

CHAPTER 9. SUMMARY

In the series of studies of this thesis, the results were summarized in Fig. 9, and...

1. The alteration of metabolic, hormonal and neural pressor factors and modulation of IRs in skeletal muscle due to FAT-induced BP elevation were investigated in rats. Rats were fed FAT or CHO from 5 weeks of age for 3 or 16 wk. After 16 wk, BP was significantly higher in the FAT group than in the CHO group. Total adipose tissue weight was significantly higher in the FAT group. Plasma glucose, insulin and leptin levels were significantly higher in the FAT group. In addition, urinary NE and Epi were significantly higher in the FAT group. On the other hand, after 3 wk of the experimental diets, total adipose tissue and plasma leptin levels were already significantly higher in the FAT group. Glucose infusion rate during the euglycemic clamp test was significantly lower in the FAT group. In soleus and gastrocnemius muscles, IRs were significantly lower in the FAT group after 16 wk of feeding. These results suggest that long-term FAT feeding aggravates multiple metabolic and hormonal pressor factors, resulting in activated SNS and elevated BP. In addition, decrease in muscle IRs with FAT-feeding is associated with severe insulin resistance and may be associated with FAT related BP elevation.

2. To clarify a mechanism responsible for FAT-related BP elevation, renal SNA, renal BF and urinary sodium excretion rate were investigated in rats. Rats were fed FAT or CHO from 5 weeks of age. After 20-21 weeks of feeding, fasted rats were anesthetized with urethane (1 g/kg, i.p.) and treated with the usual surgical procedure. Body fat accumulation was significantly greater in the FAT group than in the CHO group. MAP and renal SNA were significantly higher in the FAT group than in the CHO group. In addition, renal BF and urine sodium excretion rate were significantly lower in the FAT group than in the CHO group. These results suggest that decreased renal BF and urinary sodium excretion rate in the FAT group are due to increased renal SNA, which contributes to BP elevation derived from to excess body fat accumulation with FAT-feeding in rats.

3. Whether elevations of renal SNA and BP could be observed by leptin injection

into WAT was examined in rats. Injections of leptin (10 and 100 ng/ml/kg) into WAT evoked the activation of renal SNA dose-dependently. Circulating sympathetic nerve activators, such as leptin, insulin, glucose and lactate, were unchanged by any doses of leptin. In addition, BP was not affected by leptin injections during a 90 min experimental period. These data suggested that leptin activated the afferent nerves through the sensors in WAT, resulting in elevation of renal SNA. The novel control pathway of renal SNA by leptin is possible to contribute to FAT-related BP elevation.

4. The effects of systemic insulin injection on arteriole and capillary diameter and blood flow rate in rat cremaster muscle were investigated. Subcutaneous insulin injection (1 U/kg) significantly increased serum insulin levels at 15 min as compared with saline injection. At 15 and 30 min after insulin injection, blood glucose levels were significantly lower compared to saline injected controls. Arteriole diameter was significantly increased at 15 and 30 min, while capillary diameter was not modified by insulin. Arteriole erythrocyte flow velocity was significantly increased at 15 and 30 min. In addition, capillary erythrocyte flow velocity was increased at 15 and 30 min. These results demonstrate that calculated blood flow rates in capillary and arteriole are increased after insulin injection. Therefore, insulin elevates blood flow rate in rat skeletal muscle microvasculature.

In conclusion of this thesis, long-term FAT-fed rats elevated SNS activity, resulting in BP elevation. Especially, elevated renal SNA would closely associate with antinatriuresis and contribute to BP elevation in the rats. These activations of SNS would be induced by multiple metabolic and hormonal abnormalities, such as excess body fat accumulation, hyperinsulinemia, insulin resistance, hyperglycemia, hyperleptinemia and excess synthesis of leptin in WAT. On the other hand, insulin also had vasodilator effects in skeletal muscle microcirculation which has an important role for BP regulation.