Shimane J. Med. Sci. Vol. 2, pp. 124—132, 1978

Experimental and Clinical Studies on the Relationship between Genetic Hypertension and Glucose Metabolism

(hypertension/glucose tolerance/insulin)

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(Received December 28, 1978)

Spontaneously hypertensive rats (SHR) showed a mild deviation of glucose metabolism, as detected by glucose tolerance test (GTT). The morphological changes in the pancreatic islets of SHR may possibly be related to the hormonal alteration in genetic hypertension. In light of these experimental results GTT was applied for study in the following 3 groups of humans : the normotensives with or without a family history of cerebral stroke (5 each) and 5 hypertensives with no apparent secondary cause.

Higher serum glucose and insulin levels were obtained at 1 hour of GTT both in the hypertensives and the normotensives with a family history of cerebral stroke.

Serum lipid levels were altered by glucose administration, particularly serum cholesterol level was decreased by about 10 mg/dl at 1 hour after glucose administration both in rats and humans, with or without hypertension.

The slight intolerance detected by GTT in genetic hypertension both in rats and humans may be used as a parameter in the detection of genetic predisposition to hypertension or cerebral stroke.

Clinical and epidemiological studies indicated that hypertensives tend to show higher serum glucose levels than do normotensives (1—5). The relationship between hypertension and glucose metabolism remains to be clarified in the approach to the pathophysiology or the pathogenesis of hypertension, particularly essential hypertension and the metabolic disorders of glucose including diabetes mellitus.

To determine the relationship between essential hypertension and glucose tolerance, we applied the glucose tolerance test (GTT) first to spontaneously hypertensive rats (SHR), one of the most suitable models for human essential hypertension (6—10), and then to humans with essential hxpertension.

MATERIALS AND METHODS

Experimental Study

Glucose tolerance test (GTT) was applied to 3 strains of adult female rats—

stroke-prone SHR (SHRSP) (11), stroke-resistant SHR (SHRSR), which developed cerebral stroke spontaneously over 80% and less than 10%, respectively, and Wistar-Kyoto rats (WK), from which SHR had been derived. After body weight and blood pressure (12) were measured, 15 rats of each strain were fasted for about 12 hours during the previous night. From each strain, 5 rats were decapitated and 10 rats were given 3 ml of 20% glucose orally. Five rats of each group were sacrificed at 1 hour and 2 hours, respectively, after glucose administration.

Blood was collected into heparinized tubes. Serum levels of glucose, cholesterol and triglyceride in each GTT phase were measured by the method of Technicon Auto-Analyser II (13). Serum total protein was also determined using a protein refractometer (ATAGO-T2). In this experiment, the pancreas was fixed in Zenker's solution, and serially sectioned for microscopical observation, and the areas of the islets were measured by a quantitative picture analysing system, MOP-AM 03 (KONTRON).

TABLE I. *Age, Body Weight, and Blood Pressure in 6-month-old Female WK, SHRSR, and SHRSP used for Glucose Tolerance Test (GTT)*

	Fasting			1 hr after glucose administration			2 hrs after glucose administration		
Strain	Age (days)	BW (g)	BP (mmHg)	Age (days)	BW (g)	BP (mmHg)	Age (days)	BW (g)	BP (mmHg)
WK (15)	166±0	225±5	126±4	166±0	215±5	124±4	166±0	205±7	123±4
SHRSR (15)	169±1*	233±7	164±7**	174±2**	222±6	165±7**	169±2	225±4	154±13
SHRSP (15)	180±2**	214±3	203±7**	182±1**	204±4	202±8**	180±2**	212±3	199±8

WK : Wistar-Kyoto rats, SHR : Spontaneously hypertensive rats, SHRSR : Stroke-resistant SHR, SHRSP : Stroke-prone SHR, BW : Body weight, BP : Tail blood pressure. ( )No. of rats—5 rats were sacrificed at each GTT phase. Values represent mean±SE. Statistically significant difference from WK (* : $0.01 < p < 0.05$, ** : $p < 0.01$).

Age, body weight and blood pressure in these experimental groups are listed in Table I.

Clinical Study

GTT was performed on 15 men ranging in age from 30's—50's and who were rural inhabitants in a mountainous Daiwa Village in Shimane Prefecture. Fifty grams of glucose (150 ml of Toleran) was given orally to the following 3 groups in the morning (9 a.m.), following an overnight fast : Group 1 ; 5 of the normotensives with no particular family history of cerebral stroke, Group 2 ; 5 of the normotensives with a family history of cerebral stroke, and Group 3 : 5 of the hypertensives not treated with Thiazide which may affect glucose metabolism (14). In these groups, serum levels of glucose, insulin, total cholesterol and triglyceride were measured in each GTT phsae.

The enzyme methods for glucose, total cholesterol and triglyceride, and the double antibody method for insulin were used, respectively.

In this study, through anamnesis and routine physical examination, congenital and valvular heart diseases, and secondary hypertension were checked. Blood pressure was measured with the subjects in the sitting position, and WHO's definition of hypertension was applied ; systolic blood pressure levels of 160 mmHg or over and/or diastolic blood pressure levels of 95 mmHg or over. The family history of cerebral stroke in the examinees was graded tentatively according to the "hereditary score" : When stroke had occurred in one or both parents, 2 or 4 points were given, respectively. Stroke in grandparents was counted as 1 point for each and added to the score in the case there was no occurrence of stroke in the parent(s). Obesity index was computed from weight and body weight using Minowa's chart (15). The

TABLE II. *Age, Blood Pressure, Obesity Index and "Hereditary Score" in 3 Groups of Examinees*

Group	Age (yr)	Blood pressure (mmHg) Systolic	Diastolic	Obesity index (%)	"Hereditary score"
Group 1	41±4	108±7	70±6	−2±5	0.0±0.0
Group 2	49±6	118±4	75±1	+2±2	2.8±0.5**
Group 3	55±2*	163±8^{++}**	97±5^{+}*	+3±2	1.6±0.4**

Group 1 : The normotensives without family history of cerebral stroke. Group 2 : The normotensives with obvious family history of cerebral stroke. Group 3 : The examinees with essential hypertension. Values represent mean±SE. Statistically significant differences from Group 1 (* : $0.01 < p < 0.05$, ** : $p < 0.01$) and from Group 2 ($^{+}$: $0.01 < p < 0.05$, $^{++}$: $p < 0.01$).

increase of 20% or over in relative body weight was defined as obesity. Electrocardiogram (ECG) was also taken. Other biochemical laboratory tests were performed to determine the general physical state of the examinees. Such tests included serum total protein and albumin, and serum GOT (glutamic oxaloacetic transaminase), GPT (glutamic pyruvic transaminase), ZTT (zinc sulfate turbidity test), ALP (alkaline phosphatase) and amylase for the liver and the pancreas conditions. Age, blood pressure, obesity index and "hereditary score" in 3 groups of examinees are listed in Table II.

RESULTS

Experimental Study

The results of glucose tolerance test (GTT) are shown in Tables III, IV and V. The mean of serum glucose level at each GTT phase was higher in both SHRSP and SHRSR than in WK. The differences were statistically significant between SHRSR and WK at 2 hours after glucose administration (Table III). The mean of serum total cholesterol level was higher in WK and lowest in SHRSP at each GTT phase. The level was decreased by about

10 mg/dl at 1 and 2 hours after glucose administration in each strain (Table IV). The mean of serum triglyceride level, which was lowest in WK, was also decreased by about 40—60 mg/dl at maximum at 1 hour after glucose administration in all 3 strains (Table IV). On the other hand, the mean of serum total protein level at each GTT phase did not significantly differ among the 3 strains and was not affected by glucose administration (Table V).

TABLE III. *Serum Glucose Level in Glucose Tolerance Test in WK, SHRSR and SHRSP*

Strain	Serum glucose level (mg/dl)		
	Fasting	1 hr after glucose administration	2 hrs after glucose administration
WK	115±6	140±8^{+}	134±3^{+}
SHRSR	115±8	161±11^{+}	166±5$^{++}_{**}$
SHRSP	121±16	156±6	150±6

WK, SHRSR and SHRSP : Refer to Table I. Values represent mean±SE. Statistically significant differences from WK (* : $0.01 < p < 0.05$, ** : $p < 0.01$) and from "fasting" ($^{+}$: $0.01 < p < 0.05$, $^{++}$: $p < 0.01$).

TABLE IV. *Serum Total Cholesterol and Triglyceride Levels in Glucose Tolerance Test in WK, SHRSR and SHRSP*

Strain	Serum cholesterol level (mg/dl)			Serum triglyceride level (mg/dl)		
	Fasting	1 hr after glucose administration	2 hrs after glucose administration	Fasting	1 hr after glucose administration	2 hrs after glucose administration
WK	103±7	91±4	90±3	89±9	32±2^{++}	54±6^{+}
SHRSR	93±4	80±2*$^{+}$	77±3*$^{+}$	130±23	81±15*	90±14*
SHRSP	79±5*	71±2**	68±3**	114±19	70±6^{+}**	80±6*

WK, SHRSR, and SHRSP : Refer to Table I. Values represent mean±SE. Statistically significant differences from WK (* : $0.01 < p < 0.05$, ** : $p < 0.01$) and from "fasting"($^{+}$: $0.01 < p < 0.05$, $^{++}$: $p < 0.01$).

TABLE V. *Serum Total Protein Level in Glucose Tolerance Test in WK, SHRSR and SHRSP*

Strain	Serum total protein level (g/dl)		
	Fasting	1 hr after glucose administration	2 hrs after glucose administration
WK	7.7±0.3	7.6±0.2	7.6±0.2
SHRSR	7.8±0.1	7.4±0.1	7.4±0.1
SHRSP	8.1±0.2	7.7±0.1	7.9±0.1

WK, SHRSR and SHRSP : Refer to Table I. Values represent mean±SE.

As for microscopical findings of the pancreas, moderate arterial and/or arteriolar wall thickening was observed in the hypertensive strains. No marked fibrosis was found in the exocrine tissue in any of these strains. Although there was no particular difference in these microscopical findings among 3 strains, the mean area of single islet was significantly larger in SHRSP and SHRSR than in WK, while the mean of the counted number of islets in a unit area (100 mm^2) of a section of the pancreas was not significantly different among these 3 strains (Table VI).

TABLE VI. *Comparison of the Number and the Area of Pancreatic Islets among WK, SHRSR and SHRSP*

Strain	No. of animals	Mean count of islets in 100mm^2 of pancreas tissue	Mean area of single islet ($10^{-2}mm^2$)
WK	5	86±4	1.08±0.07
SHRSR	5	78±5	1.49±0.13**
SHRSP	5	66±12	1.54±0.11**

WK, SHRSR and SHRSP : Refes to Table I. Values represent mean±SE.
** : Statistically significant difference from WK ($p < 0.01$).

Clinical Study

All indices except for "hereditary score" were not significantly different between Groups 1 and 2, as shown in Table II. However, both systolic and diastolic blood pressure in Group 3 were significantly higher than those in Groups 1 and 2. Ages of those in Group 3 were significantly different from those in Group 1 but not in Group 2. There were no particular electrocardiographical abnormalities in Groups 1 and 2, but in Group 3, there were 2 with ST, T changes as represented by the Minnesota Codes as IV and V, and 1 with atrial fibrillation. There were no particular abnormalities or statistically significant differences among 3 groups regarding biochemical parameters.

Fasting serum glucose level in GTT remained within normal range in all 3 groups. However, at 1 and 2 hours of GTT, serum glucose level was higher in Groups 2 and 3 than Group 1. Particularly at 1 hour, the difference between Groups 1 and 2 was statistically significant. Serum insulin levels at 1 and 2 hours were also higher in Groups 2 and 3 than Group 1 (Fig. 1).

Serum lipid levels in GTT changed with glucose administration. Serum cholesterol level decreased by about 10 mg/dl at 1 hour after glucose administration, and such was also noted in rats (Tables IV and VII). However, such a constant reduction was not seen in serum triglyceride levels (Table VII).

DISCUSSION

Relationship between essential and genetic hypertension and the metabolic

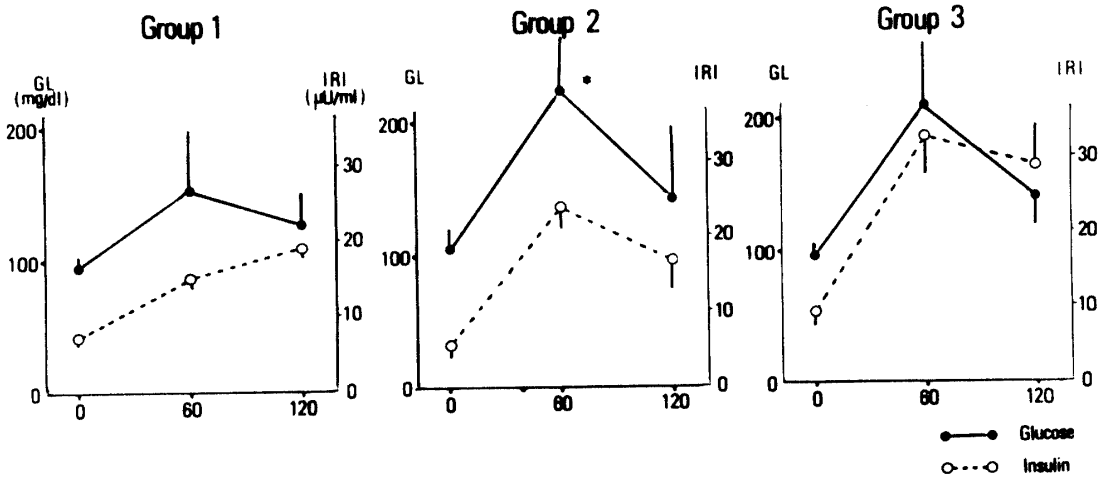

Fig. 1. Serum glucose and insulin levels in glucose tolerance test in 3 groups of examinees.
Group 1 : Normotensive without family history of cerebral stroke
Group 2 : Normotensive with obvious family history of cerebral stroke
Group 3 : Examinees with essential hypertension
* : Statistically significant difference from Group 1 ($p < 0.05$)

TABLE VII. *Serum Total Cholesterol and Triglyceride Levels in Glucose Tolerance Test in 3 Groups of Examinees*

Group	Serum cholesterol level (mg/dl)			Serum triglyceride level (mg/dl)		
	Fasting	1 hr(⊿) after glucose administration	2 hrs(⊿) after glucose administration	Fasting	1 hr(⊿) after glucose administration	2 hrs(⊿) after glucose administration
1	147±1	143±2 (−4±2)	140±1 (−7±1)	89±13	88±11 (−1±5)	80±10 (−9±5)
2	166±15	154±15 (−12±1**)	156±15 (−10±1)	135±28	133±29 (−2±5)	121±20 (−15±11)
3	178±19	171±18 (−7±2)	172±19 (−6±3)	145±42	147±39 (+2±3)	146±42 (+1±3)

Group 1, 2 and 3 : Refer to Table II. Values represent mean±SE.
⊿ : Changed value from "fasting". Statistically significant difference from Group 1 (** : $p < 0.01$)

disorders of glucose has to be studied as diabetes mellitus and hypertension are both typical "adult diseases", and the comprehensive control mechanisms of the nervous and hormonal systems are involved in both diseases. However, analyses of the relationship in humans are complicated, because various genetic or environmental factors affect both blood pressure and glucose metabolism. For example, obesity may affect both glucose metabolism and hypertension. Therefore, in order to clarify the relationship between essential hypertension and glucose metabolism, we carried out experimental studies, applying the glucose tolerance test (GTT) to SHR, as already reported (16, 17).

The etiology of essential hypertension or cerebral stroke in Japan may be different from that in Western countries. Especially, in rural areas such as in

Akita or Shimane Prefectures, the inhabitants have been raised in a traditional manner. These areas have the highest prevalence and incidence rates of hypertension and cerebral stroke, respectively, in Japan. However, their serum total cholesterol levels are lower and obesity indices are less than those seen in urbanized populations such as in Osaka City where the incidence of stroke is far less than in Akita (18−20). These epidemiological studies were ascertained in our experimental studies : SHR, particularly SHRSP with severe hypertension had lower serum cholesterol levels and less body weight as shown in Tables I and IV. A high fat diet lowered blood pressure in SHR and prevented cerebral stroke in SHRSP (21). In these respects, SHR may be regarded as the most appropriate model for the type of the hypertension most prevalent in Japan.

Our previous studies indicated that the higher serum glucose level or lower glucose tolerance in SHR was already apparent in the prehypertensive state, and suggested a possible relationship between hyperglycemia and catecholamine metabolism at the initial stage of spontaneous hypertension (16).

In the present studies, we attempted to determine the relationship between serum glucose and lipid levels in GTT, both of which are related to hypertension and cerebral stroke. In our clinical studies, we assessed the relationship between essential hypertension and glucose tolerance, and compared the findings with results from experimental studies on SHR. In epidemiological studies, the normal serum glucose level at each GTT phase of the Japanese male at different ages was studied. One report stated that the serum glucose level at 1 hour after glucose administration increased by about 6 mg/dl with an increment of 10 years in age (22). Other workers found no difference in these levels between the examinees in their 40's and 50's (23). Thus, the difference in GTT between groups 1 and 3 cannot be ascribed only to effects of ageing.

Serum glucose levels at 1 hour and 2 hours in GTT were higher both in SHR and in humans with essential hypertension than each control group (Table III and Fig. 1). Serum lipid levels in GTT of both rats and humans also showed a similar tendency. For example, serum total cholesterol level tended to decrease at 1 hour after glucose administration (Tables IV and VII). However, serum triglyceride levels in humans, the means of which might be lowest at 2 hours of GTT, were not necessarily decreased by glucose administration, while these levels of rats were definetely decreased (Tables IV and VII). Glucose metabolism was reported to be closely related to triglyceride or free fatty acid metabolism as described by "glucose fatty acid cycle" (24). However, such rapid responses of both serum triglyceride and cholesterol after glucose administration as observed in this study have not been described in detail. One of the explanations for such responses may be as follows : Serum non-esterified free fatty acid (NEFA), which is also rapidly lowered after glucose administration (25), might be related to cholesterol metabolism via acetoacetyl Co A.

Serum insulin level of GTT in humans with essential hypertension (Group

3) tended to be highest in each GTT phase. This may correspond to higher serum insulin levels at "fasting" in SHR as already reported (17). And, in SHR, such a hormonal response may be related to the morphological changes of the pancreatic islets (Table VI) (26).

In the clinical study, we evaluated the family history of cerebral stroke, applying the "hereditary score" to each examinee (Table II). Interestingly, the normotensives with an obvious family history of cerebral stroke, (Group 2), showed higher levels of serum glucose and insulin at 1 and 2 hours in GTT than did those in Group 1 (Fig. 1). Our results parallel those in a report from Germany stating that normotensives with a family history of hypertension showed higher serum insulin levels after intravenous glucose administration (4).

At present we do not have a satisfactory explanation for the lower glucose tolerance in Group 2. However, it should be kept in mind that the experimental results of lower glucose tolerance in the prehypertensive, young SHR (16), may be related to catecholamine metabolism, which was reported to be increased; norepinephrine and dopamine-β-hydroxylase (DBH) was elevated in the blood (27−29).

Therefore, we consider it is necessary to follow-up the examinees in these 3 groups, and to increase the number of examinees. GTT may thus serve as a useful tool in assessing parameters related to essential hypertension or cerebral stroke, both clinically and epidemiologically.

The authors wish to gratefully acknowledge the pertinent advice and encouragement of Dr. Yoshio Komachi, Director, Department of Epidemiology and CVD Mass-examination, the Center for Adult Diseases, Osaka, Professor Shinya Note, Department of Internal Medicine, Shimane Medical University, and Professor Yorinori Hikasa, Department of Surgery, Faculty of Medicine, Kyoto University.

This study was supported by grants from NIH, U. S. A. (HL 1775), the Science and Technology Agency of the Government of Japan, Japan Society for the Promotion of Medical Science, Mitsubishi Foundation, Japan Tobacco and Salt Public Corporation, Foundation for Adult Diseases and Foundation for Metabolic Diseases.

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