Chlorpromazine and Anesthetic Agents on Tissue Non-Protein Sulfhydryl Compounds in Normothermic and Hypothermic Rats.* (22077)

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Previous work(1,2) has shown that cold and restraint lower the concentration of non-protein sulfhydryl compounds (NPSH). Adrenalin also decreases liver and kidney NPSH (3) and it was later observed that some anesthetics alter liver NPSH. To determine the effect of anesthetics and chlorpromazine on tissue NPSH and the effect of cold on tissue NPSH of anesthetized animals, the NPSH in liver and kidney was measured on normothermic and hypothermic rats.

Methods and materials. The 210 adult Sprague-Dawley female rats were divided into the following groups: 52 control animals; 18 animals were given chlorpromazine hydrochloride; 17 were anesthetized with ether; 14 with nitrous oxide, 16 with phenobarbital sodium (phenobarbital), 39 with pentobarbital sodium (nembutal), 38 with thiopental sodium (pentothal), and 16 with thiamylal sodium (surital). Each group of treated animals was divided into 2 categories. Approximately one-half of the animals in each group was maintained at normal body temperature while the remaining animals were exposed in a cold room (0°C ± 1°C) and body temperature fall was regulated at 5°C per hour. All exposures were 4 hours in duration so that the body temperature of the hypothermic animals was approximately 18°C at the time of sacrifice. Chlorpromazine was injected intraperitoneally. These animals were in very light anesthesia exhibiting some reflex response to deep pain. Animals exposed to gaseous anesthetics (ether and nitrous oxide) were placed in a large glass chamber and the anesthetics and oxygen admitted at a rate to keep animals in very light surgical anesthesia. If animals were more deeply anesthetized, they would not survive the 4-hour exposure. Animals anesthetized with the barbiturates were injected intraperitoneally with phenobarbital, 20 mg/kg; thiamylal, 25 mg/kg; pentobarbital, 70 mg/kg; thiopental, 75 mg/kg initially, and thereafter sufficient to keep the animal in a relaxed state. In the barbiturate anesthesia experiments, the animals were maintained in surgical plane of anesthesia. The animals were then sacrificed and the organs removed immediately and frozen in dry ice. The NPSH was measured by a modification of the method of Benesch and Benesch(4).

Results. As may be seen from Table I, all anesthetized animals experienced a drop in liver NPSH. In the groups anesthetized with phenobarbital, thiamylal and thiopental, there was a significantly greater drop in the hypothermic categories than in the normothermic categories. However, in the groups given chlorpromazine, ether, nitrous oxide, and pentobarbital, exposure to cold did not have the usual effect of further decreasing the liver NPSH.

Ether, nitrous oxide, phenobarbital, and pentobarbital produced a significant decrease in kidney NPSH. Thiamylal and chlorpromazine had no effiect; whereas thiopental produced a slight increase. Cold had no effect on the kidney NPSH of animals given ether, nitrous oxide, phenobarbital and thiamylal. The thiopental and chlorpromazine groups exposed to cold showed a decrease in kidney NPSH.

Thiopental appeared to increase the blood NPSH (105 ± 7.1 μM% to 133 ± 4.8 μM%, P = <.05). No significant change in blood NPSH was observed when chlorpromazine hydrochloride was administered.

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TABLE I. Effect of Chlorpromazine and Anesthetics on Liver and Kidney Non-Protein Sulfhydryl Compounds in Normothermic and Hypothermic Rats.

Treatment	Body temp., °C	No. of animals	μM % NPSH in liver	Probability† With control	Probability† Hypothermic with normothermic	μM % NPSH in kidney	Probability With control	Probability Hypothermic with normothermic
Control	39	52	852 ± 7*			508 ± 6		
Chlorpromazine hydrochloride	20	9	567 ± 15		<.20	396 ± 17		<.01
	39	9	604 ± 21	<.01		499 ± 18	<.50	
Ether	18	10	693 ± 17	"	<.10	421 ± 17		>.50
	39	7	619 ± 28			432 ± 28	<.05	
Nitrous oxide	18	8	579 ± 21	"	"	406 ± 21		>.40
	39	6	488 ± 24			404 ± 11	<.01	
Phenobarbital sodium	18	8	597 ± 24	"	<.01	500 ± 24		>.05
	39	8	705 ± 13			450 ± 17	<.02	
Pentobarbital sodium	18	19	636 ± 12	"	>.10	401 ± 35		>.10
	39	20	655 ± 20			341 ± 23	<.01	
Thiopental sodium	18	20	540 ± 15	"	<.01	415 ± 10		<.01
	39	18	658 ± 18			551 ± 17	<.05	
Thiamylal sodium	18	8	582 ± 19	"	"	512 ± 16		>.50
	39	8	679 ± 16			516 ± 17	>.50	

* Stand. error of the mean. † P is probability derived from t values where $t = \frac{\text{Difference between means}}{\text{Stand. error of difference}}$.

Discussion. Hypothermia and stress depress metabolism in rats(5) and also decrease NPSH in actively metabolizing tissues(1,2). Since many anesthetic agents depress metabolism and produce a tendency toward hypothermia, it is not surprising that anesthetics decrease tissue NPSH. Adrenalin has been shown to lower the tissue NPSH(3). The sympatho-adrenal system is activated by most anesthetics(6), thus the lowered levels of the liver NPSH noted in these experiments may have been due to the activation of this system.

The usual effect of cold of lowering the liver NPSH was observed in the animals anesthetized with phenobarbital, thiopental, and thiamylal. However, it appears that chlorpromazine and pentobarbital may have paralyzed the mechanism activated by cold which decreases liver NPSH. Most anesthetics which caused a lowering of kidney NPSH also prevented any further diminution by exposure to cold. The only exceptions were chlorpromazine and thiopental. Since thiopental contains a sulfur atom, it is possible that the higher kidney levels in the normothermic category may represent concentrations of sulfhydryl groups from the anesthetic in the excretory process. Increased blood levels of NPSH were also observed when this drug was given. Since thiamylal was given at only one-third the level of thiopental, this slight effect would not be seen. The decrease in kidney NPSH in the hypothermic thiopental and chlorpromazine groups is essentially the same effect as that observed when control animals were exposed to cold and restraint(7).

Summary. 1. Female rats were divided into groups and given chlorpromazine or anesthetic agents. One-half of each group was exposed to cold. The total non-protein sulfhydryl concentration (NPSH) of liver and kidney was determined and compared with similar values for control animals. Chlorpromazine and all anesthetics produced a decrease in liver NPSH. Cold further decreased the NPSH of animals anesthetized with phenobarbital, thiamylal, and thiopental; however, cold had no effect on liver NPSH of the chlorpromazine and pentobarbital groups. 2. Ether, nitrous oxide, and phenobarbital de-

creased kidney NPSH. No change was observed in the chlorpromazine and thiamylal groups, but a slight increase in kidney NPSH occurred in the thiopental group. The possible relationship of anesthetics on tissue NPSH and metabolism is discussed.

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Effect of Administered Ascorbic Acid on Nitrogen Metabolic Response to Thermal Trauma. (22078)

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Numerous investigators have confirmed Cuthbertson's(1) observations of an increase in urinary nitrogen excretion by injured patients and animals. Lowered excretion of ascorbic acid, decreased adrenal and plasma ascorbic acid content, and decreased tissue ascorbic acid "saturation" as judged by load tests have also been observed during the period of increased urinary nitrogen excretion (2-5). These changes in ascorbic acid and nitrogen metabolism may be interrelated; ascorbic acid may be important in adrenal cortical function, and there is evidence to indicate that the nitrogen metabolic changes after injury are dependent, in part, on the level of adrenal activity. Ascorbic acid administered subcutaneously to normal rats was shown by Noble and Toby(6) to reduce urinary nitrogen excretion for at least 34 hours, the period of their observations. Further, rats traumatized by leg clamping and given ascorbic acid, either subcutaneously or orally, excreted less nitrogen in the first 34 hours after injury, the period of their observations, than rats similarly injured but not given ascorbic acid.

Accordingly, we have investigated the effects on nitrogen excretion of supplemental ascorbic acid given to rats with severe thermal injury throughout the period of negative nitrogen balance (2½ weeks following injury).

Methods. Thirteen male young adult albino rats of the Wistar strain were adapted over a period of 6 days to the force-feeding of a liquid diet(7,8). From the end of the adaptation period to the end of the experiment, each of the animals was given 10 cc of the diet 2 times daily. According to chemical analysis, each animal received 640 mg of nitrogen every 2 days. By calculation, this diet yielded about 0.2 calorie per gram of body weight per day and was made up, on a caloric basis, of 18% protein, 63% carbohydrate, and 19% fat. Six days after rats reached full feeding, they were placed in metabolism cages from which acidified urine and feces were collected every 2 days. Total nitrogen in urine, feces, and diet was determined by micro-Kjeldahl analysis(9). Urinary amino nitrogen was estimated by the colorimetric ninhydrin technic(10); no correction was made for urea which reacts with ninhydrin to the extent of 3%. Rats were weighed every other day. After a 12-day control period, all rats were lightly etherized and deep thermal injuries produced over 30-35% of their body surfaces by dipping their clipped backs into hot water (73°C) for 30 seconds

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