Discussion
&
Conclusion
7. Discussion

Basal pancreatic and islet blood flows were augmented in GK rats compared with control Wistar rats (Svensson et al., 1994a, 1994b). Vagotomy has been shown to decrease the augmented islet blood flow in diabetic F1 hybrids (Svensson et al., 1994) and GK rats (Atef et al., 1994) to values similar to those seen in vagotomized control rats. The same effect was achieved after treatment with atropine (L. Jansson, unpublished work), suggesting that a nervous cholinergic mechanism is, at least in part, responsible for the increased islet blood flow in the GK rat model. Later experiments have suggested that it is likely that ambient hyperglycemia accounts for this nervous-system-mediated islet blood flow increase (Carlsson et al., 1997). In the present study, we confirmed that glucose administration leads to an acute increase in islet blood flow in normal wistar rats (Jansson 1994), whereas a decrease is seen in diabetic rats (Svensson et al., 1994). The glucose-induced islet blood flow increase in normal wistar rats could be due to a complex interplay between nervous-system mediated and metabolically induced signals (Jansson, 1994; Brunicardi et al., 1996). The mechanisms underlying the glucose-induced decrease in islet blood flow in diabetic rats is unknown; however, nervous signaling pathways are likely to be involved (Svensson et al., 1994).

Administration of vildagliptin and PKF-275-055 pre-treatment had no effects on total pancreatic and islet blood flow in glucose administered normal wistar rats. Annika et al., reported GLP-1 prevented the glucose-induced increase in total pancreatic and islet blood flow in hyperglycemic rats. In contrast, vildagliptin and PKF-275-055 pre-treatment augmented the glucose-induced mild elevation total pancreatic and islet blood flow in diabetic rats. The mechanism underlying the vildagliptin and PKF-275-055 induced elevation in pancreatic and islet blood flow in diabetic rats is unknown; there may be a difference in the plasma GLP-1 levels that induce changes in blood flow (Svensson et al., 1994). Serum insulin concentrations were increased in these animals, thereby confirming the incretin effect of the hormone. Regarding the finding of an elevation in the pancreatic and islet blood flow response to hyperglycemia after vildagliptin and PKF-275-055 administration in the rats, it may be speculated vildagliptin and PKF-275-055 induced prolong effect of GLP-1 may cause peripheral vasodilatation. In salt-sensitive rodent models GLP-1 treatment has shown antihypertensive,
cardioprotective and renoprotective actions (Yu et al., 2003; Hirata et al., 2009). The main mechanism for the latter seems to be a natriuretic and diuretic effect of GLP-1, due to inhibition of Na⁺ reabsorption in the proximal tubule (Moreno et al., 2002) or attenuation of angiotensin II-induced phosphorylation of extracellular signal-regulated kinase-1/2 in renal cells (Hirata et al., 2009). Noticeably, increased cardiac output with no BP changes has also been reported in rats, suggesting that GLP-1 may cause peripheral vasodilatation (Poornima et al., 2008). In the present study, we confirmed that vildagliptin administration led to an elevation in cardiac output in diabetic rats, while a mild reduction in cardiac output is seen in normal wistar rats. Whereas PKF-275-055 administration led to have slight alteration in cardiac output in diabetic rats, whereas a significant reduction in cardiac output is seen in normal wistar rats. The mechanism underlying changes in cardiac output in normal and diabetic wistar rats is unknown.

Besides the GLP-1 hormones, DPP4 modulates the biological activity of neuropeptide Y cleaving the molecule after the proline or alanine residue. DPP4 inhibitors prolong the action of the neuropeptide Y (Mest and Mentlein, 2005). NPY potentiates the action of other vasoconstrictors, including norepinephrine, angiotensin, and vasopressin, which causes increase in blood pressure (Dahlof et al., 1985; Wahlestedt et al., 1990). In the present study, vildagliptin and PKF-275-055 administration showed no change in blood pressure in normal rats. One possible explanation for this discrepancy is that there may be a difference in the plasma neuropeptide Y levels that induced hemodynamic effects.

It is believed that islet blood flow coupled with the islet insulin release (Brunicardi et al., 1996; Jansson., 1994), and this association seems to depend on an intact production of nitric oxide (NO) within the islet vasculature (Moldovan et al., 2000; Svensson et al., 1994). Evidence that NO could be involved in insulin secretion was provided by Laychock et al. in 1991. Furthermore, L-arginine deficiency is associated with insulinopenia and a failure to secrete insulin in response to glucose. These authors demonstrated that sodium nitroprusside increased cGMP in rat islets and stimulated insulin secretion. Another mechanism of NO-mediated insulin secretion could be triggered by an increase of intracellular calcium (Laffranchi et al., 1995). This opens the possible involvement of Ca²⁺ channels and endothelium-derived relaxing factor, which some investigators believe is nitric oxide (Palmer et al., 1988) or nitrosothiol (Yoshimura
and Iida., 1950). In contrast, the present study demonstrated that diabetic rats showed increase in NO and decrease in insulin secretions and vice-versa in normal rats. Vildagliptin and PKF-275-055 pre-treatment to diabetic rats had shown decrease in NO, but significantly increased insulin secretions. From the present investigation, we observed that islet insulin secretions are independent of blood flow and NO and inhibition of NO by vildagliptin and PKF-275-055 pre-treatment to both normal and diabetic rats did not affect pancreatic and islet blood flow. Furthermore, vildagliptin and PKF-275-055 itself is able to mobilize intracellular Ca^{2+} in pancreatic islet both in absence and presence of glucose, suggesting inhibition of neuropeptides degradation in the cells of the islets of Langerhans and in the basolateral surfaces of pancreatic acinar cells involved in increase of intracellular calcium and enhance insulin secretion (Adeghate and Dona., 1990; Larson., 1979).

8. **Conclusion**

In conclusion, we have shown that DPP-IV inhibitors induced islet insulin secretions were observed to be independent of pancreatic islet blood flow and NO.