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Research

Antibiotics and Antiviral Agents Can Trigger Mitochondrial Dysfunction that Leads to Psychiatric Disorders

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Antibiotics and antiviral agents represent a diverse array of chemical agents that can be used to prevent and treat acute and chronic bacterial and viral infections. Unfortunately, many of these drugs have become less effective because these pathogens have developed a variety of resistance mechanisms. This requires us to develop new and different drugs that target unique aspects of bacterial and viral invasion and replication processes. By doing so, we may inadvertently create new drugs that influence other endogenous processes, including human behavior. This is because the structures of some of these new drugs may share critical shape features with naturally-occurring endogenous biochemicals and thus may interfere with their critical functions *in vivo*.

Discussion

Many antibacterial agents are inherently toxic to the host. This may be due at least in part to the unique evolutionary relationships that link molecular mechanisms of mammalian mitochondria to primordial processes that developed originally in their bacterial progenitors. Mitochondria, which are cellular organelles that generate ATP in the mammalian host cell, are the descendants of enslaved bacteria. Mitochondrial ribosomal (r)RNA in healthy cells is a critical target for new drug development. Mitochondrial rRNA has a similar structure and function to that found in bacteria and incorporates mutations more rapidly than mammalian nuclear rRNA. Given its propensity to incorporate mutations, the mitochondrial rRNA and mitochondria themselves become prone to dysfunction. Antibiotics designed to target pathogens may also exhibit high-affinity interactions with mammalian mitochondria that result in adverse effects. Minocycline is an example of a drug that promotes ATP synthesis and calcium retention in brain cell mitochondria that may have a direct impact on one or more psychiatric disorders. Antimicrobial-induced mania, or antibiomania, is a term used to address changes in mental health status that result directly from the administration of antibiotic agents.

With this in mind, we and others have proposed that mitochondrial dysfunction may be among the core issues leading to psychiatric dysfunction induced by antibiotic treatment, including depression and autism. Antibiotic-induced dysfunctional mitochondria have recently emerged as one of the root causes of several psychiatric disorders. For example, a small percentage of patients treated with ciprofloxacin ultimately develop psychosis. Behavioral changes have also been observed in response to metronidazole, ofloxacin, procaine penicillin, and clarithromycin. These findings suggest that translation-targeting antibiotics should be used with extreme caution, especially in patients diagnosed with mitochondrial translation defects. The long-term effects of antibiotics on mitochondrial function and integrity have yet to be determined.

Although eukaryotic cells can recognize bacteria and respond with rudimentary host defense, the bacterium typically has the advantage. The prokaryotic bacterial organism

has been evolving for millions of years and is capable of subverting the innate immune response. This capacity may in part be based on conserved common molecular mechanisms and intracellular components.

Antibiotic-mediated behavioral perturbations provide us with significant insight into the nature of mitochondria and their evolutionary history as enslaved bacteria. The large amount of oxygen consumed in the brain testifies to their ongoing critical activities. Given that bacterial pathogens and host cell mitochondria share common chemical communication mechanisms, antibiotic-induced mitochondrial dysfunction may be a critical feature of both micro-environmental and organism-level survival. Microbial colonization in the brain and/or comparatively high levels of antibiotics may ultimately alter the cellular energy supply and thus the frequency of antibiotic-induced behavioral disorders. Once the potential to initiate mitochondrial dysfunction has been achieved, the resulting cascading action may generate and support ongoing abnormal behaviors. Nonetheless, and despite the risk of damage to the host, antibiotics continue to serve important roles in the treatment of infectious diseases and medicine in general. In this scenario, alterations in behavior may emerge as a result of dysfunctional high-energy nerve cells. We speculate that, in susceptible individuals, as well as those maintained on high doses for extended periods, antibiotic use may convert an acute stress response into one that is more chronic in nature.

Antiviral Drugs

Most antiviral drugs inhibit replication via their actions that target specific enzyme activities (e.g., reverse transcriptase and polymerases). Several of these enzymes are similar to those involved in mitochondrial replication. This may result in dysfunction associated with energy-producing symbionts secondary to drug exposure as is the case for antibacterial agents as described above. Furthermore, several of these antiviral agents (e.g., azidothymidine, didanosine, nevirapine, trimethoprim-sulfamethoxazole, efavirenz, and tenofovir, to name a few) may directly target mitochondrial respiration, thus reducing ATP levels. The dual targeting activity of these antiviral and antibacterial compounds (i.e., interactions with both viruses and mitochondria) may be due to complementary stereospecific matching (shape) of the shared genetic material and their long evolutionary relationship with one another.

Similar to what we have described regarding antibacterial mitochondrial targeting, we might expect that some antiviral drugs may be capable of disrupting mitochondria. Thus, their capacity to alter cognitive function might also be surmised because of the associated high energy demands. Therefore, given these insights, additional studies will be needed to understand the impact of these drugs on human mitochondria and the implications with respect to human health. Importantly, the shared influence of these drugs on bacteria, viruses, and eukaryotic host cells may be based on the fact that these molecules have complementary shapes and use a shared biochemical language that has evolved simultaneously in different organisms. In and of itself, this intriguing finding may stimulate further inquiries designed to determine if pharmacological agents designed for one disorder may be efficacious in another. Additionally, this phenomenon offers novel insights into processes that contribute to the development and potential treatments for critical mental health issues, since they also have the potential to remain hidden in the affected host organism. Indeed, it may be ascertained they may also contribute to normal behavior.

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