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REVIEW

Apoptosis in the *in Vivo* Mammalian Forebrain

Krikor Dikranian,* Masahiko J. Ishimaru,† Tatyana Tenkova,* Joann Labruyere,* Y. Q. Qin,* Chrysanthy Ikonomidou,‡ and John W. Olney*

**Department of Psychiatry, Washington University School of Medicine, 4940 Children's Place, St. Louis, Missouri 63110; †Medical Research Institute, Tokyo Medical and Dental University, 2-3-10 Kanda-surugadai, Chiyodku, Tokyo, Japan; and ‡Department of Pediatric Neurology, Charité, Virchow Clinics, Humboldt University, Augustenburger Platz 1, 13353 Berlin, Germany*

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Apoptosis is a word originally introduced by Kerr, Wyllie, and colleagues for a cell death process they defined in terms of its ultrastructural appearance in nonneuronal cells from various tissues. There are very few studies providing detailed ultrastructural criteria for recognizing neuronal apoptosis in the *in vivo* mammalian brain. In the absence of such criteria, the Kerr/Wyllie description pertaining to nonneuronal cells has served as a reference standard. However, contemporary neurobiologists typically rely on cell culture models for studying neuronal apoptosis, and these models are rarely validated ultrastructurally; rather they are assumed to be appropriate models based on unvalidated biochemical tests for apoptosis. Relying on evidence generated in such cell culture models or on nonspecific cytochemical tests applied to brain tissue, many authors have recently suggested that an apoptotic mechanism may mediate neuronal death in a wide variety of human neurodegenerative diseases. Whether the cell death process in neurodegenerative diseases meets ultrastructural criteria for apoptosis has been given very little consideration. Recently, several methods have been described for triggering extensive apoptotic neurodegeneration in the developing *in vivo* mammalian brain. These methods include head trauma or treatment with several types of drugs (NMDA antagonists, $GABA_A$ agonists, or ethanol). We have performed an ultrastructural analysis of the neuronal cell death process triggered in the cerebral cortex and thalamus by these several methods and compared it with physiological cell death (PCD), a prototypic example of neuronal apoptosis that occurs naturally in the developing brain. Our findings, which are reviewed herein, demonstrate that the types and sequence of changes induced by each of the above methods are identical to those that characterize PCD. This confirms that each of these methods produces *bona fide in vivo* apoptotic neurodegeneration, and it signifies that our description of this neuronal apoptotic process, which differs in some respects from the Kerr/Wyllie description of nonneuronal apoptosis, can serve as a useful reference standard for recognizing the characteristic changes that *in vivo* neurons undergo when they are dying by an apoptotic mechanism.

INTRODUCTION

Mechanisms of cell death have attracted a great deal of attention in recent years and much of this attention has been focused on apoptotic cell death. In the neuroscience literature, it is increasingly being suggested that an apoptotic mechanism may underlie a wide variety of disease processes affecting the human brain (Bredesen, 1995; Thompson, 1995). However, evidence supporting this assumption is less than compelling, a fundamental problem being that much of the research pertaining to CNS apoptosis has been conducted in cell cultures (Kure *et al.*, 1991; Martin and Johnson, 1993; Loo *et al.*, 1993; Bonfoco *et al.*, 1995; Lesort *et al.*,

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