Interactions of Sympathomimetic and Sympatholytic Agents in Normotensive and Hypertensive Subjects

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Sympathomimetic agents and their blocking agents were administered drop-wise intravenously alone or in various combinations to 9 normotensive subjects and 16 patients with essential hypertension. Their effects on the cardiovascular reaction (heart rate and blood pressure) were compared in order to estimate the degree of stimulation of \( \alpha \)- and \( \beta \)-receptors respectively. When the \( \alpha \)- and \( \beta \) receptor stimulating effects of so-called \( \alpha \)- and \( \beta \)-receptor stimulators were completely blocked by corresponding blocking agents respectively, \( \beta \)-effect in the \( \alpha \)-stimulator and \( \alpha \)-effect in the \( \beta \)-stimulator remained in effect without any modification in the degree of responses. Simultaneous injection of \( \alpha \)-stimulator and \( \beta \)-blocker caused no change in the heart rate (\( \beta \)-effect), but produced additive increase in the blood pressure (\( \alpha \)-effect) already raised by single treatment of the \( \alpha \)-stimulator. A similar additive effect was observed also in the \( \beta \)-effect when \( \beta \)-stimulator and \( \alpha \)-blocker were injected simultaneously. Such an increase in the \( \alpha \)- or \( \beta \)-effect seemed to be due to conversion of \( \beta \) or \( \alpha \)-effect blocked by \( \beta \)- or \( \alpha \)-blocker respectively, but it was not attributable to the \( \alpha \)- or \( \beta \)-effect of the blockers themselves. The \( \beta \)-effect induced in this way, that is, the reactivity of \( \alpha \)-receptor was greater in hypertensive patients than in normotensives, and the \( \beta \)-effect induced in the same way was greater in normotensives than in hypertensive patients.

The concept of the receptor originated from the study of Langley\(^1\) in 1905 concerning the action of nicotine and curare on the skeletal muscle. In 1906 Dale\(^2\) demonstrated the inhibition of pressor action of adrenaline (Ad) or even acceleration of depressor action by preceding injection of the ergot alkaloid, and concluded that Ad had both pressor and depressor actions which stimulated accelerating and inhibiting receptors in the organ, respectively. Ahlquist\(^3\) in 1948 studied the reaction of each organ to Ad, noradrenaline (NA), and isoproterenol (ISO), and asserted the presence of two kinds of receptors, \( \alpha \)- and \( \beta \)-receptors, among adrenergic receptors. The \( \alpha \)-receptor is responsible for a vasoconstricting action, and the \( \beta \)-receptor for a vasodilating action. At that time, there was found no agent which antagonizes the \( \beta \)-receptor stimulating action, while \( \alpha \)-receptor blocking agents were already recognized. Powell and Slater\(^4\) in 1958 discovered dichloroisoproterenol (DCI) and the theory of Ahlquist suddenly drew attention. DCI inhibited the \( \beta \)-effect without affecting the \( \alpha \)-effect of Ad. And this discovery strongly supported the theory of Ahlquist, which offered a

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possible explanation for the two actions of Ad suggested by Dale.

In his paper, Ahlquist described the relative actions of NA, Ad, and ISO on various organs. In organs where the accelerating action was displayed, the order of Ad>NA>ISO was found, while the inhibiting action followed the order of ISO>Ad>NA. Furchgott similarly determined the ratio of potency of NA, Ad, and ISO in resected organs of rabbit and compared their blockade by α- and β-receptor blocking agents (hereafter α- and β-blockers). As the results, α-type of specimen showed the reaction in the order of Ad>NA>ISO, while β-type of specimen in the order of ISO>Ad>NA. These results were in agreement with the findings of Ahlquist. On the basis of these observations, NA is called an α-receptor stimulator and ISO, a β-receptor stimulator.

Using the cardiovascular reaction as an index of action, the α-receptor stimulating action is defined to the action which generally causes constriction of blood vessel and elevation of blood pressure without positive relationship with the cardiac function, while the β-receptor stimulating action is that which causes vasodilatation and acceleration of cardiac function or increase in the heart rate.

On the other hand, many reports pointed out an increase of vascular reaction in patients with essential hypertension as compared with normotensives (Goldenberg et al.,6 Doyle and Black; Conway and Torikai). We have recently obtained similar results from the experiments on digital blood pressure. In view of such increased vascular reactivity against α-receptor stimulator NA in patients with essential hypertension, vascular reactivity against β-stimulator ISO might also differ between normotensives and patients with essential hypertension. The effects of combinations of α- or β-receptor stimulator with α-receptor blocking agent phentolamine (Phent.) or β-blocking agent propranolol (Prop.) administered intravenously were examined on the cardiovascular reaction.

**Materials and Methods**

Sixteen patients with essential hypertension and 9 normotensive subjects were used. The test subjects were made to lie on the back quietly for 20 minutes, and the heart rate and systemic blood pressure (systolic and diastolic) were determined 5-6 times to ascertain the stabilization of these values. Intravenous injection of the chemicals was then started using a slow injector. The injection was carried out initially at a low speed—the speed being expressed by the amount of the solution injected per minute—followed by a stepwise increase in the rate of injection. Heart rate and systemic blood pressure were determined every minute. For the determination of heart rate, Matsuda's "cardiotachograph" or pulse meter was used, while a mercury sphygmomanometer was used for the measurement of systemic blood pressure. Digital blood pressure and blood flow were registered before injection of a stimulator, at the time of the maximum response to the stimulator, after the appearance of blocking effect, and also immediately after discontinuation of the stimulator injection leaving the blocker being injected alone. Peripheral vascular resistance calculated from these values (according to the law of Poiseuille) will be published elsewhere. Heart rate and systemic blood pressure were determined for 10-20 minutes following discontinuation of intravenous injection.

Table 1 indicates the stimulators and blockers used in the present experiments. The following solutions were used for intravenous injection:
Sympathomimetic and Sympatholytic Agents

Table 1. The $\alpha$- and $\beta$-receptor stimulators and blockers used

<table>
<thead>
<tr>
<th></th>
<th>$\alpha$-receptor</th>
<th>$\beta$-receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sympathomimetic</td>
<td>Noradrenaline</td>
<td>Isoproterenol</td>
</tr>
<tr>
<td>Sympatholytic</td>
<td>Phentolamine</td>
<td>Propranolol</td>
</tr>
</tbody>
</table>

1) NA solution: 1 mg of NA was dissolved in 500 ml of physiological saline.
2) ISO solution: 0.2 mg of ISO was dissolved in 500 ml of physiological saline.
3) Phent. solution: For injection of Phent. alone, 20 mg of it were dissolved in 500 ml of physiological saline. For simultaneous injection with a stimulator, 30 mg were used in patients with essential hypertension, and 40 mg were used in normotensives, both dissolved in 500 ml of physiological saline.
4) Prop. solution: For injection of Prop. alone, 10 or 15 mg of it were dissolved in 500 ml of physiological saline. For simultaneous injection with a stimulator, 15 mg were dissolved in 500 ml of physiological saline.

The speed of intravenous injection from the slow injector was usually divided into five steps, the amount of an injected solution per minute being 0.73–0.78, 1.25–1.34, 2.25–2.39, 3.92–4.14, and 6.96–7.24 ml.

Results

1) Effects of $\alpha$- and $\beta$-receptor stimulators

The effects on the systemic blood pressure and heart rate were reported in detail elsewhere.10,14

a) Injection of $\alpha$-receptor stimulator alone. Intravenous injection of NA, an $\alpha$-receptor stimulator, resulted in a marked increase in systolic, diastolic, and digital blood pressure in patients with essential hypertension, while heart rate decreased (Fig. 1). When the rate of injection was increased stepwise, systolic blood pressure also rose stepwise every time in all cases, and reached a level higher than 200 mm Hg at a rate of injection of 8 $\mu$g/min of NA. The elevation of diastolic pressure was not so pronounced as that of the systolic pressure, so that the pulse pressure increased as the rate of injection increased. In normotensive subjects, as shown in Fig. 2, systolic, diastolic and digital pressures similarly increased. The degree of elevation, especially that of systolic pressure, was not so remarkable as in patients with essential hypertension. Despite the injection of such a large amount as 14–15 $\mu$g/min, systolic pressure reached 150–160 mm Hg at the highest. The degree of elevation of diastolic blood pressure tended to be larger than in patients with essential hypertension. Consequently, pulse pressure did not increase even when the rate of injection was increased. Against the $\alpha$-receptor stimulator, the patients with essential hypertension reacted with a more pronounced rise in pressure than in normotensives. Both the patients with essential hypertension and the normotensive subjects showed bradycardia probably due to the reflex through the buffer nerves for the blood pressure.

b) Injection of $\beta$-receptor stimulator alone. When ISO, a $\beta$-receptor stimulator was administered intravenously, heart rate increased markedly in patients with essential hypertension as shown in Fig. 3 and in normotensive subjects as shown
Fig. 1. The changes in systemic (systolic, ○ in the upper; diastolic, ○ in the middle) and digital blood pressures (●) and in heart rate (●) after intravenous injection of noradrenaline in a patient with essential hypertension. See the text.

Fig. 2. The changes in systemic and digital blood pressures and in heart rate after intravenous injection of noradrenaline in a normotensive subject. See the text.
Fig. 3. The effects of intravenous injection of isoproterenol in a hypertensive. See the text.

Fig. 4. The effects of intravenous injection of isoproterenol in a normotensive. See the text.

In Fig. 4. As the rate of injection increased stepwise, heart rate increased more; at the highest speed of injection of 2.75 μg/min, its increase was much greater in normotensives than in patients with essential hypertension.
Fig. 5. The effects of intravenous injection of phentolamine in a hypertensive. See the text.

Fig. 6. The effects of intravenous injection of phentolamine in a normotensive. See the text.
Fig. 7. The effects of intravenous injection of propranolol in a hypertensive. See the text.

Fig. 8. The effects of intravenous injection of propranolol in a normotensive. See the text.

In some patients with essential hypertension, systolic blood pressure showed a mild rise as in the case of Fig. 3, while a decrease was seen in others. In normotensive subjects, systolic blood pressure rose in all cases. Diastolic blood
pressure decreased in all cases of normotensives and of patients with essential hypertension. Therefore, the increase in pulse pressure was greater in normotensives than in patients with essential hypertension.

2) Effects of α- and β-receptor blockers

Detailed description of the effects on the systemic blood pressure and heart rate was made elsewhere.\(^1\)

a) Injection of α-receptor blocker alone. When Phent., an α-receptor blocking agent, was injected intravenously, systolic blood pressure showed a mild decrease in patients with essential hypertension as shown in Fig. 5, while there was scarcely any change in diastolic blood pressure and heart rate. As is clearly seen in Fig. 6, systolic blood pressure showed a slight decrease in normotensive subjects. No tendency of further decrease was seen, even though the rate of injection increased to the maximum of 290 μg/min. Diastolic blood pressure and heart rate were almost unchanged as in patients with essential hypertension.

b) Injection of β-receptor blocker alone. When Prop., a β-receptor blocking agent, was administered intravenously and the speed of injection was increased stepwise, both systolic and diastolic pressure showed a tendency of gradual decrease in patients with essential hypertension as shown in Fig. 7, where heart rate also showed a similar tendency to decrease. Even though the rate of injection was raised to the maximum of 200 μg/min, the degree of decrease of blood pressure and of heart rate were extremely mild. As shown in Fig. 8, a single injection of Prop. in normotensive subjects resulted in a rather mild rise of systolic and diastolic pressure and a slight decrease of heart rate. No essential differences were found between the reaction of normotensives and patients with essential hypertension.

3) Effect of α-receptor stimulator and blocker simultaneously administered

After the effect of intravenous administration of NA was established, Phent., an α-receptor blocking agent, was injected into another vein, the rate of injection of Phent. being increased stepwise, while NA injection was kept at the same rate. In all cases of patients with essential hypertension and of normotensive subjects, as shown in Figs. 9 and 10, the blood pressure once elevated upon NA administration gradually fell to the pre-injection level, and the amount of Phent. sufficient to block the NA effect calculated on the weight basis was 56 times as much as that on the continuous administration of NA in the two groups of normotensives and patients with essential hypertension. The decreased heart rate also returned to the pre-injection level. As far as injection of both chemicals were continued, systemic pressure remained unchanged, but heart rate gradually increased both in normotensives and in patients with essential hypertension. The increase in the heart rate at this stage, as shown in Table 2, was 8/min (average of 5 cases) in patients with essential hypertension and 19/min (average of 5 cases) in normotensives.
Fig. 9. The effects of noradrenaline and phentolamine simultaneously administered in a hypertensive. See the text for details.

Fig. 10. The effects of noradrenaline and phentolamine simultaneously administered in a normotensive. See the text for details.
TABLE 2. Increase in heart rate and systolic blood pressure upon simultaneous administration of sympathomimetic and sympatholytic agents

<table>
<thead>
<tr>
<th></th>
<th>Heart rate per minute $\alpha\beta$</th>
<th>Blood pressure mmHg $\alpha$</th>
<th>Blood pressure mmHg $\beta$</th>
<th>Heart rate per minute $\alpha\beta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive</td>
<td>8(5)</td>
<td>20(6)</td>
<td>25(2)</td>
<td>11(2)</td>
</tr>
<tr>
<td>Normotensive</td>
<td>19(5)</td>
<td>6(2)</td>
<td>16(2)</td>
<td>20(2)</td>
</tr>
</tbody>
</table>

See the text for details. Number of cases in parentheses

When the injection of Phent. was continued after NA had been stopped, the heart rate stayed in the same tendency in patients with essential hypertension, while it showed a further increase in normotensive subjects. In other words, such an increase in the heart rate might well represent a $\beta$-effect of NA, a so-called $\alpha$-receptor stimulator, but it becomes apparent only when the $\alpha$-effect is suppressed. After Phent. was withdrawn, increased heart rate gradually returned to the pretreatment level.

4) Effect of $\beta$-receptor stimulator and blocker simultaneously administered

After the effect of intravenous administration of ISO had been established, Prop., a $\beta$-receptor blocking agent, was injected into another vein, the rate of injection of Prop. being increased stepwise, while ISO injection was kept at the same speed. In patients with essential hypertension as shown in Fig. 11 and normotensive subjects as shown in Fig. 12, the increased heart rate returned to the initial level in both instances. The $\beta$-stimulating action of ISO was thus completely blocked by Prop. The rate of injection of Prop. enough to block the ISO effect was 126 times as much as that of ISO in both normotensives and patients with essential hypertension. At this stage, the decreased systolic and diastolic pressures returned to the pre-injection level in patients with essential hypertension, while both the elevated systolic pressure and decreased diastolic pressure returned to the pre-injection level in normotensive subjects. As long as the injection of these two chemicals was continued, the heart rate remained unchanged, while the systemic blood pressure gradually increased in patients with essential hypertension and a similar but milder change was seen in some normotensive subjects, but no change was seen in others. The elevation of systolic blood pressure at this stage, as shown in Table 2, was 20 mm Hg (average of 6 cases) in the patients with essential hypertension, and 6 mm Hg (average of 2 cases) in the normotensives. Such elevation of blood pressure represents the appearance of $\alpha$-effect of ISO, a $\beta$-receptor stimulator. When the administration of ISO was discontinued and only Prop. was continued, elevated blood pressure promptly returned to the initial level. Withdrawal of Prop. produced no noticeable changes in the systemic blood pressure and heart rate.
Fig. 11. The effects of isoproterenol and propranolol simultaneously administered in a hypertensive. See the text for details.

Fig. 12. The effects of isoproterenol and propranolol simultaneously administered in a normotensive. See the text for details.
Fig. 13. Effects of noradrenaline and propranolol simultaneously administered in a hypertensive. See the text for details.

Fig. 14. Effects of noradrenaline and propranolol simultaneously administered in a normotensive. See the text for details.
5) **Effect of α-receptor stimulator and β-receptor blocker simultaneously administered**

NA, an α-receptor stimulator, was intravenously injected and the rate of injection was increased stepwise. As the injection was continued to maintain the sufficient effect of NA, Prop. was injected into another vein and the rate of injection was again stepwise increased. Both in patients with essential hypertension as shown in Fig. 13 in normotensive subjects as shown in Fig. 14, a further rise was noted above the elevated systemic blood pressure at the rate of Prop. injection of 70 μg/min in the former and 200 μg/min in the latter. In both groups, the heart rate at this stage was decreased to the range of bradycardia, and no further change was seen. As long as the injection of these two chemicals was continued, the systemic blood pressure kept the gradual rise. The rate of increase was greater in patients with essential hypertension (about 35 mm Hg in systolic pressure, about 20 mm Hg in diastolic pressure) than in the normotensive subjects (about 20 mm Hg in systolic pressure and about 15 mm Hg in diastolic pressure). As shown in Table 2, the rise in systolic pressure was 25 mm Hg in patients with essential hypertension (average of 2 cases) and 16 mm Hg in normotensive subjects (average of 2 cases). This additive increase in the blood pressure is due to the blocking of the β-effect of NA, an α-receptor stimulator, by Prop., together with the addition of an α-effect. The heart rate at this stage remained low.

When Prop. was discontinued and only NA was continued, the elevated systemic blood pressure and decreased heart rate were sustained in patients with essential hypertension and in normotensive subjects. As the injection of NA was discontinued, the systemic blood pressure immediately decreased and the heart rate increased, returning to the initial level.

6) **Effect of β-receptor stimulator and α-receptor blocker simultaneously administered**

The intravenous injection of ISO, a β-receptor stimulating agent, was performed and the rate of injection was stepwise increased. As the injection was continued to maintain the sufficient effect of ISO, Phent. was injected into another vein. When the speed of injection of Phent. was increased stepwise the heart rate which had increased as the effect of ISO showed a further increase in patients with essential hypertension as shown in Fig. 15, and in normotensive subjects as shown in Fig. 16. When the injection of both chemicals was further continued, the heart rate increased and reached the maximum at the rate of injection of 0.94 μg/min, the highest rate for ISO injection. The heart rate at this stage, as is clear from Table 2, showed an increase of 11/min (average of 2 cases) in the patients with essential hypertension and 20/min (average of 2 cases) in the normotensive subjects, the former showing a smaller increase than the latter. Such increase in the heart rate may be due to the block of the α-effect of ISO, β-receptor stimulator, by Phent., and may be explained as the addition of β-effect corresponding to the α-effect of ISO. No marked fluctuation was seen in the systemic blood pressure at this stage in both groups.
Fig. 15. The effects of isoproterenol and phentolamine simultaneously administered in a hypertensive. See the text for details.

Fig. 16. The effects of isoproterenol and phentolamine simultaneously administered in a normotensive. See the text for details.
When injection of Phent. was stopped and only the injection of ISO was continued, the increased heart rate and previous level of systemic blood pressure were maintained in both patients with essential hypertension and normotensive subjects. As the injection of ISO was stopped, the heart rate began to fall and the systemic blood pressure returned to the initial level, decreasing when it had increased and increasing when it had decreased.

**DISCUSSION**

Various organs in vivo take different attitude of reaction against Ad. There are two actions, excitatory and inhibitory. The biphasic action of Ad has also long been known. With the intravenous injection of Ad in animals, an initial elevation was followed by a rapid decrease and finally a level below normal blood pressure was obtained. This was again followed by gradual return to the normal level, making up a biphasic blood pressure curve. Dale found that such a pressor action of Ad was inhibited by an ergot alkaloid (ergotamine). Continuous inhibition was exerted subsequently by dibenamine and Phent., but the depressor factor of Ad was not inhibited by these chemicals. When dibenamine was intravenously injected as the pretreatment, blood pressure elevation due to Ad was inhibited, only leaving a transient hypotensive effect. On the other hand, most of the sympathetic postganglionic fibers are called adrenergic nerve, from the ending of which sympathin is said to be released. NA is probably the sympathin. Although such sympathin released from the ending of the sympathetic nerve was initially considered to consist of an exciting factor (sympathin E) and an inhibiting factor (sympathin I) for some time (Cannon and Rosenblueth). Subsequently, the presence of two kinds of receptor mechanism was considered more acceptable and satisfactory. Ahlquist proposed to call them α- and β-receptors.

When Ahlquist proposed the theory of the α- and β-receptors, there was only an α-lytic agent acting against α-receptor stimulating action, but β-lytic agents acting against β-receptor stimulating action were not yet discovered. In 1958, Powell and Slater discovered dichloroisoproterenol and the presence of β-receptor became even more certain and the theory of Ahlquist received strong support. The action of Ad on blood pressure is also due to such α- and β-action. Prior injection of dibenamine, as well as ergot alkaloid stated above, inhibited the elevation of blood pressure due to Ad, only leaving the transient hypotension. This might be explained by the presence of α- and β-receptor in blood vessels and the former being blocked by dibenamine. Since α-action or vasoconstrictor action thus disappears, Ad acts on β-receptor alone, leaving β-action or vasodilator action and hypotension.

Tainter et al. observed a more intense pressor action of α-receptor stimulator, NA than that of Ad. NA scarcely has a secondary hypotensive action such as that of Ad. Intravenous injection of NA after prior administration of dibenamine resulted in a milder elevation of blood pressure, but displays no hypotensive action as Ad dose. The more intense pressor action of NA than that of Ad is
probably due to the weaker $\beta$-effect of NA than that of Ad. While the $\beta$-action of Ad makes its $\alpha$-action weaker, the weakening of $\alpha$-action by $\beta$-action in NA is of smaller degree. As far as $\alpha$-action is concerned, Ad $>\text{NA}$ is said to be the case. ISO, a $\beta$-receptor stimulator, was found to have $\beta$-action 10 times as intense as that of Ad, while scarcely any $\alpha$-action was seen, so that it exerted no influence on the hypotensive action of dibenamine. As Ahlquist has stated, in the light of $\alpha$-receptor stimulating action, the ratio of the potency of the three above-mentioned drugs follows the order of Ad $>\text{NA} >\text{ISO}$, while the order of ISO $>\text{Ad} >\text{NA}$ is seen as far as the $\beta$-receptor stimulating action is concerned. This agrees well with the results obtained by Furchgott$^5$ with resected organs of rabbits, who found the order of Ad $>\text{NA} \gg\text{ISO}$ in $\alpha$-type specimen and ISO $\gg\text{Ad} >\text{NA}$ in $\beta$-type specimen.

According to Ahlquist, Ad is an amine with most potent action on $\alpha$- and $\beta$-receptors. From this fact and the ratio of potency stated above, NA or ISO is not pure $\alpha$-receptor or $\beta$-receptor stimulator, since NA and ISO have a slight $\beta$-action and $\alpha$-action respectively. The authors, therefore, expressed the actions of NA, Ad, ISO as $\alpha\beta$, $\alpha\beta$, $\alpha\beta$ from the standpoint of $\alpha$- and $\beta$-effect, and the blocking agents as ($\alpha$) and ($\beta$).

When NA, $\alpha$-receptor stimulator, was blocked by Phent., $\alpha$-receptor blocking agent,

$$\alpha\beta + (\alpha) \rightarrow \beta$$

thus the $\beta$-effect of NA remains, giving rise to acceleration of the cardiac function or increase in heart rate. Such $\beta$-effect was smaller in patients with essential hypertension than in normotensive subjects.

When ISO, $\beta$-receptor stimulator, was blocked by Prop., $\beta$-receptor blocking agent,

$$\alpha\beta + (\beta) \rightarrow \alpha$$

then, the $\alpha$-effect of ISO remains, giving rise to vasoconstriction, that is, blood pressure elevation. Such $\alpha$-effect was larger in patients with essential hypertension than in normotensive subjects.

In experiments of simultaneous injection of NA and Prop.,

$$\alpha\beta + (\beta) \rightarrow \alpha + \alpha$$

The $\beta$-effect of NA, $\alpha$-receptor stimulator, was inhibited by Prop., $\beta$-receptor blocking agent. Addition of $\alpha$-effect corresponding to the inhibited $\beta$-effect of NA resulted in blood pressure elevation due to intravenous injection of NA (large $\alpha$-effect) together with blood pressure elevation due to the blocking of $\beta$-effect. Therefore, the blood pressure rose more and more. Such action was stronger in patients with essential hypertension than in normotensive subjects. In some normotensive subjects this additive action was almost undetectable.

Finally, the experimental results in simultaneous injection of ISO, a stimulator of $\beta$-receptor, and Phent., an $\alpha$-receptor blocking agent, is represented by the
following formula.

$$\sigma \beta + (\alpha) \rightarrow \beta + \sigma$$

The $\alpha$-effect of ISO, a $\beta$-receptor stimulator, was blocked by Phent., $\alpha$-receptor blocking agent, and the addition of $\beta$-effect corresponding to the inhibited $\alpha$-effect of ISO resulted in an increase of heart rate, that is, another increase of heart rate induced by the blocking of $\alpha$-effect was added to the increase of heart rate already induced by intravenous injection of ISO (large $\beta$-effect). Such action was smaller in patients with essential hypertension than in normotensive subjects.

As stated in the introduction of this paper, $\alpha$-receptor stimulating action causes constriction of the blood vessels, but is unrelated with the cardiac function, while $\beta$-receptor stimulating action provokes dilatation of the vessels and acceleration of the cardiac action. After all, so far as the cardiovascular reaction is concerned, $\alpha$-receptor stimulating action can be expressed as an elevation of the blood pressure, while $\beta$-receptor stimulating action as an increase in heart rate. Table 3 summarizes the results of interaction between various sympathomimetic drugs and their blocking agents described above using the cardiovascular reaction as an index in the present study. All the results so far obtained by previous workers up to the present were carried out on each organ of animals, and the administration to the whole organism of various combination of these chemicals has scarcely been tried in order to observe the reaction of $\alpha$- and $\beta$-receptors separately. The present experiment may be the first in the study of interaction among them; that is, not only the antagonistic but synergistic action between stimulators of the receptors and their blocking agents by simultaneous injection of $\alpha$-receptor stimulator and $\beta$-receptor blocking agent or $\beta$-receptor stimulator and $\alpha$-receptor blocking agent.

The reflex action of the buffer nerves for the blood pressure should be considered. The injection of NA causes an elevation of blood pressure and a decrease in heart rate on account of the effect of pressoreceptor, by which the elevated blood pressure is somewhat decreased. At this time, Prop. injected simultaneously acts to decrease the heart rate further. Therefore, it seems that the $\alpha$-effect (pressor) added by the Prop. administration to the blood pressure already elevated by the NA injection is attributable to the inhibition of the $\beta$-effect of NA. Without the participation of pressoreceptor, it could have given rise to even a higher blood pressure. Quite similarly, the $\beta$-effect (increase in heart rate) observed on the simultaneous injection of $\beta$-receptor stimulator, ISO and $\alpha$-receptor blocking agent, Phent. should have been more manifest without the action of the buffer nerves. Based on these facts, $\beta$-effect appearing upon blocking the $\alpha$-receptor stimulator NA with $\alpha$-receptor blocking agent Phent, as well as the $\alpha$-effect appearing through blocking the $\beta$-receptor stimulator ISO with $\beta$-receptor blocking agent Prop, does not seem to originate from cardiovascular reflexes.

As is clear from Tables 2 and 3, the increase in heart rate due to $\beta$-effect appeared on blocking $\alpha$-receptor stimulator NA with $\alpha$-receptor blocker Phent.
and that of $\beta$-effect observed on the simultaneous injection of $\beta$-receptor stimulator ISO and $\alpha$-receptor blocker Phent. were smaller in patients with essential hypertension than in normotensives. On the contrary, the elevation of blood pressure of $\alpha$-effect appeared on blocking the $\beta$-receptor stimulator ISO with $\alpha$-receptor blocker Prop. and that of $\alpha$-effect observed on the simultaneous injection of $\alpha$-receptor stimulator NA. and $\beta$-receptor blocker Prop. were both greater in patients with essential hypertension than in normotensives. The problem why $\alpha$-effect is greater and $\beta$-effect smaller in patients with essential hypertension than in normotensives may well be explained by the hyperreactivity of patients with essential hypertension against NA., but a better understanding of this nature must await further investigation.

Acknowledgment

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