HEMODYNAMIC AND METABOLIC EFFECTS OF ACTIVITIES OF THE ADRENERGIC BETA RECEPTOR IN PHYSICAL EXERCISE

TAKASHI HAZEKI

It is noteworthy to study that various exercise tests are made not only in physiological field but also in clinical medicine in recent years, and particularly it is noticeable that the exercise test has been applied in the diagnosis of circulatory and metabolic disorders; and also have been used in determining prognosis accurately. Regarding physical response at the time of exercise, however, hemodynamic studies have mostly been made by many investigators up to now, but little study has been made regarding a regulatory system and changes of metabolism and few reports were seen in literatures in this connection.

Therefore, the purpose of author’s study in this paper is to observe the hemodynamic and metabolic changes closely at the time of exercise and at the same time to confirm that sympathetic nervous system and catecholamine have important relations with the regulatory system. Cannon\(^1\) has already reported that in the homeostatic mechanism of the body, the central nervous system and autonomic nervous system play an important role. Dale\(^2\) (1906) discovered that the pressor action of adrenaline changes to depressor action by pretreatment of ergotamine and he made a hypothesis that was due to the fact that there are two kinds of sympathetic nerve fibers and ergotamine has paralyzed the vasoconstrictive sympathetic nerve fiber. After that, this fact has been confirmed by many investigators. Ahtiaq\(^3\) (1948) discovered that noradrenaline, adrenaline, isoproterenol, etc. occasionally reverse according to organs and he made a hypothesis to the effect that each organ has two kinds of adrenotropic receptors and he named them as α-adrenergic receptor and β-adrenergic receptor. After that, many studies have been done regarding receptor blocking agents. The β-blocker\(^4-6\) was developed late after the study of α-blocking agent has been made and the conception concerning α and β-adrenergic receptor has thus been supported more and more strongly. In this paper, author attempted to study effects of β-adrenergic blocker on hemodynamic and metabolic aspects at the time of exercise of human. And for this purpose, author used one of the blocking agents Propranolol\(^6\) (1-isopropylamino - 3 - (1 - naphthylxoy - 2 - propanol hydrochloride) and observed effects on two aspects of resting and exercising in men who are normal individuals and hyperthyroid patients. Furthermore, author attempted animal experiment by use of rats to analyze the metabolic changes at the time of exercise more precisely.

MATERIALS AND METHODS

1. Author selected seven healthy men – ages ranging from 20 to 46 (29 years in average) as shown in Table I and six thyrotoxic patients (4 men and 2 women aged from 24 to 50, average being 44.5 years) were selected for study, whose clinical data are shown in Table II.

All these subjects were ordered to exercise on

Key Words: Physical Exercise Adrenergic Beta-Receptor Propranolol Hyperthyroidism Pyruvate Lactate Excess Lactate NEFA Oxygen Consumption Oxygen Debt

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TABLE I  ANTHROPOMETRIC DATA IN 7 HEALTHY SUBJECTS

<table>
<thead>
<tr>
<th>Name</th>
<th>Sex</th>
<th>Age (yrs.)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Body surface area (m²)</th>
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<td>28</td>
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<td>YM</td>
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<td>39</td>
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<td>56</td>
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<td>168.0</td>
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<td>1.63</td>
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<td>22</td>
<td>167.0</td>
<td>54</td>
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<tr>
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<td>24</td>
<td>168.0</td>
<td>59</td>
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<tr>
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<tr>
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<td></td>
<td>29</td>
<td>167.6</td>
<td>57.1</td>
<td>1.64</td>
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Godart bicycle ergometer at a level of 300 kpm/min for 10 minutes in a supine position with fixed pedalling speed (45–50 cycles per min.). Author observed all changes throughout the study from the beginning until 5 minutes after finish of exercise. After one hour from termination of the first exercise test, author infused 10mg of propanolol (Propanolol is designated as P. hereafter*) mixed with 20 ml of physiological saline slowly into the antecubital vein of the subjects, and 20 minutes later, similar exercise test was done again by the same procedure. Author then studied each parameter comparing before and after P. adm.

2. The oxygen consumption of hyperthyroid patients is definitely high even in resting time. In order to compare various results of hemodynamic and metabolic studies for healthy men with hyperthyroid patients, author first examined the work load of hyperthyroid patients to show the same oxygen consumption as that of healthy men at time of 300 kpm per min. Author then made similar exercise test as stated in the foregoing with 6 patients (1 male and 5 female) – ages ranging between 17 and 51, average being 29 years. All tests were made in morning and the room temperatur was kept at 18°C. All subjects were required to fast and refrain from smoking for more than 16 hours before tests. They were also required to stay at rest in a supine position at least for 30 minutes before starting the test. For the patient group, author strictly discontinued the drug before the test in order to avoid drug-effect. Estimation of hemodynamic parameters was made in every one minute. Blood pressure was examined at brachial artery by indirect methods. Author used 1 electrode tlemtent (Fukuda-electro Type 11 Tokyo) measuring heart rate and recorded electrocardiogram by chest lead V5. Author got M.T.I.* by calculation which was modified from Sarnoff's Tension-Time-Index which is regarded as a good index of myocardial oxygen consumption. The expired gas analysis was recorded by automatic continuous recording system of Electrometaboler

TABLE II  CLINICAL AND LABORATORY DATA ON 12 THYROTOXIC PATIENTS

<table>
<thead>
<tr>
<th>Name</th>
<th>Sex</th>
<th>Age (yrs.)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>BMR (%)</th>
<th>PBI (%)</th>
<th>Triosorb (%)</th>
<th>¹³¹I uptake (%)</th>
<th>S-chol (mg%)</th>
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<tr>
<td>Y. S.</td>
<td>M</td>
<td>47</td>
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<td>63</td>
<td>43</td>
<td>12.3</td>
<td>52.8</td>
<td>50.0</td>
<td>174.2</td>
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<td>M. T.</td>
<td>F</td>
<td>44</td>
<td>156.5</td>
<td>46</td>
<td>49</td>
<td>8.8</td>
<td>55.8</td>
<td>56.1</td>
<td>155.6</td>
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<td>47</td>
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<td>60.0</td>
<td>67.0</td>
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<td>M</td>
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<td>173.2</td>
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<td>10.8</td>
<td>45.5</td>
<td>164.7</td>
<td></td>
</tr>
<tr>
<td>S. S.</td>
<td>M</td>
<td>44</td>
<td>170.0</td>
<td>50</td>
<td>54</td>
<td>9.1</td>
<td>40.2</td>
<td>153.0</td>
<td></td>
</tr>
<tr>
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<td>M</td>
<td>53</td>
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<td>57</td>
<td>40</td>
<td>9.0</td>
<td>48.0</td>
<td>130.0</td>
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<td>156.7</td>
<td>46</td>
<td>55</td>
<td>13.8</td>
<td>32.3</td>
<td>139.2</td>
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<td>S. O.</td>
<td>F</td>
<td>40</td>
<td>161.6</td>
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<td>81</td>
<td>18.6</td>
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</tr>
<tr>
<td>T. A.</td>
<td>F</td>
<td>51</td>
<td>148.4</td>
<td>43</td>
<td>53</td>
<td>7.6</td>
<td>37.0</td>
<td>185.0</td>
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</tr>
<tr>
<td>N. H.</td>
<td>M</td>
<td>24</td>
<td>161.2</td>
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<td>82</td>
<td>20.0</td>
<td>59.6</td>
<td>134.5</td>
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<tr>
<td>T. A.</td>
<td>F</td>
<td>21</td>
<td>165.0</td>
<td>64</td>
<td>69</td>
<td>7.0</td>
<td>52.1</td>
<td>129.9</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
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<td>36.3</td>
<td>162.5</td>
<td>50.2</td>
<td>56.7</td>
<td>10.9</td>
<td>47.8</td>
<td>61.5</td>
<td>153.7</td>
</tr>
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</table>

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(Fukuda-Irika, Tokyo) and in this way author measured oxygen consumption in exercise and rest and oxygen debt. For estimation of metabolite in blood, author used arterial blood and for blood glucose level, author employed the autoAnalyzer method to which Hoffman's method was applied. The plasma lactate and plasma pyruvate were determined by Hohorst's method and Bücher-Latzko's method respectively.

Plasma non-esterified fatty acid was measured by Trout's method and for estimation of excess lactate, author followed Huckabee's equation.

3. Author used 20 Wister male albino rats weighing approximately 150 g and divided them into 4 groups, namely—1) control resting group, II) control exercising group, III) P. treated resting group and IV) P. treated exercising groups were forced to swim for 30 minutes in a pool filled with water of 25 ± 0.5°C. All rats had been kept in a fasting state for 16 hours. Author gave intraperitoneal injection of physiological saline only to the control group, while, on the other hand, author injected diluted P. with physiological saline (10 times dilution of normal concentration) at the rate of 0.015 mg per 100 g of the rat’s weight. The exercise test was done after 20 minutes from the intraperitoneal injection and again after 30 minutes from starting of exercise, the rats were killed with blows. The estimation of plasma lactate and plasma non-esterified fatty acid was made with whole blood collected immediately after decapitation. For estimation of metabolites in tissues, author employed Anthrone method (Seifter et al) for measuring glycogen contents in skeletal, heart muscle and liver immediately after excision from animal. The triglyceride contents in heart muscle and in epididymal fat pad were measured by Zilversmit’s method.

4. Author used 8 matured mongrel dogs weighing more or less 10 kg which have been kept in a fasting state for more than 16 hours. The dogs were anesthetized with morphine hydrochloride (2mg/kg) and hexobarbiturate (40mg/kg) and then author infused about 130 ml of 1 mol of L(+ ) sodium lactate with infusion pump into the femoral vein for 20 minutes at the rate of infusion of 9mg/kg/min. Author measured plasma lactate in arterial blood after 10 minutes and 20 minutes from starting of infusion and again after 15 minutes and 30 minutes after termination of infusion. After one hour, author made intravenous infusion of physiological saline to 3 dogs and for the other 5 dogs author infused P. (0.15 mg per kg of dog’s weight) into a femoral vein. Twenty minutes later, author again infused the same quantity of L(+) sodium lactate and made estimation at same time intervals and studied the results in comparison with each other.

The results were examined by Student’s “t” test and the statistical significant difference of each experiment under various conditions was

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**Fig.1.** Effects of propranolol on heart rate and blood pressure at rest in normal and thyrotoxic subjects.

- C: control,
- P: propranolol,
- N: Normal,
- S: systole,
- D: diastole,
- T: Thyrotoxicosis.

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confirmed to be $p<0.05$.

**Results**

1. Hemodynamic Test Results

1. Effects of Propranolol on heart rate and blood pressure at rest.

Figure 1 shows the heart rate and blood pressure at rest of individuals of healthy group and hyperthyroid patients group (hereafter called patients group). It also shows changes to be seen in heart rate and blood pressure after P. adm.

The heart rate of healthy group before P. adm. was $61.4 \pm 5.8$ per minute in mean value as against $93.7 \pm 10.39$ of patients group and it was noticed that in the difference in significance there was an increase of heart rate in the latter group. After P. adm., author did not recognize any significant changes of heart rate in healthy group, but in the patients group author recognized a decrease of 16.5 beats per minute in average in heart rate which was quite significant ($p<0.001$).

Regarding blood pressure in resting time, author observed that the average blood pressure of healthy group was $118.7 \pm 19.7$mmHg (systolic blood pressure) and $73.0 \pm 10.8$mmHg (diastolic blood pressure) against which the patients group showed these figures to be $134 \pm 31.27$mmHg and $70.17 \pm 7.9$mmHg and thus author noticed widening of pulse pressure in patients group. Regarding the effects of P. adm. on blood pressure, author did not recognize any significant changes in both systolic and diastolic blood pressure of healthy group as well as heart rate, but in patients group, author recognized a decrease of $8.8$mmHg in average in systolic blood pressure while the diastolic blood pressure either remained unchanged or even showed an increasing tendency.

2. Effects of administration of propranolol on heart rate, blood pressure and M.T.T.I. on exercising time.

Figure 2 and 3 show changes in heart rate and blood pressure level in 10 minutes of exercising time for 300 kpm per min. as compared between before and after P. adm.

The maximum increase in heart rate by exercise of healthy group was 30.7 beats per min. in average as against 73.7 beats per min. for patients group. The rate of increase in heart rate

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*Fig. 2. Effects of propranolol on blood pressure and heart rate responses to mild exercise in seven subjects.*

*Fig. 3. Effects of propranolol on blood pressure and heart rate responses to exercise in six thyrotoxic subjects.*

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for the same work load was thus higher in patients group than healthy group before P. adm. But the rate of increase in heart rate during exercise was suppressed by P. adm., healthy group indicated a 25% reduction in average and patients group indicated a 34% reduction, both groups showing significant changes. (The probability for the former group was (P<0.01) and that for the latter was (P<0.02))

The elevation of systolic blood pressure in exercise showed a similar tendency. The patient group showed an average elevation of 41.3 mmHg which is higher than healthy group (19.6 mmHg). However, after P. adm. the rate of elevation was not suppressed in healthy group, while in patient group, a significant suppression of 48% of rate of elevation was observed. (p<0.05)

Figure 4 shows the results on Modified-Tension Time-Index (hereafter called M.T.T.I.) for both groups as compared between before and after P. adm.

As it is clearly understood from the difference in heart rate and blood pressure level between two groups stated above, the M.T.T.I. of patient group showed significantly high levels both in rest and exercise. (p<0.001) Namely, the average of patient group was 3087 mmHg/sec/min at rest and 5615.5 mmHg/sec/min in exercising time as against 2314.1 mmHg/sec/min and 3110.5 mmHg/sec/min respectively of healthy group. Regarding the changes to be seen after P. adm., author observed that both healthy and patient groups showed only a decrease of 11–12% in average in resting time which was not significant at all, but the rise in these values in exercising time showed a significant decrease in patients group. (p<0.01) Author considered, therefore, that the reason why the changes of healthy group in resting and exercising time were not remarkable because the increase of ejection period was relatively long compared with the decrease in heart rate after P. adm.

II) Gas Metabolic Data

Figure 5 shows the results of oxygen consumption and oxygen debt before and after P. adm.

The oxygen consumption of patients group at rest before P. adm. showed a significantly high level, being 366 ± 48.4 ml/min in mean as against 236 ± 14.4 ml/min of healthy group. (p<0.001) For same work level, the oxygen consumption of patient group was 1160.0 ± 116.2 ml/min as against 767.7 ± 120.9 ml/min of healthy group. The absolute value of the former is definitely high, but author did not find significant difference in the rate of increase of value. The oxygen debt of patient group was 2006.7 ± 406 ml in mean as against 1025.1 ± 268.4 ml of healthy

Fig.4. Effects of propranolol on M.T.T.I in normal and thyrotoxic subjects.

Fig.5. Effects of propranolol on gas metabolism in normal and thyrotoxic subjects.
Fig. 6. Glucose, Pyruvate, Lactate, and Nonesterified fatty acids in arterial blood.
N: normal subjects, T: thyrotoxic subjects.

Group, the former showing a significantly high value. (p<0.001)
Regarding the changes in the estimated values, author noticed that oxygen consumption showed a decreasing tendency in both groups, however, the decrease in oxygen consumption in resting time of healthy group was not remarkable, but in the patient group a decrease of 79.3 ml/min in average was remarkable. (p<0.01)
In patient group, the oxygen consumption

Fig. 7. Plasma glucose, pyruvate, lactate and excess lactate concentrations during the experiment in seven healthy subjects before and after blocking of beta adrenergic receptor.

Fig. 8. Plasma glucose, pyruvate, lactate and excess lactate concentrations during the experiment six thyrotoxic patients before and after blocking of beta adrenergic receptor.

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Fig. 9. Effects of exercise on the response of plasma NEFA before and after blocking of beta adrenergic receptor in seven normal subjects.

Fig. 10. Effects of exercise on the response of plasma NEFA before and after blocking of beta adrenergic receptor in six thyrotoxic subjects.

during exercising time and the amount increased from resting time showed a significant decrease. (p<0.02)

At any rate, no change was seen before and after P. adm. in the increasing degree of oxygen consumption during exercising time. Oxygen debt showed a rising tendency in both groups after P. adm. but these changes were not significant.

3. Carbohydrate and Lipid Metabolism

I. Plasma Glucose, Pyruvate, Lactate and Non-esterified Fatty Acid (NEFA)

Figure 6 shows concentrations of some metabolites at rest prior to P. administration for healthy and patient group. The thick horizontal lines in this figure indicate average value of metabolites.

No significant difference was recognized in

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TABLE III  EFFECTS OF PROPRANOLOL, AT REST AND DURING EXERCISE AND RECOVERY, IN NORMAL SUBJECTS

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Propranolol</th>
<th>Heart-rate (beats/min)</th>
<th>Systolic blood pressure (mmHg)</th>
<th>( \dot{V}O_2 ) (ml/min)</th>
<th>( O_2 ) debt (ml)</th>
<th>Lactate (mM/L)</th>
<th>Pyruvate (mM/L)</th>
<th>Glucose (mg%)</th>
<th>NEFA (( \mu )Eq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R</td>
<td>56 80 56 R 106 128 107</td>
<td>236 659 944</td>
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<td>92 80 78</td>
<td>380 400 515</td>
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<tr>
<td></td>
<td>E</td>
<td>56 70 56 E 106 110 100</td>
<td>189 587 1180</td>
<td>1.12 1.16 1.06</td>
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<td>2</td>
<td>R</td>
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<td></td>
<td>E</td>
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<td>140 549 1053</td>
<td>0.92 1.10 1.06</td>
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<td>3</td>
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<td>E</td>
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<td>E</td>
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<td>1.05 1.03 0.98</td>
<td>0.16 0.13 0.14</td>
<td>71 61 67</td>
<td>470 375 400</td>
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B: before propranolol(P),  A: after P,  R: at rest,  E: during exercise,  r: recovery
TABLE IV  EFFECTS OF PROPRANOLOL AT REST AND DURING EXERCISE AND RECOVERY IN THYROTOXIC PATIENTS

<table>
<thead>
<tr>
<th>Group</th>
<th>Case No.</th>
<th>Heart-rate</th>
<th>Systolic blood pressure</th>
<th>$\dot{V}O_2$</th>
<th>$O_2$ debt</th>
<th>Lactate</th>
<th>Pyruvate</th>
<th>Glucose</th>
<th>NEFA</th>
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<tr>
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<td></td>
<td>(beats/min)</td>
<td>(mmHg)</td>
<td>(ml/min)</td>
<td>(ml)</td>
<td>(mM/L)</td>
<td>(mM/L)</td>
<td>(mg%)</td>
<td>(µEq/L)</td>
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<tr>
<td></td>
<td></td>
<td>R</td>
<td>E</td>
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B: before propranolol,  A: after propranolol,  R: at rest,  E: during exercise,  r: recovery
plasma glucose level and pyruvate level, but the plasma lactate level of healthy group showed at 0.89 mM/L in average as against 1.37 mM/L of patient group showing a significant difference. (p<0.02)

NEFA of the former group showed a mean value of 488.6 ± 120.5 µEq/L as against 967.5 ± 322.4 µ Eq/L for the latter, indicating a significant difference. (p<0.001)

2. Effects of propranolol on changes in plasma glucose, pyruvate, lactate, excess lactate and NEFA in exercising time

Author then studied the changes in metabolites level during exercise at regular time intervals and showed the increase and/or decrease from the time at rest in Fig. 7,8,9 and 10.

It is hard to say that plasma glucose level in both groups showed either a consistent increasing or decreasing tendency and furthermore, the changes were only negligible. After P. adm. during exercise, the plasma glucose level in healthy group was unchanged, but in patient group it showed a slight declining tendency. The plasma pyruvate, lactate and excess lactate in both groups showed a significant increase in exercising time (p<0.001) and particularly these values in patient group were big compared with healthy group. Namely, mean values of plasma pyruvate, lactate and excess lactate (excess lactate is designated as XL hereafter) of healthy group after 10 minutes from starting of exercise were 0.167 ± 0.05 mM/L, 1.58 ± 0.11 mM/L and 0.32 ± 0.03 mM/L respectively, against which these values of patient group were 0.24 ± 0.05 mM/L (p<0.02), 3.98 ± 0.42 mM/L (p<0.001) and 1.24 ± 0.82 mM/L (p<0.001) respectively.

In healthy group, both plasma pyruvate and lactate did not show any significant increase after P. adm. even after 10 minutes of exercise and XL value also only showed the average value of zero. Even in patient group after P. adm., the plasma pyruvate and lactate levels showed nearly 49% suppression of rising after exercise in 10 minutes which are quite significant changes and the probability was (p<0.02) and (p<0.001) respectively. However, the changes in XL level after P. adm. were such that there was no significant difference after exercise in 10 minutes and also in 5 minutes after termination of exercise a significant decrease was recognized. (p<0.001)

At any rate, as illustrated in the left diagram of Fig. 9, author have confirmed in this exercise test that plasma NEFA level began to show a declining tendency in healthy group immediately after exercise and maximum declining period was reached within 3–5 minutes, and restoration of the previous value or overshooting were obtained in 7–10 minutes, thus showing a biphasic change.

It is also illustrates in the left diagram of Fig. 10 that a biphasic change is shown in patient group in exercise. After exercise in 5 minutes, the plasma NEFA level restored the previous value and then continued to rise. Author compared the overshoot level of patient group with healthy group at 5 minutes after termination of exercise and found that it showed an average increase of 376 µEq/L in patients against the average of 143 µEq/L of healthy group. The plasma NEFA level of patient group showed such a significant high value. (p<0.02)

The effects of P. adm. are illustrated in the right diagram of each figure. In both groups, the initial lowering phase showed a slow shift in the latter half due to P. adm. and the increase in rebound overshoot after dropping phase greatly reduced and recovery to advancement was only observed after 5 minutes from termination of exercise.

At this time, the amount of NEFA level which increased from the level at rest was decreased by P. adm. In healthy group p value was less than 0.005, and it was less than 0.001 in patient group after P. adm., indicating a significant decrease of rebound overshoot level.

It has been shown above that these results were obtained by giving the same work load to healthy group and patients group (6 subjects) and the effects of P. adm. for the two groups. On the other hand, author studied about the same points by giving the equivalent work load to the remaining 6 patients which requires the same amount of oxygen as healthy man’s oxygen consumption in 300 kpm/min exercise time and showed the results en bloc in Table III and IV.

Author confirmed in this study that the changes in hemodynamic parameter and blood metabolites showed exactly the same tendency in two patient groups. The response for hyperthyroidism in exercise was varied not only in hemodynamic but also metabolic aspects and this fact gave suggestion that the sympathetic nerve stimulation which is considered to exist at the background of this disease has a close interrelationship with thyroid hormone. Author have to emphasize that the oxygen debt of patient group was significantly higher than healthy group, and it well be discussed latter. (p<0.001)
Adrenergic Beta-Receptor in Physical Exercise

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Control | Propranolol

Fig.11. Effects of swimming exercise on plasma lactate in fasting rats.

**Glycogen Contents**

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CONTROL | PROPRANOLOL

Fig.12. Effects of swimming exercise on glycogen contents in rat skeletal muscle.

Fig.13. Effects of swimming exercise on glycogen contents in rat heart muscle.

It is shown that results of animal experiments clarify the basic mechanism of changes of blood metabolite and tissues which were seen during β-adrenergic blocking by P.

**IV Results of Animal Experiments**

(I) Carbohydrate Metabolism

1) Results of Rat Swimming Exercise

Twenty male albino rats were prepared which were divided into 4 groups as stated previously. Author used whole blood in measuring plasma lactate and NEFA. Figure 11. shows the plasma lactate level of each group (thick horizontal lines indicate the respective mean value.)

The plasma lactate level of P. treated group in resting time was rather low, showing mean value of $1.29 \pm 0.23$ mM/L as against $1.46 \pm 0.21$ mM/L of control group, but no significant difference was noted. On the other hand, in the exercise groups, author found that a control group showed mean value of $2.96 \pm 0.64$ mM/L indicating an increase of plasma lactate, against P. treated group showed mean value of $1.64 \pm 0.28$ mM/L indicating no significant difference from the level of resting group. Glycogen contents were measured in skeletal, heart muscle.
and liver for investigating production process the decline of plasma lactate concentrations during exercise made by P. treatment as in man, and showed results in Fig. 12, 13 and 14.

Glycogen contents in skeletal and heart muscle of P. treated resting group showed mean values of $213 \pm 15.9\; \text{mg/100g}$ and $325.5 \pm 40.4\; \text{mg/100g}$ respectively and $232.5 \pm 25.4\; \text{mg/100g}$ and $348.5 \pm 6.1\; \text{mg/100g}$ of control resting group, indicating that no significant difference was seen in glycogen contents in tissues between two groups. After the exercise test completed, in control group, the glycogen contents in skeletal and heart muscle showed mean values of $140.5 \pm 13.6\; \text{mg/100g}$ and $222.8 \pm 15\; \text{mg/100g}$ respectively, indicating significant decreases. In P. treated groups, however, the mean value of the former was $222.3 \pm 21.7\; \text{mg/100g}$ and the latter $312.8 \pm 27.3\; \text{mg/100g}$, thus indicating that no significant difference was seen in glycogen contents in tissues from resting group in spite of exercise. In P. treated groups, glycogenolysis was suppressed in muscular tissues resulted and this was considered to be one of the metabolic actions of β-adrenergic receptor.

At any rate, the glycogen contents in liver showed a significant decrease by exercise in spite

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**Fig. 14.** Effects of swimming exercise on glycogen contents in rat liver.

**Fig. 15.** Effects of saline on plasma lactate changes during L-lactate loading in dogs.

**Fig. 16.** Effects of propranolol on plasma lactate changes during L-lactate loading in dogs.

*Japanese Circulation Journal Vol. 37, February 1973*
of P. adm. This was quite an interesting result to suggest that the activation of phosphorylase might be varied depending on tissues.

2) For the purpose of investigating β-adrenergic receptor whether it has any influence on the disappearing process of lactate, author examined the plasma lactate level at regular time intervals during and after exogenous infusion of 1 mol of L(+) sodium lactate to anesthetized fasting dogs at the rate of infusion of 9 mg/kg/min. It is shown that changes of plasma lactate level in percentage from before starting drop infusion in Fig. 15 and 16.

Fig. 15 shows the results obtained in two times drop infusion of L(+) sodium lactate before and after intravenous administration of physiological saline was done. Author confirmed that there was practically no difference of lactate in plasma concentrations in the test of first and second drop infusion.

On the other hand, as indicated in Fig. 16, after P. adm., the increase in plasma lactate concentrations was suppressed despite drop infusion of the same amount of L(+) sodium lactate and further, prompt restoration to the previous level was obtained. From these findings, author came to find that β-adrenergic receptor gives influence on disappearing process of lactate from blood (possibly increased usage in tissues).

(II) Results in Fat Metabolism

Figure 17 shows NEFA level of four groups. In two resting groups, no significant change was observed by P. adm. and the mean plasma NEFA concentration of control group was

![Graphs showing effects of swimming exercise on triglyceride (TG) contents in rat heart muscle and epididymal fat pad (EFP).](image-url)

*Japanese Circulation Journal Vol. 37, February 1973*
Fig. 19. Schematic presentation of oxygen consumption curves on physical exercise.

538.0 ± 39.1 μEq/L as against 499.0 ± 57.4 μEq/L of P. treated group. In the exercising group, however, the increase in plasma NEFA level in P. treated group was suppressed showing similar effects of P. adm. in man’s exercise group. The mean value of P. treated group was 648.0 ± 66.2 μEq/L as against 846.0 ± 66.0 μEq/L of control group, indicating a significant change. (p<0.01)

Figure 18 shows triglyceride contents in tissues.

Author did not find any difference among these four groups as far as triglyceride contents in heart muscle and in epididymal fat pad.

DISCUSSION AND CONCLUSION

An attempt to clarify the fact that the adrenergic β receptor has close connections with a regulatory system of various hemodynamic and metabolic changes to be seen in exercise, exercise tests to men and animals were done and compared changes by administration of propranolol which is thought to be a specific β-adrenergic blocker. Hartman demonstrated for the first time that catecholamine activity rises during muscular work and this was verified by Cannon soon afterwards. Raab using a non-specific chemical method, reported an increase in epinephrine-like compounds in human blood during exercise. Von Euler and Liljestrand showed and increase urinary excretion of both epinephrine and norepinephrine after prolonged work. Many investigators have reported existence of higher level of sympathetic response during exercise. Various symptoms of hyperthyroidism, increased oxygen intake in tissues and hemodynamic abnormalities greatly resemble sympathicotonia and symptoms shown by exogenous administration of catecholamine. It was already reported that hemodynamic abnormalities, etc. are blocked by reserpine24,25 guanethidine24–26 or by epidural anesthesia27 and many reports have been made regarding the relationships between hyperthyroidism and catecholamine or between catecholamine and thyroid hormone27–36 but generally speaking, it is considered that circulatory abnormalities in hyperthyroidism are mediated by β-adrenergic receptor. Author selected hyperthyroid patients, among other non-thyroid patients, as subjects for study of exercise test by ergometer. Because these patients were considered to be convenient for various observations in the state of normal and hyperactive sympathetic conditions. However, it cannot be denied that it is non-physiological for a man to do exercise in a supine position and it is generally believed that the changes in hemodynamic parameter depending on body position cannot be neglected38,39 At any rate, there is little danger in exercising in a supine position for patients and perform blood sampling and various measurements can be done without difficulties.

Author gave the same work load of 300 kpm/min for 10 minutes to both healthy men and 6 hyperthyroid patients selected from 12 patients. Although this work load was quite light to healthy men, it was possible to find changes in hemodynamic parameter and metabolites in blood and moreover, as in the case of hyperthyroidism, it was possible to give this work load to the patients unless they have very serious circulatory or nervous disturbance, so author considered the same work load to be suitable for

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this exercise test. Sowton and Malmberg reported that hemodynamic aspects are influenced by repeating exercise, while Grimby mentioned that the influence of the first exercise could be avoided in exercise within 20 minutes or in lighter exercise. Author paid a special attention to this point in this study and attempted to avoid psychological effects such as anxiety or fear to perform exercise test on subjects as much as possible by giving preliminary sample test (1/2-1/4 of main test) a few days before the main test and each subject was given one to 2 hours-time interval between each exercise test. In the hemodynamic changes after β-adrenergic blocking, author observed slight bradycardic effect in healthy group although blood pressure did not show any change. The patients group, on the other hand, showed a significant decrease in heart rate and about 12% decline of systolic blood pressure. From these findings, author came to know that the sympathetic nerve activity of healthy group in resting time is not so high whereas it is pretty high in patient group. Regarding the changes during exercise, author observed a decrease of rapid heart rate and suppression of rise of systolic blood pressure. Recently, most of investigators reported that in healthy group, a decrease in heart rate could be recognized after blocking of β-adrenergic receptor, though no change was seen in blood pressure. Estimation of cardiac output was not done in this experiment. In some reports regarding cardiac output measured in resting and exercise, discussions were made by investigators regarding decrease in heart rate after β-adrenergic blocking, whether stroke volume shows changes or not. Author observed effects of P. adm. on cardiac work according to M.T.P.I. as index and recognized a significant decrease during exercise, showing suppression of increase in cardiac work. However, some investigators reported that the heart size changes observed after P. adm. and this point still leaves a question to be studied further.

It was interesting to note that β-adrenergic block with P. has thus proved to modify and not to abolish the hemodynamic response in physical exercise, thus indicating that at least a part of this response is of adrenergic nature.

Among the reports of many investigators concerning cardiac response before and after blocking β-adrenergic receptor, Bishop and Chamberlain and Schröder reported that they have examined the effects of β-blockade on the cardiac output response to exercise in man, but have not observed any consistent or significant change. A very interesting point in the results of these investigations is the conclusion that sympathetic stimulation of the heart is not necessary for a normal response to exercise. On the other hand, some investigators reported significant decrease in cardiac output. In this connection, Braunwald observed that heart rate, cardiac output and mean arterial pressure were slightly, although consistently, reduced in normal subject and the changes were observed at both maximal and submaximal levels of work. And he also mentioned that the fact that P. resulted in a small but significant reduction of cardiac output at rest indicates that sympathetic nervous stimulation of the heart is of some importance in maintaining cardiac output even at rest, at least when the subject is upright. The reduction of cardiac output during exercise appears to be due to interference with two fundamental mechanisms. First, the increase in heart rate is less after β-adrenergic blockade, and second, the normal augmentation of myocardial contractility is almost certainly prevented. Thus they indicated that sympathetic stimulation of the heart contributes to the response in physical exercise, its importance in increasing the cardiac output appears to be relatively small at least in normal subject. However, even if nervous control of the heart is not of major importance in increasing the cardiac output during exercise, it may be of significance in allowing the heart to make rapid adjustment to changes in demand. In this connection, some investigators have reported that in dogs subjected to cardiac denervation, both the heart rate and cardiac output increase more slowly than normal as exercise is begun, even though the final cardiac output achieved does not appear to be significantly reduced.

The fact that cardiac output and heart rate still increase in response to exercise after administration of P. may be attributed to the fact that the blocking of endogenous sympathetic nerve stimuli may be less effective than the blocking on infused catecholamine, that this dose level is incomplete to block β-adrenergic receptor and or that several mechanisms may serve to mitigate the loss of sympathetic stimulation of the heart. Namely, withdrawal of vagal impulses may be responsible in part for the increase in heart rate that still occurs on exercise after β-adrenergic blocking. In addition, an increase in venous return to the heart can still occur as a
result of systemic venoconstriction and pumping action of the skeletal muscles, besides which it is supposed that some metabolic factors are related to the increase in cardiac output during exercise after β-adrenergic blocking.

Regarding the gas metabolism, author found that the oxygen consumption showed the decreasing tendency in both groups at rest and during exercise after β-adrenergic blocking. The changes were significant in patients group, but it was not significant in healthy group. On the other hand, oxygen debt showed the increasing tendency in both groups after β-adrenergic blocking, but the changes were not significant in both groups. In order to analyze more precisely those changes induced by P., author represented the schema of oxygen consumption curve in Fig. 19.

From this Figure, it was recognized that the reduction in oxygen consumption induced by P. is according to the slowly rising of this curve and to the decreasing of maximum value. Therefore, it gave a suggestion that the sympathetic nervous system could also play a significant role in early physiological responses to muscular exercise. In this study, author did not find that there is a significant reduction in oxygen consumption at rest in healthy group after P. adm. But other many reports have shown that oxygen consumption was reduced even in healthy men after P. adm. Braunwald et al. showed that at submaximal levels of work, oxygen consumption was unchanged, the fall in cardiac output after β-adrenergic blocking being fully compensated for by a increase in arteriovenous oxygen difference. In spite of a fixed amount of work is to be performed before and after β-adrenergic blocking, in this study author recognized that the oxygen consumption during exercise was reduced by P. adm. Its reduction is in part probably due to some hemodynamic effects of P. That is; reduction in cardiac work, increasing arteriovenous oxygen difference and reduction in myocardial oxygen uptake. These hemodynamic effects of P. can not completely explain the reduction of oxygen consumption observed in this study, therefore it suggested that the β-adrenergic receptor might have several influences on the metabolic changes to physical exercise. Hyperthyroid patients had a significantly higher basal control level of plasma lactate and NEFA. But no significant difference was observed in plasma glucose and pyruvate levels between two groups. Therefore, it gave a suggestion that plasma lactate and NEFA level was influenced by thyroid status. Author then studied the changes in blood metabolites level in exercising time before and after β-adrenergic blocking. Despite extensive study there is still no consensus regarding the changes in the plasma glucose during exercise. Some investigators reported that exercise increased the plasma glucose level, and against that there were some reports that exercise have a blood glucose lowering action. These differences were probably due to the duration and degree of exercise test and or to the complexity of glucose homeostasis in man. In this study, author observed that the plasma glucose level during exercise showed a slight declining tendency in patients group only after P. adm.

It has been known that lactate is produced in muscular tissue immediately after the onset of exercise, and is released into the blood stream. Huckabee showed that both production and removal of lactate are active function of every tissue of the body except for the erythrocytes, and urinary excretion of lactate is usually so little by comparison with the rate of production or absorption which occur elsewhere, which is negligible.

In spite of the same work load were performed in both groups, plasma pyruvate and lactate level in patients group during exercise were significantly higher than that in healthy group. However, author recognized that P. had a suppressive effects on plasma pyruvate and lactate level in both groups. Conceivably, XL which was calculated from Huckabee’s equation, was also decreased by P. adm. It was suggested, therefore, that an improvement of anaerobic metabolism within tissues will be made after P. adm. Huckabee indicate that XL could be used as an index of the extent of anaerobic metabolism in tissues, and then that it was closely correlate the respiratory oxygen debt following the exercise. In contrast to his opinion, Wasserman showed that anaerobic metabolism should be differentiated from the oxygen debt. Oxygen debt includes not only the oxygen deficit due to anaerobic oxidation process during the conversion of pyruvate to lactate but also the oxygen deficit which occurs during exercise and which has been called by Margaria et al. the “alactic acid” oxygen debt. There were not many reports that XL not necessarily correlate the respiratory oxygen debt.

Even if a specific condition which β-adrenergic
receptor was blocked by P. adm. in this study, author recognized that the production of XL might be suppressed by P., but oxygen debt showed a slight increase in tendency after β-adrenergic blocking. Therefore, it appears that the relationship between XL and oxygen debt is not always closely related. This point leaves a question to be studied further. In order to determine β-adrenergic receptor have whether significant role upon the lactate production in tissues during exercise, author made animal experiments using rats with swimming exercise. In this experiments, author observed that plasma lactate level in rats were altered by P. adm. in similar pattern to that of man, and that glycogen contents in skeletal and heart muscle in P. treated rats were not reduced even after exercise. These facts gave a suggestion that changes induced by P. adm. are probably caused by a decrease of the glycogen splitting enzyme phosphorylase, since the activation of glycogen phosphorylase is depend upon the catecholamines which enhance the synthesis of cyclic 3', 5' AMP which in turn promote the conversion of the inactive phosphorylase b into the more active phosphorylase a67–69. It resulted in the inhibition of lactate production in muscular tissue. But author found that the glycogen contents in the liver variably reduce after the exercise regardless of pretreatment with P. Therefore, these results suggested that there is some difference in the process which the glycogen phosphorylase is activated between the muscular tissue and the liver70. In the facts, the glucagon which was not blocked by β-adrenergic blocking could also have some influence upon the activating process of liver phosphorylase.

In attempt to study the β-adrenergic receptor whether has any significant influence upon the removal of lactate, author infused L(+)-sodium lactate at the rate of 9 mg/kg/min into the femoral vein in anesthetized dogs. The plasma lactate level was measured in constant time interval during and after its infusion. In the control dogs which P. was not administered, author confirmed that there was practically no difference in plasma lactate level in the test of first and second drop-infusion.

However, in the P. treated dogs it has been demonstrated that P. suppressed the increasing of plasma lactate level and also it promote the disappearance rate of lactate in the blood.

Some investigations reported that catecholamines elevate a lactate level and delay a disappearance rate of lactate. In considering these facts, it was recognized that β-adrenergic receptor could also have some influence upon the disappearing process of lactate, so that it was concluded that the decreasing of plasma lactate level during exercise after β-adrenergic blocking appears to be due to the two mechanisms. First, the production of lactate is blocked after β-adrenergic blockade, and second, the disappearance rate of lactate is promoted. Many reports71–74 concerning the changes to be observed in plasma NEFA in exercising time are seen in literatures, but no agreement has been reached in their opinion as yet as regards the mode of exercise test, required time and extent of the test, difference in blood sampling site, etc. In this study, author observed a biphasic changes of plasma NEFA level during exercise by following steps; (a) when exercise starts there is rapid decrease of plasma NEFA concentration generally explained by an increased uptake of fatty acids or oxidation. (b) When exercise continues, the plasma NEFA concentration trends to normalize, apparently due to increased fatty acids mobilization from adipose tissue. (c) After exercise there is short peak in the plasma NEFA level, generally explained by a continued increase in fatty acids mobilization when the demand for fatty acids in the muscle is decreasing. Some investigators reported many fat mobilizing substances. Among others fat mobilizing substances it was recongized that catecholamine is the most rapid and the strongest fat mobilizer, and so that it was suggested that catecholamine is closely relate to the fat mobilizing mechanism. Hyperthyroid patients showed a significantly higher basal control level of plasma NEFA and higher overshoot level of NEFA after exercise, however, these changes were significantly blocked by P. adm.

Moreover, author observed that the increments of plasma NEFA level in rats after the exercise were suppressed by P. adm. in similar pattern to that of man. From results above mentioned, it was concluded that the fat mobilizing mechanisms in adipose tissue are mediated by β-adrenergic receptor. However, author observed that no marked triglyceride changes after exercise in heart and epididymal fat pad are occured regardless pretreatment with P. Its results suggested that stored energy in these tissue is rich and so that significant changes in triglyceride contents can not be induced by this work load level which was used in this study, and
or that another factor besides \( \beta \)-adrenergic receptor may have some influence on the lipid metabolism. Some investigator\(^7\) reported that \( \alpha \)-adrenergic receptor activities is potentiated after blocking of \( \beta \)-adrenergic receptor. Therefore, it is difficult to classify the form of the adrenergic receptor regarding the lipid metabolism in adipose tissue. In that sense, it suggested that in order to study more precisely the fat mobilizing mechanism in adipose tissue, the estimation of the plasma glycerol concentration in addition to the plasma NEFA and the triglyceride contents in tissue, better be done. The reason was that glycerol is not reutilized in adipose tissue and so that it may be a good index which indicate the “true” rate of hydrolysis of triglyceride in adipose tissue.

From these facts, it has been clarified that \( \beta \)-adrenergic receptor have a significant role on carbohydrate and lipid metabolism. Lundholm and \textit{Svedmyr}\(^7\) showed that the calorigenic effect of catecholamine in the rabbit has been shown to be intimately associated with an increase in the production and metabolism of lactic acid. \textit{Steinberg et al}^9 and \textit{Havel et al}^8 demonstrated, that the increased mobilization and metabolism of free fatty acids were of importance for the calorigenic effects of catecholamine in man.

In considering of these results, it was suggested that the reduction in oxygen consumption after \( \beta \)-adrenergic blocking which is observed in this experiment was probably due to (a) the reduction in cardiac work hemodynamically, and due to (b) the suppressive effect on the production of lactate and due to (c) the suppressive effect on the both mobilization and metabolism of NEFA metabolically.

Therefore, it was concluded that \( \beta \)-adrenergic receptor activities may have important role not only on hemodynamic responses but also the metabolic changes to physical exercise, however, it was hardly to say that this receptor could have influence upon the both responses during exercise at a same level.

### Summary

The hemodynamic and metabolic effects of \( \beta \)-adrenergic blockade by the use of propranolol has been studied to clarify the physiological significance of \( \beta \)-adrenergic receptor activities during exercise in man and animals. Seven healthy men and twelve thyrotoxic patients were the subjects in this study. All these subjects were examined on bicycle ergometer at a moderate work load for 10 min. in a supine position. No significant changes of hemodynamic parameter induced by P. was observed in healthy men, but in patients group, significant decrease of systolic blood pressure and heart rate were observed at rest. Inhibitory effects of P. on heart rate, systolic blood pressure and cardiac work (M.T.T.I.) were marked during exercise in both group. All the metabolic effects including oxygen consumption, plasma pyruvate, lactate and XL production were suppressed with P. in both groups. Mobilization of NEFA induced by exercise were also modified, but plasma glucose was kept invariable during the experimental course. Oxygen debt showed a slight increasing tendency in both groups after P. adm. But the changes were not remarkable. Moreover, in attempt to analyze more precisely these metabolic changes in exercising time, author had animal experiments using rats and made exercise test. In rats treated with P., the plasma lactate concentration did not so increase and the glycogen contents in skeletal and heart muscle were not reduced by swimming exercise probably due to blocking on the activation of phosphorylase. But it was found invariably to reduce the glycogen contents in the liver regardless of pretreatment with P.

Plasma NEFA in animals showed the similar pattern to that of man, but no marked triglyceride changes in heart and epididymal fat pad were observed. For the purpose of investigating whether \( \beta \)-receptor has any influence on the disappearance rate of lactate, author infused 1 mol of L(+)-sodium lactate at the rate of 9 mg/kg/min into the femoral vein of 8 anesthetized dogs, the plasma lactate concentration in a arterial blood was measured at a constant time interval before and after P. adm. It has been demonstrated that P. promote the disappearance rate of lactate from blood in this experiment.

It is concluded that \( \beta \)-adrenergic receptor play an important role on the hemodynamic and the metabolic changes to muscular exercise and the mechanisms have been discussed.

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