Abstract  The focus of this article is on the cellular uptake mechanism of the family of binary actin ADP-ribosylating toxins from clostridia. These toxins are special-type AB toxins, because they are composed of two nonlinked proteins, which have to assemble on the surface of eukaryotic cells to act cytotoxically. The enzymatically active component (A), ADP-ribosylates G-actin in the cytosol of target cells. This leads to a complete depolymerization of the actin filaments and, thereby, to rounding up of cultured cells. The second component of these toxins, the binding/translocation component (B), mediates the transport of the enzyme component into the cytosol.


Introduction  Bacterial exotoxins represent well known pathogenic factors for several serious human diseases. By definition, these proteins act independently of the presence of the bacteria that produce them. After secretion by the bacteria, the toxins bind to eukaryotic target cells and are taken up into the cytoplasm by a series of steps including: (a) docking of the toxin to specific receptors on the cell surface; (b) receptor-mediated endocytosis; (c) translocation of the toxin into the cytosol, where they modify specific substrate proteins. This
causes structural alteration and functional changes of these proteins and finally leads to various cellular effects, including cell death.

There are two commonly used routes by which toxins are taken up (Fig. 1) (for a review see Sandvig and Van Deurs 2002). In the first pathway, the toxins translocate from early acidic endosomal compartments into the cytosol. This pathway, which is used by diphtheria toxin, the anthrax toxins or the Clostridium botulinum neurotoxins, can be specifically blocked by the drug bafilomycin A1, which is an inhibitor of endosomal acidification (Werner et al. 1984). During the so-called retrograde uptake pathway, the toxins also reach acidic endosomes but then they are transported to the endoplasmic reticulum (ER) via late endosomes and the Golgi apparatus. These toxins translocate from the ER into the cytosol. This pathway can be inhibited by brefeldin A, an inhibitor of vesicle trafficking between the Golgi apparatus and the ER. However, to enter the cytosol of host cells, the toxins have to cross at least one cellular membrane. For this purpose, bacterial toxins are organized in different functional domains: an enzymatically active domain (A-domain) and a binding/translocation domain (B-domain). The B-domain mediates the transport of the A-domain across membranes into the cytosol of target cells. The A-domain enzymatically modifies substrate proteins, which have essential functions for the host cells. These proteins serve either as central elements in signal transduction pathways,