Abstract

Mitochondrial dysfunction is a key factor in the pathophysiology of psychiatric disorders and may serve as a modulator and predictor of therapeutic response. Understanding the mitochondrial effects of antipsychotics and antidepressants is crucial to relate their therapeutic and adverse effects to mitochondrial functions. In this study, we used mitochondria isolated from pig brain as an *in vitro* model and evaluated the effects of selected antidepressants and antipsychotics on mitochondrial parameters. Selected antipsychotics (aripiprazole, brexpiprazole, cariprazine, chlorpromazine, clozapine, haloperidol, levomepromazine, loxapine, lurasidone, olanzapine, quetiapine, risperidone, ziprasidone, and zotepine) and antidepressants (agomelatine, bupropion, escitalopram, fluoxetine, paroxetine, sertraline, and vortioxetine) were tested. The activities of electron transport chain complexes I, II+III, and IV, citrate synthase, malate dehydrogenase, and monoamine oxidases, as well as mitochondrial respiration, ATP production, and hydrogen peroxide formation were measured. The results showed that the majority of tested antipsychotics and all tested antidepressants (except bupropion for complex II+III) significantly inhibited the activity of the electron transport chain complexes. Full inhibitors of complex I-linked respiration were antipsychotics aripiprazole, cariprazine, haloperidol, quetiapine, risperidone, and zotepine; among antidepressants, only vortioxetine. Full inhibitors of complex II-linked respiration were antipsychotics clozapine, lurasidone, quetiapine, and risperidone. Significant changes in ATP production were observed with antipsychotics brexpiprazole, cariprazine, loxapine, lurasidone, and all tested antidepressants. All tested antipsychotics and antidepressants agomelatine, and vortioxetine significantly affected hydrogen peroxide formation. Escitalopram, fluvoxamine, and sertraline fully inhibited monoamine oxidase A activity, while escitalopram and paroxetine fully inhibited monoamine oxidase B activity. The results of this research suggest that long-term inhibition of oxidative phosphorylation may affect ATP deficiency in neurons and contribute to neuronal damage at high concentrations of psychotropic drugs. The mitochondrial effects of the tested psychotropic drugs are likely related to their adverse effects, and the activation of compensatory mitochondrial mechanisms and monoamine oxidase inhibition may play a role in the therapeutic effects of antipsychotics and antidepressants.

Key words: Antidepressants, Antipsychotics, ATP, Electron Transport Chain, Mitochondrial Respiration, Monoamine Oxidase, Oxidative Phosphorylation, Reactive Oxygen Species