Cytokine-Mediated Apoptosis in Rat β-Cells Is Preceded by Downregulation of Bcl-2 and Bax-Ω Expression

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Proinflammatory cytokines have been shown to cause death in isolated rodent and human islet cell preparations. Depending on the species and the experimental conditions, they predominantly induce necrosis or apoptosis. In single rat β-cells, the combination of interleukin-1β and γ-interferon leads to a progressive increase in the number of apoptotic cells: after 7 days of culture, these cytokines cause apoptosis in ±30% of the cells. Their effect was blocked in the presence of *N*-methyl-L-arginine (NMA), a specific inhibitor of inducible NO synthase, indicating its NO dependency. It was not reproduced with one of the cytokines alone. We have investigated whether the cytokine-induced apoptosis is the result of an alteration in the cellular expression of anti- and proapoptotic proteins. After 3 days' exposure to interleukin-1β + γ-interferon, Bcl-2 mRNA and protein were clearly decreased, whereas Bax-α mRNA and protein levels remained unchanged. However, a strong downregulation was measured in Bax-Ω, a Bax-splice-variant protein, which has been described in other rat tissues. The reduction in Bcl-2 and Bax-Ω expression was not observed when NMA was added in the medium. It was absent after culture with one of the cytokines. It is concluded that cytokine-mediated apoptosis in rat β-cells is preceded by an NO-dependent downregulation of Bcl-2 and Bax-Ω, alleged antiapoptotic proteins, whereas no changes occur in Bax-α, a proapoptotic regulator. These data suggest that downregulation of Bcl-2–related antiapoptotic proteins can be responsible for apoptosis of rat β-cells.

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