NOTE

Endocrine Function in a Case of $\beta$-Adrenergic Hyperdynamic Circulatory State

HISAKO FUSHIMI$^1$, YASUO KOBAYASHI$^1$, TIAKI KOYAMA$^1$, MASAHIKO MIYATA, TADASHI YAMADA$^1$, YOSHIHIKO MATSUYUKI$^1$, TORU SUGASE$^2$, KENJI SHIMA$^{3*}$ and SEIICHIRO TARUI$^4$

$^1$Department of Medicine, Sumitomo Hospital, Kita-ku, Osaka 530, $^2$Health Administration Department, Teishin Hospital, Tennoji-ku, Osaka 543, $^3$Central Laboratory, School of Medicine, Osaka University, Fukushima-ku, Osaka 553 and $^4$Second Department of Internal Medicine, Osaka University, Fukushima-ku, Osaka 553

Synopsis

Endocrine functions were investigated in a case of "$\beta$-adrenergic hyperdynamic circulatory state". This state was diagnosed by (1) typical symptoms of cardiac awareness, (2) physical findings (increments of pulse rate and blood pressure by changing positions or walking), (3) increase in cardiac output ($5.25\text{l/min} \rightarrow 14.03\text{l/min}$) and decrease in circulatory time ($10.8\text{sec} \rightarrow 5.5\text{sec}$) by isoproterenol infusion ($0.02\lg/min/kg\text{ body weight}$), (4) rapid loss of symptoms and above findings by propranolol treatment (30mg per os daily) and reappearance by discontinuing medication.

The mechanism of insulin response to glucose has been a controversy as to whether the secretion is transmitted by $\beta$-receptor or independent glucose receptor. And in this physiologic $\beta$-adrenergic state, it was found that insulin responses in IVGTT and OGTT were within normal limit. When $\beta$-adrenergic condition was corrected by propranolol treatment, insulin responses were shown lowered, though in the normal range. This could be reproduced by discontinuing medication. Insulin, glucagon and growth hormone secretions caused by arginine were also found normal, but during the period the patient was on propranolol therapy, all responses were decreased, within the normal range. These results do not positively support the idea that glucose receptor is linked to $\beta$-receptor. They do not either agree with the contention that secretions of insulin, glucagon and growth hormone induced by arginine are mediated through $\beta$-receptors.

The concept of $\alpha$- and $\beta$-adrenergic receptor was proposed by Ahlquist (1948). Since then, it has been developed greatly in the various medical fields in cooperation with discoveries of many $\alpha$- and $\beta$-stimulating or blocking agents. In endocrinology, it has been proposed also that $\alpha$- and $\beta$-receptors play an important role in hormone secretion, especially insulin release induced by glucose which had been intensively studied and suggested to be dependent on $\beta$-adrenergic activity (Cerasi et al., 1972). This concept has been disputed recently by some authors (Robertson and Porte, 1973; Hedstrand and Aberg, 1974), who reported the glucose receptor was independent of $\beta$-receptor. Thus, these receptors still provide materials for controversy.

On the other hand, "hyperdynamic $\beta$-
"adrenergic circulatory state", the symptoms of cardiac awareness, increased responsiveness of heart rate to various stimuli, and hyperkinetic circulation due to increased \( \beta \)-adrenergic receptor reactivity, in short, hypersensitivity of \( \beta \)-receptor was reported (Frohlich et al., 1969). To our knowledge, endocrine functions in this syndrome were not reported previously. Our purpose of this report is to evaluate endocrine functions in this patient, diagnosed to have hypodynamic \( \beta \)-adrenergic circulatory state.

Case Report

A 58-year-old Japanese house wife was admitted to the hospital on Dec. 27, 1974, for her high blood pressure. Past history revealed partial gastrectomy 7 years ago due to gastric ulcer. Nothing was remarkable in her family history. Mild hypertension was found 13 years ago but the patient had not been treated. Seven years ago, while she was under bed rest during postoperative days, blood pressure was normal. Following discharge, her systolic blood pressure rose to 200-220 mmHg and no antihypertensive drugs were effective for lowering blood pressure (\( \beta \)-blocker was not used). She also complained of occasional diarrhea, palpitation and perspiration. Gradual loss of weight (from 51 kg to 34 kg on admission) took place during the last 7 years.

The patient was a short and undernourished woman (height, 140 cm; weight, 34 kg), alert and cooperative. B.P. was 180/90 on supine position (right after lying down), pulse rate was 76 (regular). No abnormalities were found except an operation scar in the epigastrium by physical examination.

Laboratory findings: RBC 367\( \times 10^4 \), Hb 66\%, C. I. 0.70, Hct 32\%, WBC 4700 with normal differential counts. Serum Na, K, Cl, creatinine, total protein and its electrophoretic pattern were within normal range. Liver function tests were normal. Irosorb: 276 mg/100 ml, serum Fe: 127.4 \( \mu \)g/100 ml, serum total cholesterol: 172 mg/100 ml, \( \beta \)-lipoprotein: 1.6 mm (in normal range), triglyceride: 45 mg/100 ml, phospholipid: 174 mg/100 ml, NEFA: 0.11 mEq/l. Electrophoretic pattern of serum lipoprotein was normal. Kidney function tests: PSP 45\% at 15 min. Fishberg concentration test 1016, 1023 and 1022. RPF: 556 ml/min, GFR: 100 ml/min, (No difference between right and left kidney in either RPF or GFR was found). Plasma renin activity: 1.4 mg/ml/hr. Cold pressor test was positive. Aschner and Gzermak tests were negative. ECG showed possible left ventricular hypertrophy. Double Master’s test was positive only right after exercise.

The patient was treated with 10 mg of propranolol three times \emph{per os} a day (30 mg in total). All symptoms (cardiac awareness, palpitation and diarrhea) and also abnormal physical findings (rapid and remarkable increase in pulse rate and blood pressure by standing up slowly from the supine position or walking) subsided rapidly. They appeared by discontinuing medication just as before the treatment and disappeared again by treatment. The treatment was interrupted twice for the tests. Since then, the medication has continued. Her mild anemia was brought to almost normal. She gained weight of 6 kg for the last 1 year and has been free from subjective symptoms and physical findings.

Methods

Heart rate and blood pressure were investigated in various positions and before, during and after the intravenous administration of isoproterenol. \emph{Isoproterenol infusion test}: Effects of intravenous infusion of 0.02 \( \mu \)g isoproterenol/kg body weight/min on heart rate, cardiac output and circulation time were measured as follows. The patient was made to fast and all medication was discontinued overnight.
One two-channeled scintillation detector was placed on the skin of the chest wall over the third interspace slightly left to the left midclavicular line and the other detector on the skin of the proximal end of the left femoral artery of the patient in the supine position. Twenty microcuries of $^{131}$I-RISA in a volume of precisely 2 ml was injected into the right antecubital vein, while tourniquetting a blood pressure cuff, and it was deflated rapidly. The time constant of the rate meter was set at 0.5 sec. The passage of the radioactive bolus through heart and then femoral artery had been recorded until the radioactivity equilibrium values were recorded. Then the intravenous infusion of isoproterenol was started and when the patient showed tachycardia with arrhythmia (18 min after the start of infusion), 100 $\mu$Ci of $^{131}$I-RISA was injected and recorded as above. Circulating time from the elbow to the femur before and during the infusion was calculated. Cardiac output before and during the infusion was calculated from the area under the precordial curve according to Bauer (1965). This isoproterenol infusion test was made before and during propranolol treatment. Besides this, instead of isoproterenol, normal saline was infused in the same way for the control study.

**Endocrinological studies:** Urinary excretion of 3-methoxy-4-hydroxy mandelic acid (VMA) was determined by the Pisano's method (Pisano et al., 1962). Metanephrine and normetanephrine was determined by Branjes et al. (1964). Cyclic AMP was measured with Cyclic AMP Radioimmunoassay Kit from Schwarz-Mann Co. In arginine or glucose tolerance test, the patient was made to fast overnight and no medicines were given in the morning.

**Oral glucose tolerance test:** 100 g glucose load of Toleran G (Takeda Co.) was used. Insulin was determined with Dinabot Insulin Riaikit. For growth hormone (GH) determination, Dinabot Riaikit was used. For glucagon, 30 K antibody was used. These tests were repeated by discontinuing medication.

**Results**

Changing positions or walking caused remarkable tachycardia and increase in blood pressure (Fig. 1). As shown in Fig. 2 and 3, pulse rate and cardiac output increased rapidly and circulation time was shortened remarkably by isoproterenal infusion before treatment, whereas they showed no detectable changes by isoproterenal infusion during propranolol treatment similar to the control experiment by normal saline infusion. No significant changes in amounts of urinary VMA, metanephrine and normetanephrine were detected before and during the period of propranolol treatment. There was found no significant difference in urinary cyclic AMP before and during propranolol treatment (Table 1). Changes in blood sugar and IRI levels
during oral and intravenous glucose tolerance tests were shown in Fig. 4. Plasma IRI response to oral glucose was slightly reduced during the treatment compared with the one before therapy. Blood sugar and insulin responses to intravenously administered glucose before and during treatment were almost identical on different occasions. Arginine tolerance test with or without propranolol treatment was repeated three times by interrupting the treatment. Two of them were shown in Fig. 5. Each of insulin, glucagon and GH response to arginine was normal and all responses were slightly diminished during the treatment on every occasion.

![Fig. 3. Circulation time and cardiac output before and during isoproterenol infusion before propranolol treatment. See the text for calculation of circulation time and cardiac output.](image)

![Fig. 4. Blood glucose and insulin response to glucose given orally (OGTT) and intravenously (IVGTT) before and during propranolol treatment.](image)

![Fig. 5. Serum insulin (IRI), glucagon (IRG) and growth hormone (GH) response to arginine load before and during propranolol treatment. Top and bottom row represent two tests made on different occasions by discontinuing propranolol treatment. Ten percent 300 ml arginine solution was infused dropwisely from a cubital vein at a speed of 10 ml per min, being started right after 0 time blood sample was drawn, for 30 min.](image)
Discussion

Pheochromocytoma was ruled out by the following findings: (1) As far as this patient was kept under under bed rest, blood pressure was normal, (2) Contents of VMA, metanephrine and normetanephrine in urine were within normal limit and there were no significant differences between the values before and during the treatment, (3) Rapid and complete loss of symptoms and findings by the propranolol treatment (30 mg daily). Renal hypertension was differentiated by normal kidney function tests and urinalysis and normal renin activity. No positive data which supported secondary hypertension were found. Essential hypertension was not likely because of its lability in positions and complete loss of hypertension by bed rest or propranol treatment. Tachycardia due to anemia was neglected because the patient developed the same symptoms and the same physical and laboratory findings by discontinuing propranolol treatment even after a remarkable improvement of anemia took place.

The so-called hyperdynamic \( \beta \)-adrenergic circulatory state is a syndrome of hyperresponsiveness of \( \beta \)-adrenergic receptor, proposed by Frohlich et al. (1966). It had been reported by various names except for the one mentioned above, such as essential hyperkinemia (Starr and Jonas, 1943) and hyperkinetic heart syndrome (Gorlin, 1962). It has been studied intensively in Japan by Miyabara (Miyabara et al., 1970 and 1973; Miyabara and Hirano, 1968). Although the question of the terminology and complete establishment of the concept of this syndrome still remains controversial (Bourne et al., 1970), this syndrome has been approved well recently (Kokubu and Ueda, 1973; Naito and Arakawa, 1973).

The case in this paper with (1) typical symptoms and physical findings, (2) hyper-reaction to isoproterenol, (3) magnificent disappearance of those abnormalities by propranolol treatment and (4) reproducibility of both conditions by giving or discontinuing propranolol seems to have provided enough terms for diagnosis of hypersensitivity of \( \beta \)-adrenergic receptor.

On the other hand, \( \beta \)-receptor has been proposed to play an important role in the hormonal secretion. Currently whether or not \( \beta \)-adrenergic receptor might be postulated glucose receptor has been lively debated. Kotler and his associates (1966) and later Wray and Sutcliffe (1972) proposed hypoglycemic effects of propranolol was attributed to interference with sympathetic stimulation of glycogenolysis in skeletal muscle and with the sympathetic suppression of insulin secretion. Then Cerasi and his associates (Cerasi et al., 1972) suggested that \( \beta \)-adrenegic receptor linked to glucose receptor in the beta cells. This hypothesis was disputed by Robertson and Porte (1973), concluding that insulin response induced by glucose was independent of \( \beta \)-adrenergic receptors. This was supported further by Hedstrand and Aberg (1974), who observed blockade of \( \beta \)-adrenergic receptor made no difference in the insulin response to glucose.

Therefore it seemed important to study endocrinologic functions including insulin secretion in this case with physiologic hypersensitivity of \( \beta \)-receptor. Insulin release induced by glucose given orally or intravenously was found within normal range. Supposing that there were no separate glucose receptors within the pancreatic islet, insulin response should be hyperactive. This is not the case in our patient.

The result does not support positively the idea that glucose and \( \beta \)-receptor are linked. The data that insulin, glucagon and GH responses to arginine were all normal before treatment, do not support that these responses to arginine are mediated through \( \beta \)-receptors. Recent studies have not clarified receptor mechanisms yet and
it is not known whether all reactions linked to β-receptors respond simultaneously in any case. There may be some left not involved. A possibility that pancreas β-receptor is not involved can not be excluded in this case. Besides, we cannot neglect effects of propranolol on insulin secretion induced by glucose and on insulin, glucagon, and G.H. secretion induced by arginine, though they were very little. Therefore, it might be concluded our study does not support positively the idea that these receptors are mediated through β-receptors.

The data that basal GH levels and GH responses to arginine showed no increments in this patient before the treatment and resulted in slight decrease on propranolol therapy, are not in accordance with the report of normal human subjects by Imura et al. (1971). Discrepancy in our case seems to be derived from the hypersensitive state of β-receptor.

The occurrence of large amounts of cyclic AMP in urine was established by Butcher and Sutherland (1962). β-receptor is related to adenyl cyclase system (Robinson et al., 1967), but in our patient no significant change was noticed in urinary excretion of cyclic AMP before and during treatment. It is partly because the increment in urinary cyclic AMP is usually small (Ball et al., 1972) and partly because the patient was inactive due to occurrence of her various symptoms on activity. It is also reported that in patients with labile hypertension, excretion of urinary cyclic AMP was not increased (Hamet et al., 1973) as in our case.

References