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Influence of Several Autonomic Drugs on Sodium Nitroprusside and Oxotremorine-Induced Hypothermia in Immature and Mature Mice

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Abstract □ Sodium nitroprusside and oxotremorine each produced body temperature depression that was independent of age. Atropine inhibited oxotremorine hypothermia in both age groups, but was ineffective in modifying thermal responses to nitroprusside in both age categories. Pilocarpine administration did not alter oxotremorine activity at either age level, while nitroprusside hypothermia was enhanced and partially reversed, respectively, in immature and mature mice. Nicotine and tetraethylammonium chloride were unable to modify hypothermia produced by oxotremorine and nitroferricyanide in adult mice. Nicotine enhanced nitroprusside hypothermia in 10-day-old mice, while temperature depression due to oxotremorine was unaffected in the same age group. Administration of tetraethylammonium chloride to immature animals treated with oxotremorine and nitroprusside resulted in greater temperature depression. Chlorpromazine, which produced no change in oxotremorine or nitroprusside hypothermia in 10-day-old mice, partially blocked oxotremorine-induced hypothermia in mature animals; the weak parasympatholytic phenothiazine produced no significant difference in hypothermia when given prior to nitroprusside in the adult group.

Keyphrases □ Hypothermia, mice—sodium nitroprusside, oxotremorine induced □ Oxotremorine, sodium nitroprusside-induced hypothermia—autonomic drugs effect □ Autonomic drugs effect—oxotremorine, sodium nitroprusside-induced hypothermia □ Age of mice, effect—induced hypothermia

The mammalian body "thermostat," because of its vast complexity, is susceptible to the action of various drugs and agents, particularly those that mimic or interfere with neurotransmitter substances. Oxotremorine, the active metabolite of tremorine, was shown to produce hypothermia in rodents through a central cholinergic mechanism (1, 2).

Age has been shown to modify the effects of certain centrally acting drugs in rats (3, 4). These animals are born functionally immature with poorly developed nervous systems. Bagdon and Mann (5) demonstrated the age factor in mice with the drug chlorpromazine. The hypothermia normally seen in mature mice in response to chlorpromazine administration was reversed in immature animals to marked hyperthermia.

During routine screening procedures in this laboratory, it was discovered that sodium nitroprusside induces a pronounced fall in the body temperature of mice. It was the purpose of this investigation, therefore, to compare the hypothermia caused by oxotremorine with that induced by sodium nitroprusside with respect to alteration by several autonomic drugs in order to ascertain the mechanism of action and to observe the effects of age on the thermic response.

EXPERIMENTAL

Young (10-day-old) and adult male mice (1398) of the Huntingdon Farms (HTF) strain were utilized in this investigation.

The drugs employed were as follows: oxotremorine,[1] sodium nitroprusside,[2] atropine sulfate,[3] pilocarpine nitrate,[3] nicotine,[4] tetraethylammonium chloride,[5] and chlorpromazine hydrochloride.[6] All solutions were freshly prepared with sterile water distilled in the laboratory.

A model 43 Telethermometer equipped with a No. 402 probe[7] was used for obtaining oral and rectal temperatures. The animals were kept at a constant environmental temperature of 23–24° for 24 hr. prior to and including the time of the experimental course.

All injections were given as a fixed dose in a volume of 0.05 ml. for immature mice and 0.25 ml. for mature mice. Calculation of doses for the immature mice was based upon an average weight of 4.5 g. obtained from preliminary experiments in this laboratory. Mature male mice, weighing from 20 to 25 g., received doses calculated on the basis of 22.5 g./mouse.

The agonists with their concentration and dose were: oxotremorine (0.0045%; 0.5 mg./kg.) and sodium nitroprusside (0.045%; 5 mg./kg.).

[1] Nutritional Biochemicals Corp.
[2] Baker Chemical Co., Phillipsburg, N. J.
[3] Merck & Co., Inc., Rahway, N. J.
[4] Eastman Organic Chemicals, Rochester, N. Y.
[5] Etamon, Parke, Davis & Company, Detroit, Mich.
[6] Thorazine, Smith Kline & French Laboratories, Philadelphia, Pa.
[7] Yellow Springs Instrument Co.

Table I—Effect of Sodium Nitroprusside or Oxotremorine (Agonists) Given 15 Min. after Saline (Antagonist) on the Body Temperature of Mature Mice

Treatment	Mice, No.	Weight, g.	Initial Temperature	Antagonist Temperature[a]	Agonist Temperature[b]	Temperature Change[c]	Compared to Saline: Drug-[d] Induced Change	Compared to Saline: t	Compared to Saline: P
Saline–saline	30	22.0	37.53°	37.77°	37.61°	−0.16°			
Saline–NTPR[e]	107	23.1	37.43°	37.91°	34.37°	−3.54°	−3.38°	26.06	0.001
Saline–OTMN[f]	114	22.5	37.85°	37.99°	34.28°	−3.71°	−3.55°	22.65	0.001

[a] Temperature 15 min. after antagonist injection. [b] Temperature 15 min. after agonist injection. [c] Antagonist–agonist temperature difference. [d] Sodium nitroprusside or oxotremorine. [e] Sodium nitroprusside. [f] Oxotremorine.

Table II—Effect of Sodium Nitroprusside or Oxotremorine (Agonists) Given 15 Min. after Saline (Antagonist) on the Body Temperature of Immature Mice

Treatment	Mice, No.	Weight, g.	Initial Temperature	Antagonist Temperature[a]	Agonist Temperature[b]	Temperature Change[c]	Compared to Saline: Drug-[d] Induced Change	Compared to Saline: t	Compared to Saline: P
Saline–saline	40	4.71	26.70°	27.57°	27.79°	+0.22°			
Saline–NTPR[e]	91	4.67	26.48°	27.33°	26.46°	−0.87°	−1.09°	9.09	0.001
Saline–OTMN[f]	103	4.85	26.74°	27.51°	26.21°	−1.30°	−1.52°	13.15	0.001

[a] Temperature 15 min. after antagonist injection. [b] Temperature 15 min. after agonist injection. [c] Antagonist–agonist temperature difference. [d] Sodium nitroprusside or oxotremorine. [e] Sodium nitroprusside. [f] Oxotremorine.

Concentrations and doses of the antagonists used in the experiment were: atropine sulfate (0.045%; 5 mg./kg.), pilocarpine nitrate (0.0009%; 0.1 mg./kg.), nicotine (0.0023%; 0.25 mg./kg.), tetraethylammonium chloride (0.0023%; 0.25 mg./kg.), and chlorpromazine hydrochloride (0.009%; 1 mg./kg.).

The animals were grouped according to age and treatment regimen. Experiments were performed at the same time each day to minimize temperature variation.

Groups of 12 animals were weighed individually on a triple-beam Ohaus balance, and their weights were recorded at the start of the experiment. Immediately following weight determination, the animals were confined singly in beakers for a 2-hr. period, during which food and water deprivation was accomplished to preserve metabolic stability. Following the 2-hr. conditioning period, oral (immature) and rectal (mature) temperatures were recorded. In the younger mice, oral temperatures were noted because their small size did not permit taking rectal temperatures without extreme discomfort to the animal. Subcutaneous administration of the antagonist occurred immediately after initial temperature recordings, whereupon the mice were returned to their containers for 15 min. At the end of this period, temperatures were again noted and the agonist was injected intraperitoneally. Fifteen minutes after the latter challenge, final temperatures were recorded. Control animals were subjected to an identical treatment procedure with the exception that either antagonist or agonist was replaced with saline.

In the comparison of mean temperature changes (*i.e.*, temperature before and after administration of agonist), statistical significance was determined by the use of Student's t distribution. Temperature differences were considered to be significant at the probability level of 5% or less. Temperature alterations attributed to antagonist or agonist were ascertained through a comparison with their saline counterparts. Antagonist effect on agonist hypothermia was determined through comparison of saline–agonist with antagonist–agonist treatments.

RESULTS AND DISCUSSION

The effects of sodium nitroprusside on the body temperature of mature male and immature (mixed sex) albino mice at a dosage level of 5 mg./kg. are outlined in Tables I and II. Temperature changes attributed to the agonist were significant for both age groups, with probability levels reaching 99.9%. In 107 mature mice, sodium nitroprusside caused an average temperature depression

Table III—Effect of Various Autonomic Drugs Given 15 Min. before Sodium Nitroprusside on the Body Temperature of Mature Mice

Treatment	Mice, No.	Weight, g.	Initial Temperature	Antagonist Temperature[b]	Agonist Temperature[c]	Temperature Change[d]	NTPR[e] Temperature Change	Compared to Table I Saline and NTPR Controls: Temperature Change	Compared to Table I Saline and NTPR Controls: t	Compared to Table I Saline and NTPR Controls: P
Atropine–saline	30	24.4	37.76°	38.10°	37.73°	−0.37°		−0.21°	2.19	0.05
							−3.45°			
Atropine–NTPR	30	22.2	37.64°	37.87°	34.05°	−3.82°		−0.28°	1.98	0.05
Pilocarpine–saline	30	21.5	37.48°	37.98°	37.80°	−0.18°		−0.02°	0.21	–[a]
							−2.92°			
Pilocarpine–NTPR	30	24.2	36.94°	37.61°	34.51°	−3.10°		+0.44°	3.05	0.01
Nicotine–saline	30	22.0	37.74°	38.17°	38.03°	−0.14°		+0.02°	0.10	–[a]
							−3.50°			
Nicotine–NTPR	30	23.3	37.71°	38.10°	34.46°	−3.64°		−0.10°	0.64	–[a]
TEA[f]–saline	30	24.0	37.45°	37.56°	37.40°	−0.16°		0.0°	0.10	–[a]
							−3.10°			
TEA–NTPR	30	23.2	38.17°	38.37°	35.11°	−3.26°		+0.28°	1.95	0.10
CPZ[g]–saline	30	23.6	37.05°	37.13°	35.69°	−1.44°		−1.28°	11.35	0.001
							−2.03°			
CPZ–NTPR	30	24.0	37.42°	37.70°	34.23°	−3.47°		+0.07°	0.53	–[a]

[a] No significance. [b] Temperature 15 min. after antagonist injection. [c] Temperature 15 min. after agonist injection. [d] Antagonist–agonist temperature difference. [e] Sodium nitroprusside. [f] Tetraethylammonium chloride. [g] Chlorpromazine HCl.

Table IV—Effect of Various Autonomic Drugs Given 15 Min. before Sodium Nitroprusside on the Body Temperature of Immature Mice

Treatment	Mice, No.	Weight, g.	Initial Temperature	Antagonist Temperature[b]	Agonist Temperature[c]	Temperature Change[d]	NTPR[e] Temperature Change	Compared to Table II Saline and NTPR Controls Temperature Change	*t*	*P*
Atropine–saline	30	4.88	26.79°	27.54°	27.44°	−0.10°		−0.32°	2.81	0.05
							−0.74°			
Atropine–NTPR	30	4.93	26.27°	27.28°	26.44°	−0.84°		+0.03°	0.18	–[a]
Pilocarpine–saline	30	4.84	26.94°	27.60°	27.70°	+0.10°		−0.12°	0.90	–[a]
							−1.35°			
Pilocarpine–NTPR	30	4.65	27.13°	28.08°	26.83°	−1.25°		−0.38°	2.73	0.05
Nicotine–saline	30	4.59	26.68°	27.70°	28.42°	+0.72°		+0.50°	5.08	0.001
							−2.50°			
Nicotine–NTPR	34	4.90	26.79°	28.32°	26.54°	−1.78°		−0.91°	6.82	0.001
TEA[f]–saline	38	4.97	26.02°	26.95°	27.64°	+0.69°		+0.47°	4.17	0.001
							−1.96°			
TEA–NTPR	30	4.74	26.62°	27.57°	26.30°	−1.27°		−0.40°	2.89	0.05
CPZ[g]–saline	30	4.71	26.12°	27.57°	27.84°	+0.27°		+0.05°	0.52	–[a]
							−1.37°			
CPZ–NTPR	27	4.97	27.16°	27.94°	26.84°	−1.10°		−0.23°	1.60	–[a]

[a] No significance. [b] Temperature 15 min. after antagonist injection. [c] Temperature 15 min. after agonist injection. [d] Antagonist–agonist temperature difference. [e] Sodium nitroprusside [f] Tetraethylammonium chloride. [g] Chlorpromazine HCl.

of 3.38°, while 91 immature animals exhibited a mean decrease in body temperature of 1.09°.

At the dosage level of 0.5 mg./kg., oxotremorine gave mean drops of 3.55 and 1.52°, respectively, in 114 mature and 103 immature albino mice. Again, these temperature changes were significantly different from the controls at the probability level of 99.9%.

A paucity of information exists in the literature with respect to age variation for oxotremorine. Bowman and Osuide (6) have shown the hypothermic action of tremorine to be independent of age in 4-day-old chicks. It has been shown in this investigation that the intraperitoneal administration of oxotremorine elicited body temperature depression for both age groups.

Subcutaneous injections of atropine sulfate (5 mg./kg.) produced a significant decrease from control values in the body temperature of mature animals (Table III). This 0.21° drop was probably mediated through the ganglionic blocking ability of the alkaloid (7). When this agent was administered prior to sodium nitroprusside, a significant increase in hypothermia (0.28°) was realized. These results indicate that the increased hypothermia was representative of positive summation (agonist plus antagonist).

Ten-day-old mice responded to the action of atropine in a manner similar to that of the mature group (Table IV). A temperature depression, which was 0.32° lower than the saline control value of +0.22°, was significant at the 95% probability level. Temperature depression brought about by the combination of atropine and sodium nitroprusside in this age group was not significantly different from saline–sodium nitroprusside treatment. The lack of positive summation for atropine and this agonist indicates that nitroprusside may block the gangliolytic action of atropine. On the other hand, atropine may produce a partial blockade of nitroprusside hypothermia.

From the results in Table III, it can be seen that pilocarpine, when injected subcutaneously at a dosage level of 0.1 mg./kg., was not significantly different from saline on the body temperature of the older animals. In mature mice, this cholinomimetic agent was able to reverse partially the hypothermic action of sodium nitroprusside at the probability level of 99% (Table III). It is possible that this antagonism was carried out through the capacity of pilocarpine to stimulate sympathetic ganglia and to release catecholamines from the adrenal medulla (8).

As observed in mature animals, oral temperature changes in the pilocarpine-treated juveniles were not different from the saline-treated control group, yet this diaphoretic agent was able to augment the hypothermic action of sodium nitroprusside (Table IV). It is, therefore, concluded from the results of this investigation that the effect of pilocarpine on sodium nitroprusside hypothermia varies according to age; slight antagonism occurs in the mature group, while the immature animals show hypothermic enhancement.

In adult mice treated with nicotine (0.25 mg./kg.), no significant effect was noted. As shown in Table III, nicotine was not able to modify hypothermia produced by sodium nitroprusside.

Table V—Effect of Various Autonomic Drugs Given 15 Min. before Oxotremorine on the Body Temperature of Mature Mice

Treatment	Mice, No.	Weight, g.	Initial Temperature	Antagonist Temperature[b]	Agonist Temperature[c]	Temperature Change[d]	OTMN[e] Temperature Change	Compared to Table I Saline and OTMN Controls Temperature Change	*t*	*P*
Atropine–saline	30	24.4	37.76°	38.10°	37.73°	−0.37°		−0.21°	2.19	0.05
							−0.20°			
Atropine–OTMN	30	24.5	37.02°	37.13°	36.56°	−0.57°		+3.14°	18.04	0.001
Pilocarpine–saline	30	21.5	37.48°	37.98°	37.80°	−0.18°		−0.02°	0.21	–[a]
							−3.86°			
Pilocarpine–OTMN	30	22.3	37.94°	37.97°	33.93°	−4.04°		−0.33°	1.86	0.1
Nicotine–saline	30	22.0	37.74°	38.17°	38.03°	−0.14°		+0.02°	0.10	–[a]
							−3.41°			
Nicotine–OTMN	30	23.9	38.14°	38.45°	34.90°	−3.55°		+0.16°	0.95	–[a]
TEA[f]–saline	30	24.0	37.45°	37.56°	37.40°	−0.16°		0.0°	0.10	–[a]
							−3.55°			
TEA–OTMN	30	23.1	38.18°	38.49°	34.78°	−3.71°		0.0°	0.04	–[a]
CPZ[g]–saline	30	23.6	37.05°	37.13°	35.69°	−1.44°		−1.28°	11.35	0.001
							−1.60°			
CPZ–OTMN	30	22.4	37.35°	37.51°	34.47°	−3.04°		+0.67°	3.94	0.001

[a] No significance. [b] Temperature 15 min. after antagonist injection. [c] Temperature 15 min. after agonist injection. [d] Antagonist–agonist temperature difference. [e] Oxotremorine. [f] Tetraethylammonium chloride. [g] Chlorpromazine HCl.

Table VI—Effect of Various Autonomic Drugs Given 15 Min. before Oxotremorine on the Body Temperature of Immature Mice

Treatment	Mice, No.	Weight, g.	Initial Temperature	Antagonist Temperature[b]	Agonist Temperature[c]	Temperature Change[d]	OTMN[e] Temperature Change	Compared to Table II Saline and OTMN Controls Temperature Change	*t*	*P*
Atropine–saline	30	4.88	26.79°	27.54°	27.44°	−0.10°		−0.32°	2.81	0.05
							+0.17°			
Atropine–OTMN	38	5.09	27.46°	27.94°	28.01°	+0.07°		+1.37°	10.54	0.001
Pilocarpine–saline	30	4.84	26.94°	27.60°	27.70°	+0.10°		−0.12°	0.90	–[a]
							−1.62°			
Pilocarpine–OTMN	30	4.70	26.59°	27.65°	26.13°	−1.52°		−0.22°	1.74	0.1
Nicotine–saline	30	4.59	26.68°	27.70°	28.42°	+0.72°		+0.50°	5.08	0.001
							−2.17°			
Nicotine–OTMN	30	4.90	25.35°	27.03°	25.58°	−1.45°		−0.15°	1.16	–[a]
TEA[f]–saline	38	4.97	26.02°	26.95°	27.64°	+0.69°		+0.47°	4.17	0.001
							−2.25°			
TEA–OTMN	30	4.84	26.67°	27.48°	25.92°	−1.56°		−0.26°	2.04	0.05
CPZ[g]–saline	30	4.71	26.12°	27.57°	27.84°	+0.27°		+0.05°	0.52	–[a]
							−1.44°			
CPZ–OTMN	30	4.95	26.46°	27.73°	26.56°	−1.17°		+0.13°	0.95	–[a]

[a] No significance. [b] Temperature 15 min. after antagonist injection. [c] Temperature 15 min. after agonist injection. [d] Antagonist–agonist temperature difference. [e] Oxotremorine. [f] Tetraethylammonium chloride. [g] Chlorpromazine HCl.

In Table IV, nicotine has been shown to produce a rise in the body temperature of 10-day-old mice at the dosage level of 0.25 mg./kg. In 30 animals treated with this compound, a mean elevation of 0.5° was observed, which was significant at the 99.9% probability level. When administered 15 min. before sodium nitroprusside, this agent approximately doubled agonist-induced temperature depression. The possibility exists that the agonist drug may have inhibited nicotine pyresis in these animals. It is proposed that the immature mammalian thermoregulatory system modifies the effect of nicotine on sodium nitroprusside temperature reduction.

Tetraethylammonium chloride administration, at a dosage level of 0.25 mg./kg., resulted in no alteration of the thermoregulatory ability of adult mice. When administered prior to sodium nitroprusside, a very slight temperature inhibition of borderline significance was observed. In young animals of this species, tetraethylammonium chloride produced a significant rise in body temperature, amounting to 0.47°. As observed with nicotine, this ganglionic blocking agent further enhanced the temperature depression of sodium nitroprusside; again, the possibility exists that the agonist drug may have inhibited the hyperthermia caused by tetraethylammonium chloride.

It is probable that nicotine and tetraethylammonium chloride act in the same fashion because they both produced qualitatively similar responses when administered alone or prior to sodium nitroprusside. It was reported that these two compounds have in common an ability to stimulate the release of epinephrine from the adrenal medulla (9). It is possible that these agents may produce hyperthermia in young animals through this mechanism and that the administration of sodium nitroprusside inhibits this response. Potentiation of nitroprusside hypothermia may result from inhibition of sympathetic ganglia in the presence of a poorly developed thermoregulatory system.

Chlorpromazine hydrochloride has been shown to achieve a temperature deficit of 1.28° in the mature age group. These results agree with those of Kopera and Armitage (10), who demonstrated the ability of chlorpromazine to cause hypothermia in mice. From the results given in Table III, it can be seen that either nitroprusside blocked the temperature effects due to chlorpromazine or the latter agent caused a partial reversal of nitroprusside hypothermia. Chlorpromazine did not alter the body temperature in young animals and failed to alter the action of nitroprusside.

Tables V and VI show that the effect of atropine sulfate on oxotremorine temperature depression is similar for both age groups. In both cases, a complete inhibition of oxotremorine hypothermia occurred and was significant at the probability level of 99.9%. Lomax and Jenden (11) blocked the hypothermic response of oxotremorine in rats with atropine. The observations of these investigators have been confirmed by this study.

The administration of pilocarpine nitrate (0.1 mg./kg.) 15 min. prior to oxotremorine caused a very slight enhancement of agonist hypothermia in both age groups; it was of borderline significance in each case (Tables V and VI). Therefore, the effect of age was not demonstrated for pilocarpine modification of oxotremorine hypothermia.

Oxotremorine-induced temperature drops were not modified by the prior administration of nicotine in mature mice. The immature animals showed no significant change in agonist hypothermic response when treated with oxotremorine in combination with nicotine. Because nicotine caused hyperthermia in immature mice (Table VI), it is possible that oxotremorine inhibited this rise in temperature. Conversely, nicotine could have enhanced oxotremorine hypothermia (negative summation).

Age has been shown to modify effects of tetraethylammonium chloride on oxotremorine-induced temperature depression. In the older group of mice, the administration of tetraethylammonium chloride did not affect the hypothermia caused by oxotremorine. Everett *et al.* (12) demonstrated that this antagonist was ineffective in blocking the temperature-lowering effect of tremorine in mice. These results lend support to their claim that the hypothermic action of tremorine is central in origin. A slight increase in the agonist hypothermic response was noted in immature mice after the administration of tetraethylammonium chloride (Table VI). A significant difference was present at the probability level of 95%. Oxotremorine may also inhibit the thermogenic effect of tetraethylammonium chloride in this age group.

A partial blockade of oxotremorine activity by chlorpromazine was observed in the mature group, which was probably caused by the weak parasympatholytic effect of the phenothiazine (13, 14). Conversely, it is also possible that oxotremorine may have interfered with the hypothermia elicited by chlorpromazine. Preadministration of chlorpromazine in the younger animals produced no change in the hypothermia due to oxotremorine. The effect of chlorpromazine on oxotremorine-induced hypothermia has thus been shown to be modified by age.

Although the means by which sodium nitroprusside causes a fall in body temperature has not been elucidated as a result of this study, a comparison of its activity with that of the centrally acting oxotremorine in the presence of various autonomic drugs in mature mice has provided strong evidence for a different mechanism of action. While the administration of atropine resulted in a complete blockage of oxotremorine-induced depression of body temperature, no such inhibition was observed with sodium nitroprusside following the parasympatholytic agent. On the other hand, pilocarpine failed to modify oxotremorine hypothermia, whereas this parasympathomimetic partially inhibited nitroprusside hypothermia.

SUMMARY AND CONCLUSIONS

1. Sodium nitroprusside and oxotremorine each produced a hypothermic response that was independent of age in the mouse.

2. The effect of atropine on oxotremorine-induced hypothermia appeared to be uninfluenced by age. In both cases, a complete inhibition of agonist hypothermia occurred.

3. The prior administration of atropine enhanced sodium nitroprusside-induced hypothermia, indicating the existence of positive summation in the mature group. This antagonist was unable to alter nitroprusside hypothermia in immature animals. Nitroprusside may block atropine-induced changes.

4. Pilocarpine effects on oxotremorine-induced hypothermia were unaffected by age.

5. The action of pilocarpine on sodium nitroprusside-induced hypothermia was age related, because slight antagonism occurred in the mature group while immature animals showed hypothermic enhancement.

6. The influence of nicotine on sodium nitroprusside-induced hypothermia was affected by age. Agonist hypothermia was not modified in the mature group; hypothermia was enhanced in the immature group. Nicotine pyresis may be antagonized in the younger group.

7. Oxotremorine temperature depression was not modified by nicotine in mature mice. In the immature animals, this agonist may have inhibited nicotine hyperthermia; conversely, nicotine may have enhanced oxotremorine hypothermia (negative summation).

8. Tetraethylammonium chloride produced effects on sodium nitroprusside hypothermia which were qualitatively similar to those of nicotine. It has been suggested that these antagonistic drugs act in a comparable manner.

9. Age was shown to modify the effect of tetraethylammonium chloride on oxotremorine-induced temperature depression. Agonist hypothermia was not affected by tetraethylammonium chloride in the mature group. Slight enhancement was shown in the immature animals. Oxotremorine may have inhibited tetraethylammonium chloride hyperthermia.

10. Sodium nitroprusside-induced hypothermia was not affected by chlorpromazine in the immature age group. In the mature animals, either nitroprusside blocked chlorpromazine hypothermia or the latter agent partially reversed nitroprusside hypothermia.

11. Chlorpromazine demonstrated no effect on oxotremorine-induced hypothermia in the immature animals. Partial antagonism was noted in the mature group. Oxotremorine may have inhibited chlorpromazine-induced hypothermia.

12. Evidence has been provided that oxotremorine and sodium nitroprusside each produce hypothermia in mature mice *via* a different mechanism. The parasympathomimetic agent, pilocarpine, did not alter oxotremorine-induced hypothermia, while this drug partially inhibited that of sodium nitroprusside. Conversely, atropine inhibited hypothermia attributed to oxotremorine but failed to modify that of nitroprusside.

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