Mitochondrial angiotensin receptors in dopaminergic neurons. Role in cell protection and aging-related vulnerability to neurodegeneration

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Résumé en anglais	The renin-angiotensin system (RAS) was initially considered as a circulating humoral system controlling blood pressure, being kidney the key control organ. In addition to the 'classical' humoral RAS, a second level in RAS, local or tissular RAS, has been identified in a variety of tissues, in which local RAS play a key role in degenerative and aging-related diseases. The local brain RAS plays a major role in brain function and neurodegeneration. It is normally assumed that the effects are mediated by the cell-surface-specific G-protein-coupled angiotensin type 1 and 2 receptors (AT1 and AT2). A combination of in vivo (rats, wild-type mice and knockout mice) and in vitro (primary mesencephalic cultures, dopaminergic neuron cell line cultures) experimental approaches (confocal microscopy, electron microscopy, laser capture microdissection, transfection of fluorescent-tagged receptors, treatments with fluorescent angiotensin, western blot, polymerase chain reaction, HPLC, mitochondrial respirometry and other functional assays) were used in the present study. We report the discovery of AT1 and AT2 receptors in brain mitochondria, particularly mitochondria of dopaminergic neurons. Activation of AT1 receptors in mitochondria regulates superoxide production, via Nox4, and increases respiration. Mitochondrial AT2 receptors are much more abundant and increase after treatment of cells with oxidative stress inducers, and produce, via nitric oxide, a decrease in mitochondrial respiration. Mitochondria from the nigral region of aged rats displayed altered expression of AT1 and AT2 receptors. AT2-mediated regulation of mitochondrial respiration represents an unrecognized primary line of defence against oxidative stress, which may be particularly important in neurons with increased levels of oxidative stress such as dopaminergic neurons. Altered expression of AT1 and AT2 receptors with aging may induce mitochondrial dysfunction, the main risk factor for neurodegeneration
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