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# Effects of Guanfacine on Sympathetic Nerve Activity and Hemodynamics

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Guanfacine, an alpha2–adrenoceptor agonist, exerts hypotensive effect by acting mainly via receptors located in the central nervous system. Although there are several reports which suggested the peripheral action, the quantitative studies of the peripheral and central actions have not been extensively performed yet. In rabbits anesthetized with urethane, arterial pressure (AP), heart rate (HR) and renal sympathetic nerve activity (RNA) were recorded simultaneously. Guanfacine was administered intravenously in cumulative dose of 10, 30, 100, 300 μg/kg; HR showed bradycardia in dose-related manner. The drug initially elevated AP which was followed by hypotensive phase with dose-dependency, while RNA markedly decreased at the initial hypertensive phase and returned to the control level gradually. The initial elevation in AP, representing the stimulating action on alpha receptor on the arterial wall was 14% at the dose of 300 μg/kg. When plasma norepinephrine concentration was assayed to evaluate the action on presynaptic alpha2–receptor, the value was depressed by 28% from each control level. Thus, these drugs have agonistic action on alpha2–receptor. However, as for the action on sympathetic nervous system, Gf exerted the hypotensive action more dominantly on the peripheral presynaptic alpha2–receptor.

**Key Words**
Alpha2–adrenoceptor agonists,
Guanfacine,
Renal sympathetic nerve activity,
Peripheral action,
Central action.

## INTRODUCTION

Recently, several kinds of alpha2–adrenoceptor agonist are available for the treatment of hypertension(1). Although there are some reports on these agents, it is not clear yet how the agents exerts effect on peripheral and central receptors quantitatively. The effect of Clonidine was examined very widely(1,2), however, guanfacine which has more specificity on alpha2–receptor has not been examined well(3).

The antihypertensive effect of the drug is mediated, at least in part, by a way of the central nervous system where it acts as an alpha-adrenoceptor agonist. This, in turn, leads to reduced sympathetic nervous activity and decreased blood pressure(2). Therefore the drug is classified as centrally acting antihypertensive one.

On the other hand, peripheral factors operative at the level of the sympathetic terminal varicosity may have either a presynatic or postsynaptic action. The amount of norepinephrine released by nerve impulses may be controlled by presynaptic receptors(4). The stimulation of presynaptic receptor suppresses the norepinephrine release from the sym-

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pathetic nerve terminal. These mechanisms may contribute to the hypotensive effects to some extent.

The aim of our study is to measure the effect of Guanfacine(Gf) with regard to hypotensive potency. For the above purpose, the effects of the drugs on arterial pressure (AP), heart rate (HR), renal sympathetic nerve activity (RNA) and plasma norepinephrine (NE) were examined in anesthetized rabbits.

## METHODS AND MATERIALS

1. Surgical Procedure

Adult rabbits, weighing from 2.5 to 3.0 kg, were anesthetized with urethane (1200mg/kg) administered intraperitoneally. After a tracheotomy was performed, each rabbit was ventilated on mixture of oxygen and room air using a Harvard type respirator pump.

The right femoral vein was cannulated for intravenous administration of drugs. Arterial pressure was recorded through a cannula inserted into the left femoral artery. The rectal temperature was also monitored and maintained at 38 ℃ with a heat pad.

Effect sympathetic nerve activity was recorded from a branch of the left renal nerve. The nerve was exposed under a binocular microscope and placed on silver-silver bipolar electrode. The nerve activity was recorded using a high gain amplifier and measured in arbitrary unit of integrated amplitude.

2. Protocol for Intervention

After all parameters were stabilized and the control level was obtained, Guanfacine (Gf) was administered intravenously in cumulative dose of 10, 30, 100, 300 $\mu$g/kg. The effects of the drugs were observed for 10 minutes. The followed administration was repeated at an interval of 30 minutes. The statistical analysis of the present report was performed with values obtained in each dose.

The values of paramenters were measured at 3 points after the administration, i.e., at the points of immediately, 3 minutes and 10 minutes. The relative % change was calculated in the comparison with the control value obtained just before the administration.

Plasma noradrenalin (NA) and adrenalin (A) was measured before and 10 minutes after the administration in maximum dose using HPLC–ECD method.

3. Data Analysis

For the data analysis, mean values of AP and RNA were employed. The results are expressed as mean ± S.E.M. in figures. Statistical analysis was performed

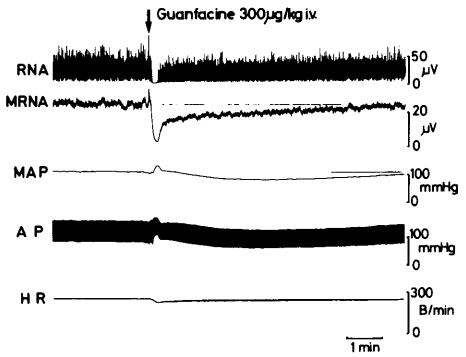



**Figure 1.** Typical changes of RNA, AP and HR induced by Guanfacine(300 $\mu$g/kg).

Immediately after the administration at arrow, arterial pressure (AP) showed an increase which was followed by hypotension. In contrast, renal nerve activity (RNA) showed marked initial decrease which was followed by gradual recovery. On the other hand, heart rate (HR) showed minimum value imediatly after the administration. m: mean

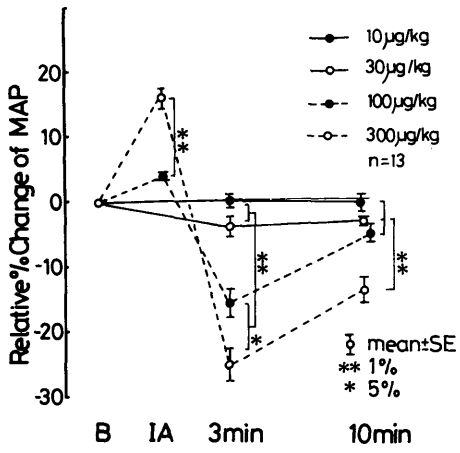



Figure 2. Summarized results of mean AP (MAP) by each doses.
The coordinate shows relative % change from the control level. On the abscissa the time after the administration is shown. The number (n) of animals was 13. B: before, IA: immediately after, min: minute

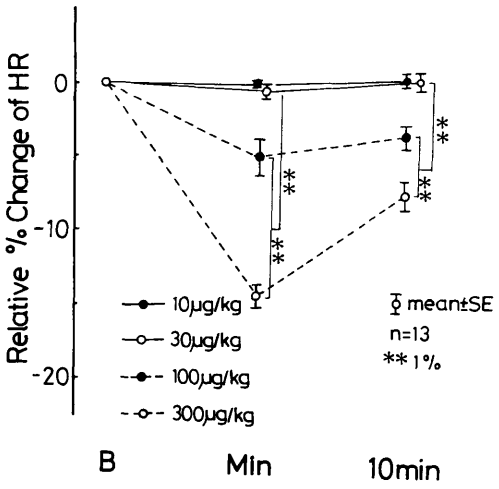



Figure 3. Effects of Gf on HR
The figure summarises results of HR. HR also decreased in dose-related mode. The minimum value was obtained immediately after the administration.

with Student's test or ANOVA test(5). Significance was accepted at the $P < 0.05$.

4. Materials

The drugs used in this experiment were as in the following.: Guanfacine (Sandoz), Gallamine (Teikoku Sangyo Co), Urethane (Wako Chem. Co.).

## RESULTS

As shown in figure 1, AP was increased immediately after the administration of Gf in a dose of 300 $\mu$g/Kg. On the other hand, RNA showed remarkable suppression at the same phase. This response indicated that the initial suppression in RNA might be developed by baroreflex. After this phase, AP changed into hypotension which was followed by gradual elevation in association with RNA. However, even at the period when RNA returned to the control value, AP was still lower than the control.

1. Effects of Gf on hemodynamics

Figure 2 summarizes the results of mean AP. Initial hypertension, as well as followed hypotension, showed dose-related change. The the value of initial hypertension was +14% at the maximum dose. Then it tured to hypotension and showed minimum value of −24% at 3 minutes. AP remained to be a hypotensive level and showed hypotension (−20%) at 10 minutes after the administration of maximum dose.

Figure 3 shows the changes in HR. HR also decreased in dose-related mode. The minimum value was obtained immediately after the administration. The value was −14% at the maximum dose. HR gradually returned to the control level but was still lower at 10 minutes. The value was 8% at

the maximum dose.

2. Effect of Gf on RNA and plasma catecholamine

The left panel of figure 4 summarizes the results of RNA. At the initial period when AP was elevated (14% at maximum dose), RNA was depressed (7%). After the suppression, the values returned to the control and finally went over the control value.

On the right panel of figure 4 summarizes correlation of AP and RNA at the dose of 100 $\mu$g/kg and 300 $\mu$g/kg. As the figure clearly shows, at 10 minutes after the administration, there is a discrepancy between the AP and RNA. While RNA was above the control, AP was still below the control. This phenomenon suggested the suppression of secretion of catecholamines from nerve terminal. Figure 5 depicts the values of adrenalin and noradrenalin on the left panel. It also shows the relative % change of the both catecholamines. The suppression was more marked in noradrenalin(46%) and less in adrenalin(12%) with statistical significance.

## DISCUSSION

In the present study, it was indicated that the drug was potent hypotensive agent capable of reducing sympathetic nerve activity by stimulating presynaptic alpha2–receptor.

Alpha2–receptors are located both in the brain and the periphery. In the brain stem they modulate sympathetic outflow(2). Peripheral alpha2–receptors activate both presynaptic receptors and

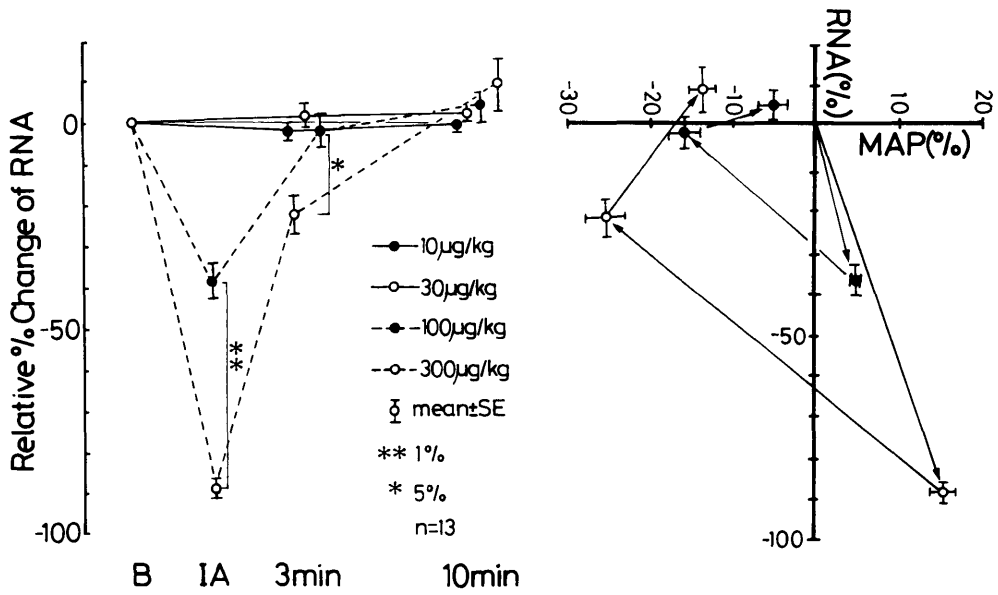



Figure 4. Effects of Gf on RNA and its correlation with MAP

On the left panel represents the results of RNA.

On the right panel summarizes correlation of AP and RNA at the dose of 100 $\mu$g/kg and 300 $\mu$g/kg. Note that RNA went over the control value while MAP below the value.

receptors in blood vessel's wall(4).

There are many reports on the central action of drugs. The agonists like Clinidine(Cl) are usually reported to act mainly via alpha2−receptors located centrally(2). The sedative effect of the drugs may also be indicative of a central nervous action(6). The neurogenic hypothesis is supported by the therapeutic activity of Cl and related alpha2−agonist drugs as well. These reports(7) showed that alpha2−adrenoceptor agonists induced a dose-related fall in plasma norepinephrine levels, which presumably reflects the reduction in central sympathetic activity and, at least in part, underlies the fall in blood pressure. Furthermore, RNA was suppressed in awaked dogs in the use of Cl(8). However, the comparison among the drugs was not clearly shown in terms of the selectivity.

As for the baroreflex sensitivity, there are several reports(9) of assessment by its influence on baroreflex sensitivity for heart rate. Since administration of Cl into the cisterna magna potentiated the cardiovascular depressor reflex in animals, the potentiation of the baroreflex by this drugs was suggested. Furthermore, Cl produced an increase in baroreflex sensitivity in patients with essential hypertension as well. From our results, Gf had this action as well.

The presynaptic alpha2−receptor has been considered to be important in an autoinhibitory feedback loop, whereby the transmitter itself influences subsequent NA release from moment to moment(4). A discrepancy between the decrease in blood pressure and the reduction in sympathetic nervous activity has also been demonstrated after acute administration of Cl in dogs, cats and rabbits. A peripheral component of the effect on sympathetic activity might account for the decrease in AP. A marked decrease in AP could then be accompanied by changes in plasma NA concentration, reflecting the sympathetic overflow from the synaptic cleft.

In the present study the presynaptic effects of the drug was speculated by the relationship of NA and RNA. With an understanding of single nerve recording(10), poor correspondence of RNA with NA may indicate the inhibition of release of NA from sympathetic nerve terminal. In fact, a significant decrease in plasma NA concentration occurred within 10 minutes of a single intravenous dose of drugs. Because adrenaline which was released from the adrenal grand showed

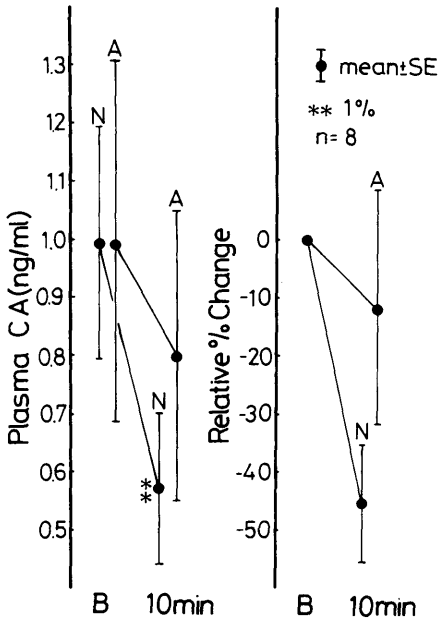



**Figure 5.** Effects of Gf on catecholamins
The left panel depicts the values of adrenalin and noradrenalin which was obtained 10 minutes after the administration in 8 rabbits.
The right panel shows the relative % change of the both catecholamines. N: noradrenalin A: adrenalin

very small change, it was suggested that the central action was very small and that the drug has mainly the presynaptic effect.

There are several published studies(12) of postjunctional alpha2–receptors in human subjects. These indicate that peripheral alpha2–receptors appear to contribute to the overall peripheral vascular resistance in human subjects as in animals. The initial pressor effect was found to be due to vasoconstriction resulting from the stimulation of peripheral alpha-adrenoceptors. Although the pressor responsiveness to intravenous alpha-agonists with a range of receptor selectivity can be used as an index of selectivity, the respose should be measured without modulation of baroreflex(3,13).

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