

CHAPTER 2. REVIEW OF PREVIOUS REPORTS

Relationships between FAT and BP

Several reviews described about association between dietary fats and BP in human (12-14). In a review, it is indicated a direct association between diets high in saturated fats and BP, and many populations that have low MAP levels eat a diet low in total fat and saturated fatty acids (14). In addition, clinical study suggested that reduce saturated and total fat could substantially contribute to lowering of BP (15). On the other hand, a number of trials have failed to show a significant BP effect by varying the dietary content of fat or by exchanging polyunsaturated for saturated fatty acids (12). The effect of polyunsaturated fatty acids on BP was inconsistent. One review emphasized a role for polyunsaturates as hypotensive agents (13), but the other described that polyunsaturated fatty acids did not always lower BP (12, 14).

In many animal studies, FAT related BP and obesity was concomitant with the BP elevation in the almost all studies (16-23). Since FAT usually causes obesity in relative short-term, FAT-related BP elevation is not likely to precede obesity (17). FAT-related BP elevation would be able to associate with insulin resistance, hyperinsulinemia, increased levels of plasma catecholamine, dyslipidemia, baroreceptor reflex impairment, activation of renin-angiotensin system and so on (16-18, 20-23). The pressor effect by FAT would be stronger in the diets high in saturated than in polyunsaturated fatty acids (13, 19).

Relationships between FAT or obesity and SNA

Bray described in his review (24) that chronic FAT lowers basal level of SNA compared with CHO in rats. Some strains of genetic obese rats and hypothalamic obese rats have lowered basal SNA (24). He hypothesized lowered SNA would be essential for development of increase in deposition of body fat by FAT. On the contrary, SHR with obesity and obese Zucker rat increase SNA (25, 26). Kaufman et al. (17, 18) measured both urinary catecholamines excretion and BP in FAT-fed rats. One of them

demonstrated that FAT elevated both SNA and BP compared with control-diet in rats (17). Another study suggested that adrenal medullary catecholamines, rather than activation of SNS, played a role in the hypertensive response to FAT (18). No other studies, however, have reported elevated SNA with FAT-related BP elevation. Thus, it has been still obscure whether or not FAT is involved in higher SNA.

It is recognized that the renal regulation of urine volume and sodium reabsorption plays a dominant role in the long-term control of BP and that the renal sympathetic nerves control kidney functions (25, 27-30). Only a few studies have investigated the relationships between basal renal SNA and genetic obesity or FAT-fed rats in association with BP (26, 31, 32). A study directly measured the basal levels of efferent renal SNA in genetic obesity. In Zucker rats fed a high-salt diet (8.0% NaCl) for 2 wk, the basal efferent renal SNA was higher with elevation of MAP in obese Zucker than in normotensive lean Zucker rats (26). However, under a condition of a low-salt diet (0.4%) feeding, BP was not higher, but renal SNA was significantly greater in obese Zucker rats (26). Since BP is complicatedly regulated, elevation of renal SNA would not always elevate BP. Two studies investigated renal SNA directly or indirectly in FAT-fed rats did not find higher renal SNA compared with CHO-fed rats (31, 32). One of them, BP was not higher in the FAT than in the CHO and another was not measured. It has been not reported that basal renal SNA is higher in FAT-related BP elevation than in control CHO-feeding.

Role of insulin on BP regulation

Insulin directly increases renal tubular reabsorption and SNA (8, 10). Previous studies demonstrated that either acute or chronic insulin administration elevates BP and SNA (33-36). On the other hand, considerable studies in human and animals failed to find a hypertensive effect of insulin (16, 37-42). In addition, investigations including some of these studies did not increase plasma NE levels or urinary NE excretion after insulin administration (41-43). Although these studies were conducted under euglycemic condition, hypoglycemia per se activates SNS (44, 45). Therefore, insulin-induced

elevation of SNA in some of previous studies might be caused by both hyperinsulinemia and hypoglycemia.

A previous finding suggested that BP elevation in FAT-fed rats was caused by insulin-induced activation of SNS (17). The study has shown that fasting plasma insulin levels significantly correlated with systolic BP. This is the only study that FAT-related BP elevation is associated with insulin-induced increased SNA (17).

Interestingly, insulin has itself depressor effects on vascular bed. It has been documented that insulin dilates vessels in skeletal muscle (46). Systemic administration of insulin induced increase in skeletal muscle blood flow (47-50). The increase in blood flow was induced by vasodilation and capillary recruitment (47, 49). In other studies, insulin's vasodilator action was observed with topical application of insulin (51, 52). Furthermore, it has shown that isolated skeletal muscle arterioles dilate in response to increasing concentrations of insulin (10, 53). These previous studies measured the hemodynamic of muscle tissue or the diameter of arteriole (not capillary).

Role of insulin resistance and skeletal muscle insulin receptor on blood pressure regulation

An association between obesity-related hypertension and insulin resistance has been described (7, 20). In the previous study in FAT-fed dogs, it was demonstrated that the more specific the index of insulin resistance (fasting insulin < whole body glucose uptake at 2 mU/kg/min < insulin ED50 dose), the stronger the relationship between the change in MAP and the change in insulin-mediated glucose uptake (20). It is considered that insulin resistance induces elevation of SNA and BP by itself as well as compensatory hyperinsulinemia. Shimosawa et al. have demonstrated that insulin inhibits NE release by electrical stimulation in isolated mesenteric arteries of rats, suggesting that insulin attenuated NE overflow from peripheral sympathetic nerve endings (54). The inhibitory effect of insulin on NE overflow was reduced in SHR having insulin resistance compared with WKY rats (55).

Insulin-induced vasodilation diminishes vascular resistance in vascular bed. Many

of human studies have suggested diminished skeletal muscle vasodilation by insulin in states of insulin resistance (56-59). In addition, previous study demonstrated in cultured HUVEC that insulin-stimulated NO production was blocked by inhibitors of tyrosine kinase and PI 3-kinase (60). In a few animal studies, insulin-mediated vasodilation and elevation of erythrocyte flow velocity in arteriole were blunted by a tyrosine kinase inhibitor in hamster cheek pouch (61). Another study demonstrated in isolated rat soleus muscle that generation of cGMP by NO donor SNP was decreased in obese Zucker compared with lean Zucker rats, suggesting impaired NO/cGMP signaling (62). Furthermore, the maximal activity of NOS was significantly decreased in insulin-resistant obese Zucker muscles (62). These findings suggested that insulin resistance decreased insulin-mediated vasodilation by weakened NO production in skeletal muscles. Baron et al. (63) suggested in a human study that diminished insulin-induced vasodilation associated with pathophysiology of hypertension.

Decreased insulin binding at maximal insulin concentrations in isolated soleus muscle in FAT-fed rats has been reported, suggesting that IR in skeletal muscle is decreased by FAT feeding (64, 65). These studies, however, did not measure BP. It is thought that decreased insulin receptor contents associate with marked insulin resistance. The relationship between the decrease in IRs and FAT-related BP elevation has been not clarified.

Role of leptin in blood pressure regulation

In a previous report, in 110 subjects with essential hypertension and 29 healthy normotensive controls, plasma leptin levels were significantly higher in the hypertensive subjects than in the normotensive subjects (66). In addition, some studies have demonstrated that chronic or acute administration of leptin increased BP in rats (67, 68). A recent report has been demonstrated BP elevation in obese and non-obese hyperleptinemic mice (69). These findings suggest that hyperleptinemia contributes to BP elevation. Intravenous and central administrations of leptin increased plasma catecholamine levels in animals (70, 71). Leptin has also shown to increase sympathetic

activities in interscapular brown adipose tissue, kidney, hindlimb and adrenal gland (11). Several acute and chronic studies suggest that increased plasma leptin elevates renal SNA or BP (11, 68, 72).

Circulating leptin would act in the CNS through the blood brain barrier (71, 73-75). Intracerebroventricular injection of leptin elevated SNA and BP in rats (76). These data suggest that increase in circulating leptin produced in the WAT accompany with obesity would act in the CNS and may be responsible for elevation of BP through the elevation of SNA. Nijima recently suggested that there is an afferent signaling system from leptin sensors in WAT (77). In addition, he demonstrated that leptin injection into WAT reflexively activated efferent SNA to WAT, brown adipose tissue, adrenal medulla, pancreas and liver (78). These data suggested that leptin controls metabolic functions by reflex modulation. However, it has not been investigated whether leptin elevates efferent renal SNA and BP through the afferent signaling system from WAT.