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Effects of Psychotropic Drugs on Pressor and Behavioral Responses to Brain Stimulation in Unrestrained, Unanesthetized Rats

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KAWASAKI, H., S. WATANABE AND S. UEKI. *Effects of psychotropic drugs on pressor and behavioral responses to brain stimulation in unrestrained, unanesthetized rats.* PHARMAC BIOCHEM. BEHAV. **10**(6) 907–915, 1979—Electrical stimulation of the posterior hypothalamus (PH) and the mesencephalic reticular formation (MRF) in unanesthetized, unrestrained rats with chronic electrode implants and an arterial cannula elictied a rise in blood pressure accompanied by behavioral changes such as exploration, flight or escape responses. Pentobarbital inhibited both the pressor and behavioral responses to PH and MRF stimulation. Chlorpromazine, diazepam and imipramine depressed the pressor response to PH stimulation rather than that to MRF stimulation with affecting the behavioral responses. It is concluded from these results that chlorpromazine, diazepam and imipramine exert their action on the neural pathway involved in the pressor response rather than on that inducing behavioral responses, whereas pentobarbital affects more extended brain areas related to these neural systems.

Blood pressure Behavior Brain stimulation Posterior hypothalamus Mesencephalic reticular formation Psychotropic drugs Chlorpromazine Diazepam Pentobarbital Imipramine Rat

ELECTRICAL stimulation of the hypothalmus or other caudal structures elicites an immediate rise of blood pressure in various species of animals and this pressor response is suppressed by several psychotropic drugs such as pentobarbital [14, 16, 18, 19],, diazepam [1, 4, 13, 18, 19], chlorpromazine [13, 16, 18, 19] and imipramine [17]. There is general agreement that suppression of the pressor response of psychotropic drugs is due to the reduction of the increased sympathetic outflow occuring after stimulation and that peripheral effects are not responsible. However, the exact sites of action of these drugs in the central nervous system has not been clarified.

Although the pressor response elicited by stimulation of the central sympathetic area has been used for the evaluation of drugs acting on the central nervous system, most experiments have been performed using anesthetized animals. The anesthetics such as barbiturates and urethane used in these experiments also inhibit the cardiovascular response to hypothalamic stimulation [3,14]. Thus, it is very likely that the results obtained under anesthetized conditions might be different from those obtained in unanesthetized animals.

In addition to the cardiovascular response, stimulation of the central sympathetic area also causes various emotional responses which are suppressed by psychotropic drugs [7, 10, 17].

We therefore attempted to investigate not only cardiovascular and behavioral responses to electrical stimulation of the posterior hypothalamus (PH) and mesencephalic reticular formation (MRF) but also the effects of some psychotropic drugs on these responses in unanesthetized and unrestrained animals.

METHOD

Animals

Fourty-nine male Wistar King A strain rats supplied by Kyushu University Institute of Laboratory Animals were used. The animals weighed between 280–300 g at the beginning of the experiment. All animals were given food and water *ad lib* and housed in groups in an air conditioned room with a 12-hr light/dark cycle (lights on at 08:00). After the arterial cannula implantation the animals were transfered to individual cages.

Surgery

Under anesthesia with pentobarbital-Na, 45 mg/kg intraperitoneally, the animal's head was fixed in a stereotaxic instrument. Bipolar electrodes composed of stainless steel wire of 0.2 mm in diameter, insulated except

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for the last 0.5 mm of the tips, were chronically implanted into the posterior hypothalamus (anterior:4.6 mm, lateral:0.5 mm, horizontal:−2.5 mm) and the mesencephalic reticular formation (anterior:1.5 mm, lateral:1.5 mm, horizontal:−1.5 mm) according to De Groot's brain atlas [6]. Each electrode was fixed to the skull with two screws and dental cement and soldered to a connector socket which was also covered with dental cement. The animals were allowed 10 days for recovery from surgery before chronic arterial cannulation.

For the direct measurement of blood pressure, chronic cannula implantation was carried out with a modification of the technique described by Mizogami *et al.* [12]. Figure 1 illustrates the position of cannula in the body of rat as well as provides a diagram of the arterial cannula itself. The cannula was composed of thin polyethylene tubing. Two sizes of tubing (PE 10 and PE 20) were jointed together by heated air. Several small bulges necessary for fixing the cannula to the femoral artery were also constructed on the PE 20 and PE 10 tubing. The animals were anesthetized with ether. A 1–2 cm incision was made on the neck and the inguinal region. The left femoral artery was isolated carefully and the cannula (PE 10) was inserted into the abdominal aorta, approximately 10 mm below the bifurcation of the left renal artery. The other end (PE 20) was lead beneath the skin to the incision on the neck, where it was exteriorized for a distance of 20 mm. The cannula was previously filled with heparinized saline (500 units/ml). The exposed cannula was plugged with a stopper made of stainless wire. After the operation 100,000 units of procaine penicillin were injected intramuscularly. The animals were caged individually in order to prevent the exposed part of the cannula from being bitten off by other rats. A recovery period of 4 days after surgery was allowed before commencing the experiment.

Testing Procedure

The animals were lightly wrapped with a light cotton towel. The cannula stopper was removed. The cannula was then gently flushed with 0.05 ml of heparinized saline (500 units/ml) and attached into a polyethylene tube extension previously filled with 200 units /ml of heparinized saline and connected to a TOYO SOCKI LPU-0.5-360-0-III pressure transducer. Arterial blood pressure was recorded on a SANEI SOCKI 8S rectigraph via a SANEI SOCKI SYS-180 biophysiograph. While the blood pressure was being recorded, 200 units/ml of heparinized saline were injected intraarterially via the extension tubing in a volume of 0.05 ml.

The lead wire for electrical stimulation of the brain was attached to the connector socket on the animal's head. Electrical stimulation was made through a NIHON KODEN MSE-3R electronic stimulator. In order not to restrain the rat from moving freely, the lead wire and the extension tubing joined to the indwelling cannula were made a sufficient length and hung from a flexible arm able to be moved in any direction.

After connecting the cannula and lead wire, the animal was moved to an open-topped Plexiglas cage (30×30×30 cm) which was placed in a soundproof box (50×70×55 cm). The box was illuminated with a 20 w fluorescent lamp and ventilated during the experiment. Arterial blood pressure was measured simultaneously with observing behavior through the window of soundproof box. After the animals adapted themselves to the cage and became calm, the posterior hypothalamus and mesencephalic reticular formation were

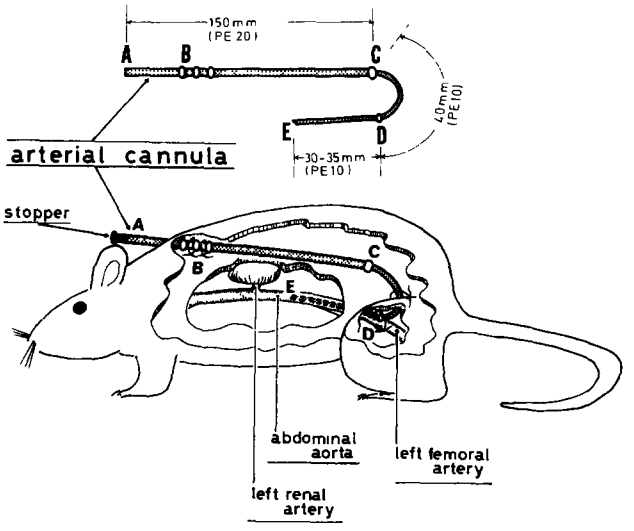

FIG 1. Schematic diagram showing the arterial cannula and its position in the abdominal aorta in the rat.

stimulated electrically. Square wave pulses (1.0 msec, 50 Hz) were given for 5 seconds and the stimulus intensity was varied from 1.2 to 5.0 V. The stimulus voltage was increased until steady optimal responses were obtained. Drugs were administered intraperitoneally after the above mentioned procedures were done.

All data in blood pressure experiments were analyzed by Student's *t*-test.

After completion of the experiments, the animals were anesthetized with ether, and their brains were perfused with saline and 10% Formalin through the carotid arteries. After the brain was removed and fixed, 50 μ thick frozen sections were made and stained with cresyl violet, and the site of the electrodes was verified histologically. Figure 2 shows the posterior hypothalamus and mesencephalic reticular formation in representative sections.

Drugs

The following drugs were employed: pentobarbital sodium (TANABE), chlorpromazine hydrochloride (Contomine, TAKEDA), diazepam (ROCHE) and imipramine hydrochloride (Tofranil, FUJISAWA). Pentobarbital was dissolved in isotonic saline and diazepam was suspended in 0.5% carboxy-methylcellulose. All drugs were injected intraperitoneally in a volume of 0.1 ml per 100 g of body weight. In the case of repeating drug administration in the same animal, the interval between administrations was more than 7 days

RESULTS

Blood Pressure in Untreated Rats

When the rat was moved into the Plexiglas cage from the home cage, marked exploratory behavior such as searching the cage, rearing, sniffing, preening and scratching were observed and the mean arterial blood pressure was 151±9 mm Hg (mean ±SD, N=49). A moderate rise of approximately 10 mm Hg in blood pressure was observed whenever the animal showed rearing, sniffing or preening behavior. As the

FIG. 2 Representative electrode placements in the posterior hypothalamus (PH) and mesencepahlic reticular formation (MRF) in two different rats.

exploratory behavior decreased, mean blood pressure gradually fell to 132±10 mm Hg (mean±SD) after 15 min. After 30 min, the rat became calm and continued to sit in one corner of the cage. During this period, mean blood pressure was 122±11 mm Hg (mean±SD) and very stable. This was the lowest blood pressure obtained in the experiment. Although the blood pressure of the rat was low and stable while sitting, when the animals began to move, especially in the case of grooming behavior, the blood pressure showed an elevation of approximately 10–20 mm Hg. When the animals stopped moving, blood pressure returned to the baseline level.

Pressor and Behavioral Responses to Posterior Hypothalamic and Mesencephalic Reticular Stimulation

Electrical stimulation of the posterior hypothalamus (PH) and mesencephalic reticular formation (MRF) elicited an immediate rise in the arterial blood pressure. Figure 3 shows the responses obtained by increasing the stimulation voltage in the unanesthetized, unrestrained rat. When the voltage was less than 1.2 V, no pressor response was obtained. The pressor responses to PH or MRF stimulation consisted of a rapid rise in blood pressure occuring simultaneously with the initiation of stimulation and a return to baseline pressure after the termination of stimulation. High intensity stimuli, however, caused biphasic pressor responses in approximately half of the rats, i.e. a rapid rise during stimulation followed by a slow rise after discontinuance of stimulation (post-stimulatory pressor response).

Electrical stimulation of PH and MRF also elicited various behavioral changes. Stimuli of less than 1.2 V induced no behavioral changes. In the case of PH stimulation, when the voltage was between 1.5 V and 1.8 V, the animals opened their eyes widely and lifted up their heads simultaneously with stimulation and then looked around the cage during stimulation. MRF stimulation with the same range of voltage induced piloerection, exophthalmos and fast respiration. During the stimulation, some animals maintained a sitting position while others moved backwards slightly. When the stimulus intensity was increased to 2.0 V-2.2 V, PH stimulation caused sudden arousal, a high degree of locomotion with exploration, rearing, walking backwards and circling, and eventually running or jumping. MRF stimulation with the

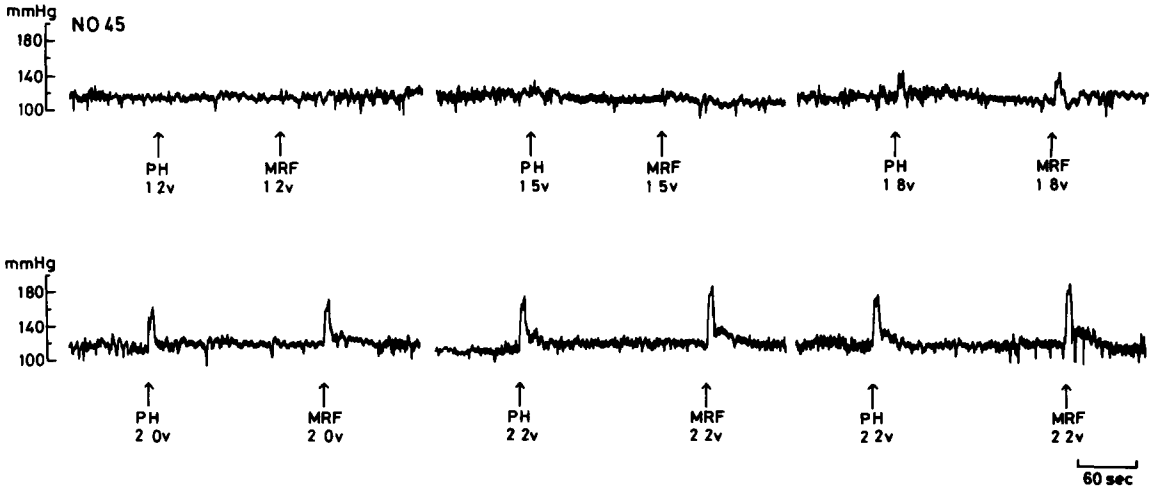

FIG. 3. Representative record of blood pressure response to electrical brain stimulation in the unanesthetized, unrestrained rat. The posterior hypothalamus (PH) and mesencephalic reticular formation (MRF) were electrically stimulated (1 msec, 50 Hz, for 5 sec) at the point indicated by the arrows. The stimulus voltage was increased from 1.2 V to 2.2 V.

TABLE 1

CHANGES IN THE MEAN RESTING BLOOD PRESSURE OF UNANESTHETIZED, UNRESTRAINED RATS AFTER INJECTION OF PSYCHOTROPIC DRUGS

test drugs	n	before	Changes in mean blood pressure time after injection (min) 5	10	20	30	60
saline	8	130 ± 13	1.6 ± 2.7	−0.6 ± 2.6	−0.5 ± 5.9	−0.9 ± 4.1	1.2 ± 7.9
pentobarbital							
5 mg/kg IP	5	135 ± 9	−0.4 ± 3.2	−1.6 ± 3.7	2.4 ± 6.2	−0.6 ± 4.4	0.4 ± 6.0
10 mg/kg IP	7	124 ± 8	0.3 ± 6.3	−2.1 ± 8.7	−1.4 ± 6.3	2.4 ± 6.3	4.7 ± 8.9
chlorpromazine							
1 mg/kg IP	5	121 ± 5	−2.2 ± 2.5*	−3.8 ± 3.7	2.0 ± 5.1	1.8 ± 3.9	4.4 ± 3.4
2 mg/kg IP	7	126 ± 6	−11.4 ± 12.8*	−6.5 ± 10.3	−10.3 ± 7.6*	−5.3 ± 8.2	−3.3 ± 4.9
5 mg/kg IP	7	122 ± 10	−9.7 ± 11.4*	−8.4 ± 7.5*	−12.3 ± 7.7†	−9.8 ± 6.2†	−3.7 ± 7.5
diazepam							
1 mg/kg IP	4	128 ± 7	2.0 ± 3.7	−2.3 ± 4.7	2.3 ± 1.9	5.3 ± 1.8*	7.0 ± 6.2
2 mg/kg IP	5	123 ± 9	2.0 ± 5.1	4.0 ± 10.1	−1.4 ± 5.3	−7.6 ± 5.3*	−1.4 ± 9.3
5 mg/kg IP	5	117 ± 7	6.4 ± 6.3	2.0 ± 7.8	−3.8 ± 10.4	−6.4 ± 3.8*	−0.4 ± 6.1
imipramine							
2 mg/kg IP	3	114 ± 4	8.6 ± 2.6†	5.0 ± 1.4*	4.7 ± 2.4	4.3 ± 3.4	6.7 ± 2.6
5 mg/kg IP	3	123 ± 2	13.7 ± 4.5†	9.7 ± 6.5†	10.3 ± 5.0*	6.3 ± 3.4*	12.0 ± 9.2
10 mg/kg IP	7	118 ± 6	5.9 ± 12.3	2.9 ± 11.7	−0.1 ± 5.5	4.9 ± 6.9	−1.4 ± 3.3
20 mg/kg IP	3	120 ± 16	−13.3 ± 5.7†	−16.0 ± 5.7†	−12.0 ± 5.8*	−5.6 ± 2.1	−6.3 ± 2.9

All data show mean ± SD (mmHg). *$p<0.05$, †$p<0.01$ significant difference vs saline control

same range of intensity elicited flight, escape, walking backwards, circling and running, these responses always appearing with a delay of 2–3 sec after the initiation of stimulation. The behavioral changes induced by PH stimulation usually subsided as soon as the stimulus was turned off, but the changes elicited by MRF stimulation continued for about 3–5 min after stimulation.

Supramaximal stimuli induced violent behavior such as very fast running, furious jumping and the animals tried to escape from the cage making blood pressure unable to be recorded. Therefore, the submaximal stimulus causing the optimal response was used as a control. The mean control voltage was 2.85±0.58 V (N=49, mean ±SD) for PH stimulation and 2.52±0.41 V (N=47, mean±SD) for MRF stimulation. The pressor responses induced by stimulation of PH and MRF were 60.4±5.7 mm Hg (mean±SD) and 60.9±7 mm Hg (mean±SD), respectively. The voltage of MRF stimulation was significantly lower than that of PH stimulation ($p<0.001$). The threshold stimulation intensity capable of inducing behavioral changes was lower than that inducing a pressor response.

Effects of Psychotropic Drugs on Resting Blood Pressure

Changes in mean resting blood pressure after the injection of various psychotropic drugs are summarized in Table 1. Pentobarbital had no effect on resting blood pressure. Chlorpromazine caused a significant fall in blood pressure. Diazepam slightly elevated blood pressure within 10 min after injection but significantly decreased the blood pressure 30 min after injection of 2 and 5 mg/kg. Imipramine, 2 and 5 mg/kg, caused a significant rise in blood pressure but blood pressure was significantly decreased at a dose of 20 mg/kg.

Effect of Pentobarbital

A total of 11 rats were used in this series of experiments. Pentobarbital at doses of 5 (N=5) and 10 mg/ (N=5) caused a reduction in spontaneous motor activity and ataxia was observed at a dose of 10 mg/kg within 10 min after injection. During this period, the animals showed an increase of eating behavior including heterophasia without any changes in blood pressure. Pressor responses induced by PH and MRF stimulation were significantly inhibited by pentobarbital, 5 and 10 mg/kg (Fig. 4) No significant difference between PH and MRF stimulation was found with regard to the inhibitory effect of pentobarbital on the pressor response. Pentobarbital at a dose of 10 mg/kg also suppressed behavioral changes elicited by the stimulation of PH or MRF.

Effect of Chlorpromazine

A total of 10 rats was used in this series of experiments. Intraperitoneal injection of chlorpromazine at doses of 1 (N=5), 2 (N=7) and 5 mg/kg (N=7) caused a reduction in spontaneous motor activity, and at doses of 2 and 5 mg/kg, ataxia was observed within 5 min after injection. During this period, a transient fall of approximately 20 mm Hg in blood pressure frequently occurred in association with the movement of the rat. Chlorpromazine caused a dose-dependent inhibition of the pressor response induced by PH and MRF stimulation (Fig. 5) and at doses of 2 and 5 mg/kg ($p<0.01$ at 2 mg/kg, $p<0.05$ at 5 mg/kg) inhibited the response to PH stimulation more than that to MRF stimulation (Fig. 6). This effect of chlorpromazine lasted over 2 hours. When the pressor response was inhibited by chlorpromazine, in 8 of 17 rats, the post-stimulatory pressor response was abolished

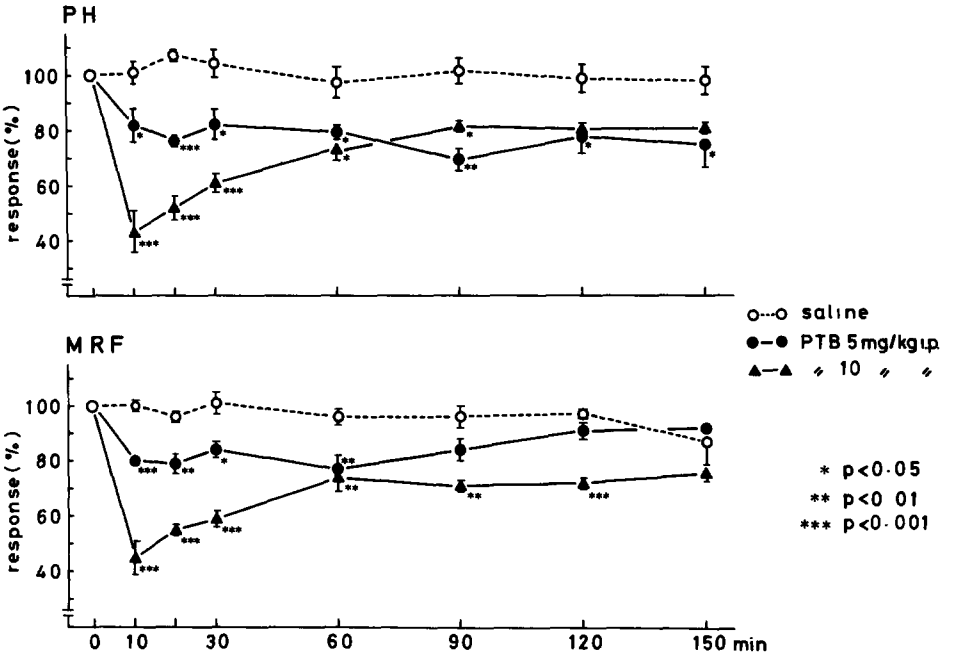

FIG. 4 Effect of pentobarbital (PTB) on the pressor response to electrical stimulation of the posterior hypothalamus (PH) and mesencephalic reticular formation (MRF) in unanesthetized, unrestrained rats. The ordinate represents the percent pressor response, and the abscissa the time in min after drug injection. Vertical bars indicate S.E.M. Asterisks indicate significant differences vs saline control.

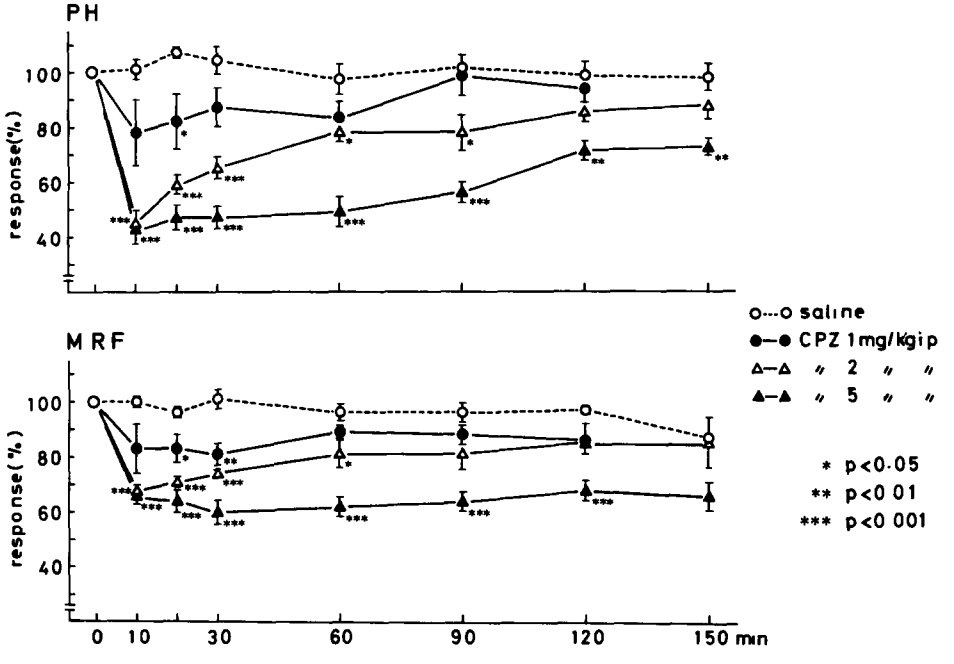

FIG.5. Effect of chlorpromazine on the pressor response to electrical stimulation of the posterior hypothalamus (PH) and mesencephalic reticular formation (MRF) in unanesthetized, unrestrained rats. Vertical bars represent S.E.M. The ordinate, abscissa and statistical details are the same in Fig. 4

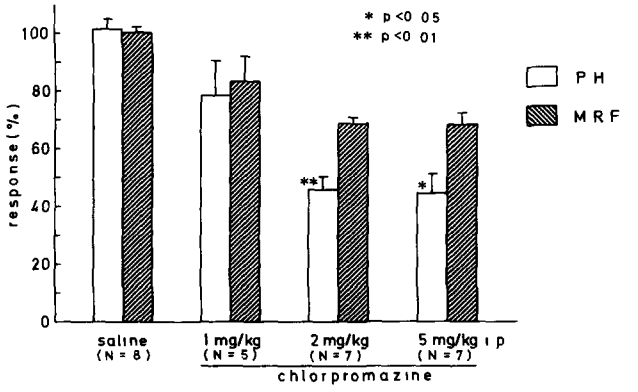

FIG. 6. Changes in the pressor response to electrical stimulation of the posterior hypothalamus (PH) and mesencephalic reticular formation (MRF) in unanesthetized, unrestrained rats at 10 min after injection of chlorpromazine. Vertical bars indicate S.E.M The ordinate is the same as in Fig. 4. Asterisks indicate significant differences of the PH response vs MRF response.

and replaced by a post-stimulatory depressor response, i.e. a transient fall after termination of the stimulation.

The behavioral changes elicited by PH and MRF stimulation were hardly suppressed by any dose of chlorpromazine, even when the pressor response was markedly inhibited.

Effect of Diazepam

A total of 14 rats were used in this series of experiments.

Diazepam at a dose of 1 mg/kg IP (N=4) caused a slight increase of spontaneous motor activity. All of the animals injected with doses of 2 (N=5) and 5 mg/kg (N=5) showed a reduction in motor activity and ataxia within 10 min after injection. During this period, the animals also showed a large increase of eating behavior including heterophasia which was always accompanied by a great rise of 50–60 mm Hg in arterial blood pressure. The hypertension during eating behavior was observed only when the rat swallowed the food but not during chewing. Diazepam at doses of 1, 2 and 5 mg/kg caused a significant inhibition of the pressor response induced by PH and MRF stimulation (Fig. 7). Although there were no significant differences between PH and MRF stimulation, diazepam seemed to inhibit the response to PH stimulation more than that to MRF stimulation ($p<0.1$ at 2 mg/kg). The effect of diazepam on the pressor response continued for more than 3 hours.

The behavioral changes elicited by PH and MRF stimulation were hardly affected by any dose of diazepam even when the pressor response was markedly inhibited.

Effect of Imipramine

A total of 16 rats was used in this series of experiments. Imipramine (2 (N=3), 5 (N=3), 10 (N=7) and 20 (N=3) mg/kg IP) caused a dose-related reduction in spontaneous motor activity. A dose of 20 mg/kg produced ataxia within 5 min after injection. Low doses of imipramine (5, 10 mg/kg) did not cause any significant behavioral changes but instead produced marked spontaneous fluctuations of arterial blood pressure, never observed in the normal state, as seen in Figure 8. At a high dose of 20 mg/kg, however, this lability of blood pressure was not observed.

Imipramine at doses of 10 and 20 mg/kg significantly inhibited the pressor response induced by PH and MRF stimulation (Fig. 9). There were not significant differences

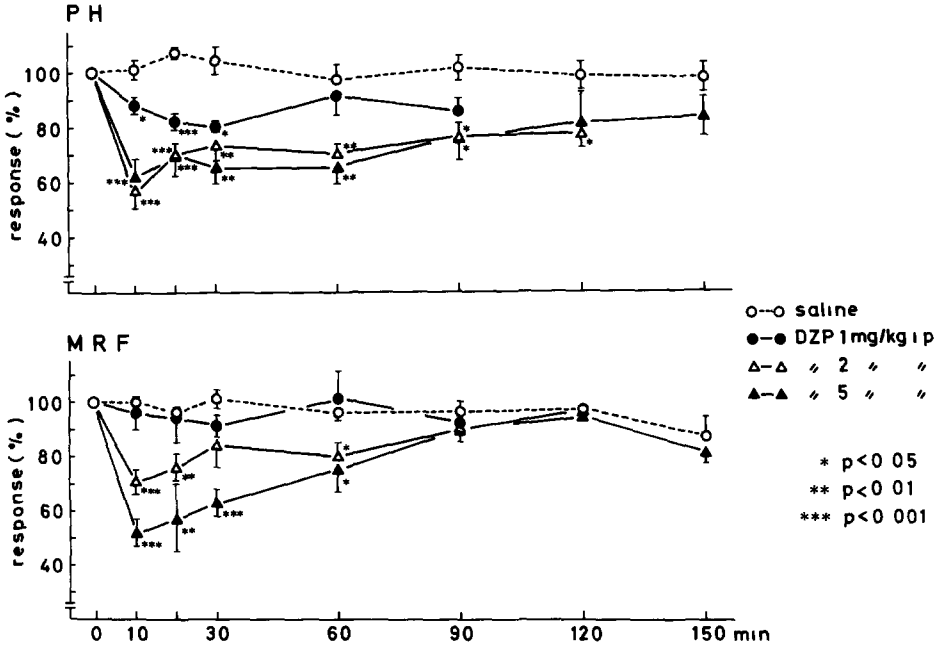

FIG. 7 Effect of diazepam on the pressor response to electrical stimulation of the posterior hypothalamus (PH) and mesencephalic reticular formation (MRF) in unanesthetized, unrestrained rats Vertical bars indicate S.E.M The ordinate, abscissa and statistical details are the same as in Fig. 4

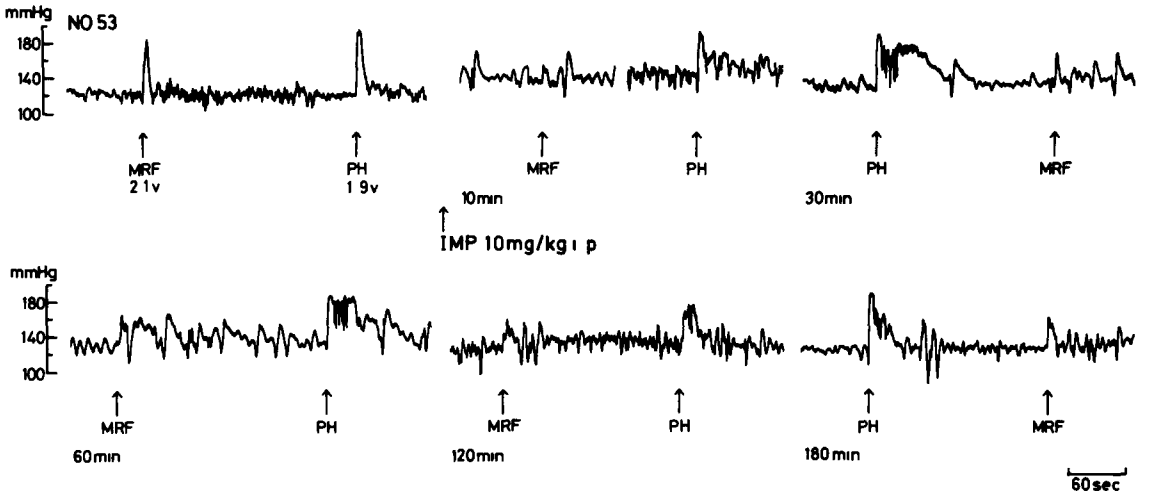

FIG. 8. Representative record of the effect of imipramine 10 mg/kg IP on the pressor response to electrical stimulation of the posterior hypothalamus (PH) and mesencephalic reticular formation (MRF) in the unanesthetized, unrestrained rat. Arrows indicate the electrical stimulation of PH and MRF.

between PH and MRF stimulation, but at a dose of 20 mg/kg, imipramine showed a tendency to inhibit the response to PH stimulation more strongly than that to MRF stimulation. Imipramine at doses of 5 and 10 mg/kg greatly changed the pattern of pressor response to the brain stimulation. The post-stimulatory pressor response was markedly potentiated. However, after injection of a dose of 20 mg/kg, the post-stimulatory pressor response was abolished and a post-stimulatory depressor response was observed. These effects of imipramine lasted for over 3 hours.

Behavioral changes elicited by PH and MRF stimulation were hardly affected by any doses of imipramine, even when the pressor response was suppressed.

DISCUSSION

In the present experiment, an arterial cannula was chronically implanted into the abdominal aorta via the femoral artery of the rat. This technique has several advantages in that the surgical procedure is easy and the animal

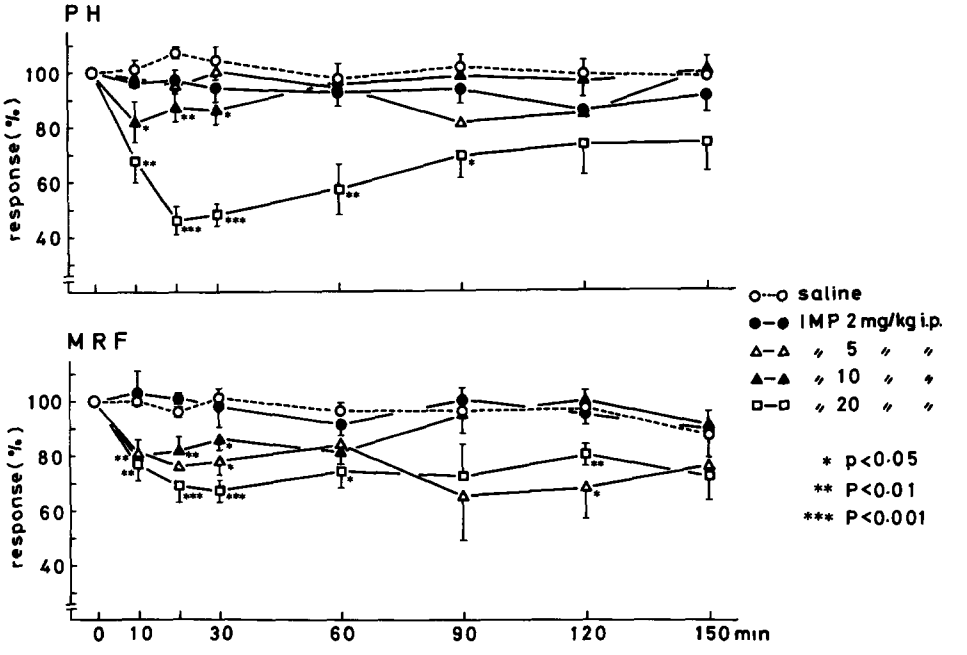

FIG 9 Effect of imipramine on the pressor response to electrical stimulation of the posterior hypothalamus (PH) and mesencephalic reticular formation (MRF) in unanesthetized, unrestrained rats. Vertical bars indicate S E.M. The ordinate, abscissa and statistical details are the same as in Fig. 4

can be saved from the influences of surgery itself in comparison with the method described by Week and Jones [22], in which midline laparotomy is necessary. This cannula was useful for about 2 weeks in measuring blood pressure. Some animals did, however, develop hindlimb paralysis from 3 to 10 days after cannula implantation. The paralysis was due to an aneurysm grown at the tip of cannula. In such animals it was impossible to measure blood pressure. By diminishing the floor space of the home cage and limiting spontaneous locomotion of the animals, we have succeeded in reducing such accidents and thus the cannula can be used for more than 3 weeks. An important advantage of this method is that blood pressure can be continuously recorded in freely moving rats without using anesthetics which can markedly influence cardiovascular function [3, 14].

By means of this method, blood pressure changes accompanying various types of behavior were investigated. Soon after the animals were placed in the experimental cage, higher blood pressure was recorded along with marked exploratory behavior. This is presumably due to an increase in sympathetic tone resulting from the elevated emotional level of the animal in a novel environment. As the animal adapted to its environment and became emotionality stable, blood pressure was gradually lowered. Electrical stimulation of PH and MRF elicited a sharp rise in arterial pressure of the rat. The pressor response to PH and MRF stimulation was heightened with increased stimulus intensity, and subsided as soon as the stimulation was turned off. The present results confirmed the previous findings that blood pressure rose after electrical stimulation of PH in unanesthetized, unrestrained rats [13] and after MRF stimulation in anesthetized rats [8]. The rise in blood pressure seen after PH or MRF stimulation is due to increased sympathetic nerve activity, probably mediated via the pressor center in the medulla oblongata [5, 21]. The pressor response to MRF stimulation was more marked and the stimulus threshold was lower as compared with the response to PH stimulation. In addition to the pressor response, PH and MRF stimulation elicited various behavioral changes. Morpurgo [13] and Bunag and Efferakeya [3] have reported that PH stimulation elicited behavioral changes such as arousal, escape and flight reactions in awake rats. In the present experiment, the rat showed marked exploratory behavior with rearing in response to stimulation. The escape and flight reactions were observed only with very high stimulation voltage. In contrast to PH stimulation, MRF stimulation produced mainly escape and flight reactions but little exploratory behavior. The behavioral response to PH stimulation was evoked simultaneously with the start of stimulation and disappeared soon after withdrawal of the stimulus, whereas that to MRF stimulation invariably appeared 2 to 3 seconds after stimulation and lasted for several minutes even after the termination of stimulation. The difference in behavioral changes induced by either PH or MRF stimulation may be due to a difference in ascending and descending neural systems which are activated by this form of stimulation. The pressor response to PH and MRF stimulation was markedly inhibited by pentobarbital. This effect is central in origin since pentobarbital has little effect on peripheral sites [14]. Furthermore, pentobarbital reduced the pressor responses to PH and MRF stimulation by approximately the same extent and also suppressed the behavioral changes seen after PH or MRF stimulation. The present results are consistent with the report that pentobarbital inhibited all of the several autonomic responses induced by hypothalamic stimulation in the unanesthetized cat [8]. It is suggested that pentobarbital exerts its effect on extended brain areas and has little selectivity in its action. Thus, pentobarbital at subhypnotic doses already causes a significant inhibition of the pressor response to PH and MRF stimulation, and affects many brain regions. When centrally acting drugs are tested in animals anesthetized with barbiturates, the results obtained should be carefully evaluated.

Chlorpromazine produced a dose-related inhibition of the pressor response to either PH or MRF stimulation. This is in agreement with the results obtained by Morpurgo [13] in unanesthetized, unrestrained rats. Furthermore, in the present experiment, the pressor response to PH stimulation was more significantly depressed by chlorpromazine than that to MRF stimulation. This suggests that the site of action of chlorpromazine is located in the hypothalamic area. This assumption is also supported by the fact that chlorpromazine has little effect on EEG arousal response to MRF stimulation [11]. Chlorpromazine, on the other hand, has a relatively potent α-adrenergic blocking action [20]. The suppressive effect of chlorpromazine on the pressor response could be explained by its peripheral sympathetic blocking action. However, if a peripheral α-blocking action accounted for the effect of chlorpromazine, no difference should exist between the pressor responses to PH and MRF stimulation. That was not the case in the present experiment. It therefore seems likely that the effect of chlorpromazine is central in origin.

Diazepam caused a dose-dependent inhibition of the centrally evoked pressor response and more markedly depressed the pressor response to PH stimulation than that to MRF stimulation, although no significant difference was found. These findings of the present experiment are in agreement with the results reported by Morpurgo in awake rats [13] and by others in anesthetized cats [1, 4, 18, 19] It has been postulated that diazepam acts on the supramedullary sympathetic center with little or no effect on the peripheral sympathetic structures [1]. The effect of diazepam on the pressor response appears similar to that of chlorpromazine and is different from that of pentobarbital in this respect.

Imipramine, which blocks the uptake mechanism of norepinephrine [2], caused a marked reduction of the centrally evoked pressor response and depressed the response to PH stimulation rather than that to MRF stimulation at doses of 10–20 mg/kg. We could not observe a potentiation of the pressor response after imipramine, although Przuntek *et al* [15] had found that antidepressants potentiated the blood pressure rise induced by hypothalamic stimulation in anesthetized cats. On the contrary, it was reported that imipramine depressed not only the pressor response but also increased splanchnic discharges during hypothalamic stimulation, although in anesthetized rabbits [17] It is therefore suggested that the site of action of imipramine is central in origin and is likely located in the hypothalamic area rather than in MRF.

On the other hand, imipramine in doses of 5–10 mg/kg caused a great change in the pattern of pressor response and markedly potentiated the post-stimulatory pressor response, i.e. a gradual rise in blood pressure was seen after termination of the stimulus, which might have been due to epinephrine being released from the adrenal medulla [9]. The potentiation of the post-stimulatory pressor response may be attributable to inhibition of the epinephrine uptake mech-

anism by imipramine. This is supported by our finding that chlorpromazine which has α-adrenergic blocking activity completely inhibited the post-stimulatory pressor response.

Behavioral changes evoked by electrical stimulation of PH and MRF were hardly affected by chlorpromazine, diazepam and imipramine even when the pressor response was markedly reduced. However, pentobarbital inhibited both the pressor and behavioral responses. This is in agreement with the finding of Morpurgo [13] that the behavioral responses to hypothalamic stimulation were not inhibited by chlorpromazine or diazepam in rats. However, it is well known that psychotropic drugs exert an inhibitory effect on the behavioral response to electrical stimulation of the hypothalamus such as attack and rage reactions in cats [7, 10] and in rabbits [17]. Discrepancies in the results of different investigatiors may be due to the differences in the animal species employed, experimental conditions and the type of behavioral response observed.

Based on the present results it is suggested that chlorpromazine, diazepam and imipramine exert their action on the central pathway involved in the pressor response rather than in the behavioral response, and, in contrast to pentobarbital, these three drugs act on more discrete brain areas and are more selective in action.

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