with GSK3β activation. By inducing oxidative stress and disrupting cellular signaling, cadmium generates reactive oxygen species (ROS), resulting in mitochondrial dysfunction and inflammation.[7] These processes activate GSK3β, which further promotes tau hyperphosphorylation and amyloid-beta accumulation, worsening neurodegenerative conditions.[8] Research indicates that cadmium exposure significantly increases GSK3β activity, leading to cognitive decline and synaptic dysfunction in AD.[9] However, gaps

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remain in understanding the precise molecular mechanisms, including how cadmium modulates upstream signaling pathways, the dose-response relationship, and the long-term impacts of low-level cadmium exposure on AD progression. This study aims to investigate the molecular interactions between cadmium and GSK3β in AD using bioinformatics tools. By identifying key molecular targets and pathways involved in cadmium-induced GSK3β activation, the research seeks to develop antioxidant treatments and novel drug candidates to mitigate cadmium's neurotoxic effects and slow AD progression.

MATERIALS AND METHODS

Selection of Protein

This study targets Glycogen synthase kinase-3β (GSK3β) for molecular docking analyses due to its crucial role in AD. It examines cadmium's binding affinity and its mechanisms of GSK3β activation to identify potential novel drug candidates for AD treatment.

Acquisition of Target Protein

Structural data for Glycogen Synthase Kinase-3β (GSK3β) was sourced from the Protein Data Bank using PDB ID 1i09 and utilized for bioinformatics analyses, including molecular docking and ligand interactions.

Preparation of Target Protein

Water molecules were removed, and polar hydrogen atoms were added to stabilize the protein structure, optimizing it for further bioinformatics analyses using Discovery Studio software.

Acquisition of Ligands

Structural information for cadmium acetate [$Cd(C_2H_3O_2)_2$] (molecular weight: 230.50 g/mol) was sourced from PubChem (CID: 10986) and used for molecular docking analyses in this study.

Ligand Preparation

The ligand structures were downloaded in SDF format and saved separately for molecular docking analyses.

Software Utilized

The software tools used in this study include Discovery Studio and PyRx for the preparation and docking simulations of the ligand.

Molecular Docking and Dynamics

PyRx software performed molecular docking to assess cadmium's binding affinity with GSK3β, analyzing binding energy and potential interactions. Binding free energy (ΔG_bind) was calculated as

$$\Delta G = \Delta G_{vdW} + \Delta G_{Hbond} + \Delta G_{elec} + \Delta G_{tor} + \Delta G_{desolv}$$

where ΔG_{vdW} represents the Van der Waals term for docking energy, $\Delta G_{Hbond}$is the Hydrogen bonding term, ΔG_{elec} refers to the Electrostatic term, ΔG_{tor} denotes the Torsional free energy term for the ligand transitioning from the unbound to the bound state, and ΔG_{desolv} stands for the Desolvation term in the docking energy.[10] Receptor-ligand interactions were analyzed using Discovery Studio Visualizer version 2021, including non-covalent interactions, π-lone pair, π-alkyl, π–π stacking, and π–π T-shape stacking interactions.[11]

For AutoDock Vina, a grid dimension of 30 Å x 30 Å x 30 Å and a cluster radius of 1 Å were used. The Cα coordinates of the selected backbone binding residues in the protein receptor were defined as the center for the docking space. Default settings were applied for other docking parameters. The resulting geometries were ranked based on the binding free energy, with the lowest energy poses selected for further analysis.

RESULTS

Table 1 shows the binding affinities (in kcal/mol) of cadmium to glycogen synthase kinase-3β (GSK3β) across nine binding modes. More negative values indicate stronger binding, and all modes reflect favorable affinities. The strongest binding occurs in Mode 1 (-3.4 kcal/mol), followed by Mode 2 (-3.3 kcal/mol), while Mode 9 shows the weakest affinity at -2.8 kcal/mol.

In Figure 1, the interaction of cadmium with the GSK3β enzyme was explored through molecular docking, revealing nine distinct binding modes. These modes represent different ways in which cadmium interacts with various regions of the enzyme.

Table 2 details nine binding modes of cadmium acetate with various receptor residues, emphasizing interaction types and counts. Each mode features conventional hydrogen bonds and van der Waals interactions. While conventional hydrogen bonds range from one to four per mode, van der Waals contacts consistently range from four to nine. Carbon hydrogen bonds appear only in Mode 5. Interacting residues

Table 1: Binding affinities (Kcal) of - cadmium acetate with GSK3β in different modes

Mode Number	*Binding Affinity (Kcal)*
1	-3.4
2	-3.3
3	-3.1
4	-3.1
5	-3.0
6	-3.0
7	-2.9
8	-2.9
9	-2.8

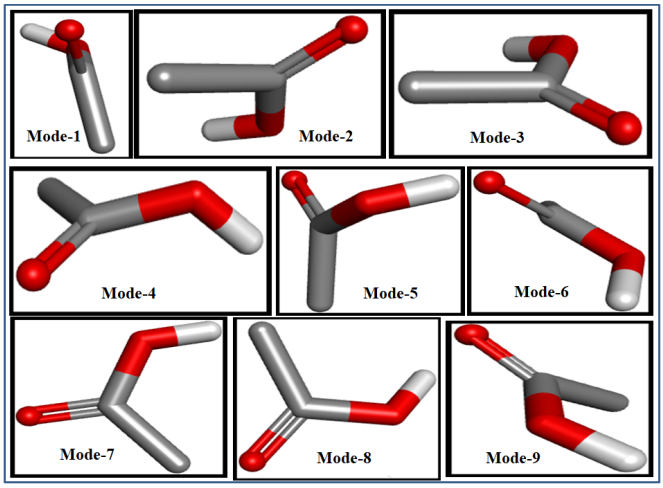

Figure 1: Modes of the interaction of cadmium acetate with GSK3β enzyme

include arginine (Arg), serine (Ser), leucine (Leu), and glycine (Gly) from subunits A and B, showcasing a diverse binding landscape.

Water molecules participate in the hydrogen bonding network only in Modes 4, 6, 7, 8, and 9, while the other modes do not include water in their hydrogen bond interactions. Overall, the table illustrates that cadmium acetate binds flexibly with receptor residues through various bonding interactions, with select modes also involving water, showcasing a multi-faceted binding mechanism.

Figure 2 depicts four binding modes (Modes 1–4) of cadmium acetate with a protein structure. Each mode features a complete protein view on the left and a close-up of the binding site on the right, showcasing a color-coded ribbon model that highlights key regions and secondary structures. The close-up images on the right detail the interactions between cadmium acetate and specific protein residues. Hydrogen bonds are shown with colored arrows or lines, with pink representing hydrogen bond donors and green as acceptors. In Mode 1, Cadmium acetate binds with Arg223, Ile228, and Leu227 through conventional hydrogen bonds and additional van der Waals interactions. Mode 2 also binds with Arg223 and Ser215, showing a slightly altered residue arrangement. Mode 3 involves fewer bonds with Leu153 and Ala143, while Mode 4 binds with Ser55 and Cys76 in a simpler configuration.

Figure 3 illustrates the binding modes (Modes 5–9) of cadmium acetate within a protein structure, with each mode represented by two images per row. The left images feature a color-coded ribbon model of the protein, highlighting structural elements like alpha-helices, beta-sheets, and loops, which show cadmium acetate's binding locations.

The right side provides close-up views of interactions between cadmium acetate and specific protein residues, with hydrogen bonds indicated by pink arrows for donors and green arrows for acceptors. In Mode 5, cadmium acetate

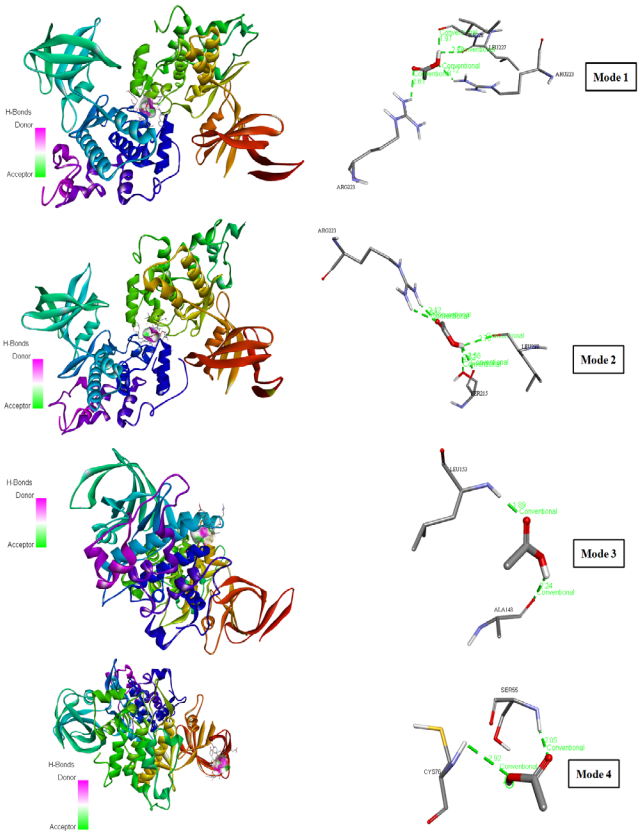

Figure 2: Interacting amino acids of GSK3β enzyme with the Mode 1, 2, 3, and 4 of cadmium acetate

forms conventional hydrogen bonds with Leu153, Ala143, and Thr152. Mode 6 shows bonding with Glu211 and Val208, while Mode 7 features a hydrogen bond with Asp264. Mode 8 displays a different orientation with Asp264, and Mode 9 includes interactions with Arg96 and Ser203, highlighting the unique residue interactions in each mode across various protein regions.

Figure 4 illustrates nine distinct interaction modes between a central molecule and surrounding amino acid residues, emphasizing van der Waals forces, carbon-hydrogen bonds, and conventional hydrogen bonds. Each mode, from Mode 1 to 9, represents a unique orientation of the central molecule in relation to nearby residues, labeled with their names and chain positions (e.g., ARG A:216).

Van der Waals interactions (depicted as light green circles) indicate proximity, while carbon-hydrogen bonds (shown as light green dashed lines) and conventional hydrogen bonds (represented as dark green solid lines) reflect stronger, directional connections. For instance, Mode 1 demonstrates hydrogen bonding with residues TYR A:216, LEU A:229, and ARG B:216, while Mode 7 primarily involves weaker van der Waals interactions with residues like SER B:205. These diverse interaction patterns suggest that each binding mode plays a distinct role in the molecule's stability, influencing its binding affinity and specificity within the binding pocket.

Table 2: Molecular docking result analysis of different modes of cadmium acetate with GSK3β enzyme

Different modes of cadmium acetate	*Type of bond*	*No. of bonds*	*Contacting receptor residues*	*No. of H_2O cloud*
Mode-1	Conventional hydrogen bonds	4	Arg B:223, Arg A:223, Ile A:228, Leu A:227	0
	Van der waals	8	Tyr B:216, Phe A:229, Gly A:230, Leu B:227, Ile B:228, Ser A:215, Gly B:230, Ser B:215	
Mode-2	Conventional hydrogen bonds	3	Arg B:223, Ser A:215, Leu A:227	0
	Van der waals	7	Ile B:228, Gly B:230, Ser B:215, Leu B:227, Gly A:230, Tyr A:216, Arg A:223	
Mode-3	Conventional Hydrogen Bonds	2	Leu B:153, Ala B:143	0
	van der Waals	6	Gln B:151, Tyr B:146, Gly B:253, Ser B:147, Leu B:250, Thr B:152	
Mode-4	Conventional Hydrogen Bonds	2	Ser A:55, Cys A:76	1
	van der Waals	4	Asp A:77, Val A:54, Ser A:78, Leu A:75	
Mode-5	Conventional Hydrogen Bonds	2	Leu A:153, Ala A:143	0
	Carbon Hydrogen Bonds	1	Thr A:152	
	van der Waals	5	Leu A:250, Tyr A:146, Ser A:147, Gly A:151, Gly A:253	
Mode-6	Conventional Hydrogen Bonds	2	Glu A:211, Val A:208	1
	van der Waals	6	Asn A:213, Asp A:233, Thr A:235, Tyr A:234, Arg A:209, Leu A:207	
Mode-7	Conventional Hydrogen Bonds	1	Asp B:264	1
	van der Waals	7	Val B:263, Ser A:203, Ile A:217, Phe A:67, Ser B:261, Asp A:181, Lys A:183	
Mode-8	Conventional Hydrogen Bonds	1	Asp A:264	1
	van der Waals	9	Lys B:183, Ser B:219, Asp A:260, Asp B:181, Phe B:67, Ile B:217, Ser B:203, Val A:263, Ser A:261	
Mode-9	Conventional Hydrogen Bonds	2	Arg B:96, Ser B:203	1
	van der Waals	5	Gly B:202, Ile B:217, Lys B:207, Arg B:180, Ala B:204	

DISCUSSION

The analysis of Cadmium acetate's interactions with Glycogen Synthase Kinase-3β (GSK3β) sheds light on its potential role in AD pathology. GSK3β is a critical enzyme in cellular signaling and is known to regulate glycogen metabolism, apoptosis, and, significantly, tau phosphorylation—a key player in AD pathology (Rayasam *et al*., 2009).[12] Overactivation of GSK3β contributes to hyperphosphorylation of tau protein, leading to the formation of neurofibrillary tangles, one of the primary pathological markers of AD.[13,14] The present study, using molecular docking analysis, reveals nine binding modes of Cadmium acetate with GSK3β, highlighting variations in binding affinities, interaction types, and contacting residues, which may influence GSK3β activity in AD progression.

Binding Affinities and Interaction Patterns

The molecular docking data in Table 1 shows that Cadmium acetate binds to GSK3β with moderate affinities across nine binding modes, with binding energies ranging from -3.4 kcal/mol (Mode 1) to -2.8 kcal/mol (Mode 9). The negative

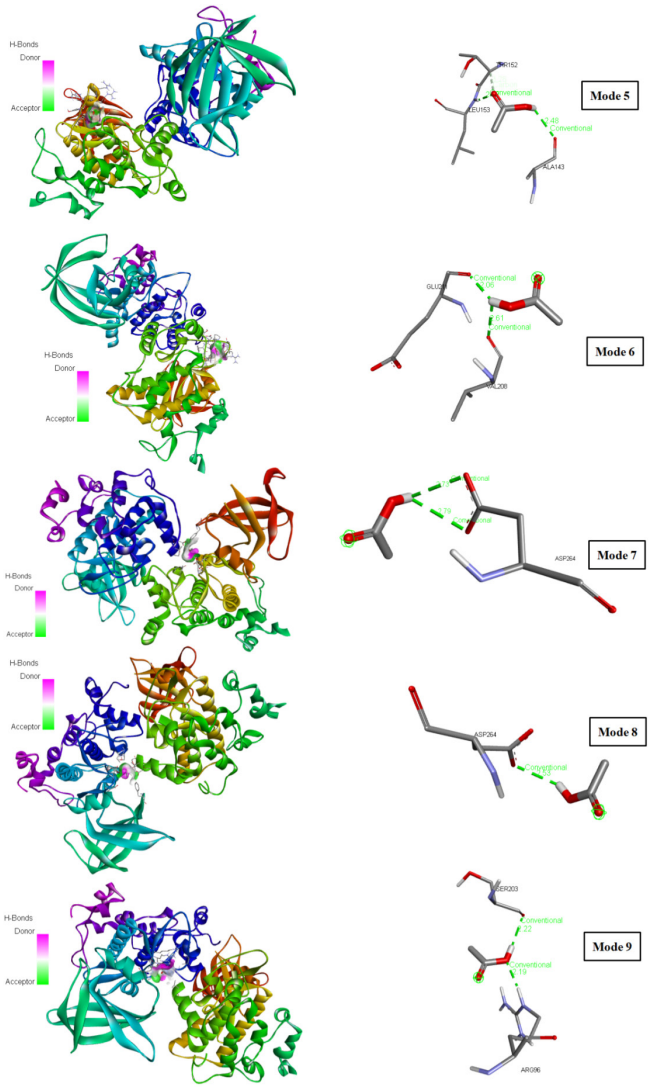

Figure 3: Interacting amino acids of GSK3β enzyme with mode 5, 6, 7, 8 and 9 of cadmium acetate

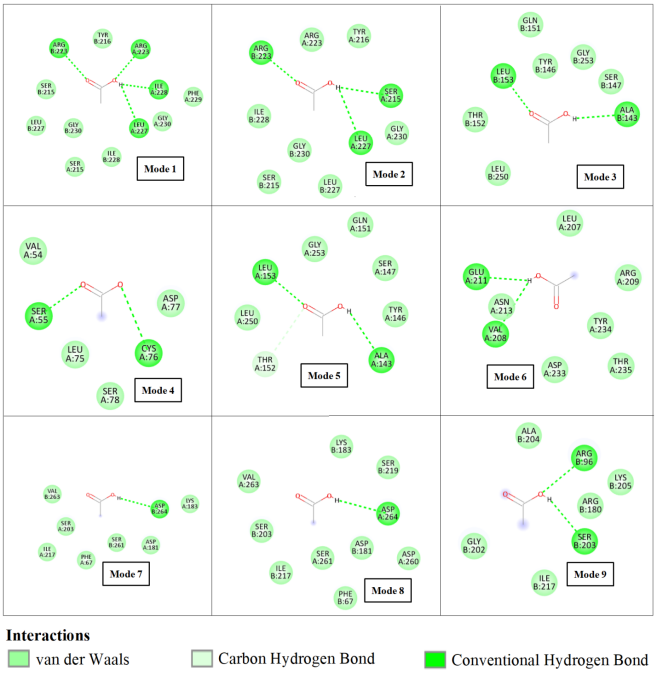

Figure 4: Bonds formed by the different modes of cadmium acetate with the different amino acids of GSK3β enzyme

binding energies indicate favorable interactions in all modes, suggesting effective binding in various orientations.[15] Mode 1 exhibits the strongest affinity at -3.4 kcal/mol, closely followed by Mode 2 at -3.3 kcal/mol, while affinities decrease slightly in other modes.

Table 2 and Figures 1-4 provide insights into the types of interactions and involved residues. All modes primarily feature conventional hydrogen bonds and van der Waals interactions, with Modes 1 and 2 showing the most hydrogen bonds (four and three, respectively). Interacting residues in Mode 1 include Arg223, Ile228, and Leu227, contributing to a stable binding configuration. Other modes, such as Mode 5, display unique interactions, including carbon-hydrogen bonds, indicating distinct binding site preferences.

Implications for Alzheimer's Disease Pathology

The multi-mode binding of Cadmium acetate with GSK3β raises important implications regarding its influence on GSK3β activity and, consequently, on AD pathology. GSK3β's overactivation is linked to tau hyperphosphorylation, leading to neurofibrillary tangles—a hallmark of AD.[13,14] The interaction of cadmium acetate with key residues within the GSK3β enzyme might influence its conformation and functional state, potentially affecting downstream signaling pathways associated with tau phosphorylation.[16]

The binding patterns in Modes 1 and 2 suggest that Cadmium acetate may induce subtle conformational changes in GSK3β by stabilizing certain residues through hydrogen bonding and van der Waals interactions. This stabilization could disrupt the enzyme's active site or regulatory regions, altering kinetics. Specifically, Mode 1 engages critical residues like Arg223 and Ile228, potentially inhibiting GSK3β's function and increasing tau phosphorylation, leading to tau accumulation and promoting Alzheimer's disease pathology.[17]

Preventive Measures for Cadmium Neurotoxicity

Preventing cadmium exposure is critical, given its role as a neurotoxin in AD pathology.[6] Strategies include reducing environmental contamination through stringent industrial regulations, promoting dietary interventions rich in antioxidants, and using chelation therapies to mitigate cadmium accumulation in neural tissues.[7,18] Further exploration of inhibitors specific to cadmium-GSK3β interaction offers promising pathways for therapeutic intervention.

Expanded Mechanisms of Inhibitors

The inhibitors discussed in this study primarily block cadmium's binding to GSK3β by altering key residues such as Arg223 and Ser215. Studies conducted by Zhu *et al.* reveal similar findings, aligning with the observations in

this research.[19] Mechanistically, these inhibitors stabilize the active or allosteric sites of GSK3β, preventing conformational changes induced by cadmium.[20] In vivo studies are necessary to validate these findings, focusing on pharmacokinetics and long-term efficacy in preventing neurodegenerative outcomes.

Neurodegeneration Mechanisms

Cadmium-induced neurodegeneration is mediated through oxidative stress, inflammation, and GSK3β activation, which accelerates tau hyperphosphorylation and amyloid plaque deposition.[21] These processes disrupt synaptic integrity, ultimately impairing cognitive functions.[6,22] Addressing these pathways provides a comprehensive understanding of cadmium's role in AD and lays the groundwork for targeted therapeutic strategies.

Drug Design Strategies to Mitigate Pathological Effects

Given the potential of cadmium acetate to modulate GSK3β activity, designing therapeutic agents to counteract these effects may be a promising strategy for Alzheimer's disease treatment. Several drug design approaches can be explored: Competitive inhibitors for GSK3β could be developed to prevent cadmium binding by targeting the same or adjacent sites. By enhancing binding affinity to residues like Arg223, Ile228, and Leu227, these inhibitors may block cadmium's interaction, thereby mitigating GSK3β's aberrant activity.[12] This strategy could significantly reduce the neurotoxic effects associated with cadmium exposure.

Allosteric Modulators

Another strategy involves designing allosteric modulators that bind to sites distinct from Cadmium acetate's binding sites but induce conformational changes that either stabilize GSK3β in an inactive form or enhance its natural regulatory mechanisms. Such allosteric modulators could promote non-toxic conformations, minimizing GSK3β's overactivation and preventing excessive tau phosphorylation. This approach offers an advantage as it circumvents direct competition with Cadmium acetate, targeting the enzyme through an indirect pathway.[13]

Chelation Therapy

Chelation therapy offers an alternative approach to address cadmium toxicity in neurons. Chelating agents bind metal ions, potentially reducing cadmium levels and decreasing their binding to GSK3β. Agents designed to target cadmium without affecting essential metals, like calcium or magnesium, could effectively mitigate cadmium-induced GSK3β dysregulation.[18] Existing chelators, such as EDTA derivatives, may be modified for cadmium specificity.

Selective GSK3β Inhibitors

Selective inhibition of GSK3β, while sparing other kinases, is a promising strategy. Developing inhibitors that mimic cadmium acetate's binding interactions, especially in high-affinity modes like Mode 1, can stabilize GSK3β in a non-pathogenic state. Tailoring these inhibitors to utilize specific amino acid residues through hydrogen bonding and van der Waals interactions can enhance stability and prevent pathological interactions.[12, 14]

Structure-Guided Drug Design

Leveraging the structural insights from Figures 2-4, drug design can target molecules that disrupt cadmium acetate's binding or alter GSK3β's interaction surfaces. Compounds mimicking the binding orientations and residue interactions seen in Modes 5 and 6 could stabilize GSK3β in inactive conformations, reducing its pathological effects. Additionally, small molecules targeting residues involved in van der Waals interactions, such as Tyr216 and Leu227, can enhance GSK3β modulation specificity, minimizing side effects.[23]

CONCLUSION

The binding analysis of Cadmium acetate with GSK3β offers valuable insights into its potential impact on AD pathology. The distinct interaction modes and binding affinities suggest that Cadmium acetate can alter GSK3β's activity by stabilizing certain residues and potentially modifying the enzyme's active conformation. Given GSK3β's role in tau hyperphosphorylation and neurofibrillary tangle formation, these interactions could facilitate the progression of AD. Based on this study, several drug design strategies emerge, including competitive inhibitors, allosteric modulators, chelation therapy, and selective GSK3β inhibitors. Leveraging structure-guided approaches can further refine these strategies, aiming to prevent or counteract the pathological effects induced by Cadmium acetate in GSK3β-related pathways. Future research should focus on validating these findings in cellular and animal models to explore the therapeutic potential of these strategies for AD intervention.

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PEER-REVIEWED CERTIFICATION

During the review of this manuscript, a double-blind peer-review policy has been followed. The author(s) of this manuscript received review comments from a minimum of two peer-reviewers. Author(s) submitted revised manuscript as per the comments of the assigned reviewers. On the basis of revision(s) done by the author(s) and compliance to the Reviewers' comments on the manuscript, Editor(s) has approved the revised manuscript for final publication.