1.5. First pass insulin metabolism

1.5.1. The liver is a primary site for insulin metabolism

The liver plays a major role in the metabolism of insulin (Duckworth et al., 1988). Approximately 70% of portal insulin is removed by hepatocytes during first-pass effect before entering the systemic circulation, but this percentage varies widely under different conditions.

Hepatic uptake of insulin is not a static process, but rather is influenced by both physiological and pathophysiological factors (Duckworth et al., 1988). In addition, the hepatic insulin uptake is incompletely understood and involves several different systems and controls.

Since most hepatic uptakes are a receptor-mediated process, at physiological concentrations, uptake is mediated primarily by the insulin receptor with a smaller contribution from nonspecific processes. At higher concentrations, non-receptor processes start to assume greater importance, very high concentrations of insulin (500-2000 μIU/ml) result in a decrease in the fractional uptake although total uptake is increased (Jochen et al., 1989). Prolonged increases in portal insulin levels also result in reduced clearance due to receptor down-regulation.

Hovorka et al., 1993 used a five-compartment model to reflect insulin distribution in systemic plasma, hepatic plasma, and interstitial fluid and insulin binding to the liver and peripheral receptors, and it included receptor-mediated and non-receptor-mediated insulin degradation. The mean residence time of endogenously secreted insulin was 71 min; 62 min found bound to the liver receptor, the time of binding to peripheral receptors was 6 min, and 3 min in blood or interstitial fluid, 80% of the