

Antibiotics and the Mitochondria

LINKS:

Antibacterial drugs and their interference with the biogenesis of mitochondria in animal and human cells

http://www.ummafrapp.de/skandal/felix/antibiotics/antibacterial_drugs.pdf

The biogenesis of mitochondria, VI. Biochemical basis of the resistance of *Saccharomyces cerevisiae* toward antibiotics which specifically inhibit mitochondrial protein synthesis.

<http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=224865&blobtype=pdf>

Biogenesis of mitochondria. XI. A comparison of the effects of growth-limiting oxygen tension, intercalating agents, and antibiotics on the obligate aerobe *Candida parapsilosis*.

<http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=2107676&blobtype=pdf>

Biogenesis of Mitochondria: Analysis of Deletion of Mitochondrial Antibiotic Resistance Markers in Petite Mutants of *Saccharomyces cerevisiae*.

<http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=235632&blobtype=pdf>

Influence on Mitochondria and Cytotoxicity of Different Antibiotics Administered in High Concentrations on Primary Human Osteoblasts and Cell Lines

<http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1797653&blobtype=pdf>

Structural basis for selectivity and toxicity of ribosomal antibiotics

<http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1083859&blobtype=pdf>

Familial streptomycin ototoxicity in a South African Family: A mitochondrial disorder

<http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1051117&blobtype=pdf>

The Renal Mitochondrial Toxicity of Beta-Lactam Antibiotics: *In Vitro* Effects of Cephaloglycin and Imipenem

<http://jasn.asnjournals.org/cgi/reprint/1/5/815>

Cephaloridine Induces Translocation of Protein Kinase C δ Into Mitochondria and Enhances Mitochondrial Generation of Free Radicals in the Kidney Cortex of Rats Causing Renal Dysfunction

http://www.jstage.jst.go.jp/article/jphs/98/1/49/_pdf

Mitochondrial DNA Deletions and Chloramphenicol Treatment Stimulate the Autophagic Transcript ATG12

<http://www.landesbioscience.com/journals/autophagy/article/prigioneAUTO3-4.pdf>

Chloramphenicol-induced Mitochondrial Stress Increases p21 Expression and Prevents Cell Apoptosis through a p21-dependent Pathway^{*}

<http://www.jbc.org/cgi/reprint/280/28/26193>

Inhibition of mammalian mitochondrial protein synthesis by Oxazolidinones

<http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1479116&blobtype=pdf>

Ciprofloxacin does not inhibit mitochondrial functions but other antibiotics do

<http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=171543&blobtype=pdf>

In vitro and in vivo immunomodulatory effects of anti-Pneumocystis carinii drugs.

<http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=163313&blobtype=pdf>


The Sensitivity of Rat Liver and Yeast Mitochondrial Ribosomes to inhibitors of protein synthesis

<http://www.jbc.org/cgi/reprint/249/21/6806>

ABSTRACTS:

[Antimicrob Agents Chemother.](#) 1990 Jan;34(1):167-9.



FREE full text article
in PubMed Central  [Links](#)



Ciprofloxacin does not inhibit mitochondrial functions but other antibiotics do.

[Riesbeck K](#), [Bredberg A](#), [Forsgren A](#).

Department of Medical Microbiology, University of Lund, Malmö General Hospital, Sweden.

At clinical concentrations, ciprofloxacin did not inhibit mitochondrial DNA replication, oxidative phosphorylation, protein synthesis, or mitochondrial mass (transmembrane potential). No difference in supercoiled forms of DNA was observed.

The tetracyclines and chloramphenicol inhibited protein synthesis at clinically achievable concentrations, while rifampin, fusidic acid, and clindamycin did not.



1: [Chem Biol Interact.](#) 2008 Jun 17;173(3):187-94. Epub 2008 Mar 21.  
[Links](#)

Interaction of beta-lactam antibiotics with the mitochondrial carnitine/acylcarnitine transporter.

[Pochini L](#), [Galluccio M](#), [Scumaci D](#), [Giangregorio N](#), [Tonazzi A](#), [Palmieri F](#), [Indiveri C](#).

Department of Cell Biology, University of Calabria, Via P.Bucci 4c, 87036 Arcavacata di Rende, Italy.

The interaction of beta-lactams with the purified mitochondrial carnitine/acylcarnitine transporter reconstituted in liposomes has been studied. Cefonicid, cefazolin, cephalothin, ampicillin, piperacillin externally added to the proteoliposomes, inhibited the carnitine/carnitine antiport catalysed by the reconstituted transporter. The most effective inhibitors were cefonicid and ampicillin with IC₅₀ of 6.8 and 7.6mM, respectively. The other inhibitors exhibited IC₅₀ values above 36 mM. Kinetic analysis performed with cefonicid and ampicillin revealed that the inhibition is completely competitive, i.e., the inhibitors interact with the substrate binding site. The K_i of the transporter is 4.9 mM for cefonicid and 9.9 mM for ampicillin. Cefonicid inhibited the transporter also on its internal side. The IC₅₀ was 12.9 mM indicating that the inhibition was less pronounced than on the external side. Ampicillin and the other inhibitors were much less effective on the internal side. The beta-lactams were not transported by the carnitine/acylcarnitine transporter. Cephalosporins, and at much lower extent penicillins, caused irreversible inhibition of the transporter after prolonged time of incubation. The most effective among the tested antibiotics was cefonicid with IC₅₀ of 0.12 mM after 60 h of incubation. The possible in vivo implications of the interaction of the beta-lactam antibiotics with the transporter are discussed.

[Mol Cell.](#) 2007 May 11;26(3):393-402.   [Links](#)
Comment in:
[Mol Cell.](#) 2007 May 25;26(4):460-2.

The site of action of oxazolidinone antibiotics in living bacteria and in human mitochondria.

[Leach KL](#), [Swaney SM](#), [Colca JR](#), [McDonald WG](#), [Blinn JR](#), [Thomasco LM](#), [Gadwood RC](#), [Shinabarger D](#), [Xiong L](#), [Mankin AS](#).

Pfizer Inc., 2800 Plymouth Road, Ann Arbor, MI 48105, USA.

The oxazolidinones are one of the newest classes of antibiotics. They inhibit bacterial growth by interfering with protein synthesis. The mechanism of oxazolidinone action and the precise location of the drug binding site in the ribosome are unknown. We used a panel of photoreactive derivatives to identify the site of action of oxazolidinones in the ribosomes of bacterial and human cells. The in vivo crosslinking data were used to model the position of the oxazolidinone molecule within its binding site in the peptidyl transferase center (PTC). Oxazolidinones interact with the A site of the bacterial ribosome where they should interfere with the placement of the aminoacyl-tRNA. In human cells, oxazolidinones were crosslinked to rRNA in the PTC of mitochondrial, but not cytoplasmic, ribosomes. Interaction of oxazolidinones with the mitochondrial ribosomes provides a structural basis for the inhibition of mitochondrial protein synthesis, which is linked to clinical side effects associated with oxazolidinone therapy.



1: [Autophagy](#). 2007 Jul-Aug;3(4):377-80. Epub 2007 Jul 5. [Links](#)

Comment on:

[Free Radic Biol Med](#). 2007 Jan 1;42(1):32-43.

Mitochondrial DNA deletions and chloramphenicol treatment stimulate the autophagic transcript ATG12.

[Prigione A](#), [Cortopassi G](#).

Department of Neuroscience and Biomedical Technologies, University of Milan-Bicocca, Monza, Italy.

Deletion mutations of mitochondrial DNA (mtDNA) accumulate somatically on a cell-by-cell basis with age, resulting in decreased cell function in muscle and substantia nigra. In osteosarcoma cells deletions incapacitate mitochondria and induce the autophagic transcript ATG12, which is involved in an early step of the mammalian autophagy pathway. We discuss here which consequences of mtDNA deletions could induce ATG12, and provide two new pieces of data. Our previous studies demonstrated that mtDNA deletions decreased mitochondrial ATP production and proteasomal function, induced the AMPK transcript (likely as a consequence of bioenergetic depletion), and decreased the intracellular concentration of 20 amino acids (possibly as a consequence of decreased proteasomal activity). Deletions eliminate essential tRNAs for mitochondrial protein synthesis, as well as essential components of mitochondrial multisubunit enzymes; therefore, the increased level of ATG12 could result from decreased bioenergetic function, increased oxidative damage, or decreased mitochondrial protein synthesis. However, the bioenergetic inhibitor rotenone does not induce ATG12. We show here that chloramphenicol, which inhibits mitochondrial protein synthesis, induces ATG12, and that mtDNA deletions result in an increased burden of oxidatively damaged protein. Thus, mtDNA deletions could induce ATG12 through a mechanism such as the following: deletions > mitochondrial protein synthesis inhibition or ROS > proteasome inhibition > amino acid depletion > ATG12.

1: [Antimicrob Agents Chemother.](#) 2007 Jan;51(1):54-63. Epub 2006 Nov 6.



Influence on mitochondria and cytotoxicity of different antibiotics administered in high concentrations on primary human osteoblasts and cell lines.

[Dewelhenke N](#), [Krut O](#), [Eysel P](#).

Klinik und Poliklinik für Orthopädie, Universitätsklinikum Köln, Joseph-Stelzmann-Str. 24, 50931 Köln, Germany. Nicole.Dewelhenke@uk-koeln.de

Osteomyelitis, osteitis, spondylodiscitis, septic arthritis, and prosthetic joint infections still represent the worst complications of orthopedic surgery and traumatology. Successful treatment requires, besides surgical débridement, long-term systemic and high-concentration local antibiotic therapy, with possible local antibiotic concentrations of 100 microg/ml and more. In this study, we investigated the effect of 20 different antibiotics on primary human osteoblasts (PHO), the osteosarcoma cell line MG63, and the epithelial cell line HeLa. High concentrations of fluoroquinolones, macrolides, clindamycin, chloramphenicol, rifampin, tetracycline, and linezolid during 48 h of incubation inhibited proliferation and metabolic activity, whereas aminoglycosides and inhibitors of bacterial cell wall synthesis did not. Twenty percent inhibitory concentrations for proliferation of PHO were determined as 20 to 40 microg/ml for macrolides, clindamycin, and rifampin, 60 to 80 microg/ml for chloramphenicol, tetracyclin, and fluoroquinolones, and 240 microg/ml for linezolid. The proliferation of the cell lines was always less inhibited. We established the measurement of extracellular lactate concentration as an indicator of glycolysis using inhibitors of the respiratory chain (antimycin A, rotenone, and sodium azide) and glycolysis (iodoacetic acid) as reference compounds, whereas inhibition of the respiratory chain increased and inhibition of glycolysis decreased lactate production. The measurement of extracellular lactate concentration revealed that fluoroquinolones, macrolides, clindamycin, rifampin, tetracycline, and especially chloramphenicol and linezolid impaired mitochondrial energetics in high concentrations. This explains partly the observed inhibition of metabolic activity and proliferation in our experiments. Because of differences in the energy metabolism, PHO provided a more sensitive model for orthopedic antibiotic usage than stable cell lines.

: [Biochem Pharmacol.](#) 2009 Mar 1;77(5):888-96. Epub 2008 Nov 12.



[Links](#)

Inhibitory modulation of the mitochondrial permeability transition by minocycline.

[Gieseler A](#), [Schultze AT](#), [Kupsch K](#), [Haroon MF](#), [Wolf G](#), [Siemen D](#), [Kreutzmann P](#).

Institute of Medical Neurobiology, Otto-von-Guericke University Magdeburg,
Leipziger Str. 44, D-39120 Magdeburg, Germany.

The semi-synthetic tetracycline derivative minocycline exerts neuroprotective properties in various animal models of neurodegenerative disorders. Although anti-inflammatory and anti-apoptotic effects are reported to contribute to the neuroprotective action, the exact molecular mechanisms underlying the beneficial properties of minocycline remain to be clarified. We analyzed the effects of minocycline in a cell culture model of neuronal damage and in single-channel measurements on isolated mitoplasts. Treatment of neuron-enriched cortical cultures with rotenone, a high affinity inhibitor of the mitochondrial complex I, resulted in a deregulation of the intracellular Ca²⁺-dynamics, as recorded by live cell imaging. Minocycline (100 µM) and cyclosporin A (2 µM), a known inhibitor of the mitochondrial permeability transition pore, decreased the rotenone-induced Ca²⁺-deregulation by 60.9% and 37.6%, respectively. Investigations of the mitochondrial permeability transition pore by patch-clamp techniques revealed for the first time a dose-dependent reduction of the open probability by minocycline (IC₅₀=190 nM). Additionally, we provide evidence for the high antioxidant potential of MC in our model. In conclusion, the present data substantiate the beneficial properties of minocycline as promising neuroprotectant by its inhibitory activity on the mitochondrial permeability transition pore.

[Biochem Biophys Res Commun.](#) 2008 Apr 11;368(3):631-6. Epub 2008 Feb 7.

 [Links](#)

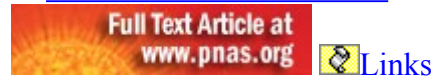
A mutation in mitochondrial 12S rRNA, A827G, in Argentinean family with hearing loss after aminoglycoside treatment.

[Chaig MR](#), [Zernotti ME](#), [Soria NW](#), [Romero OF](#), [Romero MF](#), [Gerez NM](#).

Cátedra de Bioquímica y Biología molecular, FCM-UNC, Haya de la Torre, S/N Ciudad Universitaria, 2do, Piso, Pabellón CP 5016, Argentina.

Mutations in mitochondrial DNA (mtDNA) have been found to be associated with sensorineural hearing loss. We report the clinical, genetic, and molecular characterization of one Argentinean family with aminoglycoside-induced impairment in two of their members. Clinical evaluation revealed the variable phenotype of hearing impairment including audiometric configuration in these subjects. Mutational analysis of the mtDNA in these pedigrees showed the presence of homoplasmic 12S rRNA A827G mutation, which has been associated with hearing impairment. The A827G mutation is located at the A-site of the mitochondrial 12S rRNA gene which is highly conserved in mammals. It is possible that the alteration of the tertiary or quaternary structure of this rRNA by the A827G mutation may lead to mitochondrial dysfunction, thereby playing a role in the pathogenesis of hearing loss and aminoglycoside hypersensitivity. However, incomplete penetrance of hearing impairment indicates that the A827G mutation itself is not sufficient to produce clinical phenotype.

1: [Proc Natl Acad Sci U S A](#). 2008 Dec 30;105(52):20888-93. Epub 2008 Dec 22.



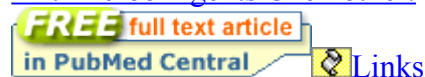
Genetic analysis of interactions with eukaryotic rRNA identify the mitoribosome as target in aminoglycoside ototoxicity.

[Hobbie SN](#), [Akshay S](#), [Kalapala SK](#), [Bruell CM](#), [Shcherbakov D](#), [Böttger EC](#).

Institut für Medizinische Mikrobiologie, Universität Zürich, Gloriastrasse 32, CH-8006 Zurich, Switzerland.

Aminoglycoside ototoxicity has been related to a surprisingly large number of cellular structures and metabolic pathways. The finding that patients with mutations in mitochondrial rRNA are hypersusceptible to aminoglycoside-induced hearing loss has indicated a possible role for mitochondrial protein synthesis. To study the molecular interaction of aminoglycosides with eukaryotic ribosomes, we made use of the observation that the drug binding site is a distinct domain defined by the small subunit rRNA, and investigated drug susceptibility of bacterial hybrid ribosomes carrying various alleles of the eukaryotic decoding site. Compared to hybrid ribosomes with the A site of human cytosolic ribosomes, susceptibility of mitochondrial hybrid ribosomes to various aminoglycosides correlated with the relative cochleotoxicity of these drugs. Sequence alterations that correspond to the mitochondrial deafness mutations A1555G and C1494T increased drug-binding and rendered the ribosomal decoding site hypersusceptible to aminoglycoside-induced mistranslation and inhibition of protein synthesis. Our results provide experimental support for aminoglycoside-induced dysfunction of the mitochondrial ribosome. We propose a pathogenic mechanism in which interference of aminoglycosides with mitochondrial protein synthesis exacerbates the drugs' cochlear toxicity, playing a key role in sporadic dose-dependent and genetically inherited, aminoglycoside-induced deafness.

[Antimicrob Agents Chemother](#). 2006 Jun;50(6):2042-9.



Comment in:

[Antimicrob Agents Chemother](#). 2007 Mar;51(3):1130; author reply 1130.

Inhibition of mammalian mitochondrial protein synthesis by oxazolidinones.

[McKee EE](#), [Ferguson M](#), [Bentley AT](#), [Marks TA](#).

Indiana University School of Medicine--South Bend, IN 46617, USA.
McKee.6@nd.edu

The effects of a variety of oxazolidinones, with different antibacterial potencies, including linezolid, on mitochondrial protein synthesis were determined in intact mitochondria isolated from rat heart and liver and rabbit heart and bone marrow. The results demonstrate that a general feature of the oxazolidinone class of antibiotics is the inhibition of mammalian mitochondrial protein synthesis. Inhibition was similar in mitochondria from all tissues studied. Further, oxazolidinones that were very potent as antibiotics were uniformly potent in inhibiting mitochondrial protein synthesis. These results were compared to the inhibitory profiles of other antibiotics that function by inhibiting bacterial protein synthesis. Of these, chloramphenicol and tetracycline were significant inhibitors of mammalian mitochondrial protein synthesis while the macrolides, lincosamides, and aminoglycosides were not. Development of future antibiotics from the oxazolidinone class will have to evaluate potential mitochondrial toxicity.

[J Med Genet.](#) 1997 Nov;34(11):904-6.



[Links](#)

Familial streptomycin ototoxicity in a South African family: a mitochondrial disorder.

[Gardner JC](#), [Goliath R](#), [Viljoen D](#), [Sellars S](#), [Cortopassi G](#), [Hutchin T](#), [Greenberg J](#), [Beighton P](#).

Department of Human Genetics, University of Cape Town Medical School, Observatory, South Africa.

The vestibular and ototoxic effects of the aminoglycoside antibiotics (streptomycin, gentamycin, kanamycin, tobramycin, neomycin) are well known; streptomycin, in particular, has been found to cause irreversible, profound, high frequency sensorineural deafness in hypersensitive persons. Aminoglycoside ototoxicity occurs both sporadically and within families and has been associated with a mitochondrial DNA (mtDNA) 1555A to G point mutation in the 12S ribosomal RNA gene. We report on the molecular analysis of a South African family with streptomycin induced sensorineural deafness in which we have found transmission of this same predisposing mutation. It is now possible to identify people who are at risk of hearing loss if treated with aminoglycosides in the future and to counsel them accordingly. In view of the fact that aminoglycoside antibiotics remain in widespread use for the treatment of infections, in particular for tuberculosis, which is currently of epidemic proportions in South Africa, this finding has important implications for the family concerned. In addition, other South African families may potentially be at risk if they carry the same mutation.

: [J Biol Chem.](#) 2005 Jul 15;280(28):26193-9. Epub 2005 May 19.





[Links](#)

Chloramphenicol-induced mitochondrial stress increases p21 expression and prevents cell apoptosis through a p21-dependent pathway.

[Li CH](#), [Tzeng SL](#), [Cheng YW](#), [Kang JJ](#).

Institute of Toxicology, College of Medicine, National Taiwan University, Taipei 100, Taiwan.

Pretreatment of HepG2 and H1299 cells with chloramphenicol rendered the cells resistant to mitomycin-induced apoptosis. Both mitomycin-induced caspase 3 activity and PARP activation were also inhibited. The mitochondrial DNA-encoded Cox I protein, but not nuclear-encoded proteins, was down-regulated in chloramphenicol-treated cells. Cellular levels of the p21(waf1/cip1) protein and p21(waf1/cip1) mRNA were increased through a p53-independent pathway, possibly because of the stabilization of p21(waf1/cip1) mRNA in chloramphenicol-treated cells. The p21(waf1/cip1) was redistributed from the perinuclear region to the cytoplasm and co-localized with mitochondrial marker protein. Several morphological changes and activation of the senescence-associated biomarker, SA beta-galactosidase, were observed in these cells. Both p21(waf1/cip1) antisense and small interfering RNA could restore apoptotic-associated caspase 3 activity, PARP activation, and sensitivity to mitomycin-induced apoptosis. Similar effects were seen with other antibiotics that inhibit mitochondrial translation, including minocycline, doxycycline, and clindamycin. These findings suggested that mitochondrial stress causes resistance to apoptosis through a p21-dependent pathway.

: [Biofactors](#). 2008;32(1-4):31-9.   [Links](#)



Mitochondrial production of reactive oxygen species: role of complex I and quinone analogues.

[Fato R](#), [Bergamini C](#), [Leoni S](#), [Lenaz G](#).

Dipartimento di Biochimica G. Moruzzi, University of Bologna, 40126 Bologna, Italy.
romana.fato@unibo.it

Mitochondrial reactive oxygen species (ROS) are mainly produced by the respiratory chain enzymes. The sites for ROS production in mitochondrial respiratory chain are normally ascribed to the activity of Complex I and III. The presence of specific inhibitors modulates reactive oxygen species production in Complex I: inhibitors such as rotenone induce a strong ROS increase, while inhibitors such as stigmatellin prevent it. We have investigated the effect of hydrophilic quinones on Complex I ROS production in presence of different inhibitors. Some short chain quinones are Complex I inhibitors (CoQ2, idebenone and its derivatives), while CoQ1, decylubiquinone~ (DB) and duroquinone (DQ) are good electron acceptors from Complex I. Our results show that the ability of short chain quinones to induce an oxidative stress depends on the site of interaction with Complex I and on their physical-chemical characteristics. We can conclude that hydrophilic quinones may enhance oxidative stress by

interaction with the electron escape sites on Complex I while more hydrophobic quinones can be reduced only at the physiological quinone reducing site without reacting with molecular oxygen.




1: [Biochem Pharmacol](#). 2009 Mar 1;77(5):888-96. Epub 2008 Nov 12.   [Links](#)

Inhibitory modulation of the mitochondrial permeability transition by minocycline.

[Gieseler A](#), [Schultze AT](#), [Kupsch K](#), [Haroon MF](#), [Wolf G](#), [Siemen D](#), [Kreutzmann P](#).

Institute of Medical Neurobiology, Otto-von-Guericke University Magdeburg, Leipziger Str. 44, D-39120 Magdeburg, Germany.

The semi-synthetic tetracycline derivative minocycline exerts neuroprotective properties in various animal models of neurodegenerative disorders. Although anti-inflammatory and anti-apoptotic effects are reported to contribute to the neuroprotective action, the exact molecular mechanisms underlying the beneficial properties of minocycline remain to be clarified. We analyzed the effects of minocycline in a cell culture model of neuronal damage and in single-channel measurements on isolated mitoplasts. Treatment of neuron-enriched cortical cultures with rotenone, a high affinity inhibitor of the mitochondrial complex I, resulted in a deregulation of the intracellular Ca²⁺-dynamics, as recorded by live cell imaging. Minocycline (100 microM) and cyclosporin A (2 microM), a known inhibitor of the mitochondrial permeability transition pore, decreased the rotenone-induced Ca²⁺-deregulation by 60.9% and 37.6%, respectively. Investigations of the mitochondrial permeability transition pore by patch-clamp techniques revealed for the first time a dose-dependent reduction of the open probability by minocycline (IC₅₀)=190 nM). Additionally, we provide evidence for the high antioxidant potential of MC in our model. In conclusion, the present data substantiate the beneficial properties of minocycline as promising neuroprotectant by its inhibitory activity on the mitochondrial permeability transition pore.

[Pharmacogenet Genomics](#). 2008 Dec;18(12):1095-102.    [Links](#)

Frequency of mitochondrial 12S ribosomal RNA variants in an adult cystic fibrosis population.

[Conrad DJ](#), [Stenbit AE](#), [Zettner EM](#), [Wick I](#), [Eckhardt C](#), [Hardiman G](#).

Department of Medicine, University of California, San Diego Gilman Drive, LA Jolla, CA 92093-0724, USA.

In adult cystic fibrosis patient populations, gram-negative bacteria, particularly *Pseudomonas aeruginosa*, frequently require aggressive therapy including systemic antibiotics, bronchodilators and airway clearance techniques. Aminoglycosides

including tobramycin are used frequently to control these chronic airway infections. They, however, cause important nephrotoxic and ototoxic effects that can significantly alter the quality of life. We investigated the genetic predisposition to aminoglycoside ototoxicity in a typical unscreened North American cystic fibrosis population by screening for variants in mitochondrial 12S ribosomal RNA and noted several polymorphisms occurred at higher frequencies than expected and were associated with clinically significant cases of hearing loss. In the population studied, both patients possessing the 1555A>G transition exhibited profound ototoxicity after nontoxic dosing of tobramycin. We also identified new homoplasmic genetic variations in the mitochondrial 12S ribosomal RNA, several of which occurred in highly conserved regions of the gene and were present in patients with moderate-to-severe ototoxicity after exposure to aminoglycosides.

1: [Free Radic Biol Med.](#) 2008 Nov 15;45(10):1395-402. Epub 2008 Aug 14.



[Links](#)

Doxorubicin increases the susceptibility of brain mitochondria to Ca(2+)-induced permeability transition and oxidative damage.

[Cardoso S](#), [Santos RX](#), [Carvalho C](#), [Correia S](#), [Pereira GC](#), [Pereira SS](#), [Oliveira PJ](#), [Santos MS](#), [Proença T](#), [Moreira PI](#).

Department of Zoology, Faculty of Sciences and Technology, University of Coimbra, 3000-354 Coimbra, Portugal.

This study was aimed at investigating the effects of subchronic administration of doxorubicin (DOX) on brain mitochondrial bioenergetics and oxidative status. Rats were treated with seven weekly injections of vehicle (sc, saline solution) or DOX (sc, 2 mg kg⁻¹), and 1 week after the last administration of the drug the animals were sacrificed and brain mitochondrial fractions were obtained. Several parameters were analyzed: respiratory chain, phosphorylation system, induction of the permeability transition pore (PTP), mitochondrial aconitase activity, lipid peroxidation markers, and nonenzymatic antioxidant defenses. DOX treatment induced an increase in thiobarbituric acid-reactive substances and vitamin E levels and a decrease in reduced glutathione content and aconitase activity. Furthermore, DOX potentiated PTP induced by Ca²⁺. No statistical differences were observed in the other parameters analyzed. Altogether our results show that DOX treatment increases the susceptibility of brain mitochondria to Ca(2+)-induced PTP opening and oxidative stress, predisposing brain cells to degeneration and death.

[Biochem Biophys Res Commun.](#) 1989 Nov 15;164(3):1281-7.





[Links](#)

Effect of anthracycline antibiotics on the reconstituted mitochondrial tricarboxylate carrier.

[Stipani I](#), [Capalbo MI](#), [Zara V](#).

Department of Pharmaco-Biology, University of Bari, Italy.

The effect of anthracycline antibiotics on the activity of the partially purified and reconstituted tricarboxylate carrier system of the rat liver mitochondria was studied. It was found that the citrate/citrate exchange activity is inhibited by Br-daunomycin and with less potency by doxorubicin, daunomycin, epirubicin and idarubicin. The inhibition of the citrate transport activity is concentration and time-dependent. Cardiophilin protects against the inhibition by Br-daunomycin and the reconstituted citrate transport activity depends upon the ratio of cardiophilin/Br-daunomycin.

: [Biochem Pharmacol](#). 1995 Mar 1;49(5):727-34.  [FULL-TEXT ARTICLE](#)  [Links](#)

Toxicity of cephalosporins to fatty acid metabolism in rabbit renal cortical mitochondria.

[Tune BM](#), [Hsu CY](#).

Department of Pediatrics, Stanford University School of Medicine, CA 94305-5119.

Cephaloglycin (Cgl) and cephaloridine (Cld) are acutely toxic to the proximal renal tubule, in part because of their cellular uptake by a contraluminal anionic secretory carrier and in part through their intracellular attack on the mitochondrial transport and oxidation of tricarboxylic acid (TCA) cycle anionic substrates. Preliminary studies with Cgl have provided evidence of a role of fatty acid (FA) metabolism in its nephrotoxicity, and work with Cld has shown it to be a potent inhibitor of renal tubular cell and mitochondrial carnitine (Carn) transport. Studies were therefore done to examine the effects of Cgl and Cld on the mitochondrial metabolism of butyrate, the anion of a short-chain FA that does not require the Carn shuttle to enter the inner matrix, and the effects of Cgl on the metabolism of palmitoylcarnitine (PCarn), the Carn conjugate of a long-chain FA that does enter the mitochondrion by the Carn shuttle. The following was found: (1) Cgl reduced the oxidation and uptake of butyrate after in vitro (2000 micrograms/mL, immediate effect) and after in vivo (300 mg/kg body weight, 1 hr before killing) exposure; (2) Cld caused milder in vitro toxicity, and no significant in vivo toxicity, to mitochondrial butyrate metabolism; (3) like Cld, Cgl reduced PCarn-mediated respiration after in vivo exposure, but, unlike Cld, it did not inhibit respiration with PCarn in vitro; (4) the Carn carrier was stimulated slightly by in vitro Cgl but was unaffected by in vivo Cgl; (5) in vivo Cgl had no effect on mitochondrial free Carn or long-chain acylCarn concentrations in the in situ kidney; (6) Cgl increased the excretion of Carn minimally compared with the effect of Cld; and (7) cephalixin, a nontoxic cephalosporin, caused mild reductions of respiration with butyrate and PCarn during in vitro exposure, but stimulated respiration with both substrates after in vivo exposure. Conclusions: Cgl has essentially the same patterns of in vitro and in vivo toxicity against mitochondrial butyrate uptake and oxidation that both Cgl and Cld have against TCA-cycle substrates. Cld has little or no in vivo toxicity to mitochondrial butyrate metabolism, whereas in vivo Cgl is as toxic as Cld to respiration with PCarn. The greater overall in vivo toxicity of Cgl to mitochondrial FA metabolism, with lower cortical concentrations and AUCs than those of Cld, supports earlier evidence that Cld is less toxic than Cgl at the molecular level.

Toxicity of cephaloridine to carnitine transport and fatty acid metabolism in rabbit renal cortical mitochondria: structure-activity relationships.

[Tune BM](#), [Hsu CY](#).

Cephaloridine (Cld), the most widely studied nephrotoxic cephalosporin, has significant structural homology with carnitine, which facilitates the transport of long-chain fatty acids into the mitochondrial inner matrix. Because of this homology, and evidence of a role of lipids in cephaloglycin (Cgl) nephrotoxicity, protocols were designed to compare the effects of Cld and Cgl on renal cortical mitochondrial carnitine transport, on long-chain fatty acylcarnitine-mediated respiration and on the in situ mitochondrial pools and urinary excretion of carnitine and acylcarnitines. The following was found: 1) both cephalosporins reduced carnitine-facilitated pyruvate oxidation (CFPO) and palmitoylcarnitine-mediated respiration (PCMR) by 40 to 50% in mitochondria exposed in vivo (300 mg/kg b.wt., 1 hr). CFPO could be decreased by reduction of carnitine uptake, pyruvate oxidation or carnitine acetyltransferase activity; 2) neither cephalosporin reduced mitochondrial carnitine acetyltransferase or carnitine palmitoyltransferase; 3) with in vitro exposure (2000 micrograms/ml, immediate effect) Cgl had no significant toxicity to mitochondrial CFPO. Cld inhibited CFPO in a dose-dependent manner, up to 100% at 2000 micrograms/ml; this effect was reduced by increasing carnitine concentrations; 4) in vitro Cld prevented the potentiation of PCMR by preloading with carnitine, reduced mitochondrial acylcarnitine/carnitine exchange by 70% and reduced PCMR by 30%; 5) in vivo Cld increased mitochondrial-free carnitine in the in situ kidney by 100%; and 6) in vivo Cld increased the fractional renal excretion of carnitine from 0 +/- 0 to 0.29 +/- 0.03 and the fractional excretion of long-chain acylcarnitines from 0.06 +/- 0.01 to 0.79 +/- 0.17.(ABSTRACT TRUNCATED AT 250 WORDS)


The renal mitochondrial toxicity of beta-lactam antibiotics: in vitro effects of cephaloglycin and imipenem.

[Tune BM](#), [Hsu CY](#).

Department of Pediatrics, Stanford University School of Medicine, CA 94305.

The nephrotoxic beta-lactam antibiotics cephaloridine, cephaloglycin, and imipenem produce irreversible injury to renal mitochondrial anionic substrate uptake and respiration after 1 to 2 h of in vivo exposure. Toxicity during in vitro exposure is nearly identical but is immediate in onset and is reversed by the mitochondria being washed or the substrate concentrations being increased. A model of injury that

accounts for these findings proposes that the beta-lactams fit carriers for mitochondrial substrate uptake, causing inhibition that is initially reversible and becomes irreversible as the antibiotics acylate the transporters. These studies were designed to create an environment of prolonged in vitro exposure, first, to determine whether toxicity becomes irreversible with time and, second, to study the molecular properties of toxicity. Respiration with and the uptake of succinate and ADP were measured in rabbit renal cortical mitochondria exposed for 2 to 6 h to 300 to 3,000 micrograms of cephalexin (nontoxic) or cephaloglycin or imipenem (nephrotoxic) per mL and then washed to remove the antibiotic. In vitro cephalexin reduced respiration only slightly and was therefore not studied further. Cephaloglycin and imipenem irreversibly reduced both respiration and succinate uptake. ADP uptake was unaffected by cephaloglycin and was slightly reduced by imipenem. Finally, cilastatin, which prevents the tubular necrosis produced by imipenem in vivo, reduced its mitochondrial toxicity in vitro. It is concluded that the pattern of in vitro injury of the nephrotoxic beta-lactams to mitochondrial substrate uptake and respiration evolves in a time-dependent and concentration-dependent manner, consistent with the proposed model of acylation and inactivation of substrate transporters, and that the protective action of cilastatin against imipenem occurs at least partly at a subcellular level.

[Biochem Pharmacol.](#) 1987 Oct 1;36(19):3293-7.  [Links](#)

Coordinate increases and decreases in mitochondrial RNA and ATP syntheses produced by propranolol and rifampicin.

[Buss WC](#), [Jaramillo E](#), [Piatt MK](#).

Department of Pharmacology, University of New Mexico, School of Medicine, Albuquerque 87131.

A variety of compounds were examined for their capacity to alter RNA synthesis in isolated rat cardiac and hepatic mitochondria. The beta-adrenergic blocking agents propranolol and butoxamine, and the antiarrhythmic agent quinidine, produced a concentration-dependent stimulation of RNA synthesis in cardiac and hepatic mitochondria. In contrast, the antitubercular antibiotic rifampicin produced a concentration-dependent inhibition of RNA synthesis in cardiac and hepatic mitochondria. Propranolol, as a representative compound which stimulated RNA synthesis, was also found to stimulate ATP synthesis in isolated mitochondria, whereas rifampicin inhibited ATP synthesis. Coordinate increases and decreases in RNA and ATP syntheses suggest that agents which stimulate or inhibit RNA synthesis may rapidly alter ATP synthesis. This finding is consistent with the rapid turn-over of mitochondrial RNA with a messenger function (1.4 and 3.3 min in isolated rat cardiac and hepatic mitochondria), and it suggests that mitochondrial RNA must continue to be synthesized to maintain inner membrane systems required for ATP synthesis. Stimulation of RNA and ATP syntheses by propranolol through membrane stabilization or other actions represents a heretofore unrecognized action of propranolol which may contribute to its beneficial therapeutic effects.

: [Insect Mol Biol](#). 2007 Dec;16(6):799-802.



[Links](#)

Tetracycline treatment influences mitochondrial metabolism and mtDNA density two generations after treatment in *Drosophila*.

[Ballard JW](#), [Melvin RG](#).

Ramaciotti Centre for Gene Function Analysis, School of Biotechnology and Biomolecular Sciences, University of New South Wales, Sydney, Australia.
w.ballard@unsw.edu.au

Tetracycline is commonly used to clear *Wolbachia* from infected insects. Studies then compare specific biochemical and/or life-history traits between infected and uninfected individuals with the same genetic background. We investigated the potential for tetracycline to influence mitochondrial efficiency and mitochondrial (mt)DNA density two generations after treatment in *Drosophila simulans*. We observed that antibiotic treatment resulted in a decline in inorganic phosphate incorporated into ATP per mole of oxygen consumed (ADP:O ratio). Further, tetracycline treatment caused a significant increase in mtDNA density in naturally *Wolbachia*-uninfected but not in naturally *Wolbachia*-infected lines suggesting a dosage effect. These data suggest that the current practice of comparing *Wolbachia*-infected and *Wolbachia*-uninfected insects two generations after tetracycline treatment needs to be re-evaluated.

1: [Toxicol In Vitro](#). 2004 Dec;18(6):797-803.



[Links](#)

Proliferative responses observed following vancomycin treatment in renal proximal tubule epithelial cells.

[King DW](#), [Smith MA](#).

School of Public Health, University of Texas-Houston Health Science Center, Houston, TX 77030, USA. dking@mdanderson.org

Vancomycin (VAN) is a glycopeptide antibiotic used to treat gram-positive infections. Nephrotoxicity is a common side effect observed with vancomycin therapy. However, the mechanism of vancomycin-induced nephrotoxicity has not been fully characterized. In this study we examined the effect of vancomycin on cellular proliferation in renal proximal tubule cells. A dose- and time-dependent increase in cell number and total cellular protein was observed following vancomycin exposure. Vancomycin exposure also caused an increase in BrdU incorporation followed by the accumulation of renal proximal tubule cells in G(2)/M phase of the cell cycle. These effects were inhibited by pretreatment with the mitogen-activated protein kinase inhibitor, PD098059, suggesting an association between the cell proliferative effect of VAN and the induction of the mitogen-activated protein kinase signaling pathway.

Mitochondrial function in renal proximal tubule cells was assessed using oxygen consumption and ATP concentrations. We observed an increase in oxygen consumption and ATP concentrations following short-term exposure to vancomycin. Together, our data suggest that vancomycin treatment produces alterations in mitochondrial function that coincide with a cell proliferative response in renal proximal tubule epithelial cells.