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Antibiotics May Trigger Mitochondrial Dysfunction Inducing Psychiatric Disorders

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Clinical usage of several classes of antibiotics is associated with moderate to severe side effects due to the promotion of mitochondrial dysfunction. We contend that this may be due to perturbation of unique evolutionary relationships that link selective biochemical and molecular aspects of mitochondrial biology to conserved enzymatic processes derived from bacterial progenitors. Operationally, stereo-selective conformational matching between mitochondrial respiratory complexes, cytosolic and nuclear signaling complexes appears to support the conservation of a critically important set of chemical messengers required for existential regulation of homeostatic cellular processes. Accordingly, perturbation of normative mitochondrial function by select classes of antibiotics is certainly reflective of the high degree of evolutionary pressure designed to maintain ongoing bi-directional signaling processes between cellular compartments. These issues are of critical importance in evaluating potentially severe side effects of antibiotics on complex behavioral functions mediated by CNS neuronal groups. The CNS is extremely dependent on delivery of molecular oxygen for maintaining a required level of metabolic activity, as reflected by the high concentration of neuronal mitochondria. Thus, it is not surprising to find several distinct behavioral abnormalities conforming to established psychiatric criteria that are associated with antibiotic usage in humans. The manifestation of acute and/or chronic psychiatric conditions following antibiotic usage may provide unique insights into key etiological factors of major psychiatric syndromes that involve rundown of cellular bioenergetics via mitochondrial dysfunction. Thus, a potential window of opportunity exists for development of novel therapeutic agents targeting diminished mitochondrial function as a factor in severe behavioral disorders.

MeSH Keywords: **Antibiotics, Antineoplastic • Bacteria • Behavior • Mitochondria • Neoplastic Processes • Psychiatry**

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Background

Antibiotics represent an arsenal of chemical agents to fight against bacterial infections. The success of this therapy is evident between 1940–1970, where twenty novel classes of antibiotics were discovered [1]. These antibiotics vary, concerning their structure and mechanism of action. Today, many of these drugs are not so effective because bacteria develop resistance, revealing a major challenge for our society [2]. They have at least four ways of rendering these drugs ineffective. The first is through modification, e.g., Beta-lactamase. Over 190 bacterial proteins, including enzymes, like these exist [3]. These proteins cleave the antibiotic, so it cannot reach and interact with its target site. The second method involves changing the structure of the targeted site. This is seen in *Streptococcus pneumonia* [4] and is possible because the bacteria obtains DNA from other bacteria via recombinational events [5]. The third way resistance to antibiotics occurs is by targeting new sites, e.g., methicillin-resistant *Staphylococcus aureus* (MRSA). Instead of just relying on the original penicillin binding proteins to maintain bacterial membrane integrity, this strain of bacteria obtained DNA from an unknown bacterial donor. It has a new gene called *mecA* which codes for an *alternative protein*, called penicillin-binding protein 2a (PBP2a) [6,7]. Beta-lactam antibiotics are not capable of targeting these alternative proteins and thus, MRSA infections can be lethal. The last method involves a decreased uptake of the antibiotic, and if it does get into the cell, it is pumped out at a faster rate. These types of resistance are now prevailing in many species and strains of bacteria, in part, because of our propensity to use these agents too frequently [8]. In time, bacteria with these resistant processes will emerge as the predominant form of the bacteria and will be difficult to kill. As we respond to these bacterial survival mechanisms we also inadvertently create drugs, which have the potential to influence other processes, e.g., human behavior. This occurs because our drug discovery process fine tunes itself as resistance develops and we simultaneously develop stereo specific overlaps with naturally occurring bio-chemicals, altering their actions downstream.

Discussion

In addition to the above concerns in antibiotic development, many of the agents exhibit toxic effects on the host [9,10]. In part, we surmise, this is due to unique evolutionary relationships that link selective biochemical and molecular aspects of mitochondrial biology to primordial processes in bacterial progenitors [11,12]. The mitochondrion is an enslaved bacterium, normally producing significant amounts of ATP in comparison to glycolysis [13]. The mitochondrial rRNA in healthy cells is of critical importance in drug development. It has a similar structure and function to that found in bacteria, and it has a

higher level of mutations compared to the nuclear rRNA. This creates the scenarios where the mitochondria become prone to dysfunction [14–16]. Antibiotics that are supposed to target pathogens will also bind to mitochondria with high affinity and cause side effects [17]. An example of this is seen with minocycline. It inhibits ATP synthesis and calcium retention in the mitochondria of brain cells [18]. The commonality of these antibiotic-induced side-effects lead physicians to create a term for this phenomenon called antimicrobial-induced mania, or antibiomania, since it can occur in neural tissues due to higher metabolic rates [19–21].

We and others propose that mitochondria dysfunction may be part of the core problem for abnormal behaviors induced by antibiotic treatment, e.g., depression, autism, etc. [16,22–27]. Dysfunctional mitochondria have recently become a center of interest in explaining mental disorders [28–33]. Ciprofloxacin induces a small percent of treated patients to develop psychosis [34–36]. In this regard, gamma-aminobutyric acid (GABA) receptor binding is inhibited by ciprofloxacin. Importantly, the 18 kDa translocator protein (TSPO) localized to the outer mitochondrial membrane, previously designated as the peripheral-type benzodiazepine receptor, has been found to be temporally enhanced in the striatum and substantial nigra pars compacta in a neuro-inflammatory rat model of Parkinson's Disease [37] or diffuse nerve injury [38]. Interestingly, a reversal of repeated social stress-induced anxiety-like behavioral outcomes in rodents has been linked to the off-target peripheral effects of the widely used benzodiazepine lorazepam on TSPO activation [39]. More precisely, *in vivo* positron emission tomography (PET) scanning using the TSPO-specific ligand [¹¹C]DPA713 has demonstrated enhanced signal in select brain areas due to *in vivo* microglial activation as a result of aging and neuronal degeneration [40,41]. Once ciprofloxacin treatment stops, the behavior returns to normal. Interestingly, a subtype A of GABA receptor (GABA_A) is regulated by the level of mitochondrial reactive oxygen species (mROS) at inhibitory synapses of cerebellar stellate cells [42]. Behavioral changes are not limited just to ciprofloxacin, but also occurs with exposure to metronidazole [43], ofloxacin [44], trimethoprim-sulfamethoxazole [45], cotrimoxazole [46], procaine penicillin [47] and clarithromycin [48,49].

Additional examples of mitochondrial dysfunction, which are antibiotic-induced, are extensive and not limited to psychiatric behavior. Aminoglycosides have been used for decades, and they are still considered to be effective for treating bacterial infections [50]. However, there is a high risk of damage to sensory cells inside the inner ear when exposed to this antibiotic due to reactive oxygen species (ROS) being released from the mitochondria [15,51–55]. Another experiment demonstrated that binding of aminoglycosides to the human mitochondrial H69 hairpin is the most likely factor in causing the side effect [56]. Moreover, tetracycline [57] also works by

manipulating gene expression via the Tet-on/Tet-off system. In addition to gene manipulation, it will also induce unnecessary stress upon the mitochondria by disrupting translation [58]. Therefore, translation-targeted antibiotics must be used with extreme caution, especially in patients that have mitochondrial translation defects.

Antibiotic-induced mitochondrial damage can be pronounced on neurons, as noted earlier for behavior, especially given their metabolism, which requires 20% of the oxygen entering the body. Oligomycin disrupts mitochondria by directly targeting ATP synthase activity [59]. Nigericin and distamycin disturb mitochondrial respiration via altering ion permeability of the membrane [60]. They can also inhibit anaerobic glycolysis [61]. This phenomenon suggests that aspects of antibiotic activity and cancers may be connected via energy processing [62]. Mitochondrial dysfunction is involved in the survival of cancer stem cells [63]. Thus, antibiotics can either be beneficial or disastrous in a cancer therapy setting. Examples are erythromycin, tetracycline, and glycolcyclines, which have beneficial roles in eradicating some cancer stem cell lines while chloramphenicol, a broad spectrum antibiotic, exhibits conflicting results [64]. Abuse of chloramphenicol stimulates tumor development. This drug works through the JNK and PI3k pathways, which lead to a phosphorylated c-Jun protein binding to the promoter region of the matrix metalloproteinase-13 region (MM-13) [65]. The increased levels of the MM-13 protein lead to tumor development [66].

Vancomycin is a very potent antibiotic and is prescribed against resistant *Staphylococcus aureus* (MRSA) infections [67]. However, it causes serious side effects, such as nephrotoxicity. This toxic effect occurs via altering mitochondrial activity [68]. HMOX1, a gene that is associated with cellular oxidative damage is regulated upon vancomycin exposure. Exacerbating this event is the fact that antioxidant genes are down regulated, indicating that this potent drug could be increasing oxidative stress in nephrons [69]. Despite the danger in administering this antibiotic to kill *Staphylococcus aureus*, the benefit of this drug clearly outweighs the risk of damages that can occur. The long-term effect of this agent on mitochondria has yet to be determined.

Staphylococcus aureus and *Pseudomonas aeruginosa* [70] are deadly infections, which activate neutrophils [70,71]. *Pseudomonas aeruginosa* destroys the cell by releasing pyocyanin, a permeable pigment that targets the mitochondrial respiratory chain [72]. Activation of the sphingomyelinase acid and the release of cytochrome C from the mitochondria shortly follow [72]. *Staphylococcus*, on the other hand, secretes a toxin (PVL) that creates holes in the mitochondrial outer membrane of neutrophils and stimulates apoptosis via BAX genes [73]. Although eukaryotic cells can recognize and fight bacteria, the bacterium has an advantage. The prokaryotic

bacterial organism has evolved, over millions of years, the ability to subvert the innate immune response via mitochondrial processes [74]. This strategy, in all probability, is based on conserved common molecular knowledge [75].

Clearly, a good part of the communication is within and external to the cell's organelles, whether it is the eukaryotic mitochondria or prokaryotic ribosomes, this occurs via conformational matching, providing the reason for the mechanism of action [76]. Antibiotics can bind to the bacteria cell and cause changes in the bacterial physiological responses, and the efficacy of these antibiotics is limited or enhanced by environmental factors [77,78]. The relationship that exists between antibiotics and induced ROS have been studied through biochemical, biophysical and enzymatic assays. To further prove that ROS, e.g., H₂O₂, is being produced, the promoters for oxidative stress regulator were analyzed and showed that there was significant activation of these genes due to the treatment of norfloxacin and ampicillin [79]. These results prove extensive ROS production is stimulated by antibiotics and strongly suggest that mitochondria, in general, can be involved in the response.

Not all antibiotics create free radical damage [79]. Antibiotics broadly fall into one of two major categories. They can be either *bacteriostatic*, or they can be *bactericidal*. Bacteriostatic drugs focus on inhibition of bacterial growth. On the contrary, bactericidal agents focus on killing bacteria through ROS. The mechanism of action of these antibiotics is what makes them unique. The action of bactericidal drugs can be via interfering with the tricarboxylic acid cycle, destabilizing iron-sulfur clusters, so that iron will participate in the Fenton reaction that occurs in the mitochondria, producing harmful hydroxyl radicals [80,81]. Hydroxyl radicals from the Fenton reaction also will damage nucleotides in bacteria [82] and cause the mitochondria to undergo metabolic stress [83].

A possible alternative to advance future antibiotic development involves targeting fatty acid biosynthesis because of differences found in eukaryotic and prokaryotic cells [84–86]. Key proteins that can be inhibited in bacteria are, for example, AcpS, AccBCD, FabD, and CoaA [87]. These proteins assist in enzymatic activities in simple prokaryotes and inhibit fatty acid synthesis gene expression. Platensimycin [88], platencin [89], and phomallenic acid [88] appear to destroy Gram-positive cocci, such as *Staphylococcus aureus*, *-pneumonia*, and *Enterococcus faecium*. Relatively recent work demonstrates that some gram-positive bacteria are resistant to agents targeting fatty acid synthesis pathways [90]. Problematically, studies show that certain bacterial strains grow better when they get an exogenous source of fatty acids [91,92]. Interestingly, the large microbe population in the enteric system has not been examined for this phenomenon. These microbes may affect the activation

state of white blood cells, which can enter the brain compartment and communicate with neurons [93].

Importantly, could target mitochondrial antibiotics alter cancer growth in a positive way? Since these agents are already in use, their approval status for FDA evaluation can be either shortened or exempt. In this case, they would become a highly economical anticancer therapeutic.

Conclusions

This timely mini-review brings attention to the role that mitochondria play in establishing an environment for normal overall behavior to emerge. Pathological perturbations of this process via antibiotics, demonstrate the role this enslaved bacterium performs. A large amount of oxygen consumed,

e.g., in the brain, testifies to its moment by moment critical activity [23,24,94,95]. In the shared commonality of chemical communication with bacteria, antibiotic-induced mitochondrial interactions represent a critical factor in micro-environmental and organismic survival. Thus, an enhanced microbial presence or antibiotic level may alter the energy supply of a cell and thus enhance the occurrence of an induced behavior disorder. In this case, the potential to initiate mitochondrial dysfunction becomes clear, and this cascading type of action ends in stimulating abnormal behaviors. Clearly, antibiotics have an important place in medicine; despite the risk of damage to the host. In this scenario, one may expect alterations in behavior since they will emerge from high-level energy nerve cells. We speculate that in susceptible individuals and ones using these agents for extended periods of time and non-recommended doses, antibiotics may turn an acute stress response into one that is chronic [23].

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