It may well be that different mechanisms for insulin internalization result in different intracellular processing mechanisms. This area clearly deserves further study.

As the endosomes are acidified, the receptor-insulin complex dissociates, with most of the receptors being recycled to the cell surface and the insulin being degraded inside the cell (LeRoith et al., 2004). Endosomal degradation of insulin is initiated before acidification of the vesicles. Not all of the internalized insulin is degraded in endosomes. Endosomal degradation varies depending on insulin concentration, duration of exposure, and other factors (Seabright & Smith, 1996). Even with controlled conditions, in vitro, the maximum amount typically degraded does not exceed 50%. The remainder of the insulin is delivered to other subcellular compartments including cytosol, nucleus, and lysosomes (Harada et al., 1995). The mechanism whereby insulin reaches these compartments is unknown.

The most likely explanation for this discrepancy is that degradation occurring early after exposure of cells to insulin is nonlysosomal and mostly endosomal, whereas the hormone that escapes endosomal degradation, either intact or partially degraded, is ultimately delivered to lysosomes for complete metabolism. In this system, non-lysosomal degradation is the initial step and lysosomal degradation is the final step.

1.5.3. Enzymes for insulin metabolism

The enzymatic mechanisms for insulin metabolism have not been established, but three systems have been implicated: insulin protease, glutathione-insulin transhydrogenase (GITe), and lysosomal enzymes (Duckworth & Kitabchi, 1981).

Whereas the GITe has previously been suggested as first step in the degradation of insulin, with initial cleavage of the molecule, then A and B chain degradation by