Factors Modifying Chlorpromazine Hyperthermia in Young Albino Mice

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The administration of *dextro*-tubocurarine immediately before chlorpromazine was ineffective in modifying the temperature responses of the phenothiazine in 10- and 38-day-old mice. Chlorpromazine sulfoxide, a metabolite of chlorpromazine, produced a profound temperature rise in 10-day-old mice. Morphine sulfate, when given to 10-day-old mice, produced a significant rise in body temperature, which was inhibited completely by the previous administration of nalorphine. In contrast, nalorphine was shown to be ineffective in modifying the body temperature elevation caused by chlorpromazine in this age group. Pilocarpine inhibited the thermogenic response of chlorpromazine by approximately 50 per cent. Cocaine, *dl*-amphetamine, and reserpine, although demonstrating hyperthermic activity in 10-day-old mice, were unable to modify the response of chlorpromazine on the body temperature of 10-day-old mice. Tripelennamine and insulin, which individually were without a temperature response, were also incapable of altering the temperature response elicited by chlorpromazine in 10-day-old mice. Insulin lowered the blood sugar level significantly in 10-day-old mice, a response not affected by chlorpromazine. The administration of iproniazid before chlorpromazine caused a slight augmentation of the hyperthermic response of the latter, while sodium cyanide, lysergic acid diethylamide, and brom-lysergic acid produced a marked inhibition of the hyperthermic activity of chlorpromazine in 10-day-old mice.

THE ACTION OF chlorpromazine (CPZ) on the body temperature of immature mice has been investigated (1), and it has been demonstrated that the effect of this phenothiazine on body temperature was influenced by age, the drug causing significant hyperthermia in 10- and 15-day-old mice and hypothermia in 35- and 38-day-old animals.

Because the nature of the factors which influence the hyperthermic activity of chlorpromazine is unknown, it was the purpose of this investigation to shed light on the subject by observing the influence of other drugs in the presence of the phenothiazine with the ultimate hope that insight into the mode of action of chlorpromazine might be elucidated. This study was divided into the following five areas which were believed to be involved primarily in the thermotropic activity of chlorpromazine.

(*a*) The effect of a skeletal muscle relaxant (*dextro*-tubocurarine) on the chlorpromazine temperature response was ascertained in mice 10 and 38 days of age to determine if diminished muscle tone would decrease the hyperthermia in 10-day-old mice and increase the hypothermia in 38-day-old animals. It has been reported previously that muscle relaxants by decreasing the heat production of muscle, could prevent hyperthermia if it were mediated through an increase in tone (2, 3) and could also augment hypothermia if the hypothermia were due to a loss of muscle activity normally responsible for heat production (4, 5).

(*b*) The effect on temperature of chlorpromazine sulfoxide, a major metabolite of chlorpromazine (6–8) in 10-day-old mice was investigated.

(*c*) Nalorphine has antagonized morphine hypothermia in dogs (9) and chlorpromazine hypothermia in mice, rabbits, and guinea pigs (10). It also can inhibit the *N*-demethylation of morphine in rat liver microsome preparations (11). Chlorpromazine undergoes demethylation in the liver as a means of biotransformation to a less active product (12, 13). Therefore it was of importance to see what effect morphine would have on the body temperature of 10-day-old mice and whether nalorphine could block that effect and also antagonize the chlorpromazine hyperthermia in 10-day-old mice.

(*d*) Chlorpromazine is known to depress subcortical activity (14–16), while cholinergic drugs activate this area of the brain (17, 18). Therefore, it became necessary to observe the effect of pilocarpine on chlorpromazine-induced temperature responses in 10-day-old mice.

(*e*) Amphetamine (19), lysergic acid diethylamide (19), reserpine (20), and potassium cyanide (21) are known to antagonize CPZ-induced hypothermia. Other drugs are known which increase the hypothermic activity of CPZ, such as tripelennamine (22), cocaine (23),

Received August 11, 1964, from the School of Pharmacy, Temple University, Philadelphia, Pa.
Accepted for publication October 28, 1964.
Presented to the Scientific Section, A.PH.A., New York City meeting, August 1964.
Abstracted from a thesis submitted by Walter J. Bagdon to the Graduate School, Temple University, Philadelphia, Pa., in partial fulfillment of Doctor of Philosophy degree requirements.
This investigation was supported by grant MH-07974-01 from the U. S. Public Health Service, Bethesda, Md.
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insulin (24), and iproniazid (19). Because the manner in which these various agents influence chlorpromazine hypothermia in mature animals is variable, an attempt to uncover similarities and discrepancies in their activity in modifying CPZ-induced hyperthermia in immature mice was undertaken with the eventual hope of elucidating the nature of the hyperthermic response of the phenothiazine. The brom derivative of lysergic acid diethylamide also was employed because it is closely related to lysergic acid diethylamide but devoid of an effect on the psyche (25). Because insulin was used, blood sugar determinations were performed to determine if CPZ would affect the hypoglycemia that ensued.

EXPERIMENTAL

Albino mice (1,515), (Huntingdon Farms, Inc., HTF strain) were grouped according to age (10 and 38 days old) with the age variation within a designated group not exceeding 15 hr. The 38-day-old animals were further differentiated according to sex. Food was withdrawn 15 min. and water 1 hr. before experimentation to provide for nutritional constancy. The mice were weighed on a triple-beam Ohaus balance immediately prior to the experimental procedure. Temperature recordings were taken orally with a model 43 Tele-Thermometer equipped with a No. 402 probe (Yellow Springs Instrument Co., Yellow Springs, Ohio). Each mouse was confined in a 100-ml. beaker with a screen top and kept at a constant environmental temperature of 38° for 15 min. before and throughout the experiment. The animals received all injections intraperitoneally in a fixed volume of 0.1 ml. of either the drug or distilled water (water for injection, Philadelphia Ampoule Co.) per injection. The dosage level was given as the salt of the drug in freshly prepared solutions.

The drugs and their sources were as follows: chlorpromazine hydrochloride (Thorazine, Smith Kline and French Laboratories); *dextro*-tubocurarine chloride (tubocurarine, Abbott Laboratories); chlorpromazine sulfoxide (generously supplied by Smith Kline and French Laboratories); nalorphine hydrochloride (Nalline, Merck Sharp and Dohme); morphine sulfate (Merck and Co.); pilocarpine nitrate (Merck and Co.); iproniazid phosphate (Marsilid, generously supplied by Hoffmann-La-Roche, Inc.); cocaine hydrochloride (Merck and Co.); *dl*-amphetamine sulfate (Hexagon Laboratories); tripelennamine hydrochloride (Pyribenzamine, Ciba Laboratories); reserpine (Serpasil, Ciba Laboratories); insulin injection, U.S.P. (Iletin, Eli Lilly Co.); heparin solution (Liquaemin Sodium 50, Organon Laboratories); sodium cyanide (J. T. Baker Chemical Co); lysergic acid diethylamide and brom-lysergic acid diethylamide (generously supplied by Sandoz Laboratories). All of the solutions or dilutions, as the situation demanded, were made with water for injection U.S.P. (Philadelphia Ampoule Laboratories).

The procedure was divided into the following five parts according to the nature of the drug(s) administered in conjunction with chlorpromazine.

1. Skeletal Muscle Relaxant—*dextro*-Tubocurarine

Four-hundred and sixty-two mice, 10 and 38 days old, were divided into groups according to treatment as follows:

Group A.—This group received two 0.1-ml. injections of distilled water.

Group B.—This group received one injection of 0.1-ml. of distilled water and one injection of 0.1 ml. of a solution containing *dextro*-tubocurarine (75 mcg./Kg.).

Group C.—This group received one injection of a 0.1-ml. solution containing *dextro*-tubocurarine (75 mcg./Kg.) and one injection of 0.1 ml. of solution containing 1 mg./Kg. of chlorpromazine.

Initial oral temperatures were recorded, then followed by the two injections designated for that particular group. The animals were returned to the beakers (maintained at 38°) for 30 min., after which oral temperatures were recorded again. The change in body temperature produced by *dextro*-tubocurarine against the control was compared to that produced by the simultaneous injections of both *dextro*-tubocurarine and chlorpromazine.

2. Chlorpromazine Metabolite—Chlorpromazine Sulfoxide

Thirty-nine 10-day-old mice had their oral temperatures recorded, then received chlorpromazine sulfoxide at a dosage level of 50 mg./Kg., whereupon they were returned to their beakers and maintained in an enviromental temperature of 38° for 15 min. Then they received an injection of distilled water and were returned to the beakers for an additional 30 min., when oral temperatures were recorded again. The change in body temperature produced by chlorpromazine sulfoxide was compared to that elicited by the controls. The controls used in this procedure were the 10-day-old animals employed as controls under *Part 3* of this investigation.

3. Narcotic Analgesic and Antagonist—Morphine and Nalorphine

Two-hundred and ninety 10-day-old mice were divided into six groups according to treatment. After an initial oral temperature was recorded, an injection was made; each animal was returned to his beaker for 15 min., whereupon a second injection was given. The mouse was returned again to the beaker for a period of 30 min. At the end of the 30-min. period, a final oral temperature was determined. The groups according to the sequence of injections were as follows:

Group D.—This group received water followed by water.

Group E.—This group received water followed by morphine.

Group F.—This group received water followed by chlorpromazine.

Group G.—This group received nalorphine followed by water.

Group H.—This group received nalorphine followed by morphine.

Group I.—This group received nalorphine followed by chlorpromazine.

The dosage levels of these drugs were: morphine, 5 mg./Kg.; chlorpromazine, 1 mg./Kg.; and nalorphine, 0.1 mg./4.6 Gm. The changes in temperature produced by nalorphine, morphine, and chlorpromazine were compared with that elicited by the controls. The effects of nalorphine on the temperature changes evoked by morphine and chlorpromazine were also noted.

4. Cholinergic Agent—Pilocarpine

One-hundred and forty-nine 10-day-old mice were treated as under *Part 3*, except that only two groups were used, and the sequence of injections was as follows:

Group J.—This group received pilocarpine followed by distilled water.

Group K.—This group received pilocarpine followed by chlorpromazine.

Pilocarpine was given at a dosage level of 0.1 mg./Kg. and chlorpromazine at 1 mg./Kg. The effect of pilocarpine on body temperature was determined by comparing the results obtained with pilocarpine with those elicited by the water controls in *Part 3*, while the effect of CPZ-induced hyperthermia was accomplished by comparing these results with those caused by CPZ in *Part 3*.

5. CNS Stimulants, Depressants, Enzyme Antagonists—Iproniazid, Cocaine, *dl*-Amphetamine, Tripelennamine, Reserpine, Regular Insulin, Sodium Cyanide, Lysergic Acid Diethylamide, and Brom-lysergic Acid Diethylamide

Five-hundred and seventy-five 10-day-old mice were treated as described under *Part 4*, except that the injection sequence was drug followed by water, and drug followed by chlorpromazine. The drugs employed in this phase of the experiment were iproniazid, 100 mg./Kg.; cocaine hydrochloride, 5 mg./Kg.; *dl*-amphetamine sulfate, 10 mg./Kg.; tripelennamine, 10.5 mg./Kg.; reserpine, 20 mg./Kg.; regular insulin, 4 I.U./Kg.; sodium cyanide, 0.66 mg./Kg.; lysergic acid diethylamide, 0.75 mg./Kg.; and brom-lysergic acid diethylamide, 10 mg./Kg. The effects of these drugs on body temperature were determined by comparing their results with those obtained from the controls in *Part 3*. The actual elevation in body temperature induced by chlorpromazine in the presence of the various agents was evaluated by comparing the data with those obtained in *Part 3* from CPZ when administered alone.

The effect of chlorpromazine on insulin hypoglycemia was determined by the method of Folin and Malmros (26). Readings were made with a Klett-Summerson photoelectric colorimeter. The mice were treated exactly as those in the temperature study with regard to the frequency of injections and the constancy of the environmental temperature at 38°. However, these animals were not fasted for an extended period because of their immaturity. The mice were heparinized by administering i.p. 0.01 ml. of a solution containing 5000 U.S.P. u./ml. of heparin sodium. Blood then was immediately obtained after a headblow by excising the heart and collecting the blood in a heparinized syringe. The amount of blood obtained was 0.1 ml. per determination; it was procured either from one animal or by pooling the blood from two animals.

In all of the procedures, the significance of differences between the means of drug and control, or drug and combination of drugs, was estimated by using the *t* test, and probability levels were also indicated. Probability levels below 90% were designated as insignificant.

RESULTS AND DISCUSSION

It was observed (Table I) in 10-day-old mice that *dextro*-tubocurarine, at a dosage level of 75 mcg./Kg., given immediately prior to 1 mg./Kg. of chlorpromazine, did not affect the hyperthermia associated with the administration of CPZ. Therefore, it was concluded that the hyperthermic response to CPZ was not mediated through an increase in skeletal muscle tone. In 38-day-old male and female mice, *dextro*-tubocurarine did not augment the CPZ-induced hypothermia. Accordingly, the conclusion was made that hypothermia produced by CPZ was not mediated by a curariform action, for the introduction of another skeletal muscle relaxant failed to enhance the hypothermic response. Although CPZ has a depressant effect on striated muscle (4, 5), Halpern and Liakopoulos (27) have shown that the injection of a synthetic curarizing drug with CPZ did not augment the hypothermic response of the phenothiazine. Accordingly, their results are in agreement with those obtained in this experiment with 38-day-old mice. Perhaps CPZ is incapable of producing hypothermia by the relaxation of skeletal muscle because relatively higher concentrations are required at neuromuscular junctions for it to depress muscle tone (28, 29).

Chlorpromazine sulfoxide caused a rise in temperature of approximately 1.5° over the controls at a dosage level of 50 mg./Kg. (Table II). This elevation in body temperature was significant at the 99.9% level. Although this metabolite of chlorpromazine has been shown to be less potent than the parent compound in its general pharmacologic activity, it still possesses many of the properties of the latter (30, 31), *i.e.*, the ability to cause a rise in body temperature of 10-day-old mice, as demonstrated in this study.

In Table III, morphine, when given at a dosage level of 5 mg./Kg., caused a significant temperature rise of approximately 1.5° in 10-day-old mice. The opiate has been shown to have a variable degree of activity on the body temperature of mammals which is dependent upon the species and the dose. However, morphine administration to dogs and rabbits in a wide dosage range consistently produced a drop in body temperature (32, 33); on the other hand, cats showed a temperature rise (32). Winter and Flataker (34) have produced an increase in body temperature in rats with a subcutaneous dose of 8 mg./Kg. of morphine. This effect was also noted by Herrmann (35); but with larger doses of the opiate (40 to 90 mg./Kg.), hypothermia occurred. Gunne (36) also observed temperature rises with doses of 10 and 20 mg./Kg. of morphine in rats; while with slightly larger doses (30 to 80 mg./Kg.), a fall in body temperature became more and more evident. In adult mice, Madden and Hiestand (37) obtained a drop in body temperature when morphine was administered at a dosage level of 50 mg./Kg. The hyperthermia produced by

TABLE I.—EFFECT OF *dextro*-TUBOCURARINE ON THE BODY TEMPERATURE OF CHLORPROMAZINE-TREATED MICE

	Mice, No.	Sex	Wt., Gm.	Initial Temp., °C.	Final Temp., °C.	Temp. Change, °C.	Drug-Induced Change, °C.	*t*	*P*
10-Day-Old									
Water-water	58		4.72	34.54	34.83	+0.29			
							−0.01	0.07	[a]
d-Tubo[b]-water	56		4.68	35.23	35.51	+0.28			
							+1.02	6.74	0.001
d-Tubo-CPZ[c]	65		4.79	35.41	36.71	+1.30			
38-Day-Old									
Water-water	47	M	21.20	36.20	36.20	0.00			
							+0.01	0.07	[a]
d-Tubo-water	46	M	21.97	36.48	36.49	+0.01			
							−0.42	3.02	0.01
d-Tubo-CPZ	48	M	21.72	36.42	36.01	−0.41			
Water-water	46	F	20.36	36.29	36.30	+0.01			
							+0.04	0.29	[a]
d-Tubo-water	48	F	20.97	36.40	36.45	+0.05			
							−0.50	3.67	0.001
d-Tubo-CPZ	48	F	20.02	36.26	35.81	−0.45			

[a] No significance. [b] *d*-Tubocurarine. [c] Chlorpromazine.

TABLE II.—EFFECT OF CHLORPROMAZINE SULFOXIDE ON THE BODY TEMPERATURE OF 10-DAY-OLD MICE

Treatment	Mice, No.	Wt., Gm.	Initial Temp., °C.	Final Temp., °C.	Temp. Change, °C.	Drug-Induced Change,	*t*	*P*
Drug	39	5.64	34.56	36.41	+1.85			
						+1.45	8.15	0.001
Control	48	5.26	34.53	34.93	+0.40			

TABLE III.—EFFECTS OF NALORPHINE GIVEN 15 MIN. BEFORE MORPHINE OR CHLORPROMAZINE ON TEMPERATURE CHANGES PRODUCED BY THESE AGENTS IN 10-DAY-OLD MICE

Treatment	Mice, No.	Wt., Gm.	Initial Temp., °C.	Final Temp., °C.	Temp. Change, °C.	Drug-Induced Change, °C.	*t*	*P*
						Compared to Water		
Water-water	48	5.26	34.53	34.93	+0.40			
Water-morphine	49	4.84	34.75	36.60	+1.85	+1.45	9.68	0.001
Water-CPZ[b]	48	4.87	34.19	35.79	+1.60	+1.20	6.93	0.001
Nalorphine-water	49	4.84	34.98	34.72	+0.64	+0.24	1.45	[a]
						Compared to Morphine		
Nalorphine-morphine	49	5.05	34.67	35.05	+0.38	−1.47	10.17	0.001
						Compared to Chlorpromazine		
Nalorphine-CPZ	47	5.27	34.44	35.98	+1.54	−0.06	0.31	[a]

[a] No significance. [b] Chlorpromazine.

morphine in 10-day-old mice in this experiment may be related to the lower dose employed, for it is possible that mice also may show a biphasic action of the temperature response according to the dosage level, or it may be related to a differential development of the hypothalamic regulating centers in young mice. In this part of the procedure, chlorpromazine again produced a temperature rise in 10-day-old mice similar to that recorded in Table I and in our earlier publication (1). Nalorphine, when administered at a dosage level of 0.1 mg./4.6 Gm., was without a significant effect on body temperature.

Nalorphine, when given 15 min. prior to morphine, completely blocked the rise in body temperature in 10-day-old mice in response to morphine. The ability of nalorphine to antagonize many of the pharmacological properties of morphine, including hypothermia in dogs (9), is well known. Nalorphine has been used to curtail some of the toxic manifestations of acute chlorpromazine poisoning (38) and has been shown by Frommel and associates (10) to oppose the hypothermic and hypnotic effects of CPZ. In this study, the prior administration of nalorphine failed to block the hyperthermia elicited by chlorpromazine in 10-day-old mice. Therefore, it is presumed that the action of CPZ in this respect is exerted at a different site from that occupied by the narcotic antagonist.

Table IV shows that pilocarpine, at a dosage

level of 0.1 mg./Kg., had no significant effect on body temperature. However, the effect of pilocarpine at this dosage level, when administered 15 min. before CPZ, revealed that a significant inhibition of the hyperthermic response of CPZ occurred in 10-day-old mice. Because CPZ is believed to depress subcortical activity (14–16), while cholinergic drugs activate this area of the brain (17, 18), it is possible that pilocarpine prevented CPZ-induced hyperthermia by negative summation. On the other hand, pilocarpine also is known to have a peripheral action. This effect probably was blocked by CPZ, which is known to exert a peripheral anticholinergic action (39, 40). Therefore, it is believed that a central antagonism is the more likely mode of action.

Iproniazid (Table V) was shown to have no significant effect on the body temperature of 10-day-old mice when given at a dosage level of 100 mg./Kg. When the MAO inhibitor was administered before CPZ, there was a slight potentiation of the CPZ-induced hyperthermia significant at the 90% level of probability. Because CPZ is known to undergo detoxification by the liver microsomes (7, 41), and iproniazid is able to inhibit this metabolic pathway (42), it is believed that the increase in body temperature afforded by the presence of iproniazid is due to the decreased biotransformation of chlorpromazine.

The administration of cocaine, at a dosage level of 5 mg./Kg., produced a slight elevation of the body temperature of 10-day-old mice which was significant at the 90% level of probability. This dose of cocaine did not augment the hyperthermia of CPZ, although it has been shown that cocaine can potentiate CPZ-induced hypothermia in adult rabbits (23). Bogdanski and Spector (43) have shown that CPZ can block many of the effects of cocaine, including hyperthermia. The possible reason why cocaine, in spite of its hyperthermic activity, did not increase the CPZ-induced hyperthermia may be due to its blockage by CPZ. This action demonstrated that these two agents may produce hyperthermia through different mechanisms.

Amphetamine (10 mg./Kg.) produced a temperature rise slightly greater than 0.7° and significantly different from the controls at the 99.9% level of probability. This amine is known to cause an increase in body temperature in man (44) as well as animals (3, 45). When amphetamine was given prior to CPZ in 10-day-old mice, there was no significant increase in the hyperthermic activity produced by CPZ. Again, an agent has been demonstrated which produced a temperature rise that did not significantly augment the hyperthermic response of CPZ. Askew (46) has noted that chlorpromazine partially antagonized the sharp rise in temperature following the administration of

TABLE IV.—EFFECT OF PILOCARPINE GIVEN 15 MIN. BEFORE CHLORPROMAZINE ON BODY TEMPERATURE OF 10-DAY-OLD MICE

Treatment	Mice, No.	Wt., Gm.	Initial Temp., °C.	Final Temp., °C.	Temp. Change, °C.	CPZ[b] Temp. Change, °C.	Compared to Table III Water and CPZ Controls Temp. Change, °C.	t	P
Pilocarpine-water	74	5.03	35.86	36.22	+0.36		−0.04	0.31	[a]
						+0.54			
Pilocarpine-CPZ	75	5.49	35.51	36.41	+0.90		−0.70	4.53	0.001

[a] No significance. [b] Chlorpromazine.

TABLE V.—EFFECT OF VARIOUS DRUGS GIVEN 15 MIN. BEFORE CHLORPROMAZINE ON THE BODY TEMPERATURE OF 10-DAY-OLD MICE

Treatment	Mice, No.	Wt., Gm.	Initial Temp., °C.	Final Temp., °C.	Temp. Change, °C.	CPZ[b] Temp. Change, °C.	Compared to Table III Water and CPZ Controls Temp. Change, °C.	t	P
Iproniazid-water	31	4.75	35.65	36.22	+0.57		+0.17	1.07	[a]
Iproniazid-CPZ	31	4.73	35.92	37.90	+1.98	+1.41	+0.38	2.02	0.1
Cocaine-water	33	5.13	35.59	36.28	+0.69		+0.29	1.73	0.1
Cocaine-CPZ	28	5.04	35.51	37.01	+1.50	+0.81	−0.10	0.49	[a]
dl-Amphetamine-water	35	4.87	35.26	36.39	+1.13		+0.73	4.43	0.001
dl-Amphetamine-CPZ	34	5.33	34.61	36.43	+1.82	+0.69	+0.22	1.05	[a]
Tripelennamine-water	31	4.49	34.51	35.13	+0.62	+1.33	+0.22	1.20	[a]
Tripelennamine-CPZ	34	4.92	34.94	36.89	+1.95		+0.35	1.65	[a]
Reserpine-water	31	4.78	35.05	35.75	+0.70	+1.21	+0.30	1.73	0.1
Reserpine-CPZ	35	5.43	35.23	37.14	+1.91		+0.31	1.59	[a]
Insulin-water	35	5.09	34.69	35.31	+0.62	+0.65	+0.22	1.20	[a]
Insulin-CPZ	31	4.53	34.86	36.13	+1.27		−0.33	1.66	[a]
Sodium cyanide-water	30	4.36	34.38	34.81	+0.43	+0.31	+0.03	0.18	[a]
Sodium cyanide-CPZ	32	4.14	34.62	35.36	+0.74		−0.86	4.19	0.001
LSD[c]-water	31	4.22	34.53	35.00	+0.47	+0.72	+0.07	0.42	[a]
LSD-CPZ	30	4.42	35.09	36.28	+1.19		−0.41	2.04	0.05
BOL[d]-water	31	4.17	34.82	35.56	+0.74	+0.12	+0.34	2.02	0.10
BOL-CPZ	32	4.33	35.36	36.22	+0.86		−0.74	3.72	0.001

[a] No significance. [b] Chlorpromazine. [c] Lysergic acid diethylamide. [d] Brom-lysergic acid diethylamide.

TABLE VI.—EFFECT OF CHLORPROMAZINE AND INSULIN ON THE BLOOD SUGAR OF 10-DAY-OLD MICE

Treatment	Determinations. No.	Av. mg. % with S. D.	t	P
Water-water	13	131 ± 32		
Insulin-water	13	62 ± 24	5.71	0.001
Insulin-chlorpromazine	15	55 ± 11	0.96	[a]

[a] No significance.

amphetamine in mice, and it is believed by Fabinyi-Szebehely and Szebehely (47) that the hyperthermic responses of amphetamine are central in origin. A central antagonism is believed to exist between the two drugs, thereby providing evidence for the existence of different mechanisms of action for the agents involved.

No significant effect on body temperature in 10-day-old mice was found when tripelennamine was given at a dosage level of 10.5 mg./Kg. Although this drug is known to potentiate CPZ-induced hypothermia in adult animals at this dose (22), no significant effect on the hyperthermia caused by CPZ in 10-day-old mice was noted.

Reserpine, when administered at a dosage level of 20 mg./Kg., produced a 0.3° rise. The probability of its occurrence was at the 90% level. In adult animals, reserpine is known to produce a fall in body temperature, an effect which has been observed in man (48), rabbits (49), rats (50), mice (51), and monkeys (52). Moore (53), while working with 8-day-old kittens, noted a transient thermogenic response to reserpine which he believed arose as a result of norepinephrine release from sympathetic nerve terminals. This could possibly be the reason for the slight temperature rise observed after reserpine administration in the 10-day-old mice in this experiment. Reserpine, when given prior to CPZ, had no effect on the subsequent CPZ-induced hyperthermia in 10-day-old mice. Thus, despite the fact that Hoffman (20) found that reserpine inhibited the CPZ temperature drop in adult animals, it had no effect in modifying the hyperthermic response of CPZ in 10-day-old animals. The possible reason why reserpine did not increase the hyperthermia produced by CPZ could be due to the ability of CPZ to block the release of 5-hydroxytryptamine, dopamine, and norepinephrine after the administration of reserpine (54).

The administration of insulin injection U.S.P. (4 I.U./Kg.) had no significant effect on the body temperature of 10-day-old mice. Although LeBlanc (24) has shown a potentiation of CPZ-induced hypothermia in adult animals by insulin, this study demonstrated that there was no significant effect of this drug in altering the hyperthermic response of CPZ in 10-day-old mice. The effect of insulin in this experiment on the blood sugar level of 10-day-old mice is presented in Table VI. Insulin was shown to lower significantly the blood sugar compared to the controls. The administration of CPZ 15 min. after insulin failed to exert an ameliorating action on the blood sugar level, despite the fact that CPZ alone has the ability to produce hyperglycemia (55, 56). These results are similar to those obtained by LeBlanc (24), who noted that simultaneous injections of CPZ and insulin produced a marked hypoglycemia which resembled that evoked by insulin alone.

Sodium cyanide, when given at a dosage level of 0.66 mg./Kg., had an insignificant effect on the body temperature of 10-day-old mice. When this compound was administered 15 min. before CPZ, it greatly antagonized the hyperthermia usually noted with CPZ in immature mice. It is believed by LeBlanc (57) that CPZ-induced hypothermia in adult rats is caused by the release of certain substances from mast cells and leucocytes. LeBlanc (21) further demonstrated that cyanide prevented this cell disruption and also inhibited the hypothermic response of CPZ. The marked hyperthermia obtained by CPZ in 10-day-old mice was inhibited by sodium cyanide and may be related to substances which are released from mast cells and leucocytes; but these substances must react differently in young animals, for this study demonstrated a rise in temperature rather than a fall, as noted in adult animals.

It has been observed that lysergic acid diethylamide, when given to 10-day-old mice at a dosage level of 0.75 mg./Kg., had no effect on body temperature. It has been previously shown that lysergic acid diethylamide can produce temperature changes in adult animals (19, 58). The possible explanation for the lack of temperature effects of this compound in 10-day-old mice may be due to a lack of full development of a portion of the temperature regulating area. The administration of lysergic acid diethylamide prior to CPZ had an inhibitory effect on the hyperthermic response of CPZ calculated to be probable at the 95% level. An antagonism of the behavioral and temperature effects of lysergic acid diethylamide by CPZ has been reported (59, 60). This antagonism may be the cause of the inhibition of the temperature effects of CPZ in 10-day-old mice.

Brom-lysergic acid diethylamide (10 mg./Kg.) caused a slight rise in the body temperature of 10-day-old mice significant at a 90% level of probability. When this compound was given before CPZ, there was a significant inhibition of hyperthermia due to CPZ which reached the probability level of 99.9%. Although BOL has actions which are similar to LSD_{25}'s activity, generally it is believed that BOL is devoid of psychic activity and possesses a central depressant action rather than the stimulatory action characteristic of LSD_{25} (25, 61). Recently, a lysergic acid-like delirium following the ingestion of a small amount of the brom analog has been reported (62). It is believed by these authors that these compounds are therefore similar, differing only in the degree of activity produced. The results of this investigation have revealed that both compounds significantly inhibited CPZ-induced hyperthermia and varied only in the intensity of the respective responses.

As a result of these studies, it was not possible to determine the precise mechanism by which chlor-

promazine exerted its hyperthermic activity, although it can be assumed that changes in skeletal muscle tone appear to play an insignificant role. The ability of sodium cyanide to prevent the hyperthermic response of chlorpromazine is unclear, but possibly it may be related to the prevention of mast cell disruption. It is theorized that chlorpromazine exerts a predominately central action because the chlorpromazine-induced hyperthermia was antagonized by certain centrally acting drugs employed in this investigation.

SUMMARY

1. The simultaneous administration of *dextro*-tubocurarine and chlorpromazine had no effect upon the pyrotropic activity of chlorpromazine in 10- and 38-day-old mice.

2. A metabolite of chlorpromazine, chlorpromazine sulfoxide, produced a profound temperature rise in 10-day-old mice when given at a high dosage level.

3. Nalorphine, which effectively blocked morphine-induced hyperthermia in 10-day-old mice, failed to modify CPZ-induced hyperthermia in this age group.

4. Pilocarpine inhibited the chlorpromazine temperature rise in 10-day-old mice by approximately 50%.

5. Drugs which increased the body temperature of 10-day-old mice when administered alone were cocaine, *dl*-amphetamine, reserpine, and bromlysergic acid diethylamide; while iproniazid, tripelennamine, insulin, sodium cyanide, and lysergic acid diethylamide had no effect on this age group. Many of these agents, despite their individual actions on body temperature, had no effect on the hyperthermic responses of chlorpromazine. These were cocaine, *dl*-amphetamine, tripelennamine, reserpine, and insulin. Iproniazid caused a potentiation of the temperature rise produced by chlorpromazine in 10-day-old mice; while this action was inhibited by sodium cyanide, lysergic acid diethylamide, and brom-lysergic acid diethylamide.

6. Chlorpromazine did not significantly modify the hypoglycemic response of insulin in 10-day-old mice.

7. It is theorized that the hyperthermic activity of chlorpromazine in 10-day-old mice may be related to a direct action of the phenothiazine on the maturing hypothalamic thermoregulator centers.

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