

CHAPTER 8. GENERAL DISCUSSION

Although obesity often induces hypertension in human and animals (7, 100), the mechanism is not entirely clear how BP is elevated in diet-induced obesity. The activation of SNS has been suggested as an important candidate for the cause of an obesity-related hypertension (101-103). In the present study in FAT-fed or CHO-fed rats, the strong relationship between BP elevation and SNS and pressor factors has been established.

Long-term FAT induced BP elevation with activation of SNS attending excess body fat accumulation, hyperinsulinemia, insulin resistance, hyperleptinemia and hyperglycemia (Study 1). On the other hand, short-term FAT did not induce BP elevation and SNS activation, even though the development of excess body fat accumulation, insulin resistance and hyperleptinemia was observed (Study 1). In addition, IR contents in skeletal muscle were decreased in long-term FAT compared with CHO, suggesting marked insulin resistance (Study 1). Furthermore, long-term FAT elevated renal SNA and lowered renal BF and urinary sodium excretion (Study 2). These results suggested that FAT-related BP elevation was induced by SNS activation involved with multiple metabolic and hormonal pressor factors. Especially, elevation of renal SNA would result in lowered renal BF and urinary sodium excretion, which is able to closely associate with FAT-related BP elevation. Other possible mechanisms, such as activation of renin-angiotensin system or defects of vasodilation, were not investigated in the present study. However, SNS also affects these mechanisms toward BP elevation (85, 104-106).

BP and SNS are affected by obesity-related hormones, insulin and leptin. Therefore, the second objectives of the present study were to investigate basic physiological actions of the hormones. Leptin injections (10 and 100 ng/kg) into the left perirenal WAT increased the renal SNA dose-dependently (Study 3). However, plasma levels of leptin and insulin, and blood levels of glucose and lactate were not modified by the saline and leptin injections into WAT. These data supported the previous studies that leptin activated afferent nerves through the sensors in WAT (77, 78). The present study established an additional finding that leptin in WAT stimulated renal SNA via the afferent nerve pathway. In FAT-fed rats,

increased synthesis of leptin in WAT is possible to contribute to BP elevation, in addition to elevation of plasma leptin levels.

About another obesity-related hormone insulin, its hemodynamic actions have not been well elucidated in skeletal muscle microvasculature. Thus, the study evaluated cremaster muscle microcirculation in response to systemic insulin administration (Study 4). In rat cremaster muscle microvasculature, insulin-induced increase in blood flow rate was caused by mediating vasodilation in arteriole and increasing erythrocyte flow velocity in arteriole and capillary. Since microcirculation has important roles for BP regulation (99, 107), what insulin directly dilates microvessel suggests that insulin would control BP by microvascular relaxation. It would be a reason why BP was not elevated after insulin injection. The depressor effects of insulin are likely to be diminished in the states of insulin resistance (60, 61). However, this point was not investigated in the present study.

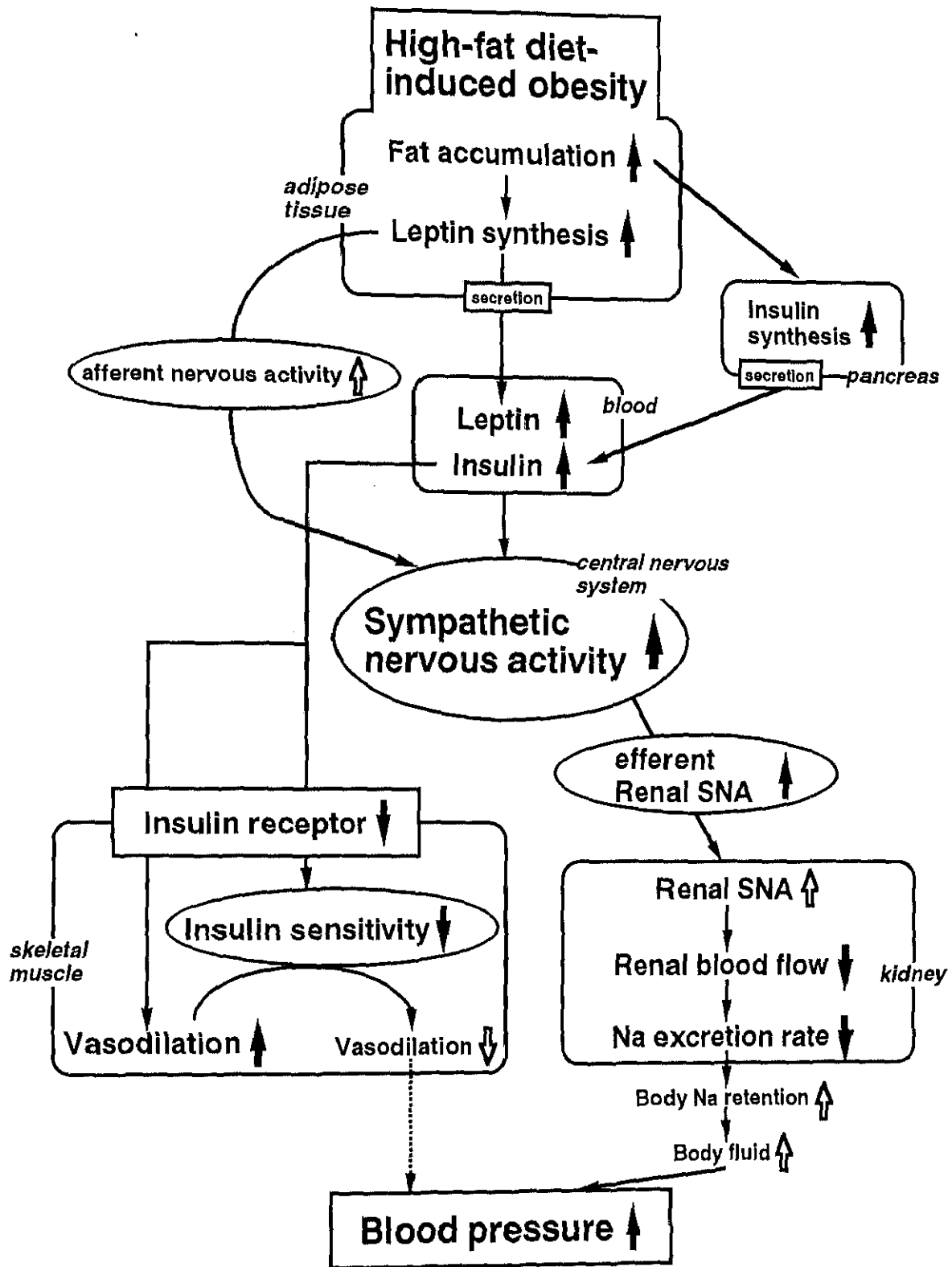


Fig. 9 A proved mechanism involving elevation of sympathetic nervous activity and blood pressure in long-term high-fat diet-fed rats.