EFFECT OF $\gamma$-AMINOBUTYRIC ACID (GABA) ON NORMOTENSIVE OR HYPERTENSIVE RATS AND MEN

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Since the discovery of a depressant action on the arterial pressure of $\gamma$-amino-butryic acid (GABA) by TAKAHASHI and his coworkers$^{1,2}$, it has become apparent that there are considerable quantitative variations between animal species and some differences between anesthetized and unanesthetized animals in its depressant action$^{3-6}$.

In the present investigation, the authors have observed effects of GABA on rats and men, and compared its depressant action between normotensive and hypertensive animals. Further, our interest has been focused on the action of oral administration of GABA.

METHODS

Experiments were performed on about 200 Wistar rats and about 50 men. All rats were fed with Oriental laboratory chow (20 gm/day), which contained proteins, carbohydrates, minerals and various vitamins in appropriate proportions, and drank tap water at liberty. Their body weights, amounts of water drunk in a day, daily excreted urine and its specific gravity were checked.

The systolic blood pressure of rats was usually measured one day a week in chronic experiments by plethysmographic method, which was essentially similar to that employed by BYROM and WILSON$^7$. Before measurements, rats were placed for five minutes in a chamber previously warmed to about 40°C, in order to make measuring easier with increasing blood flow in the tail. During measurements, unanesthetized rats were placed on a small hammock.

In men, the systolic and the diastolic blood pressure of the radial artery were measured by the auscultation method. Besides, electroencephalogram and electrocardiogram were simultaneously recorded. For recording of respiration, a thermister was introduced into the nostril, which was connected to one arm of a Wheatstone bridge. Unbalance of this input bridge induced by changes in the resistance of the thermister during respiration was amplified by a three stage direct coupled amplifier. All these phenomena were recorded by an inkwriting oscillograph.

Experimental renal hypertension in rats was produced by the clip method. Small silver clips were applied to a unilateral renal artery of 102 rats and sustained hyper-
tension appeared in about a half of them. In a few rats, hypertension was induced by bilateral constriction of renal arteries.

γ-Aminobutyric acid (GABA, mp 199-201°C) was administered orally or subcutaneously. To rats, GABA mixed with meal was orally applied. To men, it was orally administered as tablets coated with sugar.

As the conclusion of experiments, rats were killed and their various organs were examined macroscopically as well as microscopically.

RESULTS

Experiment I

I. Effect of oral GABA on normotensive rats; Twenty Wistar rats of about 58 days old were fed for 12 weeks under the condition described in methods and to ten of them, GABA (1 gm/day) was orally given for 8 weeks from the 5th week.

The group of rats whom GABA was not given drank daily 28±3 ml of water and excreted 9.0±1.5 ml of urine on the average. Increase in their body weights averaged 85±15 gm in 12 weeks. The group of GABA-fed rats drank daily 27±3 ml of water and excreted 10.0±1.6 ml of urine on the average. Increase in their body weights averaged 80±21 gm in 12 weeks.

Systolic blood pressure of 115 rats whom GABA was not given was measured at random 345 times. Its value averaged 102±8 mm Hg (81-124 mm Hg). In seven GABA-fed rats, systolic blood pressure was measured from the second week after application. Its value averaged 103±11 mm Hg (80-120 mm Hg).

At the conclusion of experiments, they were killed and their brain, lung, heart, spleen, liver and kidney were stained with Haematoxylin and examined histologically. However, no appreciable histological changes between control rats and GABA-fed rats were observed.

II. Effect of oral GABA on hypertensive rats; The blood pressure levels of experimental renal hypertensive rats tended to fluctuate considerably on the initial phase, but sooner or later became relatively stationary. More than ten mg of GABA (0.01-1 gm) per day was applied orally at such stages to hypertensive rats weighing about 200-300 gm. The depressant effect of GABA varied considerably between individuals, but it was obviously recognized in nearly all the hypertensive rats (93%), when more than 30 mg was given every day (TABLE 1).

After application of 50 mg of GABA, fall of blood pressure amounted to 28 mm Hg on the average in 7 hypertensive rats (P<0.001). In TABLE 2, the dose-effect relation of GABA in the same rats is shown.

The depressant effect of orally administered GABA appeared within one or two days in some hypertensive rats, but in others it was observed at first after a few days (FIG. 1). Thereafter, its effect was usually maintained during the administration and disappeared within one week after interruption of the applica-
tion. If GABA was again applied, the effect was observed repeatedly.

In Fig. 2, typical example of the effect of GABA on hypertensive rats is furnished. In this figure, the fluctuation in systolic blood pressure level of another hypertensive rat to whom GABA was not administered and the effect of GABA on a normotensive rat are also shown as controls.

On the other hand, no appreciable change was observed in the blood pressure

### Table 1

<table>
<thead>
<tr>
<th>Amount of administration (gm/day)</th>
<th>Systolic blood pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before administration</td>
</tr>
<tr>
<td>1.0</td>
<td>169 ± 7 (2*)</td>
</tr>
<tr>
<td>0.5</td>
<td>169 ± 5 (3)</td>
</tr>
<tr>
<td>0.1</td>
<td>161 ± 4 (4)</td>
</tr>
<tr>
<td>0.05</td>
<td>179 ± 3 (7)</td>
</tr>
<tr>
<td>0.03</td>
<td>153 ± 2 (3)</td>
</tr>
<tr>
<td>0.01</td>
<td>179 ± 6 (5)</td>
</tr>
</tbody>
</table>

* Figures indicate numbers of experiments.

### Table 2

<table>
<thead>
<tr>
<th>Amounts of administration (g/kg/day)</th>
<th>Systolic blood pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
</tr>
<tr>
<td>3.8</td>
<td>188 ± 5</td>
</tr>
<tr>
<td>0.2</td>
<td>210 ± 2</td>
</tr>
<tr>
<td>0.04</td>
<td>206 ± 5</td>
</tr>
<tr>
<td>0.16</td>
<td>161 ± 1</td>
</tr>
<tr>
<td>0.11</td>
<td>155 ± 1</td>
</tr>
<tr>
<td>0.16</td>
<td>176 ± 4</td>
</tr>
<tr>
<td>0.03</td>
<td>185 ± 2</td>
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</tbody>
</table>
levels of respective three hypertensive rats whom 50 mg of L-glutamate or L-aspartic acid were orally given every day for three weeks.

III. Effect of subcutaneous GABA on blood pressure of rats: When 5 mg of GABA in 0.1 ml were injected subcutaneously in three normotensive rats, no effect on blood pressure was observed. However, when the same amount of GABA was injected in three hypertensive rats, in two rats remarkable decreases and in another rat a slight decrease were observed. Its effect reached to peak within one or five minutes after injection and continued for more than thirty minutes.

Subsequently, the effects of GABA and reserpine were compared in the three same hypertensive rats. 0.2 mg of reserpine was subcutaneously injected.

![Graph](image-url)
The maximal fall in blood pressure was of the same order in both cases, but the effect of reserpine appeared after a longer latency and lasted for a longer period (Fig. 3).

Experiment II

I. Effect of GABA on healthy men, In eleven healthy adult men, 1-3 mg per kg of GABA was injected subcutaneously and its effects on respiration, blood pressure, electrocardiogram and electroencephalogram were observed. In nine cases, no appreciable changes took place in respiration, but in two cases remarkable acceleration occurred; in one subject respiration rate was increased from 24/min to 66/min and in another from 16/min to 33/min. The heart rate increased by 21-55/min in seven cases, but decreased by 27/min in one case. Blood pressure tended to elevate in all the cases, exclusive of one. But, the elevation of blood pressure was within 10 mm Hg, except for two cases, where increases in systolic blood pressure amounted respectively to 32 and 54 mm Hg. On the other hand, EEG and EKG were not affected by the injection of GABA.

Besides these effects, all the subjects reported some sensation of flushing similar to that induced by intravenous injection of CaCl₂, a slight numbness in the limbs, a pricking sensation in the skin, respiratory discomfort and headache. Moreover, they noticed dry mouth and subsequently increase in saliva secretion. All the objective and subjective effects of GABA were usually transient and disappeared within twenty minutes. These effects were likewise observed after the skin to be injected was previously anesthetized by novocaine.

As above described, the effect of subcutaneous GABA was not so severe, though more or less uncomfortable. However, there was one exceptional case, where striking decrease in blood pressure (by 54 mm Hg) lasted for more than one hour.

Subsequently, GABA (3 gm/day) was orally administered to four healthy persons for one month and its effect on blood pressure was observed. Oral GABA did not show any depressant effect or other appreciable side effects in all the cases.

II. Effects of GABA on hypertensive patients; GABA (3 gm/day) was applied to 25 hospitalized patients suffering from essential hypertension. GABA produced a more or less remarkable depressant effect in 22 persons (88%). The lowering of blood pressure level by oral GABA amounted to 45.8 mm Hg in systolic and to 23.2 mm Hg in diastolic pressure on the average.

The systolic and diastolic blood pressure of the treated patients were gradually lowered within 1-3 days or a few more and reached a minimal level which was usually not below the normal blood pressure level within one or two weeks after application. The lowered level was usually maintained during the application, but returned to the previous elevated level within a few days, if the treatment was interrupted.
The depressant effect of GABA was more prominent in patients of higher elevated blood pressure level and was accompanied with disappearance of self-noticed symptoms such as headache, numbness in the arm, singing in the ear.

To six normotensive patients who were admitted to the same hospital, GABA (3 gm/day) was given for about five weeks, but no appreciable change in blood pressure and no side effects were observed.

DISCUSSION

Our findings that oral GABA did not cause any depressant effect on blood pressure of normotensive animals, but in hypertensive animals it could produce a lasting lowering of blood pressure level, suggest that the reactivity of some depressant mechanism to GABA may be increased in hypertension. According to our results, this increase in reactivity may be more than 30-fold in the case of experimental renal hypertension. In the case of human essential hypertension, the increase in the reactivity may be more, because GABA could reduce blood pressure more easily in the latter case.

However, the problem, what organ is the principal site of action of GABA in hypertensive animals, is left unsettled.

SUMMARY

1. The effect of GABA on blood pressure of normotensive and hypertensive rats or men was investigated.
2. GABA, when administered orally one g per day for a month, did not cause any appreciable changes in body weight, blood pressure and other side effects in normotensive rats. No histological changes were found in their organs.
3. On the contrary, GABA reduced the elevated blood pressure of experimental renal hypertensive rats at the doses of more than thirty mg per day. Its effect was maintained during the application, and disappeared within one week after the interruption of treatment.
4. When glutamate or aspartic acid of 50 mg per day was orally applied for three weeks, no change was observed in blood pressure of hypertensive rats.
5. GABA, administered subcutaneously was also more effective in hypertensive rats than in normotensive ones.
6. Subcutaneous injections of GABA (1-3 mg per kg) on normotensive subjects produced slight uncomfortable side effects.
7. GABA, if administered orally three g per day, did not cause any appreciable effects on normotensive persons, but it lowered remarkably the elevated blood pressure of patients.
REFERENCES


