Induction of mitochondrial permeability transition by mitochondria-induced nitric oxide release from two new ruthenium nitrosyl complexes

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Nitric oxide (NO) is involved in several pathologies and physiological functions, including cell death by apoptosis, which may involve the mitochondrial permeability transition (MPT) process; cancer cells, in turn, are more resistant to undergo apoptosis. In this context, we analized comparativelly the release of NO by two new ruthenium nitrosyl complexes, the *cis*-$[Ru(dcbpy)_2(Cl)(NO)]$ and $[Ru(bpy)_2(4\text{-pic})NO]$ $(PF6)_3$ (PicNO), via mitochondrial reducing power, as well as their effects on succinate-energized isolated rat liver mitochondria itself. Conversely to our previous study with the *trans*-$[Ru(NO)(NH3)_4(py)](PF_6)_3$ (pyNO) complex (Nitric Oxide: 20, 24-30, 2009), these complexes did not significantly inhibit mitochondrial respiration or dissipate mitochondrial membrane potential, while in the presence of 10 µM Ca^{2+} they induced, between 10-100 µM, the MPT process as characterized by mitochondrial swelling inhibited by Cyclosporin A and prevented by EGTA; stimulation of mitochondrial respiration was observed instead. In addition, they stimulated reactive oxygen species generation monitored with dichlorofluorescein-diacetate. These results characterize these compounds as MPT inducers independently of any significant inhibitory affect on the respiratory chain, and therefore with a potential to induce cancer cell death by apoptosis.

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