

Pathological apoptosis by xanthurenic acid, a tryptophan metabolite:
activation of cell caspases but not cytoskeleton breakdown

ABSTRACT

These results indicate that xanthurenic acid is a previously not recognized endogenous cell death factor. Its accumulation in cells may lead to accelerated caspase activation related to aging and disease development.

INTRODUCTION

Background Xanthurenic acid is formed upon tryptophan degradation by indoleamine-2,3 dioxygenase (IDO). The end products of this degradation pathway are, alternatively, nicotinate and xanthurenic acid. IDO activity is stimulated by superoxide radicals, liposaccharides and interferon- γ . Kynurenine aminotransferase (KAT), the enzyme directly responsible for xanthurenic acid formation from 3-hydroxykynurenine, is found in the cytoplasm and mitochondria, and is highly expressed in the retina. Xanthurenic acid is present in blood and urine at concentrations of 0.7 and 5-10 μ M, respectively. A several - fold increase is observed in vitamin B6 deficiency and some diseases such as tuberculosis. Xanthurenic acid's presence in the blood is linked to malaria development, and in the lenses to senile cataract formation. Xanthurenic acid binds covalently to proteins, leads to their unfolding, and to cell death. Here, we report that xanthurenic acid induces cell death associated with caspase-3, -8, and -9 activation, nuclear DNA cleavage, and cytochrome C release. However, cell death is not associated with cytoskeleton breakdown, usually observed because of actin depolymerization by caspase-3-cleaved gelsolin.

CONCLUSION

Conclusions Our results indicate that an accumulation of the tryptophan metabolite, xanthurenic acid, leads to cleavage of caspases substrates and apoptosis. Unexpectedly, xanthurenic acid-induced apoptosis is associated with an abnormal function of cleaved gelsolin. The results indicate that xanthurenic acid is an important factor involved in aging and disease development.