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ORIGINAL ARTICLE

In silico investigation of the effects of Gentamicin on lysosomal lipid degradation and the transport system between lysosomes and smooth endoplasmic reticulum

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Summary

Introduction: Gentamicin, an aminoglycoside antibiotic, has limited clinical use due to accompanying side effects: nephrotoxicity and ototoxicity. The damage caused by Gentamicin accumulates over time, leading to cell death. Cells of renal proximal tubules are most affected, as are hair cells of the inner ear. One of the presumed mechanisms of toxicity is phospholipidosis, a disorder characterized by the accumulation of phospholipids within cells.

Aim: This study aims to investigate, *in silico,* the mechanism of Gentamicin action in the development of phospholipidosis through interactions with key proteins responsible for lipid transport between the smooth endoplasmic reticulum and late endosomes, as well as enzymes involved in lipid degradation.

Material and Methods: We defined target proteins in the KEGG database, and their expression profiles and tissue-specificities were examined using the Human Atlas database. Nine proteins met the final criteria and were further examined by molecular docking using AutoDock Vina.

Results: Most of the examined proteins showed high expression in the kidney and corresponding structures of the central nervous system. Docking analysis indicated that the interaction between Gentamicin and ORP1L protein exhibited the lowest Gibbs free energy value of - 8.1 kcal/mol. In comparison, the STARD3 protein had the highest Gibbs free energy value of -5.2 kcal/mol. Amino acid sequences to which Gentamicin binds on the selected proteins were similar within the same protein families.

Conclusion: Observed under *in silico* conditions, Gentamicin interacts with proteins that participate in lysosomal lipid degradation and transport between lysosomes and smooth endoplasmic reticulum.

Keywords: Gentamicin, nephrotoxicity, ototoxicity, phospholipidosis, molecular docking

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INTRODUCTION

Gentamicin (GM) is an aminoglycoside antibiotic used to treat infections caused by Gram-negative bacteria and certain Gram-positive *Staphylococci*. The underlying mechanism of the GM antibacterial effect is the inhibition of protein synthesis by irreversible binding to the 30S ribosomal subunits in bacterial cells. Versatile formulations of GM are used to treat infections via intravenous, intramuscular, or topical administration. The best therapeutic effects are exerted against infections caused by *Enterobacteriaceae* (*Escherichia coli, Klebsiella pneumoniae, Serratia spp.,* and *Enterobacter spp.*), *Pseudomonas aeruginosa*, and certain members of the *Neisseria, Moraxella*, and *Haemophilus* families (1). Clinical use of GM is significantly limited due to severe adverse effects that can be classified into two groups: nephrotoxicity and ototoxicity

The incidence of acute kidney injury (AKI) in GM-treated patients ranges from 2 to 55%, and the most prominent pathomorphological substrate is acute tubular necrosis (2). Cell damage inflicted by GM accumulates through time and leads to imminent cell death. Due to their proximity to the glomerular filtration membrane, tubular epithelial cells of the proximal renal tubules are most affected. In contrast, tubular cells in the distal renal tubules and collecting ducts sustain less damage (3). Though significant efforts to prevent AKI in patients undergoing GM treatment have not yielded results, as the pathophysiological mechanisms of toxicity remain unclear (2). Ototoxic GM effect occurs bilaterally and irreversibly as it gets into the perilymph and the endolymph of the inner ear (4). Chronic exposure to GM leads to degeneration of hair cells in the Organ of Corti, as reported by Groot *et al*. GM accumulates in the lysosomes of hair cells, leading to the formation of lipid inclusions (5). It has been shown that GM leads to a significant increase in plasma total cholesterol and triglycerides, and a reduction of plasma phospholipid levels (6).

Phospholipidosis is a disorder characterized by increased accumulation of phospholipids in the cell. Based on its etiopathogenesis, phospholipidosis can be congenital or acquired, and most commonly affects the lungs, liver, or kidneys. The pathophysiological and morphological substrates of phospholipidosis include pulmonary fibrosis, hepatic steatosis, acute kidney injury, or chronic kidney disease (7). Phospholipidosis can result from disruption of the phosphatidylinositol bisphosphate signaling pathway, disturbances in lipid transport, or disorders of lipid breakdown. Lysosomes are crucial for lipid homeostasis in cells. Extracellular lipid particles engulfed by the cell or endogenous lipids formed during organelle turnover undergo lipolysis in lysosomes, a process carried out by lipases (lysosomal acid lipases, LAL – Lysosomal Acid Lipase A, LIPA, and Lysosomal Acid Lipase 4, LIPL4). Subsequentially, the metabolites are transported to the smooth endoplasmic reticulum (SER) though a complex protein system comprising cholesterol transporter Niemann-Pick type C disease proteins (NPC1 and NPC2), oxysterol-binding protein-related proteins (ORP5 and ORP1L), StAR-related lipid transfer domain 3 protein [STARD3 (metastatic lymph node 64 protein, MLN 64)] and STARD3 N-terminal like protein [(STARD3NL (MLN64 N-terminal homologue, MENTHO)] and protein tyrosine phosphatase non-receptor type 1B (PTP1B) (Figure 1).

Our study aimed to identify GM-driven mechanisms underlying phospholipidosis pathogenesis by inhibiting key proteins responsible for lipid transport between the SER and late endosomes, as well as enzymes involved in lipid breakdown, using *in silico* analysis.

MATERIALS AND METHODS

Defining the target protein

To define the protein of interest, the Kyoto Encyclopedia of Genes and Genomes (KEGG) PATHWAY Database was used (https://www.genome.jp/kegg/pathway.html). This repository is a binomic online database consisting of the KEGG component (a database generated by genome sequencing, enzymatic pathways, and biological compounds) and the PATHWAY component (a database of networks of molecular interactions in the cells and their variants in specific organisms).

In accordance with the literature, the scope of the investigation focused on lysosomes, smooth endoplasmic reticulum, and their interactions. Consequently, both organelles were selected from the KEGG database, and based on the resulting network, processes and organelle interactions, target proteins were defined and used for further analysis (8).

Expression profile and tissue specificity of target proteins

Expression profiles of target proteins, as well as their tissue specificity, were determined using the Human Protein Atlas (https://www.proteinatlas.org). This comprehensive database contains all proteins discovered to date, along with their expression profiles and tissue specificity. For each protein, it was assumed to be expressed in the kidney, the inner ear, or corresponding structures in the central nervous system. The expression levels were termed as high, intermediate, low, or undetectable.

Molecular docking

Molecular docking is a technique that predicts the orientation, affinity, and interaction of a ligand at the receptor (protein) binding site.

Protein (receptor) structure information provided by crystallography was collected from the RCBS Protein Data Bank (PDB, https://www.rcsb.org) or the AlphaFold Protein Structure Database (https://alphafold.ebi.ac.uk). Structure (3D) of Gentamicin (GM) as a ligand was obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov). Molecular docking analysis was done utilizing the AutoDock Vina program (version 1.2.x, https://github.com/ccsb-scripps/AutoDock-Vina). This open-source software has shown wide application in new drug discovery (9). Upon entering two inputs into the software – the protein structure (in PDB format) and the ligand structure (in SDF format), additional modifications may be performed if needed. For our analysis, we decided to remove the surrounding water molecules from the structure of the investigated molecules. The rationale for this decision is that water molecules do not play a significant role in the binding of the investigated molecules, and that calculations of the molecules' interactions are facilitated. In addition, polar hydrogen atoms and charges are added to receptor molecules before the process is initiated to ensure ample binding sites are available. Molecular docking was performed under the condition that all the ligand bonds are rotatable, while receptor bonds do not possess this ability (9). Upon initiating the docking process, the software initiates interaction simulations between the functional groups on receptor and ligand molecules. The results are the ten most representative interactions, with calculated values of Gibbs free energy and the root-mean-square deviation (RMSD) of atomic positions. Negative values of Gibbs free energy indicate a higher likelihood of spontaneous reaction, i.e., stronger binding between the receptor and the ligand. In contrast, RMSD values are used to assess docking accuracy (9). The Gibbs free energy values calculated for target proteins were compared with the control interaction between tyrosyl tRNA synthetase (TyrRS), a known target protein (receptor) for GM (ligand).

RESULTS

We have identified 9 potential target proteins by searching the KEGG PATHWAY database: LIPA, LIPL4, NPC1, NPC2, ORP5, ORP1L, STARD3, STARD3NL, and PTP1B. Target protein function and localization are presented in **Figure 1**.

Analysis of target protein expression profiles in the Human Protein Atlas shows that kidneys exhibit high expression of NPC2, NPC1, STARD3, and PTP1B, and an intermediate level of ORP5, ORP1L, and STARD3NL. LIPA and LIPL4 were undetectable in the kidneys. Protein expression profiles in the central nervous system display spatial differences. High expression of ORP1L, STARD3, and STARD3NL is shown in the cerebral cortex; LIPA, STARD3, and STARD3NL are substantially expressed in the cerebellum, while the hippocampus also exhibits high STARD3 and STARD3NL expression. In addition, NPC1 and OPR5 show intermediate levels of expression in cerebral cortex, hippocampus, and caudate nucleus, whilst OPR5 is also present in the cerebellum. Intermediate ORP1L expression is seen in the cerebellum,

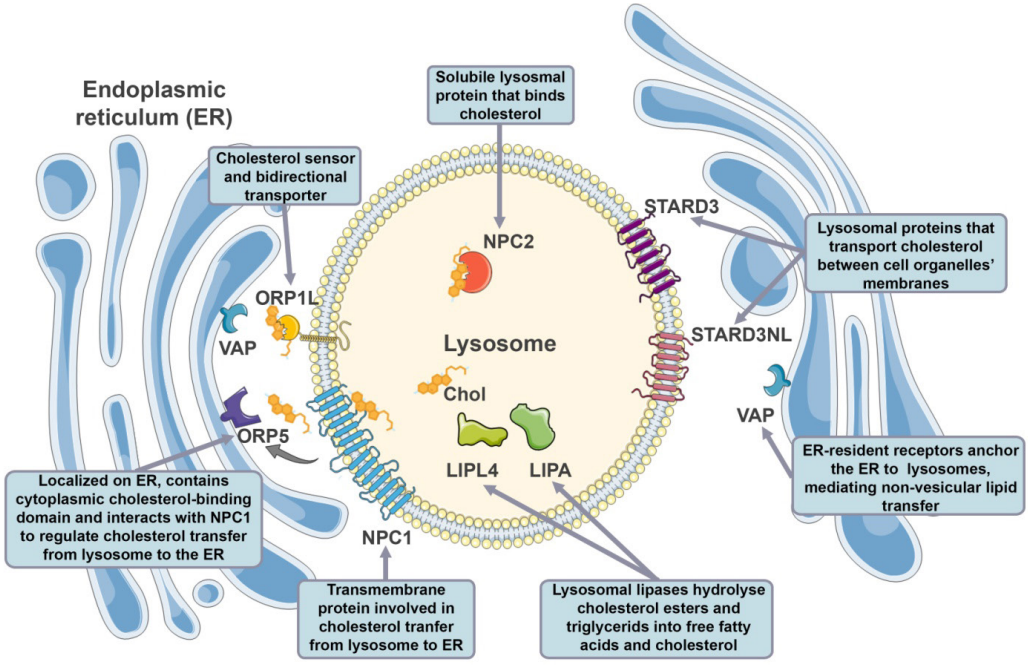

Figure 1. Potential target proteins interacting with Gentamicin to increase intracellular lipid accumulation and phospholipidosis. Chol – cholesterol, OPR1L and OPR5 – oxysterol-binding protein-related proteins, NPC1 and NPC2 – Niemann-Pick type C disease proteins, LIPL4 – lysosomal acid lipase 4, LIPA – lysosomal acid lipase A, STARD3 – StAR-related lipid transfer domain 3 protein, STARD3NL – STARD3 N-terminal like protein, VAP – vesicle-associated membrane protein. Adapted from Servier Medical Art (https://smart.servier.com), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

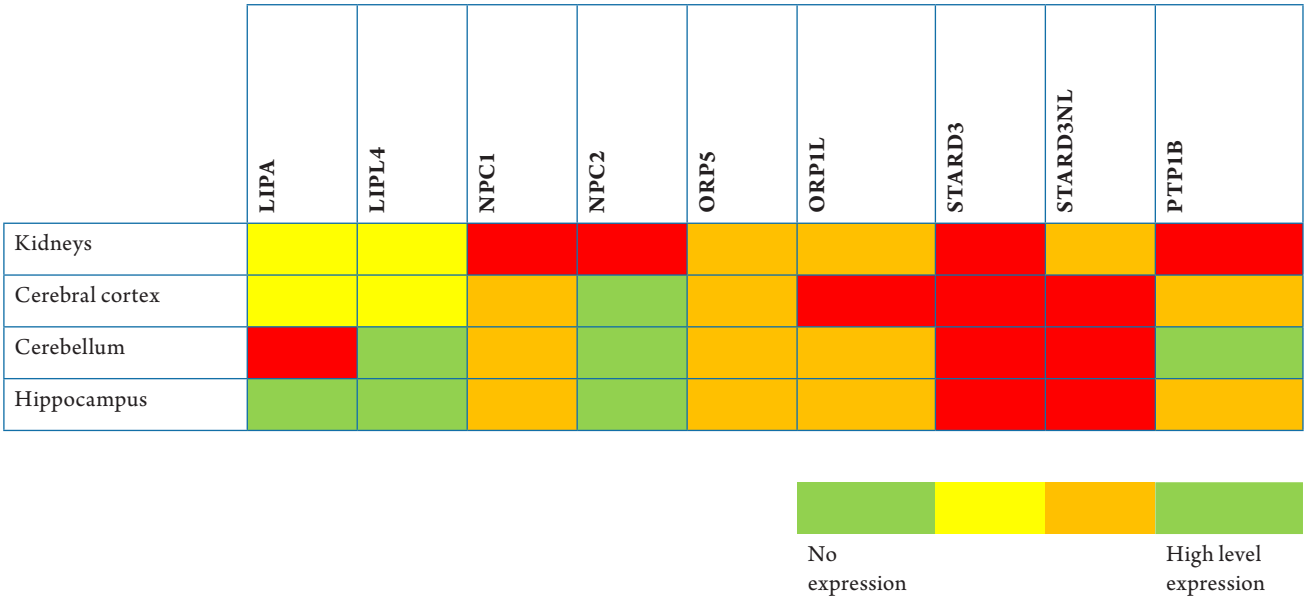

Figure 2. Heatmap of target protein expression in specific tissues. LIPA – lysosomal acid lipase A, LIPL4 – lysosomal acid lipase 4, NPC1 and NPC2 – Niemann-Pick type C disease proteins OPR1L and OPR5 – oxysterol-binding protein-related proteins, STARD3 – StAR-related lipid transfer domain 3 protein, STARD3NL – STARD3 N-terminal like protein, PTP1B – protein tyrosine phosphatase non-receptor type 1B

hippocampus, and caudate nucleus. Target protein expression levels in tissues of interest are shown in **Figure 2**.

Molecular docking was performed using AutoDock Vina, and comparisons were made based on interactions yielding RMSD values lower than 3, as higher values are considered to limit the accuracy of the analysis. Interaction of ORP1L and GM presented with the smallest value of Gibbs free energy of -8.1 kcal/mol. The interaction between the STARD3 protein and GM had the lowest Gibbs free energy of -5.2 kcal/mol. The values of Gibbs free energy of other target protein-GM interactions are shown in **Figure 3**.

In addition to the free-energy analysis of the target protein-GM interaction, we have evaluated potential GM-binding sites on target proteins of interest. The most abundant amino acid sequences present in target proteins that GM can bind to consist of lysine (Lys), serine (Ser), glutamate (Glu), and leucine (Leu) **(Table 1)**.

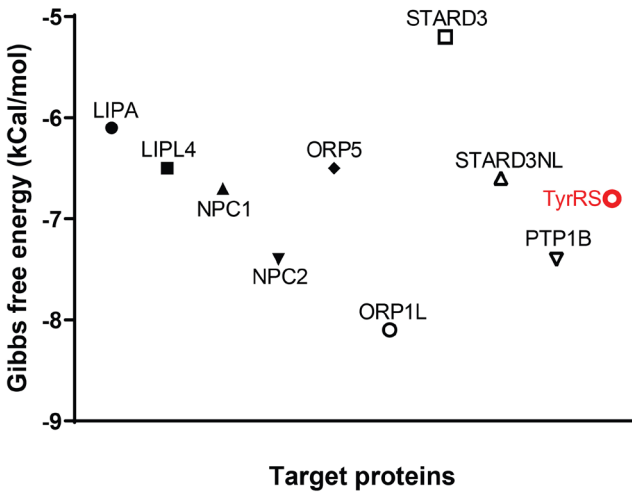

Figure 3. Gibbs free energy values in the interaction between Gentamicin and target proteins, as well as a control protein (tyrosyl-tRNA synthetase, TyrRS). For each protein, the reported values had an RMSD of less than 3 (indicating high docking precision), corresponding to a single interaction per protein. LIPA – lysosomal acid lipase A, LIPL4 – lysosomal acid lipase 4, NPC1 and NPC2 – Niemann-Pick type C disease proteins OPR1L and OPR5 – oxysterol-binding protein-related proteins, STARD3 – StAR-related lipid transfer domain 3 protein, STARD3NL – STARD3 N-terminal like protein, PTP1B – protein tyrosine phosphatase non-receptor type 1B

DISCUSSION

Gentamicin is an aminoglycoside antibiotic used in the treatment of infections caused by Gram-negative bacteria. Although a highly potent drug, its clinical use is limited due to accompanying adverse effects that affect the kidneys, inner ear, and central nervous system (1). The pathomorphological substrate underlying these effects is increased cell death resulting from disruption of various metabolic processes. One of the observed changes after GM therapy is the deposition of lipids in lysosomes and the cytoplasm, and the development of phospholipidosis (5).

We here identify potential target proteins with which GM could interact. These proteins are responsible for lysosomal degradation, lipid recognition, and transport of lipids from lysosomes to the smooth endoplasmic reticulum, where they are recycled. According to the literature, phospholipidosis, one of the consequential disorders arising from GM therapy, has been reported to occur predominantly in renal tissue and proximal tubular cells (5). The results of our work indicate that most of the examined proteins are variably expressed in the kidney, with the majority showing high to intermediate levels of

Table 1. Amino acid sequences and their target sites in the examined proteins that bind Gentamicin

Protein	Amino acid sequence at the protein binding site
LIPA	Lys107, His108, Lys109, Glu35, Asp36, Gly37, Tyr38, His290, Phe297, Ser292, Lys294, Asn295
LIPL4	Met2, Trp3, Leu4, Leu5, Phe233, Gly231, Asn291, Glu235, Trp263, Ser261
NPC1	Gln570, Leu569, Val96, Ala530, Lys95, Ala166, Val66, Val180, Gly179
NPC2	Gln387, Leu390, Phe24, Gln23, Pro474, Ser473, Val33, Asp31
ORP5	Met371, Trp372, Leu216, Pro215, Lys144, Thr143, Lys376, Trp142, Pro215, Leu133, Gln214, Thr667, Ala666
ORP1L	Trp721, Ile722, Ile655, Pro654, Val712, His713, Trp914, Gly718, Lys719, Val684, His586, Glu585
STARD3	Glu179, Ala180, Asn184, Glu181, Glu182, Glu183, Ser227, His122, Arg121, Lys229, Glu228
STARD3NL	Ser49, Ile48, Gly47, Lys46, Leu186, Val189, Glu182, Ser193
PTP1B	Pro188, Ala189, Ser190, Leu192, Pro185, Glu276, Gly277

LIPA - Lysosomal Acid Lipase, LIPL4 - Lysosomal Acid Lipase 4, NPC1, NPC2 - cholesterol transporter Niemann-Pick type C disease protein, ORP5, ORP1L - oxysterol-binding protein-related proteins, STARD3 - StAR-related lipid transfer domain 3 protein, STARD3NL - STARD3 N-terminal like protein, PTP1B - protein tyrosine phosphatase non-receptor type 1B (PTP1B), Lys - Lysine, His - Histidine, Glu - Glutamate, Asp - Aspartate, Tyr - Tyrosine, Phe - Phenylalanine, Ser - Serine, Asn - Asparagine, Met - Methionine, Trp - Tryptophane, Leu - Leucine, Gly - Glycine, Gln - Glutamine, Pro - Proline, Val - Valine, Thr - Threonine, Ile - Isoleucine

expression. In the work of de Groot *et al.*, which investigated mechanisms of GM toxicity in the inner ear, one underlying effect was the accumulation of lipid inclusions in lysosomes (5). The mechanosensory hair cells, which are most susceptible to GM-induced damage, are embryonically derived from the same progenitor, from which the rest of the central nervous system develops (6). At the same time, the neural crest contributes to the development of the inner ear's supporting structures. Our results show that most of the examined proteins are expressed at relatively high levels across multiple regions of the central nervous system. Therefore, it is plausible that GM effects on lipid breakdown and transport are one of the mechanisms underlying the reported results in mechanosensory cells.

The results of molecular docking show that GM, compared to the control protein, has stronger interactions with NPC2, ORP1L, and PTP1B. Lysosomal NPC2 plays an integral role in cholesterol binding and elimination from lysosomes. At the same time, ORP1L acts as a cholesterol sensor and facilitates bidirectional transport of cholesterol and phospholipids across lysosomal membranes. PTP1B, expressed on the smooth endoplasmic reticulum surface, maintains balanced intracellular cholesterol levels through its binding and transport (11). All three proteins interact with one another and transport lipids between cell compartments (11). *In vivo* experiments by Abdel-Gayoum *et al.* showed that GM-treated rats exhibited increases in plasma LDL-cholesterol and triglyceride levels, and a dose-dependent change in phospholipid concentration (7). Taking our results into account, the aforementioned changes in the lipid profile might result from increased intracellular lipid accumulation and necrotic cellular damage, followed by the release of their contents into the extracellular matrix and plasma. Further studies indicate that GM leads to increased expression of transporters on the surface of proximal tubular cells, thereby amplifying its accumulation within cells and its transport between cellular compartments (12). The plausible mechanisms of GM-induced phospholipidosis have been the focus of several studies (13–18), each providing an aspect of its pathogenesis, such as disturbances in phosphatidylinositol signaling, interactions with the negatively charged groups of phospholipids, and inhibition of phospholipases A1, A2, and C1. However, these studies require further investigation of the mechanisms mentioned, as none of them provides answers to all questions regarding the observed changes at the cellular level (13–18). Ioannidis *et al.* showed that GM interferes with the tricarboxylic acid cycle, leading to increased lipid accumulation in the cell (19). It can therefore be said that GM has a multifocal effect on different cellular components, with mitochondria, lysosomes, and the endoplasmic reticulum being the most susceptible. Our research focuses on two cellular organelles and their functional connection, and, according to the results, may identify another potential mechanism of GM toxicity.

Finally, we analyzed the GM-binding sites on the investigated proteins. Our results show that the sequence containing Lys, Ser, Glu, and Leu is the most prevalent, supporting the existence of a conserved sequence across different proteins. Dagil *et al.* (20) showed that GM binds to megalin, acting as a competitive inhibitor. The amino acid sequences GM interacted with consisted of Lys, cysteine (Cys), tryptophan (Trp), valine (Val), aspartic acid (Asp) and threonine (Thr). Interestingly, the same amino acid sequence was observed in one of the proteins we examined, ORP1L (20). As both ORP1L and megalin are receptors integrated in the phospholipid bilayer, although in different cellular compartments, the same binding sequences indicate a complex interaction of GM that is not only limited to one part of the cell or one cellular process.

CONCLUSION

The results of our *in silico* analysis indicate that GM interacts with proteins involved in lysosomal lipid degradation and in transport between lysosomes and the smooth endoplasmic reticulum. All investigated proteins were expressed at a high rate in the kidney and the corresponding structures of the central nervous system. The intricate involvement of GM in cellular transport mechanisms described in this work warrants further study. It could focus on assessing levels of the target protein in animal models of GM-induced toxicity.

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Author contributions: Conceptualization, N.M.; Methodology, N.M and S.S.; Formal Analysis, N.M. and J.J.; Investigation, N.M. and D.G.; Data Curation, N.M., S.S. and V.J.; Writing – Original Draft Preparation, N.M. and S.S.; Writing – Review & Editing, N.M., S.S., N.J., M.S., J.P.P., S.K., D.G., V.J., J.N.O; Visualization, N.M. and S.S.; Supervision, N.M., S.S., J.N.O.; Funding Acquisition, J.N.O. All authors reviewed and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Ethical approval: N/A

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IN SILICO ISPITIVANJE EFEKATA GENTAMICINA NA LIZOZOMALNU DEGRADACIJU LIPIDA I TRANSPORTNI SISTEM IZMEĐU LIZOZOMA I GLATKOG ENDOPLAZMATSKOG RETIKULUMA

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Sažetak

Uvod: Gentamicin je aminoglikozidni antibiotik sa ograničenom kliničkom upotrebom zbog

pratećih neželjenih efekata grupisanih u dve velike grupe: nefrotoksičnost i ototoksičnost. Oštećenja nastala gentamicinom se vremenom akumuliraju i finalno dovode do smrti ćelija. U bubregu najviše su zahvaćene ćelije proksimalnih tubula, a u unutrašnjem uhu senzorne ćelije. Jedan od pretpostavljenih mehanizama toksičnosti je fosfolipidoza, poremećaj u kome dolazi do povećane akumulacije fosfolipida u ćeliji.

Cilj: Cilj našeg rada je *in silico* utvrđivanje mehanizma dejstva gentamicina u nastanku fosfolipidoze na osnovu interakcije sa ključnim proteinima odgovornim za transport lipida između glatkog endoplazmatskog retikuluma i kasnih endozoma kao i enzima koji učestvuju u razgradnji lipida.

Materijal i metode: U *KEGG* bazi smo definisali target proteine, a u *Human Atlas* bazi pratili njihove profile ekspresije i tkivne specifičnosti. Finalne kriterijume ispunjavalo je 9 proteina koje smo dalje ispitivali u *AutoDock Vina* programu, molekularnim dokingom.

Rezultati: Većina ispitanih proteina se eksprimira u visokoj stopi u bubregu i odgovarajućim strukturama centralnog nervnog sistema. Rezultati dokinga su pokazali da je interakcija ORP1L proteina i gentamicina imala najnižu vrednost Gibsove slobodne energije i iznosila je -8.1 kcal/mol, dok je za protein STARD3 vrednost Gibsove slobodne energije bila najviša iznosila je -5.2 kcal/mol. Aminokiselinske sekvence za koje se gentamicin vezivao na ispitivanim proteinima su bile slične u okviru istih familija proteina.

Zaključak: Gentamicin u *in silico* uslovima ostvaruje interakcije sa proteinima koji učestvuju u lizozomalnoj degradaciji lipida i transportu između lizozoma i glatkog endoplazmatskog retikuluma.

Ključne reči: Gentamicin, nefrotoksičnost, ototoksičnost, fosfolipidoza, molekularni doking

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