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Abstract Title:	Heroin-induced degeneration of cortical neurons involves mitochondria-dependent apoptosis.
Authors:	**Cunha Oliveira, T.*** [1] ; Rego, A. C. [1] ; Macedo, T. ; Oliveira, C. R. [1] [1]Ctr. for Neuroscience and Cell Biology, Coimbra, Portugal
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The repeated use of drugs of abuse, namely cocaine and amphetamines, has been associated with altered neuronal function, which may involve neuronal loss. However, less information is available concerning the neurotoxicity of heroin, known to evoke neuronal dysfunction in several areas of the central nervous system. Thus, in this work we analyzed the apoptotic pathways involved in heroin neurotoxicity in rat cortical neurons. Heroin decreased by 10% the capacity to reduce a tetrazolium salt and affected the neuritic network, without affecting the integrity of the plasma membrane. Heroin also increased chromatin condensation and poly-ADP-ribose-polymerase cleavage. We further analyzed the apoptotic pathways leading to this nuclear phenotype. Western blot analysis showed that cytochrome c was increased in the cytosol of cells treated with heroin. In these cells, mitochondrial membrane potential was decreased when compared to the control, total Bcl-2 levels were decreased, and Bax levels were unchanged. Early activation of caspases -2 and -9, involved in the mitochondrial apoptotic pathway, was observed. The activity of effector caspases -3 and -6 was also enhanced, whereas caspase-8, involved in the apoptotic extrinsic pathway, was only slightly activated at later time points. Interestingly, the apoptotic morphology was completely prevented by the pan-caspase inhibitor z-VAD-fmk, indicating an important role for caspases in the neurodegeneration induced by heroin. We further determined that ionotropic glutamate receptors and opioid receptors are not involved in heroin-induced neurodegeneration. In addition, our results suggest that reactive oxygen species do not trigger caspases activation. Altogether, these data suggest an important role for mitochondria in mediating the neurotoxic effects of heroin.

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