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THE ENHANCEMENT OF CHLORPROMAZINE-INDUCED HYPOTHERMIA BY LESIONS IN THE ANTERIOR HYPOTHALAMUS

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1 Administration of chlorpromazine (Cpz), either systemically or centrally, to unanaesthetized rats at an environmental temperature of 23°C caused dose-dependent hypothermia.

2 In order to achieve equivalent hypothermia, intraventricular administration required a total dose of 20 μg Cpz and intraperitoneal administration a dose of 9.7 mg/kg body weight. Accordingly, the dose-ratio between intraventricular and intraperitoneal administration was 1 to 110. Cpz apparently exerts its hypothermic effect by acting directly on central nervous structures rather than through peripheral sites.

3 Cpz-induced hypothermia was potentiated by preoptic anterior hypothalamic (POAH) lesions but not by lesions of the ventromedial nucleus (VMN) of the hypothalamus. It was found that Cpz induced hypothermia most readily in rats with large POAH lesions (−10.4°C), less so in rats with spinal lesions (−5.5°C) at least with control rats (−2.9°C).

Introduction

Chlorpromazine (Cpz), a major tranquillizer, produces a fall in body temperature when administered systemically to man (Ayd, 1955) and animals (Kopera & Armitage, 1954; Dobkin, Gillert & Lamoureaux, 1954; Hoffman & Zarrow, 1958) in a neutral thermal environment. Because of its hypothermic effect, the drug has been proposed as an adjunct in the production and maintenance of hypothermia (Gray & Graham, 1971) and in the treatment of heat stroke (Hoagland, 1961) in clinical medicine. However, the site and mechanism of this action of Cpz is not clear. It could act on peripheral thermal elements, on the temperature regulating structures within the CNS, or on both.

In the rat, Cpz-induced hypothermia is due, in part, to increased peripheral vasodilatation (Kollias & Bullard, 1964), increased surface area by postural change (Le Blanc, 1958), decreased oxygen consumption (Courvoisier, Fournel, Ducrat, Kohlsky & Koetschet, 1953; Hoffman, 1958; Kollias & Bullard, 1964), and loss of piloerection and shivering (Kollias & Bullard, 1964). Most of these investigators have suggested that the hypothermic effect following systemic injection of Cpz is due to an action on central thermoregulating structures. Nevertheless, conflicting reports exist on the effect of intrahypothalamic injections of Cpz on the body temperature of the rat. Unexpectedly, a dose-dependent hyperthermia was seen after central administration of the drug (Rewerski & Jori, 1968; Kirkpatrick & Lomax, 1971; Rewerski & Gumulka, 1974). Kirkpatrick & Lomax (1971) even concluded that the hypothermia induced by systemically administered Cpz is mediated by sites outside the CNS. They discovered that systemic administration of *N*-methyl Cpz (a quarternary analogue of Cpz), a substance which supposedly has difficulty penetrating the blood-brain barrier, also produces hypothermia. On the other hand, direct injection of this drug (Cpz) into the preoptic anterior hypothalamus (POAH) has been shown to produce dose-dependent hypothermia in monkeys (Chai, Fann & Lin, 1976) and in hamsters (Reigle & Wolf, 1971).

The present study was undertaken to elucidate the possible locus of Cpz-induced hypothermia in rats by means of two different approaches: (1) The effects of surgical intervention of the POAH area and the spinal cord, the two proposed thermoregulating structures (Lin & Chai, 1974; Simon, 1974), on the hypothermia induced by systemically injected Cpz were determined. (2) The order of effectiveness of Cpz administered by various routes (namely, peritoneum,

jugular vein, internal carotid artery, and 4th and 3rd cerebral ventricle) on body temperature was determined.

Methods

One hundred male Sprague-Dawley rats, with body weights between 230 and 300 g at the time of surgery, were used. The rats were housed individually in wire-mesh cages in a room of 25 ± 1.0°C with natural light-dark cycles. The rats were given free access to tap water and granular young-chicken feed supplied by the Taiwan Sugar Corporation. Food and water intake, body temperature, and body weight were measured daily at 08 h 00 min. During the experiments, the rats were placed in a prone position on a board. Ambient temperature during the experiments was 23 ± 0.5°C.

Surgical intervention

Each rat underwent either ablation of CNS tissue or chronic cannula implantation in an aseptic surgical operation under general anaesthesia of pentobarbitone sodium (6 mg/100 g, i.p.). Details of the methods used to prepare chronic rats with lesions in POAH or the spinal cord have been described previously (Lin & Chai, 1974). In brief, electrolytic destruction of POAH was accomplished bilaterally with anodal d.c. current of 2 mA for 20 seconds. The stereotaxic coordinates used were 8.5 mm anterior to the ear bars, 0.8 mm lateral to the midline, and 0.8 mm above the base of the skull. In preparing spinal animals, the cervical vertabrae was exposed and complete transection was made with a spatula at the seventh cervical spinal cord (C7). Ablation of the ventromedial nucleus of the hypothalamus (VMN) was performed according to the technique of Liu & Yin (1974). The stereotaxic coordinates used were 6 mm anterior to the ear bars, 0.5 mm above the base of the skull, and 0.5 mm left or right to the midline.

Implanation of unilateral cannula in the 4th or 3rd cerebral ventricle followed methods described previously (Chai, Chen & Yin, 1971; Lin & Chai, 1972). A 22-gauge guide tube was chronically implanted into the ventricle. The drug was administered through a 10 µl Hamilton microsyringe with the tip of a 27 gauge tube passing just beyond the outlet of the guide tube. Implanation of intrajugular and intracarotid catheters was based on techniques of Corbit (1965) and Chai, Lin, Chen & Wang (1971), respectively. The left jugular vein or the left internal carotid artery was selected for chronic cannulation. Intraperitoneal injections were made by puncture through the abdominal wall. A 1 ml syringe was used for the intrajugular, intracarotid, and intraperitoneal injections.

A period of 2–6 weeks was allowed to permit the animals to recover from the surgical operation before they were used for experiments. For rats with POAH lesions or spinal transection, gradual recovery of appetite (food consumption greater than 10 g per day), an increase in body weight, and a normal range of body temperature (maintained under room temperature) were good indications of general recovery. During the control period of observation in an ambient temperature of 23°C, animals showing a rectal temperature below 37°C, above 38.9°C, or great fluctuations were excluded.

Following the experiments, the rats were killed by an overdose of pentobarbitone sodium and the heads were perfused with 10% formalin saline. The brains were removed, cut in 40 µm sections, and stained with thionin to verify the site of the brain lesions or spinal transection and the tips of the cannulae for intracerebroventricular injection. The exact location of intrajugular and intracarotid cannula was verified by gross inspection.

Drug injection

Chlorpromazine hydrochloride (supplied by Smith Kline & French Laboratories) was added to pyrogen-free distilled water just before use and adjusted to pH 7.0–7.3 in order to make the various molar solutions. The volume and the molar concentration of Cpz solutions used in different routes of injection were as follows: intraperitoneal, intravenous and intracarotid injections of 5–15 mg/kg, 2–6 mg/kg and 0.1–0.5 mg/kg Cpz, respectively, were given in 1 ml 0.9% w/v NaCl solution (saline)/kg body weight. On the other hand, fourth and third cerebroventricular injections of 10–40 µg Cpz for each route were given in 5 µl saline per animal. Control injections of pyrogen-free sterile NaCl solutions equal in volume and molarity to the Cpz solutions were given by the same routes. All the solutions used for injection were prepared in pyrogen-free glassware which was baked at 180°C for 4 h before use.

Temperature recordings

Rectal temperature was monitored with a Tri-R-6 flexible thermistor probe, and the subcutaneous temperature of the tail was monitored by a Tri-R hypodermic needle thermistor. Respiratory movements were monitored with a pneumograph, connected to a Statham SP37 transducer. All recordings were made continuously on a Grass polygraph. Shivering-like movements were observed grossly.

Results

Injections of Cpz, given either systemically or

centrally at an ambient temperature of 23°C caused dose-dependent decreases in rectal temperature, varied degrees of psychomotor depression, an initially higher rate of respiratory frequency, and an initially higher tail skin temperature (subcutaneous vasodilatation). Changes in rectal temperature were the only responses measured specifically.

Responses to thermal exposure and effects of intraperitoneal administration of chlorpromazine on lesioned animals

In this series of experiments, tests of thermal exposure preceded Cpz injection by two days. Figure 1 and Table 1 show maximum changes in rectal temperature of intact and spinal rats, rats with POAH lesions, and rats with VMN lesions after 1 h of heat (36°C) or cold (8°C) exposure. They also show the decrement in the rectal temperature of these animals in response to Cpz administration at an ambient temperature of 23°C. Abrupt exposure to heat produced significant hyperthermia, subcutaneous vasodilatation and hyperpnoea, whereas exposure to cold produced the opposite effects, marked hypothermia, subcutaneous vasoconstriction and bradypnoea. Figure 1 shows that the rise or fall in rectal temperature of rats with lesions in POAH (+3.9°C in the heat; −6.5°C in the cold) and spinal rats (+2.6°C; −4.4°C), upon heat or cold exposure, were significantly higher than those of control rats (+1.5°C; −3.0°C) and rats with lesions in VMN (+1.6°C; −3.2°C). Hence, lesions in POAH or in the cervical spinal cord (at C7) caused a thermoregulatory deficit against heat and cold. Moreover, the extent of the thermoregulatory deficit was related to the sites and size of the brain lesions. Large lesions in POAH produced more marked deviations of the rectal temperature during thermal stress (+3.9°C in the heat vs −6.5°C in the cold) than did small lesions (+2.8°C; −4.5°C). Figure 2 shows outline drawings of brain sections taken from 2 rats with large lesions in POAH (a–c and d–f) and 1 rat with small POAH lesions (g–i). On the other hand, the animals with lesions in VMN tolerated heat or cold stress as well as did the control animals.

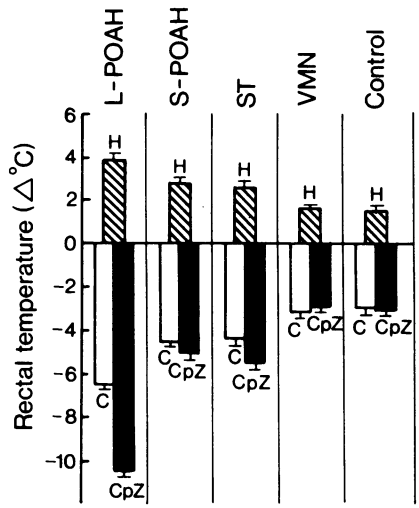

Figure 1 Temperature responses to external heat (36°C) and cold (8°C) exposure, and to an intraperitoneal dose of chlorpromazine (Cpz) (10 mg/kg; ambient temperature of 23°C) in control rats and rats with lesions in preoptic anterior hypothalamus, ventromedial nucleus of hypothalamus and spinal cord. L-POAH: large lesions in preoptic-anterior hypothalamus; 8 animals. S-POAH: small lesions in preoptic-anterior hypothalamus; 4 animals. ST: spinal transection at C7; 4 animals. VMN: lesions in ventromedial nuclei of hypothalamus; 4 animals. Control: 8 intact animals. H: heat exposure. C: cold exposure.

Table 1 Changes of rectal temperature in response to an intraperitoneal dose of chlorpromazine in control animals and in animals with lesions in the preoptic anterior hypothalamus (POAH), the ventromedial nucleus of the hypothalamus (VMN) and the spinal cord at an environmental temperature of 23°C

No. of animals	*Treatment of animals*	*Route injection and dose*	*Temperature decrement*			
			Latency	*Maximum*	*Time to maximum*	*Recovery time*
		(mg/kg)	*(min)*	*(°)*	*(min)*	*(min)*
8	Control	i.p., 10	15 ± 2.36	3.1 ± 0.24	96 ± 4.88	440 ± 16.65
8	L-POAH	i.p., 10	6 ± 1.82	10.4 ± 0.38*	390 ± 10.25	2280 ± 50.75
4	S-POAH	i.p., 10	9 ± 1.22	5.1 ± 0.26*	180 ± 12.53	270 ± 35.12
4	ST	i.p., 10	12 ± 1.02	5.5 ± 0.31*	210 ± 12.78	900 ± 42.51
4	VMN	i.p., 10	15 ± 2.20	2.9 ± 0.28	150 ± 10.45	500 ± 18.35

L-POAH: large lesions in preoptic-anterior hypothalamus; S-POAH: small lesions in preoptic-anterior hypothalamus; ST: spinal transection at C7; VMN: lesions in ventromedial nuclei of hypothalamus. Values are means ± s.e.

* Indicates statistically significant change with P values < 0.05 calculated from Student's t test.

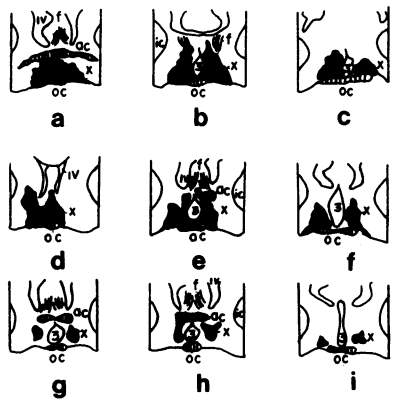

Figure 2 Drawings of photomicrographs of brain sections taken from 2 rats with chronic large lesions in preoptic-anterior hypothalamus show sites and size of lesions from rostral to caudal portions (a–c and d–f) and 1 rat with small lesions in POAH (g–i). f: fornix; ac: anterior commissure; 3: 3rd cerebral ventricle; IV: 4th cerebral ventricle; ic; internal capsule; oc: optic chiasma; x: sites of lesions.

The magnitude of the hypothermic effect of Cpz (10 mg/kg, i.p.) also depended on the location as well as the size of the lesions. The order of effectiveness of Cpz-induced hypothermia decreased from the rats with large lesions in POAH (10.4°C maximum decrement in rectal temperature) to the spinal rats (5.5°C maximum temperature decrement) and finally to the control rats (2.9°C maximum temperature decrement). Other parameters, e.g., latency, time to maximum temperature decrement, and recovery time, correlated well with the magnitude of temperature decrement produced by Cpz (see Table 2 for details).

Effect of chlorpromazine on body temperature of normal rats as related to dose and route of administration

Table 2 shows the hypothermic effect of Cpz administered via the peritoneum, femoral vein, internal carotid artery, and fourth and third cerebral routes at an ambient temperature of 23°C. It was found that the dose required to produce a drop of around 3°C in rectal temperature decreased as the route varied from central to systemic, i.e., from an intracerebroventricular route (20 μg in total) to an intracarotid route (0.25 mg/kg) and finally to an intraperitoneal route (9.75 mg/kg) of administration. In other words, direct injection of small amounts of Cpz (20 μg in total) into the cerebral ventricle produced the same hypothermic effect (3°C) as intraperitoneal injection of a large dose (9.75 mg/kg), a ratio of 1 to 110. This

Table 2 Hypothermic effect of chlorpromazine administered via peritoneum, femoral vein, internal carotid artery, and fourth and third cerebral ventricle routes at an environmental temperature of 23°C

No. of animals	*Route of administration*	*Dose*	*Temperature decrement*			
			Latency	*Maximum*	*Time to maximum*	*Recovery time*
			(min)	*(°C)*	*(min)*	*(min)*
4	Peritoneum	5 mg/kg	18 ± 2.28	2.4 ± 0.23	62 ± 4.74	180 ± 9.26
4	Peritoneum	10 mg/kg	14 ± 2.10	3.3 ± 0.23	90 ± 5.64	430 ± 15.32
4	Peritoneum	15 mg/kg	6 ± 1.02	4.5 ± 0.35	130 ± 6.37	460 ± 17.43
4	Femoral vein	2 mg/kg	15 ± 3.54	3.1 ± 0.20	85 ± 6.32	410 ± 14.28
4	Femoral vein	4 mg/kg	10 ± 1.64	3.9 ± 0.32	92 ± 8.25	510 ± 17.56
4	Femoral vein	6 mg/kg	7 ± 1.12	4.6 ± 0.32	115 ± 8.61	550 ± 20.12
4	Internal carotid artery	0.1 mg/kg	6 ± 1.25	2.2 ± 0.30	149 ± 7.47	590 ± 20.10
4	Internal carotid artery	0.25 mg/kg	6 ± 1.21	2.8 ± 0.31	155 ± 8.62	610 ± 22.30
4	Internal carotid artery	0.5 mg/kg	5 ± 0.25	3.8 ± 0.33	211 ± 20.86	650 ± 25.62
4	4th cerebroventricle	10 μg	5 ± 0.19	2.6 ± 0.19	68 ± 5.24	380 ± 16.21
4	4th cerebroventricle	20 μg	3 ± 0.27	2.9 ± 0.19	270 ± 18.75	520 ± 16.32
4	4th cerebroventricle	40 μg	2 ± 0.24	3.8 ± 0.15	377 ± 23.60	740 ± 22.56
4	3rd cerebroventricle	10 μg	6 ± 0.22	2.5 ± 0.21	71 ± 5.21	370 ± 13.32
4	3rd cerebroventricle	20 μg	4 ± 0.18	3.2 ± 0.29	160 ± 8.46	480 ± 16.34
4	3rd cerebroventricle	40 μg	2 ± 0.21	4.2 ± 0.34	362 ± 17.45	760 ± 21.63

Values are means ± s.e.

suggests that chlorpromazine exerts its effect mainly through the CNS. However, there was no significant difference in the Cpz-induced hypothermia between the routes of administration of 3rd and 4th cerebral ventricles in the range of doses being tested.

Although psychomotor depression occurred in all rats immediately after Cpz administration, some recovered much more rapidly than others. For instance, some showed rearing locomotion only 0.5 to 1.0 h after administration. However, there was no relation between recovery from psychomotor depression and degree or duration of hypothermia. Furthermore intracerebroventricular administration of Cpz induced marked hypothermia, yet there was little apparent psychomotor depression.

Administration of Cpz produced a temporary increase in subcutaneous temperature and respiratory frequency. These reactions were concomitant with the reduction of rectal temperature. However, as the rectal temperature fell 1.5 to 2.0°C, the tail temperature dropped rapidly as did the respiratory frequency. By the time the hypothermia reached its maximum, the tail temperature and the respiratory rate had returned to the resting level or even lower.

Discussion

In the present study, the most striking finding was the high correlation between the extent of thermoregulatory deficit and magnitude of Cpz-induced hypothermia. Lesions in POAH or spinal transection at C7 caused both a thermoregulatory deficit against heat and cold and an enhancement of Cpz hypothermia, compared to that seen in control animals and animals with VMN lesions. Animals with large lesions of the POAH region had a larger thermoregulatory deficit than those with small lesions in the POAH or those with spinal transection at C7. This was revealed by the changes in body temperature of groups of animals with these lesions when they were exposed to thermal stress.

The present study was concerned with the additional question of whether Cpz caused changes in body temperature by acting directly on the central or peripheral control system. For an equivalent hypothermia (−3.0°C), the effectiveness of Cpz decreased from intracerebroventricular to the intracarotid and intravenous and finally to the intraperitoneal route of administration. Hence, Cpz apparently exerts its hypothermic effect mainly through the central nervous system rather than through peripheral sites. Recent evidence has suggested that the temperature regulating system may include central nervous structures other than POAH, e.g., medulla oblongata and spinal cord (Hellon, 1971; Chai & Lin, 1973; Lin & Chai, 1974; Simon, 1974). Indeed, two distinct structures in the brain stem, namely, the POAH and medulla oblongata, have been found responsible for the Cpz hypothermia (Chai *et al.*, 1976). Furthermore, present results also showed a dose-dependent hypothermia in response to the direct injections of Cpz into third or fourth cerebral ventricle. The above data, taken together, imply that the induction of Cpz hypothermia may be attributed to a specific action of Cpz on these central thermoregulatory mechanisms in the POAH and the medullary areas.

In considering the question of the enhancement of Cpz-induced hypothermia in animals with brain lesions, the fact has to be considered that the extent or intensity of Cpz-induced hypothermia is related to the compensatory activity of the central thermoregulatory mechanisms. In intact animals, an intraperitoneal dose of 10 mg/kg of Cpz produced a maximum fall of 3.1°C in body temperature in an environment of 23°C. A displacement of 3.1°C from normal core temperature should be powerful enough to activate the various thermoreceptors in the body. The activated thermoreceptors, particularly those located in the central nervous system, then send feedback inputs (temperature-dependent) to the central control mechanisms to generate a series of compensatory reactions (e.g., vasoconstriction, bradypnoea, piloerection and shivering; Hellon, 1971). Under normal circumstances, these cold-induced compensatory reactions should counteract the Cpz-induced thermal responses and prevent further reduction of the body temperature. As a consequence, in animals with lesions in POAH and in spinal animals, the absence or reduction in the numbers of hypothalamic or spinal thermoreceptors would induce little compensatory reaction to counteract the massive Cpz-induced hypothermia and, therefore, would allow a severe reduction in body temperature, 10.4°C and 5.5°C, respectively. In addition, if we accept the phylogenetic hypothesis of 'cephalization' (that temperature regulating mechanisms that exist along the whole CNS become more concentrated in its anterior portions; Thauer, 1973) then, the present study showing that animals with large lesions in POAH underwent a more marked Cpz-induced hypothermia than spinal animals could be explained.

Finally, it should be mentioned that, in the present study, intracerebroventricular administration of Cpz induced marked hypothermia, yet there is little apparent psychomotor depression. This seems to indicate that a sedative effect on the animal is not a prerequisite for the Cpz hypothermia. The same suggestion has been made by Borbely, Huston & Baumann (1973).

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