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Drug-Induced Mitochondrial Toxicity

Abstract

Mitochondria play a critical role in generating most of cell's energy as ATP. They are also involved in other metabolic processes such as haem synthesis e.t.c. Over the years, drugs such as certain antiviral agents, lipid lowering drugs, cholesterol lowering drugs, antibiotics, analgesics and cancer therapeutics have been implicated in inducing-mitochondrial dysfunction and thus drug-induced-mitochondrial toxicity. Recent advances suggest that mitochondria DNA, mitochondrial respiratory chain, oxidative phosphorylation, mitochondrial channels and mitochondrial permeability form the bulk of the target of drug-induce toxicity. In the case of Acetaminophen (Analgesic), reaction metabolite formation including ROS, glutathione depletion, alkylation of mitochondrial proteins, membrane permeability transition (MPS)/Pore formation in the inner mitochondrial membrane and release of intermembrane proteins lead to toxicity after an over dose. For antiretroviral drugs like NRTIs, termination of mitochondrial DNA-Synthesis terminates organelle replication and some other mitochondrial processes leading to toxicity. Based on the recognition of the different interplaying mechanism, it appears most promising therapeutically to target either the initiating event or central propagating mechanism to prevent toxicity.

Introduction

Over recent years, there has been resurgence in the interest in mitochondrial network. This network plays a central role in various cellular functions and can represent a primary or secondary target for drug actions. Mitochondrial play a critical role in generating 95% of cellular ATP requirements and participates in a variety of physiological process. It is central to the progression and regulation of apoptosis (waterhouse et al., 2002).

Mitochondrial dysfunction has been implicated in numerous disease states, including neurological and cardiovascular disorders, as well as drug-induced toxicities and even aging (Amacher, 2005; Moyle, 2005). As a result of this importance and complexity, any disturbance of mitochondrial function can have detrimental and wide-reaching implications.

Xenobiotics have long been suspected of disrupting mitochondrial function leading to injury. Recent advances in understanding of the molecular mechanisms involved have revealed that they are much more complex than originally