suggest that the rate of hydrolysis of stevioside is slightly greater than that of rebaudioside A (Koyama et al. 2003b; Wingard et al. 1980), and the rate of steviol transport is in favour of absorptive direction involving both passive diffusion and carrier-mediated transport through a monocarboxylic transporter, compared to stevioside (Chatsudthipong and Muanprasat 2009).

The distribution of stevioside takes place after hydrolysis of stevioside to steviol. It has been found that accumulation of steviol is maximal in the liver, kidney and intestine (Cardoso et al. 1996). High-performance liquid chromatography (HPLC) analysis of bile showed that steviol is the major metabolite present in rats. However, analysis of urine revealed the presence of steviol glucuronide in humans (Geuns et al. 2006) and no stevioside or steviol was detected.

The metabolic conversion of stevioside to steviol occurs in the liver. The metabolic pathway of steviol involves phase I metabolism of steviol by cytochrome P450 and phase II metabolism in which steviol is conjugated with glucuronide (Roberts and Renwick 2008). There are two probable routes of stevioside excretion, via bile and urine. Steviol glucuronide is the common major metabolite found in circulation of both humans and rats. Biliary and urinary tracts appear to be the major routes for steviol glucuronide excretion. However, the extent to which this metabolite is excreted via these two routes differs between humans and rats. In the latter, the principal route is through faeces via biliary excretion of steviol glucuronide (Nakayama et al. 1986; Roberts and Renwick, 2008; Wingard et al. 1980). In humans, steviol glucuronide is predominantly excreted via the urine (Cardoso et al. 1996; Geuns 2007; Geuns et al. 2006; Wheeler et al. 2008). This is due to different molecular weight (MW) thresholds for human and rat biliary excretion of organic anions (Kwon et al. 2002). In the rat, anions with molecular weight less than 325 Da are excreted in urine and in humans, anions less than 500–600 Da are excreted in urine (Renwick 2008).

Stevioside and rebaudioside A undergo similar metabolic and elimination pathways in humans, with steviol glucuronide being excreted primarily in the urine and steviol through the faeces which account for 62% and 5.2%, respectively, of the total administered stevioside dose in a 72-h period (Wheeler et al. 2008). The excretory process probably involves renal organic anion transporters (Srimaroeng et al. 2005).

2.2 Antihyperglycaemic effect

There has been a sharp increase in the incidence of type 2 diabetes mellitus among the developing and industrialised nations, due to ageing, dietary habits and reduced physical activities. Diabetes is a chronic metabolic disorder resulting from insulin abnormalities, insulin secretion from islet β-cells, pancreatic α-cell dysfunction and relative imbalance of insulin and glucagon levels. It has been found that stevioside and Stevia extract can be used for treatment of diabetic patients (both type 1 and type 2) as it significantly decreases the plasma glucose levels (Renwick and Molinary 2010).

Stevioside and steviol both enhance insulin secretion and insulin sensitivity of the islet cells but only in presence of elevated glucose levels (Jeppesen et al. 2000, 2003; Lailerd et al. 2004). Both have a long-lasting and apparently reversible insulinotropic effect via direct action on the β-cells to stimulate insulin secretion (Jeppesen et al. 2000). Preliminary experiments in rats reveal that in STZ-induced diabetic rats, the hypoglycaemic effect of oral intake of stevioside (1, 2 or 10 mg/kg body weight(BW)/day for 15 days) is mediated via its effect on phosphoenol pyruvate carboxy kinase (PEPCK), a rate-limiting enzyme for gluconeogenesis controlling glucose production in the liver (Chen et al. 2005). Stevioside slows down gluconeogenesis in the liver via suppression of PEPCK gene expression, leading to a decrease in plasma glucose levels in diabetic rats (Giffin et al. 1993). Injection of stevioside along with glucose provokes insulin secretion, suppresses glucagon level in the plasma and decreases blood glucose response to glucose tolerance test in anaesthetised type 2 diabetic rats, which supports the fact that stevioside possesses antihyperglycaemic, insulinotropic and glucagonostatic effects in type 2 diabetic situations (Jeppesen et al. 2002).

Excessive oral intake of stevioside (500 mg/kg BW) in diabetic rats increases the insulin sensitivity of the body, as determined by the glucose-insulin index, which indicates the degree of insulin sensitivity or insulin action on glucose disposal rate followed by glucose loading (Chang et al. 2005; Lailerd et al. 2004).

Stevioside shows a direct effect on glucagon secretion as well (Hong et al. 2006), by decreasing the release of glucagon, probably by enhancing mRNA expressions of carnitine palmitoyltransferase, peroxisome proliferator-activated receptor gamma (PPARγ) and stearoyl-CoA desaturase. However, rebaudioside A affects insulin secretion stimulation in the presence of extracellular Ca^{2+}, i.e. insulin stimulation at high glucose levels disappears in the absence of extracellular Ca^{2+} (Abudula et al. 2004, 2008). Rebaudioside A stimulates insulin secretion from pancreatic β-cells via inhibition of K_{ATP}, thereby allowing β-cells to depolarise and activate Ca^{2+} channels. This inhibition of K_{ATP} is possible in the presence of a high glucose level, underscoring the glucose dependency of rebaudioside A action. However, the signalling pathway through which high plasma glucose triggers the action of rebaudioside A is still not known. Long-term consumption of rebaudioside A shows no effect on glucose homeostasis, lipid profile or blood pressure (Maki et al. 2008) and exhibits good tolerance properties.

In addition to stevioside and steviol, isosteviol, a metabolic compound of stevioside, improves lipid profile and regulates the expression of key β-cell genes, including insulin regulatory transcription factors, thereby improving glucose homeostasis, enhancing insulin sensitivity, lowering plasma triglyceride and decreasing weight of diabetic KKAy mice (Nordentoft et al. 2008). Chronic type 2 diabetes is normally accompanied by hypertension and dyslipidaemia (UKPDS Group 1998a,b). Thus, the ideal pharmacological intervention in type 2 diabetes should be aimed at lowering blood pressure, lipid and glucose concentration in the plasma. As stevioside possesses blood pressure-lowering and hypoglycaemic effects (Jeppesen et al. 2003), it has a high potential to be used clinically for the treatment of these patients. It is interesting to note that the effect of stevioside is dependent largely on