

INFLUENCE OF AGE AND SEX ON HIGH-FAT DIET-INDUCED INCREASE IN BLOOD PRESSURE

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ABSTRACT

We are studying to elucidate the reason for increase in age-related hypertension and the mechanism thereof using rats. We would like to introduce model animals and the results obtained from these animal experiments.

Based on a study regarding whether the elevation of blood pressure caused by dietary fat is due to excessive calorie intake and resulting body-weight gain or else fat itself - if so which type of fat is responsible for elevating blood pressure, it was suggested that elevated blood pressure was due to some effects specific to animal fat.

According to a study if insulin resistance involves elevated blood pressure, it became apparent that the build-up of visceral fat caused by high-fat diet together with worsening of insulin sensitivity were responsible for elevating blood pressure.

Next, we studied if there are sexual differences in dietary-fat induced hypertension and influence of male hormone. It became clear that the mechanism of elevated blood pressure caused by high-fat diet involved a condition of insulin resistance due to high-fat diet and furthermore, only when testosterone was present, the blood pressure was elevated.

In addition, we studied aging effects on hypertension due to dietary fat. As a result, it became clear that the older the person gets, more likely he/she suffers from visceral obesity and conditions of insulin resistance, making blood pressure prone to rise.

In summary, even without having excessively high calorie diet and without body weight gain, intake of excessive animal fat will cause visceral obesity and so do hypertension. Also, when taking high-fat diet, males tend to suffer from hypertension more often than females, suggesting testosterone is involved as the cause. Further, it was shown that the older the persons are, the greater the dietary effects result in, causing their blood pressures likely to increase.

Key Words: High-fat Diet, Hypertension, Obesity, Aging, Sex

INTRODUCTION

In recent years, obesity of older people has increased in this country, and more life-style related diseases are found among them. Also according to epidemiological report, the number

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of hypertensive patients increases with aging. While its mechanism is less certain, insulin is reported to be involved.^{1,2)} Attention has been also drawn towards the influence of insulin on the one's life-span.

We are carrying out animal experiments in order to understand the cause and mechanism of increase in hypertensive patients with aging. We would like to introduce model animals prepared so far and the results obtained from these animal experiments.

1. Not Excessive Calorie Intake, But Animal Fat Elevates Blood Pressures.

Relationships between dietary obesity and hypertension have been the subject of multitude of research activities. It has been postulated that as a report⁴⁾ has shown that high-fat diet induced insulin resistance and some specific fat affected the adrenal medullary function and the central nerve activity, the dietary fat itself, not excessive calories, caused elevation of blood pressure.

Therefore, we investigated:

1. whether elevation of blood pressure caused by dietary fat is due to excessive calorie intake and resulting body-weight gain or else fat itself,
2. if so which type of fat is responsible for elevating blood pressure.

Three month old male Wistar rats were fed with a half of the calories of chow provided by substituted animal diet (lard) (Fig. 1). After 5 weeks, systolic blood pressure was elevated with a significant level (Fig. 2). Body weight did not increase significantly compared with the control. Also, no elevated blood pressures were observed among the rats fed with diets that are substituted with vegetable oil (safflower oil), medium-chain triglyceride (MCT), or sucrose. It implied that elevated blood pressure was due to the effects specific to animal fats. Also, since the rats fed with diets supplemented by animal fat providing half the calories of chow showed elevated blood pressure, it suggested that the elevated blood pressure from lard diet was not due to lack of nutrients.

2. Insulin Resistance^{3,5)} Is Involved.

In the above study, we also investigated whether or not the insulin resistance caused elevated blood pressure, using 3 month old male rats by feeding the diets (high-fat diet) with half the calories being replaced by animal fat (lard). Compared with the chow group, we discovered an increase in blood insulin level, an increase in visceral fat, and worsening of insulin sensitivity (as demonstrated in the Insulin Suppression Test) (Fig 1). Blood glucose level was unchanged.

Also, when Troglitazone, an insulin resistance ameliorating drug, was added to the high-fat diet, it improved in both insulin resistance and blood pressure (Fig. 2).

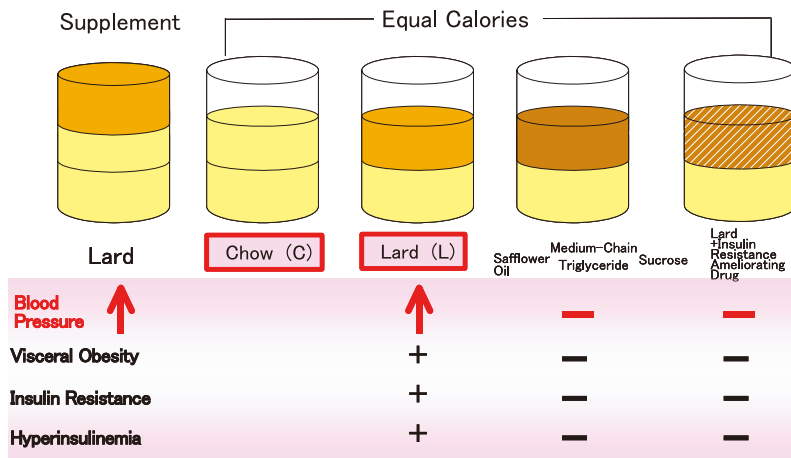
Accordingly, we found that high-fat diet-induced elevation of blood pressure involved the accumulation of visceral fat and worsening of insulin sensitivity.

3. Sex Makes Differences.⁶⁾

The above results are based on male subjects, so we studied the differences between males and females. It has been known that in general, the morbidity of essential hypertension is lower for pre-menopause females than males^{7,8)} and for genetically hypertensive model animals such as SHR, males have higher blood pressure than females.^{9,10)} We studied hypertension caused by dietary obesity in terms of differences in sex as well as involvement of male hormone.

There was no indication of elevated blood pressure, with a significance level, with 3 month

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		Chow	Lard	Safflower Oil	Medium-Chain Triglyceride	Sucrose
Visceral Fat (g)		5.9±0.77	8.1±0.48*	7.2±0.54	4.7±0.38	5.7±0.51
Blood Glucose (mM)		6.7±0.21	6.6±0.08	6.3±0.02	6.1±0.21	6.8±0.38
Blood Insulin Level (mg/ml)		4.6±0.90	7.5±1.00*	4.1±0.30	3.1±0.80	5.7±0.80

Fig. 1 Effects of Dietary Ingredients on Blood Pressure, Visceral Obesity, Insulin Resistance, and Hyperinsulinemia

*P<0.05 (compared with the chow group)

Used Wistar male rats of 3 month old. For each group, feed with diet, providing half the calories with each substitution (i.e., maintain the intake calories equal for each group), and measure body weight and blood pressure every week, and after 7–8 weeks, draw fasting blood sample without anesthesia and restraint. Insulin sensitivity was obtained through insulin suppression test. Visceral fat (fat around testicle) was weighed after slaughtering.

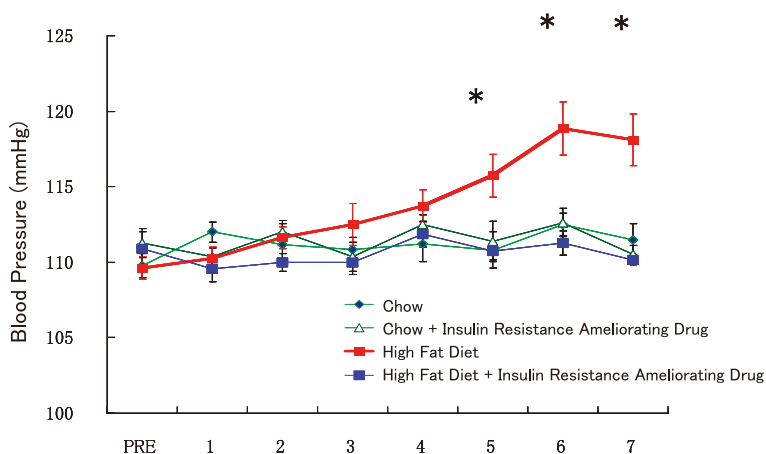


Fig. 2 Effects of High-Fat Diet and Insulin Resistance Ameliorating Drugs on Blood Pressure

*P<0.05 (compared with the control)

Splitting each dietary group into two halves, feed one half with diet containing insulin resistance ameliorating drug. See Fig.1 for details.

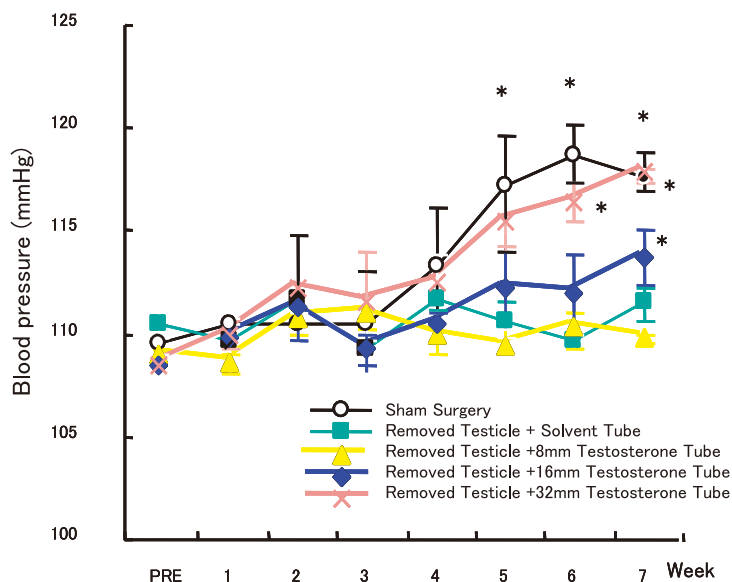


Fig. 3 Effects of Testicle Removal and Testosterone Dosing on Blood Pressure

* $P < 0.05$ (compared with the chow group)

Used Wistar male rats of 3 month old. Male and female group with sex glands removed, and group with testicles removed and with testosterone (T)-loaded tube (6, 16, and 32mm long) embedded under the skin. See Fig. 1 for details.

old female rats fed with high-fat diet. Removing ovaries did not make any changes. On the other hand, a male rat with testicle removed showed no elevated blood pressure with high-fat diet, but externally giving testosterone, a male hormone, a dose dependent blood pressure elevation was observed (Fig. 3). All the animals, with high-fat diets, showed insulin resistance. Thus, we found that high-fat diet caused a condition of insulin resistance and only when testosterone was present, the blood pressure was elevated.

4. The Older The Earlier in Blood Pressure Elevation¹¹⁾

Based on the above results, first we studied age-related blood pressure changes for males. When 3, 10, and 18 month old F344/N male rats were fed with high-fat diet, the timing of blood pressure elevation became earlier with aging (Fig. 4). There were no age-related differences in baseline blood pressures, but they showed higher values compared with Wistar rats (cf. Fig 2). We observed that the older showed an earlier increase in visceral fat, blood insulin, and leptin, and worsening of insulin resistance. Accordingly, we postulated a mechanism that the older tend to have more readily the visceral fat and insulin resistance, resulting in excreting excessive leptin from fat cells making sympathetic nerve system work actively, which in turn elevates blood pressure. For 10 and 18 month old rats, when loaded with high-fat diets, their body weight increased, with a significant level, compared with the control but this body weight increase did not appear to be involved in blood pressure elevation since the latter preceded the former.

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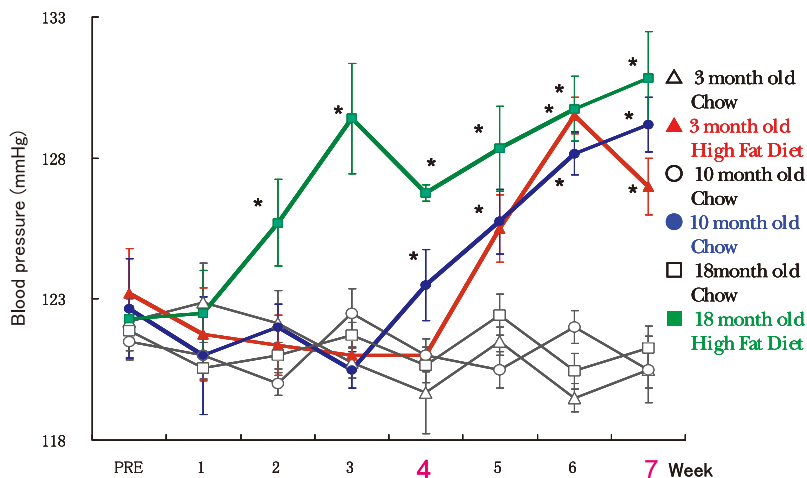


Fig. 4 Aging Effect on Blood Pressure

* $P < 0.05$ (compared with the control)

F344/N Male Rats of age 3, 10, and 18 month old. See Fig. 1 for details.

CONCLUSION

In summary, we found that even without having excessively high calorie diet and without body weight gain, intake of excessive animal fat will cause visceral obesity and so do hypertension. Also, it is suggested that males with high-fat diet are more prone to become hypertensive than females. Testosterone was implicated to be a culprit. Furthermore, post-menopause females have decreased female hormone in their blood, resulting in proportionally higher male hormone, thus potentially causing high morbidity rate of hypertension among the post-menopause females. Also, it was shown that the older the persons are, the greater the dietary effect results in, causing their blood pressures likely to increase. Based on the findings from these experimental models, we are currently working to further the understanding of the mechanism of elevated blood pressure due to visceral obesity from dietary fat.

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