Br. J. Pharmac. (1976), **57**, 43–49

HYPOTHERMIC ACTION OF CHLORPROMAZINE IN MONKEYS

C.Y. CHAI
Department of Biophysics, National Defense Medical Center, Taipei, Taiwan, Republic of China
Y.D. FANN
Kohlberg Memorial Medical Research Laboratory, Taipei, Taiwan, Republic of China
M.T. LIN
Department of Medical Research, Veterans General Hospital, Taipei, Taiwan, Republic of China

1 In the conscious monkey (*Macaca cyclopis*) intravenous administration of chlorpromazine 0.1–8.0 mg/kg produced a fall of rectal temperature of 0.3 to 3.5°C after a latency of 3.5 to 10.8 minutes. The course of hypothermia lasted from 125 to 600 min or more.

2 Direct injection of chlorpromazine 100–800 μg into the lateral or fourth cerebral ventricle produced a similar fall of 0.3 to 2.0°C but with shorter latency (2 to 3.5 min) and with a duration of 94 to 375 minutes.

3 Two distinct structures in the brain stem, namely, the preoptic anterior hypothalamus (POAH) and medulla oblongata, responded to direct injection of chlorpromazine 200 μg. The sensitivity was slightly higher in the POAH than in the medulla. Structures in between were not sensitive.

4 The results suggest that chlorpromazine works principally through the central nervous system, i.e. the POAH and medulla oblongata, to mediate its hypothermic effect.

Introduction

The hypothermic action of chlorpromazine has been well documented and much effort has been devoted toward delineating its mechanism and sites of action. Peripheral mechanisms including α-adrenoceptor blockade (Goodman & Gilman, 1970), decreased utilization of glucose and free fatty acid (Bonaccorsi, Garattini & Jori, 1964; Ghafghazi, Miya, Mennear & Chalmers, 1968) have been suggested. Systemic injection of chlorpromazine uniformly produced hypothermia in several species i.e. rats, adult mice, hamsters, guinea-pigs, ground squirrel, rabbits and dogs (L'Allemand, Brendel & Usinger, 1955; Bachtold & Pletscher, 1957; Chevillard, Giorno & Laury, 1958; Hoffman & Zarrow, 1958; Bagdon & Mann, 1965; Kirkpatrick & Lomax, 1971; Reigle & Wolf, 1971).

It has been suggested that chlorpromazine may mediate its hypothermic action through the central nervous system (CNS). Chlorpromazine inhibited the neuronal activities of the reticular formation of the brain stem (Bradley, Wolstencroft, Hosli & Avanzino, 1966). Chlorpromazine also inhibited the gamma motor neurone and the brain stem facilitatory mechanism which led subsequently to relaxation of the skeletal muscle (Domino, 1962). The highest concentration of chlorpromazine has been found in the brain of dogs after a systemic dose of this agent (Salzman & Brodie, 1956). However, experimental findings regarding chlorpromazine hypothermia induced by CNS activation are controversial. In hamsters, Reigle & Wolf (1971) found that microinjection of chlorpromazine into the preoptic anterior hypothalamus (POAH) produced hypothermia. In rats, Rewerski & Jori (1968), Rewerski & Gumulka (1969) and Kirkpatrick & Lomax (1971) reported that similar intrahypothalamic injection produced an opposite effect, i.e. hyperthermia, although systemic injection produced hypothermia.

The present investigation was designed to elucidate further the hypothermic action of chlorpromazine. The site of action of chlorpromazine hypothermia was determined by comparing the effects of this agent by various routes of administration. Emphasis was laid particularly on local injection of chlorpromazine to various sites of the brain stem from the POAH through to the medulla oblongata. An attempt was made not only to localize the structures responsible for the hypothermia but also to determine whether structures other than the POAH are sensitive to chemical agents which cause change of body temperature. Previous investigations of ours (Chai, Mu & Brobeck, 1965; Chai & Wang, 1970; Chai, Chen & Yin, 1971; Chai & Lin, 1972) and of others (Holmes, Newman & Wolstencroft, 1960) have shown that the medulla is thermosensitive and may

participate in thermo-regulation. In the present investigation, monkeys were used because little information regarding the thermal effects of chlorpromazine on this species is available.

Methods

Thirty-eight monkeys (*Macaca cyclopis*) of either sex, weighing 4–5.5 kg were used. The animals were prepared for intracerebroventricular or intracerebral administration according to the methods of Chai *et al.* (1971) and Myers & Yaksh (1969) with some modifications. In brief, each animal was anaesthetized with sodium pentobarbitone (35 mg/kg, i.v.). Under aseptic procedures, a guide cannula, made of a 21-gauge lumbar puncture needle cut to the desired length, was positioned in the lateral ventricle or fourth ventricle, or in the cerebral tissue of the brain stem by means of a stereotaxic technique. The cannulae were fixed on the skull by stainless steel screws and acrylic resin. For intracerebral injection, usually 2–4 cannulae were implanted at random into the brain stem of the animal at a time. In the area rostral to midbrain the cannulae were inserted at a right angle while in the area caudal to mid-brain at a 50° angle. This was done in order to allow the cannula to be perpendicular to the base of the brain stem. After completion of the implantation, the central occluding stylus was inserted into the cannula and was fastened by threads.

The animals were not subjected to experimentation until at least 5 to 7 days after they had recovered completely from the surgery. When the intracerebral injection was given, the central occluding stylus was removed and an injection cannula, made of a 25-gauge tubing needle with the length cut 0.5 mm longer than the guide cannula, was inserted into the guide cannula. The free end of the needle tubing was connected to a section of PE 20 polyethylene tubing and the injection was given from a 100 µl Hamilton microsyringe. Intravenous administration was directly through the saphenous vein.

A solution of chlorpromazine hydrochloride (Rhdia, France) was prepared fresh before use by dissolving it in pyrogen-free 0.9% w/v NaCl solution (saline). For intravenous injection (i.v.) a solution was prepared in which 1 ml contained the per kg dose, 0.1–8 mg; for intraventricular injection 100 µl contained the total dose, 100–800 µg; for intracerebral injection, 10 µl contained 200 µg of the agent.

The pH of the chlorpromazine solution for intracerebroventricular injection was 5.3–5.7 with a tonicity equivalent to 0.91–1.03% NaCl solution. The chlorpromazine solution for intracerebral injection was at pH 5.0 with a tonicity equivalent to 1.23% NaCl solution. Control injections of the same volume of saline adjusted to the above range of acidity and tonicity via the same routes did not produce any significant response.

Twelve hours before experimentation the monkey was allowed no food, but water was available *ad libitum*. During the experiments the animal was restrained in a monkey chair at a constant environmental temperature of 25 ± 0.5°C. Injection of the drug was made only after the animal had acclimatized to the environment and the rectal temperature had become stable. Repeat injections were made at an interval of 4–6 days.

Rectal temperature was monitored by a flexible thermistor probe (Yellow Springs Instrument Co. (YSI) 401) inserted 8–10 cm into the rectum. Cutaneous temperature was monitored by a needle thermistor probe (YSI 524) inserted into the subcutaneous tissue on the inner side of the thigh, and by a surface thermistor probe (YSI 425) adhering to the surface of the palm. Temperature signals were amplified by a YSI scanning telethermometer (model 47). Respiratory rate was monitored by means of a pneumograph. All recordings were made on a polygraph (Grass 7B). An electrocardiogram, lead II, was recorded by a separate polygraph. Heart rate was estimated by counting the number of R waves of the ECG.

At the conclusion of each experiment, 10 µl of diluted China ink was injected into the guide cannula for labelling. The animal was killed by an overdose of sodium pentobarbitone and the head was perfused with saline, followed with 10% formalin solution. The brain was then removed, and the sites of injection were verified by means of frozen sections of 30 µm thickness stained by the Weil method.

Results

General reactions after administration of chlorpromazine

The overall reactions varied with the dose of chlorpromazine. When the dose was less than 0.1 mg/kg intravenously or below 100 µg intracerebroventricularly (lateral or 4th ventricle), no apparent changes in behaviour or body temperature were observed. At higher doses the animal exhibited struggling, restlessness, polypnoea and increase of the cutaneous temperature of the palm during the first 5–15 minutes. These responses were then followed by a period of sedation, during which there was evidence of decreased muscle tonus, with extension of the extremities, sleepy appearance, and sluggishness in the corneal reflex concomitant with a drop in body temperature. The degree of hypothermia was proportional to the extent of sedation. The size of the pupil remained essentially unchanged. Half to several hours after sedation the animal gradually regained full consciousness. Rectal temperature gradually returned

as the sedation diminished; the animal often urinated at this time.

Effects of intravenous administration of chlorpromazine on body temperature

Table 1 summarizes the effects of chlorpromazine, 0.1–8 mg/kg, intravenously. In 3.5–10.8 min after the dose, the rectal temperature began to fall and reached a minimum in 40–200 minutes. The average fall in rectal temperature was 0.3–3.5°C, proportional to the dose. At a dose of 0.1 mg/kg to 4 mg/kg the temperature gradually returned to its preinjection level in 125–576 minutes. When the dose was increased to 8 mg/kg, the temperature did not return to its preinjection level even after over 600 minutes. Figure 1 shows the time course of the average change in six animals in rectal temperature, subcutaneous temperature of the thigh and cutaneous temperature of the palm, and respiratory and heart rates after chlorpromazine, 2 mg/kg, intravenously. The fall in rectal temperature (maximum 1.7°C) paralleled the fall of subcutaneous temperature of the thigh (maximum 1.8°C). The temperature reached a minimum in 150 min, then rose gradually to return to the preinjection level after 450 minutes. In contrast, after chlorpromazine injection, the cutaneous temperature of the palm rose very rapidly to 5.5°C higher than normal in 20 minutes. The rise, however, was maintained only briefly and temperature returned to the preinjection level in 150 minutes. Concomitant with the elevation of palm temperature, respiratory rates increased (9 breaths/min on average) but for only a short time (90 minutes). The time course of

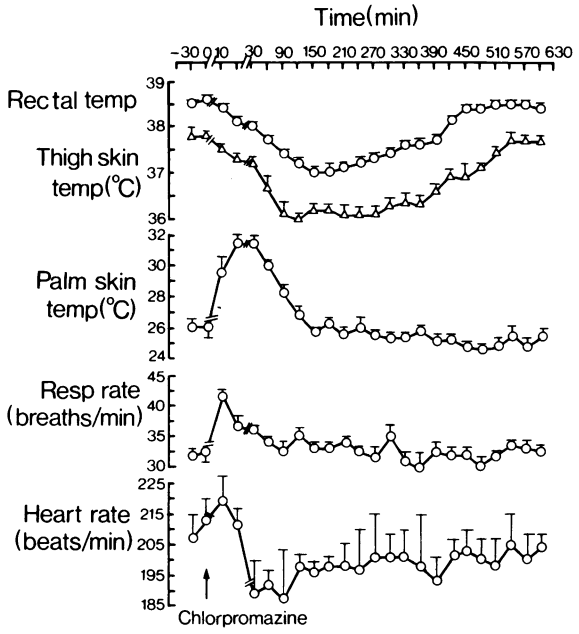

Figure 1 Changes of rectal temperature, cutaneous temperature of the thigh and palm, and respiratory and heart rates after chlorpromazine, 2 mg/kg intravenously. Administration of drug was performed at zero time. $n = 6$.

reduction of heart rate varied with different animals. In two out of six animals, a decrease occurred immediately after the chlorpromazine injection. In one

Table 1 Decrease of rectal temperature after intravenous and intracerebroventricular administration of chlorpromazine

Route of administration	*Dose*	*Latency (min)*	*Maximum fall in rectal temp. (°C)*	*Time to minimum temp. (min)*	*Time of recovery (min)*
Saphenous vein	0.1 mg/kg	10.8 ± 2.2	0.3 ± 0.1	40 ± 12	125 ± 34
	0.5 mg/kg	6.6 ± 0.8	1.2 ± 0.2	73 ± 16	234 ± 53
	1.0 mg/kg	6.2 ± 0.7	1.4 ± 0.4	102 ± 33	359 ± 83
	2.0 mg/kg	4.3 ± 0.6	1.7 ± 0.2	102 ± 10	429 ± 41
	4.0 mg/kg	4.5 ± 0.5	2.7 ± 0.2	179 ± 10	576 ± 14
	8.0 mg/kg	3.5 ± 0.3	3.5 ± 0.3	200 ± 53	*
Lateral Ventricle	100 µg	3.3 ± 0.6	0.4 ± 0.1	35 ± 10	144 ± 51
	200 µg	3.5 ± 0.4	1.2 ± 0.2	69 ± 4	168 ± 39
	400 µg	4.0 ± 0.7	1.7 ± 0.2	64 ± 8	314 ± 61
	800 µg	2.5 ± 0.4	1.9 ± 0.1	97 ± 10	229 ± 11
Fourth Ventricle	100 µg	3.5 ± 0.4	0.3 ± 0.1	24 ± 5	94 ± 23
	200 µg	3.0 ± 0.1	1.0 ± 0.1	56 ± 24	185 ± 19
	400 µg	3.2 ± 0.4	1.7 ± 0.1	75 ± 12	246 ± 51
	800 µg	2.0 ± 0.1	2.0 ± 0.1	100 ± 7	375 ± 95

Values are means ± s.e. of results from six animals.
* At this dose none of 6 animals returned to the preinjection temperature within 10 hours.

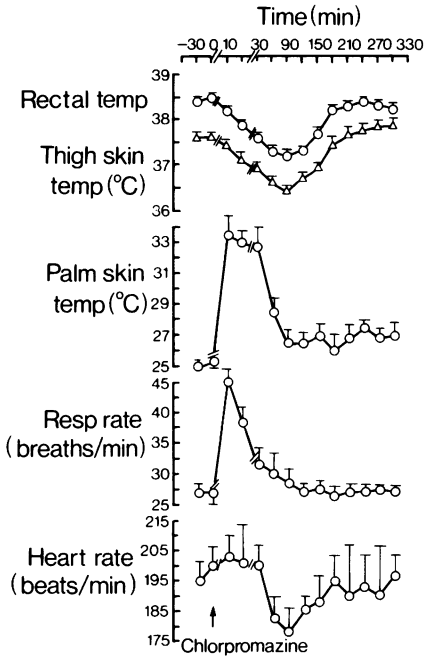

Figure 2 Changes of rectal temperature, cutaneous temperature of the thigh and palm, and respiratory and heart rates after chlorpromazine 200 μg injected into the lateral ventricle. $n = 6$.

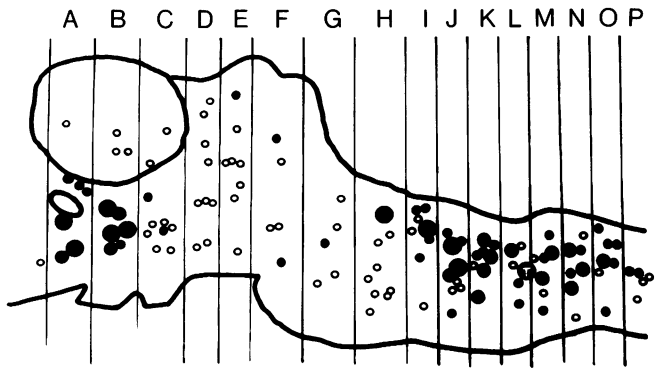

Figure 3 Sagittal section showing sites of intracerebral injection of chlorpromazine 200 μg. Areas of the brain stem are taken 1 mm from the midline. The closed circles show positive reactions and indicate that injections produced a hypothermic response greater than 0.5°C with a latency shorter than 5 minutes. The sizes of the circles illustrate the thermal reactivity: small, 0.5 to 0.8°C; medium, 0.8 to 1°C, large, above 1°C. The open circles indicate negative results, showing that either the decrease of rectal temperature was less than 0.5°C or the latency of onset longer than 5 min, or both. A = preoptic anterior hypothalamus, B = middle hypothalamus, C = posterior hypothalamus, D and E = midbrain, F to I = pons, J to P = medulla.

animal the heart rate did not show any change in the first 20 min but then decreased gradually. In three other animals the heart rate showed an initial elevation and then decreased gradually in about 30 minutes. The mean maximum decrease in heart rate was 20 beats/minute. In general, the decrease of heart rate lasted for a relatively long period (300 min average) and was frequently accompanied by changes of electrocardiogram, i.e. irregular P–R interval, S–T depression, or elevation of T wave.

Effects of intracerebroventricular administration of chlorpromazine on body temperature

Table 1 also summarizes the fall of rectal temperature after administration of chlorpromazine 100–800 μg to the lateral or fourth ventricle. The hypothermic responses from these two routes were similar. The magnitude of temperature reduction was dose-related, in a range of 0.3–2°C; the latency of onset 2.0–3.5 min; the duration of maximum reaction 24–100 min; the whole course of the hypothermic reaction 94 to 375 minutes. Figure 2 shows the result of administration of chlorpromazine 200 μg through the lateral ventricle. In general, the reactions followed the same patterns as those of intravenous and intracerebral injections. After chlorpromazine the temperature of rectum and thigh fell 1.2°C in 90 minutes. The palm temperature and respiratory rate showed a rapid but brief increase, 8.2°C and 18 breaths/min, 10 to 20 min after the injection. After chlorpromazine, the heart rate showed a slight increase and a decrease (22 beats/min) 30 min later. Cardiac arrhythmia also occurred frequently. The time course and pattern of reactions following administration of chlorpromazine into the 4th ventricle were similar.

Effects of intracerebral administration of chlorpromazine on body temperature

Figure 3 shows the sites of local administration of chlorpromazine 200 μg into the brain stem. The reactive sites were found to be confined principally to two areas i.e. the POAH and medulla oblongata. Other areas such as posterior hypothalamus, midbrain, and pons were not sensitive. Table 2 summarizes the results of intracerebral injection of chlorpromazine 200 μg. A total of 120 injections were made. Among the 17 sites of injection in the POAH, 12 produced a positive reaction, of which 5 showed a hypothermic response more than 1°C (the greatest

being, 1.8°C). Only 2 of the 10 injections in the posterior hypothalamus showed positive reactions; one of the 17 injections in the midbrain did so. Four of 19 injections in the pons produced a hypothermic response. One of these points produced a fall of more than 1°C. Among the 57 injections in the medulla, 40 showed a hypothermic response, and 4 of these produced hypothermia of more than 1°C (highest 1.5°C). If the degree of sensitivity among the various regions of the brain stem is expressed as the 'effective hypothermic index' (the extent of rectal temperature fall times the percentage of positive reactions in a particular brain area), the sensitivity is in the following descending order: POAH (0.71), medulla (0.59), pons (0.13), posterior hypothalamus (0.12), midbrain (0.04). Figure 4 shows the results of local injection of chlorpromazine 200 μg into the medulla (labelled T in Figure 3L). The pattern of reactions did not differ from those of other routes of injection. The maximum fall in rectal temperature was 1.1°C, along with a fall of thigh subcutaneous temperature (maximum 0.8°C). Palm temperature rose 5°C. Respiratory rate increased 10 breaths/minute. Heart rate decreased 27 beats/minute.

On two occasions during medullary injections, the

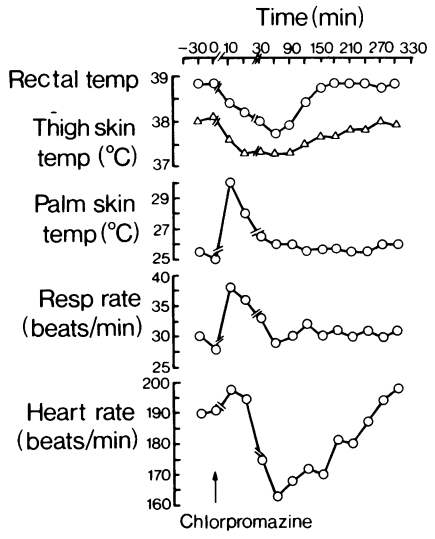

Figure 4 Changes of rectal temperature, cutaneous temperature of the thigh and palm, and respiratory and heart rates after chlorpromazine 200 μg injected into the medulla oblongata (obtained from the 'T' point in L of Figure 3). $n = 1$.

Table 2 Results of local injection of chlorpromazine (200 μg) into preoptic anterior hypothalamus, posterior hypothalamus, midbrain, pons and medulla oblongata.

	Preoptic anterior hypothalamus	*Posterior hypothalamus*	*Midbrain*	*Pons*	*Medulla*
No. of injection sites	17	10	17	19	57
No. of injection sites showing hypothermic response	12	2	1	4	40
No. of injection sites showing negative response	5	8	16	15	17
Average of fall in rectal temperature (°C)	1.0	0.6	0.7	0.6	0.8
Effective percentage	70.6%	20.0%	5.9%	21.0%	70.2%
Effective hypothermic index	0.71	0.12	0.04	0.13	0.56

Hypothermic and negative responses are explained in the text.

$$\text{Effective percentage} = \frac{\text{No. of injection sites showing hypothermic response}}{\text{No. of injection sites}} \times 100.$$

Effective hypothermic index = Average fall of rectal temperature × effective percentage.

rectal temperature, after an initial fall for periods of 155 and 180 min, rose to a level of 0.9°C and 1.5°C higher than the normal temperature, as previously reported by Chai *et al.* (1971).

Discussion

The findings show that intracerebral administration of chlorpromazine is effective in producing hypothermia. Injection of chlorpromazine 200 μg, both into the lateral and 4th ventricles produced a fall of rectal temperature from 1°C to 1.2°C, comparable to that following chlorpromazine 0.5–1 mg/kg intravenously (Table 1). This dose was 1/15 to 1/25 that of the intravenous injection (each animal weighed 5 kg on average). In some animals, an even smaller dose (1/100 that of i.v.) was sufficient. In addition, the latency of hypothermia after intracerebroventricular injection was much shorter than when the drug was administered by the intravenous route. This suggests that the hypothermic effect of chlorpromazine was in great part mediated through the CNS. Similar results have been observed in the rat (unpublished data). In this investigation, administration of chlorpromazine into the 3rd and 4th ventricles, and systemic circulation all produced hypothermia. Administration through the ventricle required a much smaller dose yet produced a greater effect. It should be noted, however, that intravenous administration of a large dose of chlorpromazine produced a greater hypothermia than that of the cerebroventricular route; 3.5°C after 8 mg/kg intravenously compared with 2°C after 800 μg intracerebroventricularly (see Table1). A peripheral component in the hypothermic action cannot be excluded.

It is generally agreed that in the POAH there resides the highest integrating mechanism of thermohomeostasis. Direct injection of pyrogen into this area induces fever (Cooper, Cranston & Honour, 1967; Lin & Chai, 1972). Injection of morphine (Lotti, Lomax & George, 1965), acetylcholine (Kirkpatrick & Lomax, 1970), or catecholamine (Myers & Yaksh, 1969) also produce very marked changes in the body temperature. However, current investigations have shown that regulation of body temperature is not limited to POAH. For example, Hardy (1973) has recorded input signals in the anterior and posterior hypothalamus and midbrain when the skin, hypothalamus or spinal cord were heated or cooled. We also have repeatedly demonstrated that cooling of the medulla oblongata and spinal cord produced subcutaneous vasoconstriction, slowing of respiratory rate, tachycardia, hypertension and increase of rectal temperature while heating produced the opposite effects, i.e., subcutaneous vasodilatation, respiratory acceleration, bradycardia, hypotension and decrease of rectal temperature (Chai *et al.*, 1965; Chai & Wang, 1970). These reactions persisted without reduction after decerebration or destruction of the POAH (Chai & Lin, 1973; Lin & Chai, 1974). Similar findings on the independence of thermosensitivity in the medulla have been reported by Lipton (1973). Rosendroff & Mooney (1971) have succeeded in inducing fever by local injection of leukocytic pyrogen not only in the hypothalamus but also in the pontine reticular formation. However, they did not explore the medulla oblongata. On the other hand, Bard, Woods & Bleir (1970) observed that chronic decerebrate cats failed to produce any effective defence actions during cold exposure and no fever response after administration of pyrogen. Cooper *et al.* (1967) injected leukocytic pyrogen into various parts of the brain and found that only injection in the POAH produced fever. Other areas, i.e. posterior hypothalamus, midbrain and pons were not responsive. It should be noted that there were few injections to areas caudal to the posterior hypothalamus.

In the present experiments, we injected chlorpromazine into the whole brain stem of monkeys and found that two distinct structures, i.e. the POAH and medulla, with the former predominant, were very sensitive in hypothermic reaction. The areas are identical with those responding to local injections of acetylstrophanthidin for hypothermia as found previously by Chai *et al.* (1971). Acetylstrophanthidin probably produces hypothermia by its acetylcholine-like action. It has been found that acetylcholine produces hypothermia when injected into the hypothalamus (Kirkpatrick & Lomax, 1970).

The above results thus are consistent with the contention that the POAH plays a very important role in temperature regulation, and that an independent but accessory mechanism for regulation exists in the medulla oblongata (Chai & Lin, 1973; Lin & Chai, 1974).

Thermoregulatory reactions, i.e., cutaneous vasodilatation of the palm, increased cutaneous temperature and respiratory acceleration were apparent shortly after the administration of chlorpromazine. It should be noted that vasodilatation occurred only on the palm and foot but not on the thigh. Since the skin of the palm is not covered with hair, this may suggest that heat dissipation is achieved principally through redistribution of more heat load to the hairless region. It should be noted that both vasodilatation and respiratory acceleration are important mechanisms for heat dissipation. Thus it appears very likely that increase of heat dissipation is the chief mechanism of the chlorpromazine-induced hypothermia, at least in the early stage after administration of the drug.

This investigation was supported, in part, by J. Aron Charitable Foundation, U.S.A. and the National Science Council, Republic of China.

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(Received August 25, 1975. Revised November 20, 1975.)