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Kynurenines and the respiratory parameters on rat heart mitochondria

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Abstract

It has been shown recently that the L-kynurenine metabolite kynurenic acid lowers the efficacy of mitochondria ATP synthesis by significantly increasing state IV, and reducing respiratory control index and ADP/oxygen ratio of glutamate/malate-consuming heart mitochondria. In the present study we investigated the effect of L-tryptophan (1.25 $\hat{1}/4$ M to 5 mM) and other metabolites of L-kynurenine as 3-hydroxykynurenine (1.25 $\hat{1}/4$ M to 2.5 mM), anthranilic acid (1.25 $\hat{1}/4$ M to 5 mM) and 3-hydroxyanthranilic acid (1.25 $\hat{1}/4$ M to 5 mM) on the heart mitochondria function. Mitochondria were incubated with saturating concentrations of respiratory substrates glutamate/malate (5 mM), succinate (10 mM) or NADH (1 mM) in the presence or absence of L-tryptophan metabolites. Among tested substances, 3-hydroxykynurenine, 3-hydroxyanthranilic acid and anthranilic acid but not tryptophan affected the respiratory parameters dose-dependently, however at a high concentration, of a micro molar range. 3-

Hydroxykynurenine and 3-hydroxyanthranilic acid lowered respiratory control index and ADP/oxygen ratio in the presence of glutamate/malate and succinate but not with NADH. While, anthranilic acid reduced state III oxygen consumption rate and lowered the respiratory control index only of glutamate/malate-consuming heart mitochondria. Co-application of anthranilic acid and kynurenic acid (125 or 625 μ M each) to glutamate/malate-consuming heart mitochondria caused a non-additive deterioration of the respiratory parameters determined predominantly by kynurenic acid. Accumulated data indicate that within L-tryptophan metabolites kynurenic acid is the most effective, followed by anthranilic acid, 3-hydroxykynurenine, 3-hydroxyanthranilic acid to influence the respiratory parameters of heart mitochondria. Present data allow to speculate that changes of kynurenic acid and/or anthranilic acid formation in heart tissue mitochondria due to fluctuation of L-kynurenine metabolism may be of functional importance for cardiovascular processes. On the other hand, beside the effect of 3-hydroxyanthranilic acid and 3-hydroxykynurenine on respiratory parameters, their oxidative reactivity may contribute to impairment of mitochondria function, too.



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Keywords

Kynurenines; Kynurenic acid; Mitochondria respiratory parameters; Cell function; Excitatory amino acid receptors; Endogenous uncoupler; ATP; ADP

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