Summary

Estrogens belong to the family of steroid hormones and regulate a variety of biological processes such as metabolism, cell growth and reproduction, via binding to estrogen receptors (alpha and beta isoforms, ERα and ERβ), which are localized in various subcellular organelles such as nucleus, cytoplasm, membranes and mitochondria. ERs control the function and the physiology of many systems such as the nervous, cardiovascular and skeletal system, via genomic and non-genomic mechanisms of action and are involved in the regulation of many pathological conditions such as breast cancer and neurodegenerative diseases. ERs can interfere with a variety of endocrine disruptors, affecting human physiology. Thus, it is very important to elucidate and characterize the biochemical and molecular mechanisms of the interaction between ERs and endocrine disruptors. In this context, the role of the mitochondrial ERβ and the potential estrogenic action of aluminum salts, in particular aluminum chlorochloride in breast cancer cells and neuroblastoma cells were investigated, in this study. The results of our studies reveal aluminum estrogenicity, which is mediated mainly by ERα. In the presence of aluminum the protein levels as well as mRNA levels of ERα are increased in human ERα-positive human breast cancer cells. This effect is accompanied by increase in the mRNA levels of several estrogen target genes and elimination of this action in the presence of the estrogen antagonist ICI182 780(ICI). In addition these actions are not observed in ERα-negative breast cancer cells. Our experimental observations also suggest that the mechanism by which aluminum affects the protein levels of ERα, is among others, through its possible involvement in estrogen receptor's degradation mechanism, affecting ERα phosphorylation at the residue Ser118. Increase in ERα protein levels, in the presence of aluminum ions, may contribute to development and progress of breast cancer. Also, through the ERα-dependent regulation of ERβ expression and action, aluminum may affects the ERβ protective effects. In agreement with this hypothesis, in the presence of aluminum ions, both protein and mRNA levels of ERβ are reduced in neuroblastoma cells. This reduction is accompanied by activation of apoptosis, and possibly it is associated with the the observed neurodegeneration, upon aluminum salts accumulation. Aluminum salts also induce perinuclear and possibly mitochondrial localization of estrogen receptors, affecting mitochondrial functions. Our studies on the characterization of the role of mitochondrial ERβ in neuroblastoma cells reveal the ability of mitochondrial targeted ERβ (mtERβ) to induce mitochondrial transcription activation via the interaction of mtERβ with both the estrogen responsive elements (EREs) and cAMP responsive elements (CREs), located in the D-loop of mitochondrial DNA. Also, the characterization of heat shock proteins and components of the complex V that as mtERβ interacting proteins contribute to the elucidation of the mechanism(s) of entrance and action of the mitochondrial estrogen receptor.

Keywords: estrogen receptors, aluminum, mitochondria, cancer, nervous system