Biological activities of mesoionic compounds: mitochondrial dysfunction and cell toxicity

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Mesoionic compounds possess potential therapeutic applications related to their structural and physicochemical characteristics. They are relatively small molecules of an aromatic nature and a high dipole moment, which favour strong electrostatic interactions of these compounds with macromolecules. Although the molecules are internally charged, they are neutral overall, and therefore can cross biological membranes in vivo. We have investigated the molecular mechanisms involved in antitumor effects of two classes of mesoionic compounds, the sydnones and 1,3,4-thiadiazolium. Sydnones were represented by SYD-1 (3-[4-chloro-3-nitro-phenyl]-1,2,3-oxadiazolium-5-olate) and 1,3,4-thiadiazolium by 4-phenyl-5-(2'-Y, 4'-X or 4-X-cinnamoyl) - 1,3,4-thiadiazolium-2-phenylamine chlorides differing from each other only in the cinnamoyl ring substituent: MI-J (X=OH); MI-F (X=F); MI-2,4diF (X=Y=F). Because mitochondria are involved in the mechanisms of cell death, we have investigated the effects of these compounds on functions-linked to energy provision in these organelles. We have shown a significant decreasing of oxidative phosphorylation efficiency, probably related with their antitumor activity. These effects seem not to be associated with the induction of oxidative stress since the mesoionics reduced processes associated with this condition, specifically the lipoperoxidation induced by iron and peroxyl radicals, the oxidation of pyridine nucleotides and the formation/open of mitochondrial pore transition, besides their ability of scavenging superoxide anion. We also showed that 1,3,4-thiadiazolium derivatives were selectively cytotoxic to hepatoma cells (HepG2), promoting cell death with apoptosis characteristics, while not affecting the viability of non-tumoral hepatocytes. Furthermore, the 1,3,4-thiadiazolium derivatives were only slightly, or not at all, transported by resistant cells overexpressing ABCG2 and MRP1, while they even produced inhibition of these transporters. Our results encourage new investigations about their mechanisms of action for future clinical tests with these compounds.

Keywords: Mesoionic compounds, Mitochondrial bioenergetics, Cell toxicity.