RELATIONSHIP BETWEEN ARRHYTHMIAS AND A LIBERATION OF ENDOGENOUS CATECHOLAMINE CAUSED BY TOXIC DOSES OF OUABAIN IN DOGS.\* 

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Abstract……A remarkable blood pressure rise associated with elevated plasma catecholamines was observed at the onset of arrhythmia when a toxic dose of ouabain was administered into dogs. The mechanism of this phenomenon may be explained as the release of endogenous catecholamines from the adrenal glands and peripheral sympathetic nerve endings brought about by a toxic dose of ouabain. Central catecholamine does not appear to be related with the above phenomenon.

Key words: Ouabain, blood pressure rise, ventricular arrhythmia, catecholamine, adrenalectomy, chemical sympathectomy

INTRODUCTION

Previous investigators have reported that the administration of cardiac glycosides produced a blood pressure rise in animals and humans (Boyajy and Nash, 1958, Williams et al., 1958, Blackmon et al., 1960, Cairns et al., 1960, Mason and Braunwald, 1964).

On the other hand, some investigators reported that the administration of cardiac glycosides did not produce an elevation of systemic blood pressure (Dresdale et al., 1959, Selzer et al., 1959). However, more recently, Mason and Braunwald observed that intravenous injections of ouabain in normal human subjects increases the mean arterial pressure (Mason and Braunwald, 1964). In general, blood pressure rise due to cardiac glycosides has been explained in part as a direct action on peripheral vessels and in part by central or refex action (Goodman and Gilman, 1970, Stark et al., 1972).

In the present experiment, a constant infusion of ouabain in dogs produced a marked vasopressor effect concomitant with arrhythmia at toxic levels. The mean blood pressure

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rise was 76 mmHg in untreated dogs. This finding is difficult to be explained only as a direct action on peripheral vessels and central or reflex action because of ouabain of the magnitude of blood pressure rise. Extensive studies have been made by many investigators to the effect that cardiac glycosides may induce the release of catecholamines from the adrenal medulla (Erlij and Medez, 1964, Ciofalo et al., 1967, Banks, 1967, Kirpekar et al., 1970, Nishikawa and Tsujimoto, 1974) and from sympathetic nerve endings especially in cardiac muscle (Cairoli et al., 1961, Tanz, 1962, Roberts et al., 1963, Ciofalo and Treece, 1973, Ozawa and Katsuragi, 1974). It was also reported that digitalis may inhibit the re-uptake of catecholamine into nerve endings (Ciofalo et al., 1967).

These findings suggest the possibility that endogenous catecholamine may be related to the pressor response of cardiac glycosides. A similar possibility has been postulated in inotropism and arrhythmia arising from cardiac glycosides which may be at least in part related with sympathetic activity under various experimental conditions (Tanz, 1962, Tanz and Marcus, 1966, Levy and Richards, 1965).

To my knowledge, no report are available concerning the relationship between pressor responses to cardiac glycosides and endogenous catecholamines. The present study was therefore undertaken in an attempt to elucidate the possibility of catecholamine liberation by ouabain related to the vasopressor effect. Therefore, these experiments were designed to explore the elevation of plasma catecholamine level in parallel with the vasopressor effect and to examine whether the depression of the sympathetic activity could suppress the vasopressor response by ouabain.

**EXPERIMENTAL METHODS**

Experiments were performed on the following five groups of dogs.

**Group I** ...... Non-treated dogs (control).

**Group II** ...... Central sympathectomy.

Ten mg of 6-hydroxydopamine (6-OHDA) per dog were administered into the lateral ventricles for chemical sympathectomy of the central nervous system (Thoene and Tranzer, 1968, Breese and Traylor, 1970, Kaplanski and Smelik, 1973, Chalmers and Reid, 1972). A stereotaxic apparatus was used for the administration of 6-OHDA into the lateral ventricles. Experiments were performed from 10 to 14 days after the above operation.

**Group III** ...... Systemic sympathectomy.

α-Methyl-p-tyrosine, an enzyme blocking agent for catecholamine synthesis was injected intraperitoneally at a dose of 250 mg/kg for the depression of sympathetic nerve activity (Spector and Udenfriend, 1965, Swedin, 1970). Two thirds of α-methyl-p-tyrosine were injected 40 hr before the experiments and one third of the total amount was injected 16 hr before the experiments respectively.

**Group IV** ...... Adrenalectomy.

Bilateral adrenal glands were surgically removed. After this procedure, 1 hr was
allowed before starting the infusion of ouabain.

Group V -----Systemic sympathectomy and surgical adrenalectomy.

In Group V, the dogs were treated with α-methyl-p-tyrosine in the same manner as shown in Group III, thereafter adrenal glands were surgically removed totally 1 hr before ouabain infusion.

Adult mongrel dogs (8-13 kg) of either sex were prepared under sodium pentobarbital anesthesia (30 mg/kg i.v.) with artificial respiration. The electrocardiogram was recorded continuously on 2nd limb lead throughout the experiments. The arterial blood pressure was monitored by means of a mercurial manometer from the catheter inserted into the left femoral artery. Right and left femoral veins were catheterized for taking blood samples for the measurement of plasma catecholamine contents and for the infusion of ouabain. Ouabain was infused constantly at a dose of 5 μg/kg per 3 minutes until standstill of the heart. Blood samples were taken for catecholamine measurement just before the infusion of ouabain and at the time of the blood pressure elevation which preceded the onset of ventricular arrhythmias by ouabain.

The measurement of plasma catecholamine was carried out by using Saito's method method (1969). An Amino-Bowman spectrophotofluorometer was used for reading the fluorescence intensity of catecholamine. In cases where the level of plasma catecholamine was over 2 μg/L in total amount, it was possible to differentiate norepinephrine from epinephrine. But, when the level was lower than 2 μg/L, the plasma catecholamine contents were shown as the total amount. Student t-test was used for a statistical analysis of the data.

RESULTS

GROUP 1 -----CONTROL

Ouabain was infused into the femoral vein of non-treated dogs at a rate of 5 μg/kg per 3 minutes. As shown in Fig. 1, ventricular arrhythmias appeared following elevation of the blood pressure at toxic doses of ouabain. The maximum rise of blood pressure (Max B.P. rise) was 76 mmHg on an average and the catecholamine level in plasma was increased to 1,824 μg/L on an average at the time of blood pressure rise. The average value of plasma catecholamine was significantly increased as compared with that obtained in non-treated dogs (0.007 μg/L) as indicated in Table 1. The toxic dose and the lethal dose of ouabain obtained in this group of animals were 57.3 μg/kg and 99.2 μg/kg in average, as shown in Table 3. The catecholamine content in tissues which was measured after cardiac arrest was 0.089 μg/g in the brain cortex, 0.141 μg/g in the brainstem and 1.446 μg/g in the myocardium, as shown in Table 2.

GROUP II -----CENTRAL SYMPATHECTOMY

In the 6-OHDA-treated dogs, ouabain produced the same pattern of pressor and arrhythmic effects as seen in control. Data obtained in one case of this group are shown in Fig. 2, in which plasma catecholamine, epinephrine in particular, was makedly
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<table>
<thead>
<tr>
<th></th>
<th>CONTROL</th>
<th>1st B.P. RISE</th>
<th>2nd B.P. RISE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLASMA EPINEPHRINE</td>
<td>N.D.</td>
<td>3.61 μg/L</td>
<td>2.76 μg/L</td>
</tr>
<tr>
<td>PLASMA NOREPINEPHRINE</td>
<td>N.D.</td>
<td>0.79 μg/L</td>
<td>N.D.</td>
</tr>
</tbody>
</table>

B.P.: BLOOD PRESSURE  N.D.: NO DETECTION

Fig. 1. Associated changes in B.P., ECG and plasma catecholamine during I.V. infusion of ouabain in control dog.

<table>
<thead>
<tr>
<th></th>
<th>CONTROL</th>
<th>B.P. RISE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLASMA EPINEPHRINE</td>
<td>N.D.</td>
<td>4.35 μg/L</td>
</tr>
<tr>
<td>PLASMA NOREPINEPHRINE</td>
<td>N.D.</td>
<td>2.77 μg/L</td>
</tr>
</tbody>
</table>

B.P.: BLOOD PRESSURE  N.D.: NO DETECTION

Fig. 2. Associated changes in B.P., ECG and plasma catecholamine during I.V. infusion of ouabain in dogs pretreated intraventricularly with 6-OHDA.

makedly increased at the time when arrhythmias and blood pressure rise were concomitantly induced by ouabain. The Max B.P. rise obtained in 8 cases was 48 ± 9 mmHg on an average and the catecholamine level in plasma at the time of Max B.P. rise was 3.476 ± 1.481 μg/L plasma on an average, as shown in Table 1. The toxic dose and the lethal dose of ouabain obtained in 8 cases were 49.1 μg/kg and 78.8 μg/L, respectively, as shown in Table 2. These values were not significantly different from those obtained in non-treated control dogs.

Catecholamine values in tissues measured in this group, were 0.015 μg/g the brain cortex, 0.032 μg/g in the brainstem and 1.032 μg/g in the myocardium as seen in Table
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**Table 1. Maximum Rise of B.P. and Plasma Catecholamine Level at Maximum B.P. Rise During an I.V. Infusion of Ouabain in Pretreated Dogs**

<table>
<thead>
<tr>
<th>GROUP</th>
<th>N</th>
<th>MAX BP RISE (mmHg) (mean±S. E.)</th>
<th>PLASMA CA AT MAX BP (μg/L plasma) (mean±S. E.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>7</td>
<td>76±28</td>
<td>1.824±0.672*</td>
</tr>
<tr>
<td>II</td>
<td>8</td>
<td>48±9</td>
<td>3.476±1.481*</td>
</tr>
<tr>
<td>III</td>
<td>8</td>
<td>49±15</td>
<td>7.111±2.670*</td>
</tr>
<tr>
<td>IV</td>
<td>6</td>
<td>54±14</td>
<td>2.233±0.560*</td>
</tr>
<tr>
<td>V</td>
<td>7</td>
<td>21±12**</td>
<td>0.019±0.009</td>
</tr>
</tbody>
</table>

CA IN UNTREATED PLASMA (μG/L PLASMA) (N=9) 0.007±0.000

* Significantly different from control (p<0.01)
** Significantly different from control (p<0.05)

Group I: Non-treated dogs (control)
Group II: Central sympathectomized dogs with 6-hydroxydopamine
Group III: Systemic sympathectomized dogs with α-methyl-p-tyrosine
Group IV: Adrenal sympathectomized dogs by bilateral adrenalectomy
Group V: Systemic and adrenal sympathectomized dogs by the combined procedures mentioned in Groups III and IV

**Table 2. Total catecholamine levels of various tissues in control dogs, central sympathectomized dogs by 6-OHDA and systemic sympathectomized dogs by α-MT**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Treatment</th>
<th>Control</th>
<th>α-MT</th>
<th>6-OHDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortex</td>
<td>0.089±0.029 (7)</td>
<td>0.029±0.005** (6)</td>
<td>0.015±0.002* (5)</td>
<td></td>
</tr>
<tr>
<td>Brainstem</td>
<td>0.141±0.044 (7)</td>
<td>0.130±0.030 (6)</td>
<td>0.032±0.003* (5)</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>1.446±0.192 (7)</td>
<td>0.301±0.062* (7)</td>
<td>1.032±0.088 (5)</td>
<td></td>
</tr>
</tbody>
</table>

* Significantly different from control (p<0.01)
** Significantly different from control (p<0.05)

α-MT: Systemic sympathectomized dogs by α-methyl-p-tyrosine at a dose of 250 mg/kg
6-OHDA: Central sympathectomized dogs by 10 mg of 6-hydroxydopamine per dog administered into the lateral ventricles

2. Accordingly, it was evident that the central sympathectomy significantly decreased catecholamine content in the brain cortex and brainstem, but did not significantly change the catecholamine content in the myocardium.

These results indicate that the chemical sympathectomy of brain induced no effect on the onset of ouabain arrhythmias and on concomitant elevations of blood pressure and catecholamine level in plasma by ouabain.

**GROUP III ……SYSTEMIC SYMPATHECTOMY**

In dogs pretreated with α-methyl-p-tyrosine, the catecholamine contents was 0.301 μg/g in the myocardium 0.025 μg/g in the brain cortex and 0.130 μg/g in the brainstem,
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Table 3. Toxic Dose and Lethal Dose under I.V. Infusion of Ouabain (5μg/kg/3min) in Pretreated Dogs

<table>
<thead>
<tr>
<th></th>
<th>TOXIC DOSE (μg/kg)</th>
<th>LETHAL DOSE (μg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean ± S. E.</td>
<td>mean ± S. E.</td>
</tr>
<tr>
<td>GROUP I (N=7)</td>
<td>57.3±4.7</td>
<td>99.2±11.6</td>
</tr>
<tr>
<td>GROUP II (N=8)</td>
<td>49.1±2.1</td>
<td>79.8±5.3</td>
</tr>
<tr>
<td>GROUP III (N=8)</td>
<td>52.2±8.4</td>
<td>88.0±11.1</td>
</tr>
<tr>
<td>GROUP IV (N=6)</td>
<td>54.1±5.1</td>
<td>83.1±8.3</td>
</tr>
<tr>
<td>GROUP V (N=7)</td>
<td>52.9±2.2</td>
<td>91.4±7.6</td>
</tr>
</tbody>
</table>

N: number of animals

Group I : Non-treated dogs (control)
Group II : Central sympathectomized dogs with 6-hydroxydopamine
Group III: Systemic sympathectomized dogs with α-methyl-p-tyrosine
Group IV: Adrenal sympathectomized dogs by bilateral adrenalectomy
Group V: Systemic and adrenal sympathectomized dogs by the combined procedures mentioned in Groups III and IV

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while catecholamine contents obtained in control dogs were 1.446 μg/g in the heart and 0.089 μg/g in the brain cortex. It was demonstrated, therefore, that the catecholamine content in the heart and brain cortex was significantly lower in sympathectomized dogs than those in control dogs. However, the brainstem catecholamine was not significantly changed by sympathectomy with α-methyl-p-tyrosine (Table 2).

The sympathectomized dogs also showed the same pattern of blood pressure elevation and arrhythmia, which was accompanied by an increase in plasma catecholamine as seen in non-treated dogs (Fig. 3). The blood pressure rise by ouabain was 49 mmHg on an average and plasma catecholamine was elevated up to 7,111 μg/L after ouabain from 0.007 μg/L of control in sympathectomized dogs (Table 1).
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![Graph showing blood pressure and ECG changes](image)

<table>
<thead>
<tr>
<th></th>
<th>CONTROL</th>
<th>B.P. RISE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLASMA EPINEPHRINE</td>
<td>N.D.</td>
<td>1.92 µg/L</td>
</tr>
<tr>
<td>PLASMA NOREPINEPHRINE</td>
<td>N.D.</td>
<td>2.97 µg/L</td>
</tr>
</tbody>
</table>

B.P. : BLOOD PRESSURE  N.D. : NO DETECTION

Fig. 4. Associated changes in B.P., ECG and plasma catecholamine during I.V. infusion of ouabain in bilaterally adrenalectomized dog.

![Graph showing blood pressure and ECG changes](image)

<table>
<thead>
<tr>
<th></th>
<th>CONTROL</th>
<th>ARRHYTHMIC PHASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLASMA EPINEPHRINE</td>
<td>N.D.</td>
<td>0.03 µg/L</td>
</tr>
<tr>
<td>PLASMA NOREPINEPHRINE</td>
<td>N.D.</td>
<td>N.D.</td>
</tr>
</tbody>
</table>

B.P. : BLOOD PRESSURE  N.D. : NO DETECTION

Fig. 5. Associated changes in B.P., ECG and plasma catecholamine during I.V. infusion of ouabain in dog pretreated with α-MT (250 mg/kg I.P.) and adrenalectomized bilaterally.

GROUP IV -----SURGICAL ADRENALECTOMY

As shown in Fig. 4 and Table 1, a marked increase in plasma level of catecholamine was induced by ouabain concomitantly with an elevation of blood pressure and the onset of arrhythmia in bilaterally adrenalectomized dogs. The blood pressure rise by ouabain was 54 mmHg on an average and the plasma catecholamine level increased

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GROUP V ...... SYSTEMIC SYMPATHECTOMY PLUS SURGICAL ADRENALECTOMY

After adrenal glands were totally removed in dogs pretreated with α-methyl-p-tyrosine, ouabain did not significantly elevate the plasma level of catecholamine even though the blood pressure was slightly elevated at toxic doses (Fig. 5). Ventricular arrhythmia, however, was induced to the same degree by ouabain as seen in other groups. As shown in Table 1, the elevation of blood pressure by ouabain was 21 mmHg on an average in group V. This value was significantly smaller than that of control group.

ORIGIN OF CATECHOLAMINE LIBERATED INTO PLASMA BY OUABAIN

In non-adrenalectomized cases of group I–III in which the total catecholamine content in plasma exceeded 2 µg/L after ouabain, epinephrine occupied 87% of the total catecholamines. On the other hand, after removal of bilateral adrenal gland, ouabain increased the norepinephrine content in blood plasma, occupying 71% of total catecholamines in 4 cases of group IV, in which the total catecholamine level was over 2 µg/L. The results obtained suggest that ouabain enhanced secretion of epinephrine from the adrenal glands and also gave rise to norepinephrine liberation from sympathetic nerve terminals.

BLOOD PRESSURE RISE AND ONSET OF ARRHYTHMIA

Two types of blood pressure rise were observed at toxic doses of ouabain in dogs. One of them was the mountain-shaped rise of blood pressure as shown in Figs. 1–4. The other was a continuous rise of blood pressure which occurred at the time of onset of arrhythmia and continued until death. This type of blood pressure rise was seen in about half of the experimental dogs of Groups I–IV. In almost all cases which showed a rise of blood pressure by ouabain, a small rise of blood pressure was observed gradually following an infusion of ouabain before the onset of the steep elevation of blood pressure combined with ventricular arrhythmia. Toxic doses of ouabain were determined by the onset of ventricular arrhythmia in this experiment. The mean toxic dose and the mean lethal dose in Groups II–V did not show significant differences from those of the control under this experimental design (Table 3).

DISCUSSION

Plasma catecholamine level increased in parallel with the rise of blood pressure at a toxic dose of ouabain in Group I–IV. On the other hand, both B.P. rise and the elevation of plasma catecholamine did not appear at a toxic dose of ouabain in bilaterally adrenalectomized dogs pretreated with α-methyl-p-tyrosine. It is of interest that the ouabain-induced B.P. rise was related to the elevation of epinephrine in plasma in 9 non-adrenalectomized dogs of Groups I–III in which total plasma catecholamines were over 2 µg/L. This evidence suggests that a toxic dose of ouabain has an ability to
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release adrenal medullary catecholamines.

On the other hand, norepinephrine occupied the major part of plasma catecholamine contents elevated by a toxic dose of ouabain in 4 adrenalectomized dogs of Group IV. This may suggest that ouabain also has the ability to increase the liberation of norepinephrine from the peripheral sympathetic nerve stores. Therefore, it may follow that ouabain has an effect to stimulate the sympathoadrenal system in vivo as well as in vitro as already observed by some investigators (Caireli et al., 1961, Tanz, 1962, Roberts et al., 1963, Eriji and Mendez, 1964, Ciofalo and Roberts, 1976, Bank, 1967, Kirpekar et al., 1970, Ciofalo and Treece, 1973, Nishikawa and Tsujimoto, 1974, Ozawa and Katsuragi, 1974).

The present studies indicate a marked vasopressor response induced by ouabain at a toxic dose. Williams et al (1958) reported that there was an average B.P. rise from 129/73 mmHg to 156/86 mmHg following digitalization in normal human subjects at rest, and suggested that the vasopressor effect is due to the increased systemic vascular resistance. Furthermore, Mason and Braunwald (1964) showed about 10 percent of the mean B.P. rise in parallel with the increased total peripheral vascular resistance in non-failure subjects. The magnitude of pressor responses in this study was larger than those previously reported (Boyajy and Nash, 1958, Williams et al., 1958, Blackmon et al., 1960, Cairns et al., 1960, Mason and Braunwald, 1964). This inconsistency may be due to the fact that they applied therapeutic doses of cardiac glycosides while the pressor effect in the present studies was observed at a toxic dose. There may also be the influence of species difference and experimental conditions on the inconsistency. The duration of the pressor effect by ouabain in this study was also longer than those observed by the investigators mentioned above. This difference may depend on the fact that about a half of experimental dogs showed a continuous B.P. rise from the onset of arrhythmia until death which may be due to the constant infusion of ouabain until death in this experiment.

Regarding the mechanism of digitalis-induced vasopressor effect, a vasoconstricting action of the vascular smooth muscle has been reported by many investigators (Mason and Braunwald, 1964, Stark et al., 1972, Leonard, 1957, Ross and Waldhausen, 1960, Braunwald et al., 1961). Ross and his coworkers (1960) have demonstrated a direct vasoconstrictor effect of digitalis on vascular smooth muscle. Stark and his colleagues (1972) indicated the neurally mediated effect of acetylstrophanthinidin through alpha-adrenergic receptors as the predominant mechanism by which peripheral vascular resistance increases. On the other hand, Billis and his coworkers (1969) suggested that central nervous system plays a much larger role in the vasoconstrictor response which is transmitted peripherally by the sympathetic nervous system. More recently, Quest and Billis (1971) demonstrated that digitalis can directly act on the carotid sinus baroreceptor and that this action is a major determinant of the cardiovascular effect. It appears to be difficult to interpret the mechanism on ouabain-induced B.P. rise at a toxic dose only by the central mediated and/or peripheral actions of digitalis on

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vascular smooth muscle as mentioned above. Because the magnitude of pressor effect was so great at a toxic dose of ouabain.

Therefore, on the basis of a concomitant elevation of plasma catecholamines at ouabain-induced B.P. rise it may be reasonable to consider that endogenous catecholamine released by ouabain may play an predominant role on the vasopressor effect at a toxic dose. Furthermore, the above consideration may be supported by the observation that the pressor effect of ouabain was inhibited by pretreatment with \(\alpha\)-methyl-\(p\)-tyrosine combined with bilateral adrenalectomy.

A small vasopressor effect was, of course, observed in this study before the onset of ventricular arrhythmia. It may be reasonable to consider a direct and neurogenic action of ouabain on the peripheral vascular muscles at non-toxic doses. In this experiment, it is difficult to consider an influence of ouabain-induced catecholamine release on the vasopressor effect by ouabain at non-toxic doses. But the above possibility may not be completely neglected if more sensitive measurements of plasma catecholamine is devised.

It is postulated by Chalmer and Reid (1972) that the central noradrenergic nerves form an essential link in the baroreceptor reflex arch because the neurogenic hypertension produced by buffer nerve section was inhibited by intracisternal treatment with 6-OHDA. Based on the above observations, it can be extrapolated that the activities of central noradrenergic ablation by 6-OHDA was examined in this study.

The central noradrenergic denervation by 6-OHDA failed to inhibit the B.P. rise by ouabain. Therefore the mechanism of B.P. rise by a toxic dose of ouabain may not be due to central mediated noradrenergic action but rather by peripheral action. The increase of blood pressure at the arrhythmic phase during infusion of ouabain is summarized in Table I and showed that pretreatment of \(\alpha\)-methyl-\(p\)-tyrosine, 6-OHDA and adrenalectomy reduce the degree of B.P. rise compared with that of control. But the level of plasma catecholamine at a toxic dose of ouabain did not correspond well with the degree of B.P. rise. Therefore the level of increased plasma catecholamine could not be correlated with the degree of B.P. rise at a toxic dose of ouabain. This may be explained by the variations of individuals in the activity of many other regulatory mechanisms of systemic blood pressure (Horrobin, 1966, Abboud, 1972, Guyton et al., 1972, Gribbin et al., 1971, Wallin et al., 1973).

It is difficult to explain the difference between the types of mountain-shaped B.P. rise as shown in Fig. 1-4 and those of continuous B.P. rise. It is also difficult to explain the reason of a recurrent B.P. rise observed in some cases of mountain-shaped B.P. rise. But it may be possible to speculate that intermittent release of catecholamine may occur in the cases of recurrent B.P. rise.

ACKNOWLEDGMENTS

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technical assistance in the fluorometric catecholamine measurements.

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