ANTIDEPRESSANTS AND CEREBRAL ENERGY METABOLISM: NEW FUNCTIONAL PROTEOMIC INSIGHTS

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Introduction: Depressive disorders are heterogeneous diseases and their complexity has led to many etiopathological hypotheses. This heterogeneity may account for the time lag between pharmacological (within hours) and therapeutic effects (within 2-4weeks) after antidepressants (ADs) administration and for the only 50-60% of responder treated patients. Alterations in brain bioenergetics were hypothesized to participate in Depression pathogenesis. Neuroimaging *in vivo* studies on patients showed abnormalities in brain energy metabolism, although not clearly demonstrated in experimental studies: some authors suggest ADs as inhibitors of mitochondrial metabolism, while others the opposite. We think that these conflicting results are due to macro-heterogeneity of cerebral areas and micro-heterogeneity of brain mitochondria, the latter not considered before in experiments evaluating ADs action.

Materials and methods: The effects of tricyclic Desipramine (15mg/kg, i.p.) and selective serotonin reuptake inhibitor Fluoxetine (10 mg/kg, i.p.) were studied on mitochondrial metabolism of frontal cerebral cortex and hippocampus of male Sprague-Dawley rats. Pharmacological treatment was started from 7th week of age and continued for 21days. Because of brain mitochondria micro-heterogeneity, the following populations were purified: non-synaptic mitochondria (FM) of neuronal perikaryon located *in vivo* in post-synaptic compartment, and intra-synaptic light (LM) and heavy (HM) mitochondria of pre-synaptic compartment. The catalytic activities of regulatory enzymes of energy-yielding metabolic pathways have been assayed: citrate synthase, succinate dehydrogenase, malate dehydrogenase for Krebs' cycle; NADH- cytochrome c reductase, cytochrome oxidase for Electron Transport Chain; glutamate dehydrogenase, glutamate-oxaloacetate- and glutamate-pyruvate-transaminase for glutamate and related amino acids metabolism.

Results: In frontal cerebral cortex, (a) both Desipramine and Fluoxetine increased cytochrome oxidase activity of FM and HM, and (b) decreased malate dehydrogenase, succinate dehydrogenase and glutamate-pyruvate-transaminase activities in LM; (c) Fluoxetine exerted a selective effect on enzymes related to glutamate metabolism, increasing the activity of glutamate dehydrogenase in FM. As regards the effects on hippocampal energy metabolism, (a) in FM, both drugs enhanced cytochrome oxidase and glutamate dehydrogenase activities, (b) in LM the overall bioenergetics was unaffected and, (c) in HM only Desipramine increased malate dehydrogenase and decreased the activities of Electron Transport Chain Complexes.

Discussion and conclusions: Desipramine and Fluoxetine showed a common pattern of modifications for enzyme activities respect to subcellular compartments: (a) in FM, energy metabolism was stimulated; (b) in LM, energy production pathways were inhibited in frontal cerebral cortex and unchanged in hippocampus; (c) in HM, the drugs induced heterogeneous modifications, because of the previously demonstrated biochemical-metabolic characteristics of these likely damaged mitochondria. These results provide new insights about ADs pharmacodynamics: upon ADs administration, noradrenaline and serotonin increase in the synaptic cleft due to inhibition of reuptake systems, consequently (a) intra-cellular signalling pathways are activated in post-synaptic compartment, increasing energy production requirements, while (b) neurotransmitter concentrations decrease in pre-synaptic compartment and inhibitory feedback signalling pathways are triggered in synaptoplasm. These results encourage further studies evaluating the same enzymatic systems in experimental animal models of Depression, in accordance with evidence that mitochondrial energy metabolism may be potential target for ADs therapeutic strategies.

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