Summary. A major challenge in current neuroscience research is to understand the molecular mechanisms leading to neuronal apoptosis in neurodegenerative diseases and after acute brain insults. Neuronal apoptosis which has a crucial function for elimination of unwanted neurons in the immature nervous system, for a long time was thought to be restricted to this type of developmental cell death. In recent years however, evidence has accumulated that apoptosis is also activated in the adult nervous system, and may contribute to pathophysiological cell death in both acute and chronic neurological and psychiatric disorders. Based on morphological and biochemical criteria, two major forms of apoptosis can be discriminated. Type I apoptosis is performed via the “classical” execution machinery whose central death mediators are members of the caspase family of cysteine proteases. In contrast, type II apoptosis does not require caspases, but is executed via alternative mechanisms. In this chapter, we will discuss the contribution of type I and type II apoptosis in acute and chronic brain disorders and evaluate the possibilities and drawbacks for the therapeutic rescue of neurons in which the apoptotic death program is already initiated.

1. INTRODUCTION

Half a century ago, Rita Levi-Montalcini and Victor Hamburger discovered nerve growth factor (NGF). Subsequently the concept was developed that target-derived growth factors promotes the survival of neurons, and that neurons not provided with trophic factors die during development (Oppenheim RW 1991). In 1972, Kerr, Wyllie, and Currie proposed the existence of an intrinsic cell death program and introduced the term apoptosis for the execution of this program (Kerr et al., 1972). Apoptosis was believed to be an active form of cell death enabling individual cells to commit suicide. In contrast, necrosis is a passive form of cell death raised by accidental damage of tissue and does not encompass activation of a specific death program. It is estimated that 50 % of all neurons generated during development undergo apoptotic cell death, and that apoptosis is essential for establishing and maintaining functional neuronal networks. The ground breaking achievements in the model system C. elegans have provided fundamental insights into the genes regulating apoptosis in humans (Horvitz, 1999). Most of these genes are highly expressed during brain development. However, this program can also be readily
activated in the adult nervous system, and may contribute to pathophysiological cell death in acute and chronic brain disorders.

2. CONTENT

2.1. Apoptosis and programmed cell death

Initial classification of cell death into the apoptosis/necrosis dichotomy was mainly based on morphological criteria: hallmarks of apoptosis include membrane blebbing, cell shrinkage and chromatin condensation and fragmentation. The cell disintegrates into apoptotic bodies which are subsequently phagocytized by macrophages, microglia, or neighbouring cells without eliciting an inflammatory response. Necrosis, on the contrary, is typically associated with early loss of plasma membrane integrity and swelling of the cell body and organelles. The rupture of the plasma membrane and subsequent release of cellular constituents evokes an inflammatory response. In recent years, significant progress has been made identifying key components of the apoptotic cell death machinery and deciphering the signalling pathways in which they are embedded. The caspase family of proteases are central executioners of most forms of apoptotic cell death. Caspase-dependent cell death is also termed “classical” apoptosis or type I apoptosis.

Figure 1: Proposed model for major cell death pathways implicated in type I apoptosis. Classical, type I apoptosis is activated by two major pathways: in the death receptor (extrinsic) pathway, executioner caspases are activated via the death receptor signaling