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CLINICAL PHARMACOLOGY OF METABOLISM-ACTIVATING AND CORRECTING DRUGS

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Abstract: This article explores the clinical pharmacology of metabolism-activating and correcting drugs, a heterogeneous group of agents designed to restore or optimize metabolic processes in pathological conditions. It provides an overview of drug classes, mechanisms of action, pharmacokinetics, clinical applications, and safety considerations. Special attention is given to the role of these agents in mitochondrial dysfunction, ischemia, metabolic syndrome, and neurodegeneration. The article highlights current evidence and emerging therapeutic strategies in both acute and chronic disease management.

Keywords: Metabolic correction, mitochondrial function, metabolic syndrome, actoprotectors.

INTRODUCTION

Metabolic imbalance lies at the core of many acute and chronic pathophysiological states, including ischemic tissue injury, metabolic syndrome, neurodegenerative diseases, and chronic fatigue syndrome. In these conditions, impaired energy production, disrupted redox balance, and altered substrate utilization contribute to organ dysfunction and disease progression. Metabolism-activating and correcting drugs — often referred to as metabolic modulators — are pharmacological agents that intervene in biochemical pathways to restore or enhance cellular metabolism. These drugs do not act as classic symptom-relieving

agents, but rather as bioenergetic regulators, influencing intracellular homeostasis. The purpose of this article is to review the pharmacodynamic and pharmacokinetic principles of these agents, outline their clinical applications, and assess their therapeutic potential in evidence-based medicine.

MATERIALS AND METHODS

Metabolism-activating drugs encompass a broad pharmacological spectrum, including coenzymes, amino acid derivatives, carnitine analogues, antioxidants, nucleotide precursors, and intermediary metabolism enhancers. A unifying feature of these compounds is their ability to modulate energy production, oxidative phosphorylation, or intermediary substrate availability, particularly in mitochondria-dense tissues such as the brain, heart, liver, and skeletal muscle.

1. Coenzyme Q10 (Ubiquinone): CoQ10 is a lipophilic molecule that plays a vital role in the electron transport chain within mitochondria, facilitating ATP synthesis through oxidative phosphorylation. Its antioxidant properties further support cellular defense against reactive oxygen species (ROS). CoQ10 supplementation is indicated in primary mitochondrial disorders, statin-induced myopathy, heart failure with preserved ejection fraction (HFpEF), and some neurodegenerative diseases such as Parkinson’s disease. The compound exhibits variable oral bioavailability due to poor solubility, which is enhanced in nanoemulsion or liposomal formulations. Peak plasma concentration occurs within 6–8 hours, with a half-life ranging from 33 to 36 hours.

2. L-Carnitine and Derivatives: L-Carnitine is an essential carrier molecule that facilitates the transport of long-chain fatty acids into mitochondria for β-oxidation. Its use is well-documented in inherited carnitine deficiency, dialysis-related carnitine loss, and hepatic encephalopathy. Acetyl-L-carnitine (ALC) demonstrates neuroprotective and cognitive-enhancing effects, possibly through modulation of acetylcholine metabolism and mitochondrial energetics. Clinical studies have shown benefit in age-related cognitive

decline and diabetic neuropathy. Carnitine is generally well-tolerated; however, long-term administration has been associated with trimethylamine-N-oxide (TMAO) production, a potential proatherogenic metabolite [1].

RESULTS AND DISCUSSION

Mildronate (Meldonium): Originally developed for ischemic heart disease, mildronate inhibits carnitine biosynthesis and shifts myocardial energy substrate preference from fatty acid oxidation to glucose oxidation, which is more oxygen-efficient. This metabolic remodeling improves ATP production under hypoxic conditions and may reduce ischemic injury. It has been used in angina pectoris, chronic heart failure, and neurocirculatory asthenia, though some of its indications remain controversial due to limited large-scale randomized trials. Pharmacokinetically, mildronate has high oral bioavailability and is excreted primarily unchanged in the urine.

Inosine and Riboxin: Inosine is a purine nucleoside with proposed ATP-enhancing and myocardial protective effects. It is believed to stimulate oxidative metabolism and RNA synthesis, although its exact mechanisms remain incompletely understood. Riboxin (inosine monophosphate) has been used in cardiology and hepatology in Eastern Europe, but its clinical efficacy has not been widely validated by Western standards. Its use has declined due to inconsistent outcomes and insufficient evidence of benefit.

Alpha-lipoic acid (ALA): ALA functions as a coenzyme in mitochondrial oxidative decarboxylation reactions and acts as a potent antioxidant capable of regenerating other antioxidants such as vitamins C and E. It is widely used in the treatment of diabetic polyneuropathy, metabolic syndrome, and non-alcoholic fatty liver disease (NAFLD). ALA improves insulin sensitivity, reduces lipid peroxidation, and supports endothelial function. Oral bioavailability is moderate and food intake significantly reduces absorption, requiring administration on an empty stomach [2].

Actoprotectors: A unique subclass of metabolism-correcting agents, actoprotectors enhance physical and mental work capacity under stress and hypoxic conditions without increasing oxygen consumption. Examples include bemitil (Metaprot) and bromantane. These drugs modulate mitochondrial enzymes and gene expression related to metabolic adaptation, and are being studied for potential application in chronic fatigue syndrome and performance enhancement. While their exact pharmacological profiles are still being elucidated, preliminary studies indicate central nervous system effects and upregulation of stress tolerance pathways.

Emerging Therapies: Recent developments in metabolic pharmacology include pyruvate-based therapies, NAD+ precursors (e.g., nicotinamide riboside), and AMP-activated protein kinase (AMPK) modulators. These agents target core elements of energy metabolism, redox balance, and cellular senescence, and are under investigation for conditions ranging from Alzheimer's disease to cancer cachexia. Their introduction represents a shift toward precision metabolic therapy, targeting specific enzyme systems or genetic deficiencies underlying metabolic dysregulation.

Safety and tolerability vary widely among this drug group. Although most agents exhibit favorable profiles due to endogenous nature or nutritional origin, high-dose or long-term use may result in unintended metabolic shifts, pro-oxidant effects, or interference with endogenous regulation. As such, rational use demands a clear indication, therapeutic goal, and monitoring strategy [3].

Beyond classical metabolic disorders, metabolism-activating and correcting drugs are increasingly recognized for their adjunctive roles in high-stress clinical environments such as intensive care units (ICUs), oncology, and rehabilitation medicine. In critically ill patients, systemic inflammation, oxidative stress, and mitochondrial dysfunction converge to produce a state known as "metabolic shutdown" or "cytopathic hypoxia," wherein cells are unable to utilize oxygen efficiently despite adequate perfusion. Under such

circumstances, agents that support mitochondrial ATP production, such as L-carnitine, nicotinamide adenine dinucleotide (NAD^+) precursors, and coenzyme Q10, are being explored for their potential to restore bioenergetic balance, reduce organ failure, and shorten recovery time. Preliminary studies suggest that these agents may improve lactate clearance, modulate immune responses, and preserve endothelial integrity — although large-scale randomized trials are still lacking [4].

In oncology, metabolic modulators are being considered not as primary anticancer agents but as cytoprotective adjuvants. Chemotherapy-induced mitochondrial damage and oxidative stress can result in profound fatigue, neuropathy, and muscle wasting — collectively referred to as cancer-related fatigue and cachexia. Drugs such as alpha-lipoic acid, acetyl-L-carnitine, and antioxidant formulations may mitigate these effects by improving mitochondrial resilience and reducing neurotoxicity. However, their use remains controversial, as some antioxidants might interfere with the pro-oxidant mechanisms of chemotherapeutic agents. Thus, careful timing, dose titration, and oncologist oversight are essential when incorporating these agents into supportive cancer care.

Rehabilitation medicine also presents fertile ground for metabolism-correcting pharmacotherapy. Patients recovering from stroke, spinal cord injury, or prolonged immobilization often display impaired mitochondrial function and anabolic resistance. Supplementation with mitochondrial cofactors such as ALC, riboflavin (vitamin B2), and magnesium may enhance neuromuscular recovery, cognitive restoration, and overall functional rehabilitation. Additionally, emerging data suggest that actoprotectors and adaptogens can increase tolerance to physical rehabilitation stress, reduce perceived exertion, and accelerate return to baseline function in elderly or deconditioned individuals.

A growing and often overlooked indication for metabolism-targeting agents is the management of chronic fatigue syndrome (CFS) and fibromyalgia — complex, multifactorial disorders characterized by impaired energy metabolism, mitochondrial

anomalies, and systemic low-grade inflammation [5]. While no cure exists, several studies have examined the benefit of L-carnitine, CoQ10, and NAD^+ precursors in improving fatigue levels, sleep quality, and exercise tolerance. The use of combination regimens that target multiple metabolic pathways simultaneously is being explored, with early trials indicating synergistic effects.

CONCLUSION

Metabolism-activating and correcting drugs constitute a valuable but complex category of therapeutic agents with growing relevance in both acute and chronic medical care. Their mechanisms span mitochondrial function enhancement, oxidative stress mitigation, substrate optimization, and cellular adaptation under metabolic stress. While some agents — such as L-carnitine, CoQ10, and alpha-lipoic acid — are supported by robust clinical data, others remain under active investigation. The future of this pharmacological domain lies in personalized approaches, combining biochemical diagnostics, pharmacogenomics, and clinical endpoints to optimize metabolic interventions. Rational prescribing, grounded in evidence and individualized assessment, will be essential to harness the full therapeutic potential of these agents.

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