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Review

# Pharmacological inhibition of mitochondrial membrane permeabilization for neuroprotection

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ABSTRACT

Recent data have provided important clues about the molecular mechanisms underlying certain neurodegenerative diseases. Most cell death in vertebrates proceeds via the mitochondrial pathway of apoptosis. Mitochondria contain proapoptotic factors such as cytochrome *c* and AIF in their intermembrane space. Furthermore, mitochondrial membrane permeabilization (MMP) is a critical event during apoptosis, representing the "point of no return" of the lethal process. Modern medicine is developing an increasing number of drugs for neurodegenerative disease, but no neuroprotective treatment has yet been established. While current treatments temporarily alleviate symptoms, they do not halt disease progression. This paper briefly reviews the pharmacological inhibition of mitochondrial membrane permeabilization for neuroprotection.

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## Introduction

Many neurons die from necrosis and apoptosis through various mechanisms such as ischemia, mechanical stress, or degeneration. Therapeutic targeting of apoptosis (rather than necrosis) appears feasible because apoptosis is a delayed event and an energy-

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dependent, regulated process. Mitochondria are considered to be the central regulators of apoptotic cell death. In various paradigms of cell death, mitochondrial membrane permeabilization (MMP) delimits the frontier between life and death (Fig. 1). Mitochondria control the intrinsic pathway of apoptosis, in which MMP ignites the activation of caspases and other catabolic enzymes, and mitochondria participate in the extrinsic pathway of apoptosis, in which they amplify the self-destructive process (Green and Reed, 1998; Hengartner, 2000; Kroemer et al., 1997). Irrespective of its initiation at the inner or outer mitochondrial membrane, MMP culminates in the functional and structural collapse of mitochondria. The functional loss of mitochondria is accompanied by the dissipation of the mitochondrial membrane potential, shutdown of ATP synthesis, and a redox imbalance. The structural disruption of mitochondria leads to the reorganization of cristae and to the release of toxic intermembrane space proteins into the cytosol. MMP has a profound impact on cellular metabolism, activates caspase-dependent and -independent executioner mechanisms, and finally results in the demise of the cell (Ferri and Kroemer, 2001; Galluzzi et al., 2008). The lethal consequences of MMP relate to the critical position occupied by mitochondria in cellular bioenergetics and the release of proapoptotic proteins into the cytosol and the nucleus. Proapoptotic proteins liberated as a consequence of MMP include activators of the caspase cascade (e.g. cytochrome *c*), as well as caspase-independent death effectors (e.g. apoptosis-inducing factor (AIF) and endonuclease G) (Garrido et al., 2006; Li et al., 2001). Indeed, mitochondrial membrane permeabilization (MMP) is the main checkpoint of programmed cell death, and lethal pathways of signal transduction are often activated in neurodegenerative diseases. Hence, pharmacological agents that target mitochondria to subvert MMP are being evaluated as therapeutic approaches for the avoidance or treatment or neurodegenerative disorders. Here, we summarize the checkpoints of mitochondrion-dependent apoptosis and review current concepts on pharmacological targeting of mitochondria for neuroprotection.

## Mitochondrial outer membrane permeabilization

MMP may affect the outer membrane through at least two distinct mechanisms. First, the activation of proapoptotic proteins of the Bcl-2 family (e.g., Bax, Bak) can lead to the generation of multimeric channels, allowing for the release of intermembrane space proteins (Zamzami and Kroemer, 2001), or alternatively to the formation of lipidic pores due to the interaction between proapoptotic Bcl-2 family members (e.g., Bax, truncated Bid) and lipids contained in mitochondrial membranes (Galluzzi et al., 2008; Green and Kroemer, 2004; Kroemer et al., 2007). Second, outer membrane permeabilization can occur upon its physical rupture, be it induced accidentally or as part of a regulated process originating at the inner membrane (the so-called mitochondrial permeability transition). Irrespective of the precise molecular mechanisms, outer membrane permeabilization culminates in the release of proapoptotic intermembrane space proteins, which trigger the execution process of apoptotic cell death.

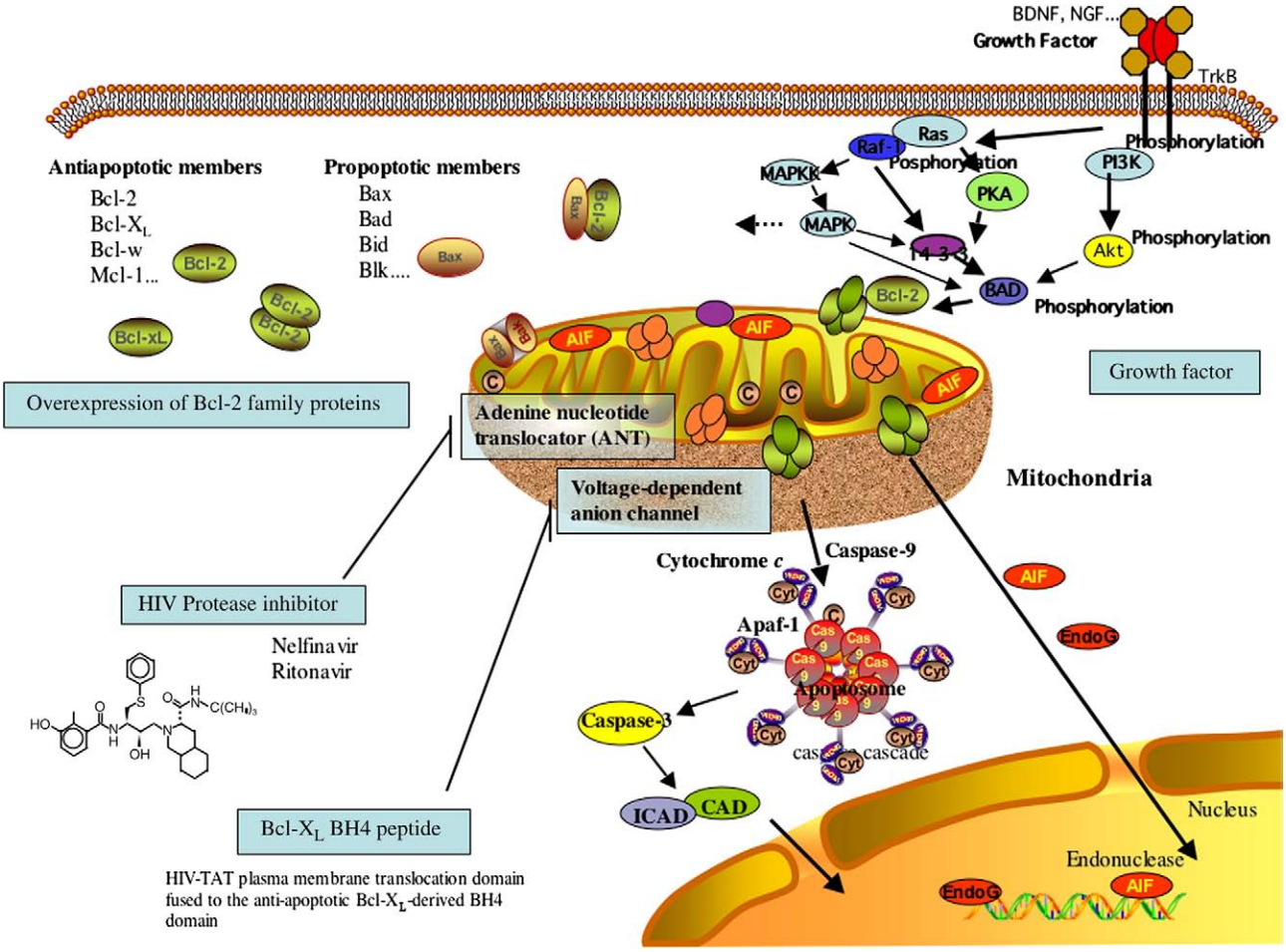


**Fig. 1.** The mitochondrial pathway to apoptosis and its inhibition for neuroprotection. The scheme summarizes the mechanisms of mitochondrial membrane permeabilization discussed in this review, as well as the post-mitochondrial effector mechanisms that are either caspase-dependent or caspase-independent. Different strategies for neuroprotection are also enumerated. For details see main text.

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