bath solution was frequently replaced. After 30 minute equilibration period, the rate and force of contraction were measured for 30 minutes.

Part I

Statistical analysis

The data were analyzed at maximal drug effect by the use of paired t-test. The changes were considered significant when the probability of chance occurrence was less than 5% ($P < 0.05$). The blood pressure in the following experiments was expressed as mean blood pressure which was calculated from $\frac{1}{3}$ pulse pressure + diastolic blood pressure. The values were expressed as mean $\pm$ s.e.m.

Results

1. Intravenous injection of hydralazine 2, 4, 6, 12, 16 mg/kg in anaesthetized rats.

The sample of tracing are shown in Fig. 1.1 - 1.3. The hypotensive response to intravenous injection of hydralazine 2, 4, 6, 12, 16 mg/kg was recorded between 10 and 30 min after the injection. Significant ($P < 0.001$) decrease in mean blood pressure occurred at 5 min and remained highly significant at 15 min (table 1.1). However, the onset of hypotensive action of hydralazine after each dose gradually reached maximum in between 15 and 30 min after administration. Therefore, the hypotensive effect of the different doses of hydralazine in this experiment was measured at the maximal hypotensive effect. Hydralazine 2, 4, 6, 12,

16 mg/kg reduced blood pressure about 50% from control of each dose (table 1.2). In an attempt to compare the hypotensive effect of the different dose of hydralazine, the percentage of mean blood pressure was calculated. The percentage of change of mean blood pressure from control produced by hydralazine 2, 4, 6, 12,16 mg/kg were 42.2 $\pm$ 1.9, 46.6 $\pm$ 3.6, 47.4 $\pm$ 1.5, 52.2 $\pm$ 2.1 and 44.5 $\pm$ 2.7, respectively (table 1.2).

The effects of hydralazine, 2, 4, 6, 12, 16 mg/kg on heart rate in anaesthetized rats were measured at 15 min after administration was shown in table 1.3. Each dose of hydralazine caused a dual response in the rate of beating of heart which was the initial bradycardia with subsequent tachycardia. This consistent response was seen immediately after hydralazine administration. The delayed response of heart rate was inconsistent in anaesthetized rats. At the maximal hypotensive drug effect, each dose of hydralazine produced significantly decrease in heart rate ($P < 0.005$ and $P < 0.05$) (Fig 1.4).

The various doses of hydralazine in anaesthetized rats caused initial transient bradycardia and followed by tachycardia. This cardiac response were called dual action of hydralazine on heart rate and the response was dose-dependent (Fig 1.3, 1.4, 1.5). In Fig.1.1 hydralazine 2 mg/kg produced on one rat, the decrease of heart rate from 370 to 350 beats/min, then rapidly increased from 350 to 360 beats/min. When the dose of hydralazine increased to 16 mg/kg, the heart rate decreased from 405.0 $\pm$ 7.4 to 317.0 $\pm$ 8.0 beats/min (Table 1.5). The mean change

of bradycardia and tachycardia in this experiment was shown in table 1.5. The bradycardia and tachycardia were expressed as percentage change in order to compare the cardiac response of different dose of hydralazine (table 1.6).

2. The result of intravenous injection of hydralazine 2, 4, 6, 12, 16 mg/kg in pithed rats.

The typical tracing of the effects of hydralazine on the example rats, 2, 4, 6, 12, 16 mg/kg are shown in Fig. 2.1, 2.2, 2.3. It can be seen that the blood pressure of pithed rat was about 50% lower than in anaesthetized rats. Hydralazine 2, 4, 6, 12, 16 mg/kg produced a significant ($P < 0.001$) lowering of blood pressure at 5 min after administration. The blood pressure remained unchanged within 15 min (table 2.1) and went down to maximal hypotensive effect (Fig. 2.4). The mean percentage change of blood pressure is calculated to compare the hypotensive effect of each dose of hydralazine. The percentage changes of mean blood pressure of hydralazine 2, 4, 6 mg/kg were 18.8 ± 2.5, 24.4 ± 3.0, 30.6 ± 3.1, respectively. Hydralazine, 12 and 16 mg/kg caused a higher reduction in mean blood pressure than low doses; the percentage changes of the mean blood pressure were 25.5 ± 1.6 and 29.9 ± 2.9, respectively.

The effect of different doses of hydralazine on heart rate was shown in table 2.3. In this experiment, hydralazine only in the dose of 2 mg/kg produced the significant increase in heart rate at 5 and 15 min

after administration ($P < 0.01$ and $P < 0.005$, respectively) (table 2.3). Furthermore, hydralazine, 4, 6, 12, 16 mg/kg produced only transient dual effect on heart rate, whereas the rate at the maximal hypotensive effect remained unchanged ($P > 0.05$) (Fig. 2.5, table 2.4).

The cardiac responses of different doses of hydralazine in pithed rats turned out to be the same as in anaesthetized rats; hydralazine produced a bradycardia and tachychcardia in a dose dependent maner (Fig. 2.1, 2.2, 2.3 and table 2.5). The mean percentage change of dual action produced by hydralazine was shown in table 2.6.

Part II

1. Antagonism of noradrenaline (10 μg) on the hypotensive effects of yohimbine (0.25 mg/kg), hydralazine (2 mg/kg) and phentolamine (2 mg/kg) in anaesthetized rats.

Statistics

The values are expressed as mean $\pm$ s.e.m.. For testing the statistical significance of different between two mean, unpaired t-test was used and a paired t-test was used for testing the difference within a group.

Group A

Antagonism of noradrenaline (10 μg) on the hypotensive effects of yohimbine (0.25 mg/kg).

A typical tracing of one rat in Fig. 3.1, shows that noradrenaline (10 μg) increased systolic blood pressure 80 mmHg from

predrug level and gradually declined. The heart rate markedly decreased and returned to normal level. These effects of noradrenaline on blood pressure and heart rate were recorded as a control in this experiment.

Yohimbine 0.25 mg/kg caused a reduction of blood pressure from 120/90 to 85/60 mmHg, whereas the heart rate was slightly increased. Thirty minutes after yohimbine administration, noradrenaline (10 μg) was injected intravenously. The systolic blood pressure increased 60 mmHg from a predrug level, while the heart rate increased slightly and remained unchanged for a period of 30 min. Although in this experiment the mean changes of systolic blood pressure produced by noradrenaline after yohimbine administration seemed to be different from the change of the blood pressure induced by noradrenaline alone (table 3.1). However, the change of systolic blood pressure was not statistically significant ($P > 0.05$) (Fig. 3.4). The heart rate was also unaffected (Fig. 3.5).

Group B

Antagonism of noradrenaline (10 μg) on the hypotensive effects and heart rate of hydralazine (2 mg/kg).

The typical tracing example is shown in Fig. 3.2. Noradrenaline (10 μg), by itself, increased the systolic blood pressure 64.0 $\pm$ 4.9 % of predrug value, whereas heart rate was reflexly decreased 38.3 $\pm$ 8.7 %. After pretreatment with hydralazine, noradrenaline (10 μg) significantly enhanced ($P < 0.005$) the elevation of the blood pressure (from 64.0 $\pm$ 4.9 to 105.9 $\pm$ 8.6 % of predrug value) (Fig. 3.4) and the heart rate was not

significanty changed ($P > 0.05$) (Fig. 3.5) from noradrenaline alone.

Group C

Antagonism of noradrenaline (10 μg) on the hypotensive effects and heart rate of phentolamine (2 mg/kg).

The typical example of tracing was shown in Fig. 3.3. Noradrenaline (10 μg), by itself, increased the systolic blood pressure 71.5 $\pm$ 6.9 % of predrug value and it decreased heart rate 21.4 $\pm$ 5.8 % of predrug value measured immediately after noradrenaline administration (table 3.1). Phentolamine (2 mg/kg) was significantly antagonized ($P < 0.001$) the increasing of the systolic blood pressure induced by noradrenaline (Fig. 3.4), and the reflexly decreased heart rate was significantly inhibited ($P < 0.05$) (Fig. 3.5).

2. The effect of haloperidol (0.214 mg/kg) on the cardiovascular effects of hydralazine (2 mg/kg) in anaesthetized rats.

The typical example of tracing was shown in Fig. 4.1. Haloperidol, by itself, decreased mean blood pressure from 85.3 $\pm$ 9.3 to 63.8 $\pm$ 9.2 mmHg and decreased heart rate from 370.1 $\pm$ 7.1 to 340.0 $\pm$ 15.4 beats/min (table 4.1). Thirty minutes after haloperidol administration, then hydralazine was injected intravenously. Hydralazine caused a further reduction of blood pressure from 63.8 $\pm$ 9.2 to 31.6 $\pm$ 2.9 mmHg, whereas the heart rate was decreased from 304.0 $\pm$ 15.4 to 206.0 $\pm$ 17.7 beats/min. The reduction in blood pressure induced by haloperidol alone was significantly from control ($P < 0.05$). The further

reduction of blood pressure induced by hydralazine after haloperidol pretreatment was significantly different from the initial prehydralazine level ($P < 0.005$). However, the effect of haloperidol alone on the reduction of heart rate was not significantly different from control ($P > 0.05$), but the effect of hydralazine on heart rate after haloperidol pretreatment was significantly decreased ($P < 0.005$) (table 4.1) (Fig. 4.3, 4.4).

3. The effect of haloperidol (0.214 mg/kg) on the cardiovascular effects of hydralazine (2 mg/kg) in pithed rats.

The typical example of tracing was shown in Fig. 4.2. Haloperidol alone decreased mean blood pressure from 38.9 ± 1.2 to 35.3 ± 1.3 in pithed rats (table 4.1), and this change of blood pressure was not significantly different from control ($P > 0.05$). After hydralazine administration, the blood pressure was reduced from 35.3 ± 1.3 to 25.3 ± 2.17 mmHg. The reduction was significant different from the initial predrug level ($P < 0.05$) (table 4.1). Haloperidol alone did not affect the heart rate; it was 268.0 ± 13.9 and 269.0 ± 10.7 beats/min before and after haloperidol administration respectively. In addition, the effect of hydralazine on heart rate after haloperidol pretreatment was not significantly decreased ($P > 0.05$) (Fig. 4.3, 4.4).

Part III

Statistical analysis.

The data were analyzed by the use of unpaired t-test. The changes were considered significant when the probability of chance occurrence was less than 5% ($P < 0.05$). The values were expressed as mean $\pm$ s.e.m.

Results

1. Chronic pretreatment of rats with hydralazine (2 mg/kg) for 15 days.

A typical example of tracing is shown in Fig. 5.1. The rate of beating and the force of contraction of isolated atria are shown in table 5.1. The rate of beating in control group was 109.1 $\pm$ 14.8 beats/min, whereas in the experimental group was 98.0 $\pm$ 11.5 beats/min. The force of contraction in control group and experimental group were 0.24 $\pm$ 0.05 g and 0.35 $\pm$ 0.05 g, respectively. However, these changes were not significantly different from the control group ($P > 0.05$).

2. Chronic pretreatment of rats with hydralazine (2 mg/kg) for 30 days.

A typical example of tracing is shown in Fig. 5.2. The effect of hydralazine on the rate of beating and force of contraction of isolated atria are shown in table 5.1. The rate of beating in the control group and experimental group were 145.4 $\pm$ 11.3 and 115.6 $\pm$ 9.8 beats/min, respectively. The force of contraction were 0.52 $\pm$ 0.08 and 0.40 $\pm$ 0.03 g, respectively. The increase in heart rate and force of contraction caused

by chronic pretreatment of hydralazine were not significant different from the control group ($P > 0.05$).