cells that contain insulin receptors and internalization mechanisms can degrade insulin. As in liver, insulin action in adipocytes correlates better with degradation than with delivery (Donner et al., 1982).

Under normal conditions, almost all insulin is uptake and degraded intracellularly or at least by membrane processes as mentioned below.

1.5.2. Cellular insulin uptake, processing and degradation

The uptake, processing, and degradation of insulin by cells are a complex process with multiple intracellular pathways (Figure 1.7).

The initial step in the action of insulin is binding of insulin to its specific receptor on the plasma membrane of cells. Receptor-bound insulin serves as a reservoir (Duckworth et al., 1998) that can return intact insulin to the blood or deliver it to another intracellular site.

After insulin binds to its receptor, the receptor–insulin complex is internalized in endocytotic vesicle. Internalized insulin can be processed through multiple pathways (Di Guglielmo et al., 1998), resulting in degradation or release from the cell intact (diacytosis or retroendocytosis). Intracellular pathways of insulin processing include degradation of insulin in endocytotic vesicles (Seabright & Smith, 1996) or delivery of intact insulin and degradation products to other subcellular sites. Locations of internalized insulin are cytosol, nucleus, Golgi, or other locations (Smith & Jarett, 1990; Khan et al., 1982). Insulin may be degraded in these sites or later transferred to the lysosomal system for degradation (Ward & Moss, 1985). Ultimately, most internalized insulin, partially degraded insulin, and insulin fragments localize to lysosomes for completion of degradation.