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Opinion

Important interactions between drugs and nutrients that influence mitochondrial metabolism

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Introduction

The pathogenesis of adverse drug reactions (ADRs) often develops as a result of medication-related interactions with the status of micronutrients, that is often related to damage of mitochondria. The withdrawal from the market of a number of drugs, such as tolcapone, cerivastatin or rosiglitazone, is directly related to the mitochondrial toxicity of these substances. In medical practice and in the context of pharmacovigilance, these interactions and disorders should receive more attention in medical and pharmaceutical practice in the future.

Mechanisms of mitochondrial toxicity of drugs

Due to their complex and vulnerable morphology (e.g. double membrane, cardiolipin) as well as the numerous elementary functions, it is not surprising that mitochondria are often the target of drug-induced damage (e.g. statins, chemotherapy). The main mechanisms of mitochondrial damage caused by drugs include:

- the inhibition of fatty acid β-oxidation,
- Disturbances of mitochondrial integrity and increase in transition pore (MPT) permeability (e.g. cardiolipin, opening of MPT),
- Lipid peroxidation and mitochondrial GSH depletion,
- the depletion of mitochondrial DNA (mtDNA)
- the uncoupling of oxidative phosphorylation (OXPHOS)
- the inhibition of enzyme complexes of the mitochondrial electron transport chain (ETK) as well as
- Depletion of mitotropic nutrients (MN) such as CoQ10, selenium or magnesium.

Mitochondrial transition pore permeability (MPTP) can lead to a loss of structural and functional integrity of mitochondrial membranes in some pathophysiological conditions. Various drugs and environmental toxins (e.g. glyphosate) induce an opening of the MPTP. This significantly alters mitochondrial structure and function, leading to lasting impairments in the cell cycle. A drop in the coenzyme Q10 level of over 25% in the cells favors the first morphological changes in the cell and promotes premature ageing.

The inhibitors of the mitochondrial (mt) respiratory chain are divided according to their site of action into inhibitors of the respiratory chain, inhibitors of oxidative phosphorylation and uncouplers (protonophores) of oxidative phosphorylation. Inhibitors of the respiratory chain, whose sites of attack are on the hydrogen and electron transporting complexes I to IV, impair substrate oxidation. Over 60 drugs are known that can inhibit respiratory chain complex I, including amobarbital, metformin and simvastatin. The nigrostriatal neurotoxin MPTP or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, which triggers the symptoms of Parkinson's disease in animal models, also inhibits complex I of the mt respiratory chain.

Clinicopathological presentation of mitochondrial damage caused by drugs (selection)

- **Liver damage:** interaction with mitochondrial glutathione pool, inhibition of fatty acid beta oxidation.

According to current research, drug-induced liver injury is responsible for more than 50% of all acute liver failures in the United States and is the most common reason why drugs are withdrawn from the market. The drug groups that often cause liver damage include analgesics (e.g. paracetamol), antiepileptic drugs (e.g. valproic acid), antibiotics (e.g. amoxicillin/clavulanic acid, tetracycline), tuberculostatic drugs (e.g. isoniazid) and cytostatic drugs (e.g. dacarbazine). Pathobiochemically, the hepatotoxicity of these substances is often associated with a disorder of mitochondrial energy metabolism in the hepatocytes

- **Muscle damage**: inhibition of enzyme complexes of mitochondrial ETK, CoQ10, MK-7 and selenoprotein depletion.

In addition to the inhibition of mevalonic acid synthesis, a number of disorders of mitochondrial function play a role in the pathogenesis of statin-induced muscle damage. These include, in particular:

- the dose-dependent depletion of the mitochondrial substrate coenzyme Q10 (ubiquinone/ubiquinol),
- the direct inhibition of enzyme complexes of the mitochondrial respiratory chai
- the impairment of transmitochondrial electron transfer and oxidative phosphorylation
- the reduction of heme A synthesis and/oras well
- the depletion of mtDNA.

Statins not only inhibit the synthesis of cholesterol, but also that of other biomolecules made up of isopentenyl pyrophosphate (isopentenyl-PP), such as the body's own ubiquinone, menaquinone-7 and selenoproteins.

A meta-analysis by the American Heart Association from 2018 describes a significant reduction in statin-related muscle complaints through daily supplementation of 100 to 600 mg of Coenzyme Q10. Coenzyme Q10 also counteracts driving factors of arteriosclerosis such as inflammation and oxidative stress in the vessels.

- **Oral antidiabetic drugs: Metformin**

The biguanides buformin, phenformin and metformin were introduced into diabetes therapy shortly after the sulfonyl urea derivatives. The complex

mechanism of action of biguanides and the interaction with the mitochondrial respiratory chain is associated with serious side effects. Gastrointestinal symptoms such as abdominal pain, diarrhea, vomiting and nausea often occur when taking it. The occurrence of cardiovascular complications and several cases of life-threatening lactic acidosis (0.25 to 1 case per 1000 patient-years) led to the measure that Buformin and Phenformin have being withdrawn from the market for example in Germany in 1978. Regular use of metformin can disrupt the dietary availability micronutrients such as magnesium and vitamin B12. A lack of magnesium increases insulin resistance by disrupting the insulin tyrosine kinase receptor; a deficiency of vitamin B12 and/or folic acid can lead to a disorder in methyl group metabolism, which also affects mitochondrial integrity.

Conclusion:

Given the ever-increasing number of drugs on the market and the frequency with which they are used, greater attention must be paid by physicians and pharmacists in daily medical and pharmaceutical practice focused in particular on the adverse effects of drug therapy on the micronutrient status in order to minimize the potential risk to the health of patients. Especially high-risk patients (e.g. the elderly, patients on polypharmacotherapy) and individuals under medication with drugs such as proton pump inhibitors, diuretics and/or statins should be monitored for drug induced micronutrient deficiencies and disruption of mitochondrial integrity.