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Do antibiotics cause mitochondrial and immune cell dysfunction? A literature review

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While antibiotics are clearly important treatments for infection, antibiotic-induced modulation of the immune system can have detrimental effects on pathogen clearance and immune functionality, increasing the risk of secondary infection. These injurious consequences may be mediated, at least in part, through effects on the mitochondria, the functioning of which is already compromised by the underlying septic process. Here, we review the complex interactions between antibiotic administration, immune cell and mitochondrial dysfunction.

Introduction

Antibiotics are key components of modern-day medicine. Yet, despite their numerous benefits, they carry a significant risk of detriment and thus represent a double-edged sword. Some harmful effects are overt and/or well recognized such as rashes, hepatic and renal dysfunction, overgrowth by opportunistic organisms, induction of resistance, and effects on the microbiome.[1] However, other adverse consequences are less well appreciated, for instance effects on the efficacy of anti-cancer medications,[2] organ–organ crosstalk[1] and the Jarisch–Herxheimer reaction, in which release of pathogen constituents such as endotoxin and DNA activate proinflammatory pathways.[3] Using a rat model of caecal ligation and puncture, Peng *et al.*[4] demonstrated that ampicillin/sulbactam improved survival but at the expense of a greater inflammatory response and more renal dysfunction.

The antimicrobial actions of antibiotics also impact directly, albeit to a lesser extent, upon mammalian cells. Antibiotics can affect immune and bioenergetic function and this may potentially compromise the host's ability to both counter the infection and maintain organ functionality. Sepsis represents a dysregulated host response triggered by an infectious process that leads to organ dysfunction.[5] As bioenergetic/metabolic shutdown is considered a likely key component underlying multi-organ dysfunction in sepsis,[6] including the immune system, there may be an additional and crucial iatrogenic contribution from antibiotics.

It is thus timely to review current knowledge of how specific antibiotic classes affect immune cell processes including chemotaxis, phagocytosis, antigen presentation, cytotoxicity and antibody production, and what is known about their impact on mitochondria. We performed a detailed search of both clinical and preclinical literature using PubMed using the following criteria: (antibiotics OR antimicrobials OR aminoglycosides OR beta-lactams OR macrolides OR quinolones OR oxazolidinone) AND (immune OR mitochondri*). All non-English reviews were excluded.

A brief overview of mitochondrial dysfunction in sepsis, with particular reference to immune cells, and the link to antibiotics

The link between antibiotics and mitochondria stems from the endosymbiotic theory, which proposes that mitochondria share common ancestry with Alphaproteobacteria such as *Rickettsia*, *Anaplasma* and *Ehrlichia*.[7] Thus mitochondria may be particularly susceptible to antibiotic mechanisms acting on nucleic acid and protein synthesis and/or transport pathways. The ensuing inhibition of mitochondrial functionality and biogenesis may compromise energy substrate availability with downstream consequences on host cell functionality. Importantly, mitochondria do not simply act as intracellular powerhouses but also play other important roles to maintain homeostasis. These include biosynthesis (e.g. nucleotides, fatty acids and cholesterol), mediation of intracellular signalling, and production and sequestration of reactive oxygen species (ROS). Mitochondrial dysfunction is implicated in multiple conditions including sepsis, neurodegeneration, ageing and cancer cell metabolism.

In sepsis, mitochondrial dysfunction is strongly associated with illness severity and poor outcomes.[6] Immune dysregulation is a major feature of sepsis and this is increasingly linked to bioenergetic dysfunction.[8–11] Specific alterations are described in immune cell mitochondrial respiratory complex activity, oxygen consumption, mitochondrial membrane depolarization, apoptosis and ROS production.[12–16] Release of mitochondrial DNA and cardiolipin are also sensed by immune cells as damage-associated molecular pathogens (DAMPs) that will further amplify the systemic inflammatory response.[16,17] After the

initial immune activation, immunoparesis follows; this can persist for weeks, if not months, predisposing the patient to secondary infection. An increasing evidence base links immunoparesis, at least in part, to bioenergetic dysfunction.[10]

Aminoglycosides

Data on immunomodulatory effects of aminoglycosides are conflicting.[18–21] In some studies, therapeutic levels of gentamicin and amikacin reduced polymorphonucleocyte (PMN) chemotaxis.[22,23] On the other hand, others reported no influence on either chemotaxis or phagocytosis but an inhibitory effect on PMN bactericidal activity.[24,25] At therapeutic doses, amikacin increased superoxide production in stimulated PMNs but this was reduced at high doses (1–5 mg/L).[26] Gentamicin, netilmicin and tobramycin, however, had no impact.[26] Gentamicin and amikacin at high concentrations (>40 mg/L) also inhibited macrophage activation.[27]

Deleterious effects of aminoglycosides on mitochondrial function are also described. This mechanism has been implicated, at least in part, in the complications of ototoxicity and nephrotoxicity[28–30] as aminoglycosides act on the mitochondrial ribosomal A site, which has structural similarity to bacterial ribosomes. This may activate phosphatidylinositol phospholipase C,[31] increasing intracellular calcium[32] and ultimately leading to a proinflammatory response via activation of extracellular signal-regulated kinases (ERKs).[33] In renal and sensory hair-cell mitochondria, gentamicin inhibited oxidative phosphorylation and mitochondrial membrane potential, increasing ROS and apoptosis.[34–42] Kanamycin reduced mitochondrial membrane potential, electron transport chain activity and ATP production in epithelial cells.[43] Aminoglycosides could also chelate mitochondrial iron, forming a highly oxidant Fe(II)–aminoglycoside complex that causes oxidative damage and death in sensory hair cells.[44] Gentamicin may mobilize iron from mitochondria in a time- and dose-dependent manner via generation of hydrogen peroxide.[45] To our knowledge, no study has yet investigated aminoglycoside effects on mitochondrial function in immune cells.

β-Lactams

β-Lactams have known immunomodulatory functions in hypersensitivity[46–48] and cancer.[49,50] However, reported effects on immune cells in the context of infection have been conflicting.[51] It remains unclear whether these effects are direct or secondary to release of pathogen-associated molecular patterns (PAMPs), which are evolutionarily conserved molecules released by killed bacteria.[52–55] Variations in β-lactam-induced endotoxin release can influence cell death processes; when added to a co-culture of PMNs and *Escherichia coli*, ampicillin and cephalosporins produced a marked release of endotoxin with resulting PMN necrosis, whereas imipenem generated significantly lower levels of endotoxin and induced apoptotic cell death.[56] β-Lactams also reduce granulopoiesis and may even cause neutropenia.[57,58] Paradoxically, amoxicillin increased dendritic cell maturation and expression of activation markers such as HLA-DR, CD86 and CD80.[48]

There are also conflicting data on chemotaxis and phagocytosis. Some studies found penicillins, carbapenems and cephalosporins had no effect on PMN chemotaxis,[59–65] whereas others reported ampicillin and cephalosporins reduced chemotaxis across a broad concentration range.[63,66,67] Yet other papers found cephalosporins and carbapenems increased chemotaxis of PMNs and murine macrophages, respectively.[68–72] Similarly, for phagocytosis, some studies found no effect of cephalosporins on PMN phagocytosis at therapeutic doses,[63,66,73] some found cephalosporins and carbapenems increased human PMN and murine macrophage phagocytosis,[68,69,72,74–76] while others reported that piperacillin, cephalosporins and meropenem reduced phagocytic activity in PMNs, monocytes and rat leucocytes, respectively.[61,67,77] Cefotaxime, faropenem, amoxicillin, clavulanic acid and imipenem increased the respiratory burst and superoxide production in PMNs.[64,76,78–80] On the other hand, meropenem reduced superoxide release but had no effect on PMN killing of *Candida albicans*.[73] In a cell-free system, ampicillin and various cephalosporins could scavenge hypochlorous acid (HOCl).[81] With this wide variation in findings, no solid conclusions can be drawn.

Data on the effects of β-lactams on cytokine release are also inconsistent. In endotoxin-stimulated PBMCs, penicillin (at 5–80 mg/L) did not affect TNF-α release over a 3 day study period.[82] However, meropenem reduced TNF-α release from endotoxin-stimulated monocytes after a 4 h incubation but did not affect IL-1α, IL-6 or IL-8.[73] By contrast, a study using endotoxin-stimulated PBMCs found that piperacillin (at 100 mg/L) and co-amoxiclav (at therapeutic doses) increased release of TNF-α, IL-1β, IL-6 and IL-8 and increased expression of TLR2 mRNA, but reduced TLR4 mRNA expression.[77–83] A further study using monocytes incubated with *Staphylococcus epidermidis*, however, found no effect of β-lactams on TNF-α release.[84] In various studies on endotoxin-stimulated monocytes, penicillin and various cephalosporins inhibited IFN-γ activity,[85] IL-10 release[86] and CD14 expression.[87] Penicillins could also conjugate with human IFN-γ, TNF-α, IL-1β, IL-4 and IL-13 but selectively disrupt IFN-γ-dependent immune responses.[85,87,88]

In terms of adaptive immunity, benzylpenicillin, carbenicillin, cefazolin and cefalotin did not affect lymphocyte mitogenic responses after 3 days of incubation.[89] However, moxalactam at different concentrations reduced chemical-induced lymphocyte proliferation.[90] Long-term ceftriaxone use increased the peripheral blood CD4/CD8 cell ratio but reduced the number of CD4+CD25+ cells.[91]

There is a scarcity of literature on the effects of β-lactams on immune cell mitochondria. Studies have mostly focused upon effects on hepatic and renal mitochondria. Cephalosporin nephrotoxicity was partially explained by effects on mitochondrial anionic substrate transport (e.g. glutamate and malate).[92,93] Cefaloglycin competitively reduced carnitine-facilitated pyruvate oxidation and palmitoylcarnitine-mediated mitochondrial respiration, thereby reducing β-oxidation of fat and inhibiting activity of the tricarboxylic acid cycle.[93] In renal mitochondria, imipenem, cefaloridine and cefaloglycin reduced mitochondrial respiration while imipenem and cefaloglycin reduced oxidation of butyrate, valerate and pyruvate as early as 30–90 min.[94] Another study demonstrated that cephalosporins and penicillins could both reduce carnitine transport in a dose-dependent manner.[95] In rat liver mitochondria, co-amoxiclav increased ATPase activity and induced opening of the mitochondrial transition pore to increase release of cytochrome c, thereby triggering

activation of caspase-9 and -3 and apoptosis.[96] In neurons, piperacillin lowered mitochondrial membrane potential, reducing respiration and ATP production, but increased mitochondrial superoxide.[97]

Glycopeptides

Naturally occurring glycopeptides are involved in both innate and adaptive immune responses, including immunoglobulins, cytokines, chemokines, complement, adhesion molecules and various receptors. Glycopeptides also affect the immune system, mostly by inducing adverse reactions via mast cell degranulation,[98–103] neutropenia and decimation of gut microbiota.[104–108] An *in vivo* murine study found that vancomycin produced neutropenia and lymphocytosis in peripheral populations but increased T-helper cells and reduced T-cytotoxic cells within the spleen.[109]

In the context of infection, there is a plethora of conflicting reports. Teicoplanin at half its MIC enhanced macrophage phagocytosis of *Staphylococcus aureus*,[110] whereas teicoplanin and vancomycin (at concentrations of 10–100 mg/L) increased intracellular killing of phagocytosed organisms in both PMNs and monocytes.[111–113] At high teicoplanin concentrations (500 mg/L), adherence, chemotaxis, phagocytosis and killing of *C. albicans* by PMNs were significantly inhibited, while vancomycin (at 0.002 mg/L) reduced PMN adherence and phagocytosis.[114] Conversely, other studies found that therapeutic concentrations of teicoplanin and vancomycin did not affect chemotaxis, adherence nor phagocytosis of human PMNs.[19,106,111,115–117]

There are similar conflicting findings in terms of cytokine release. In LPS-stimulated monocytes, vancomycin increased TNF-α, IL-6 and IL-10 and expression of multiple toll-like receptors (TLRs).[113] Other studies, however, reported a decrease in TNF-α production in PBMCs following an 18 h incubation with vancomycin,[118] and a reduction in IL-8, IL-1β and TNF-α with teicoplanin.[119]

We could find no studies investigating the effects of glycopeptides on immune cell mitochondria. Vancomycin (at ∼0.033 mg/L) inhibited protein and glycoprotein synthesis in isolated rat liver mitochondria and brain mitochondria.[120] Mitochondrial dysfunction has been postulated to be the cause of glycopeptide nephrotoxicity, particularly through an increase in ROS production. In porcine proximal tubular epithelial cell lines, vancomycin (at 2 mM concentration) increased mitochondrial ROS production, reduced mitochondrial membrane potential, impaired activity of complex I of the electron transport chain, and increased apoptosis via activation of caspase-3, -7 and -9.[121–123] These effects may be mediated by peroxidation of the mitochondrial membrane protein cardiolipin[122] and could be partially or wholly mitigated by antioxidants such as vitamin E and MitoTEMPO.[121–123] Another *in vitro* study, however, found that vancomycin (at 1, 2.5 and 5 mM concentrations) increased oxygen consumption and ATP concentrations in proximal tubular epithelial cell lines.[124]

Macrolides

The immunomodulatory effects of macrolides on the lung have been recognized since the 1970s.[125] In bronchiolitis, erythromycin reduced bronchoalveolar lavage fluid accumulation of leucocytes, particularly PMNs.[126–130] This may relate to a reduction in PMN chemotactic activity mediated by decreased production of IL-8, LTB-4 and IL-1β.[126–130] In patients with atopic diseases such as asthma and rhinosinusitis, various macrolides reduced PMN and eosinophil counts in sputum, bronchoalveolar fluid and blood, cytokine levels, PMN elastase and NADPH oxidase activity.[131–142] In patients with moderate to severe COPD, azithromycin (500 mg daily for 3 days) decreased blood leucocyte and platelet counts, lowered serum acute-phase proteins and soluble E-selectin levels, and transiently decreased serum IL-8.[143] In patients with cystic fibrosis, long-term use of clarithromycin reduced sputum cytokine levels but enhanced *ex vivo* lymphocyte proliferation.[144]

Several *in vitro* studies report that macrolides reduce pro-inflammatory cytokines and chemokines (e.g. IL-1, IL-2, IL-6, IL-8 and TNF-α),[145–147] possibly via suppression of AP-1 and nuclear factor kappa B (NF-κB) pathways[148] and by modulation of TLR expression.[149] Macrolides reduce accumulation of cells at affected sites such as the lung by suppressing induction of MCP-1 and MMP-9, thereby reducing vascular hyperpermeability.[150] Conflicting studies suggest that macrolides may or may not increase chemotaxis,[151–156] cytokine release or phagocytosis of immune cells.[157–161] Similarly, macrolides either do not affect or reduce phagocytosis[162–164] and the respiratory burst.[165–167] Finally, there are multiple conflicting reports on the effect of macrolides on immune cell proliferation and survival.[168–173]

We could not identify studies on the effects of macrolides on mitochondria in immune cells and only a few studies on mitochondria from other tissues. Erythromycin inhibited protein synthesis in mitochondria isolated from BHK-21 renal cells, but not in intact mitochondria due to their inability to penetrate the mitochondrial membrane.[174] In models of cerebral and myocardial ischaemia, rapamycin was protective; the mechanism was suggested to be via attenuation of mitochondrial dysfunction through inducing autophagy via the PI3K pathway and activation of mitochondrial K_{ATP} channels.[175] Several studies report that macrolides can increase complex I and III activity, O_2 consumption and ATP synthesis.[176,177]

Quinolones

The reported immunomodulatory effects of quinolones are more consistent, particularly in hypersensitivity reactions[178–180] but also on the gut microbiota.[181,182] Quinolones (at 5–100 mg/L) reduced pro-inflammatory cytokine and chemokine release (e.g. IL-1, IL-6, IL-8, TNF-α, IFN-γ and GM-CSF),[183–190] partially by down-regulation of NF-κB, ERK and c-Jun-N-terminal kinase (JNK).[191–193] Quinolones also increased IL-8 and TNF-α mRNA[194] and IL-2 production.[195–198]

Most reports show that quinolones do not affect chemotaxis or phagocytosis at therapeutic doses; however, at high concentrations they do inhibit both phagocytosis and the respiratory burst.[199–202] Ciprofloxacin may also increase phagocytosis and intracellular killing of organisms.[203,204]

Quinolones at concentrations of >50 mg/L can inhibit mammalian cell growth by blocking cell cycle progression.[205,206] The increase in thymidine uptake has been attributed to increasing IL-2 production.[207] In lymphocytes, proliferation was inhibited by up-regulating Fas ligand, caspase-8 and -3 activity.[208,209]

In vitro ofloxacin (at 10 or 100 mg/L) did not induce apoptosis in isolated lymphocytes.[210]

Quinolones damage mitochondria by targeting mitochondrial topoisomerases.[211] These influence mitochondrial DNA (mtDNA) topology and structural availability for DNA replication. TOP2B induces mtDNA supercoiling which, on inhibition by quinolones, accumulates and prevents mtDNA replication.[211,212] Ciprofloxacin induces mtDNA loss, decreases electron transport chain complex I activity (as this is mtDNA encoded),[213] and decreases mitochondrial membrane potential.[214] This may be beneficial in colorectal and bladder cancer where quinolones have inhibited mtDNA synthesis, reduced mitochondrial membrane potential, up-regulated Bax expression and activity of caspase-3, -8 and -9, resulting in apoptosis.[215,216] In breast cancer, quinolones reduced mitochondrial membrane potential and ATP production by suppression of the PI3K/Akt/mTOR and mitogen-activated protein kinase (MAPK)/ERK signalling pathways.[217] In lung cancer, quinolones disrupted activity of complexes I and III, reduced ATP production and increased ROS production.[218]

Oxazolidinones

Prolonged use of oxazolidinones is associated with myelosuppression, metabolic acidosis with hyperlactataemia, and peripheral and ophthalmic neuropathies. Myelosuppression occurs due to reduced maturation of myeloprogenitor cells, mediated by impaired mitochondrial protein synthesis, complex IV activity and mitochondrial oxidative metabolism.[219–222] In addition to inhibition of fatty acid synthesis,[223] these bioenergetic effects have been implicated in oxazolidinone-induced lactic acidosis.[224–226] Linezolid inhibits mitochondrial translation by binding ribosomal peptidyl transferases and interfering with the binding of aminoacyl-tRNAs.[219,221] This process impairs the coordinated assembly of the electron transport chain from mitochondrial- and nuclear-encoded genes.[227]

Multiple *in vitro* studies have shown that oxazolidinones reduce cytokine production (e.g. TNF-α, IL-6, IFN-γ and IL-1ra)[228–236] and phagocytosis, but exert no effect on killing capacity.[237] Oxazolidinones also have no effect on chemotaxis, phagocytosis or the respiratory burst.[238–240]

There are limited studies of the effect of oxazolidinones on mitochondrial functionality in muscle, liver and kidney.[222,226,224,241] One clinical study did show impaired mitochondrial complex IV in PBMCs taken from patients on long-term linezolid therapy developing lactic acidosis and weakness.[242]

Conclusions

Different classes of antibiotics exert varying immunomodulatory and bioenergetic effects with more consistent findings reported for quinolones and macrolides. This variation may be partially explained by differences in study methodology, cell types studied and underlying disease. Most studies to date have used *in vitro* or animal models and clinical data are relatively scarce. In many of these studies, supratherapeutic antibiotic concentrations have been used so the relevance to clinically relevant dosing regimens remains uncertain. Nonetheless, recommendations to increase antibiotic dose and/or frequency in critically ill patients, e.g. for quinolones and piperacillin/tazobactam, allied with an impaired ability to metabolize/excrete antibiotics due to concurrent organ dysfunction, altered volumes of distribution and protein binding, and the widening use of combination therapies to cover potentially resistant organisms will enhance the risk of potential toxicity.

No hard and fast recommendations can be made at present but we hope this review reignites interest in this forgotten area. Newer technologies should be utilized as many of the studies are now rather dated, and studies should be ideally performed on patient samples taken sequentially over the duration of a course of treatment. Better recognition of any impact on immune or bioenergetic functionality will also require concurrent therapeutic drug monitoring as wide variation in blood concentrations is recognized in critically ill patients who largely receive fixed doses of antibiotic.[243,244]

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