PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE **174**, 102–106 (1983)

Effect of Body Temperature on Salicylate-Induced Hyperventilation (41710)

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Abstract. Hyperventilation and hyperpyrexia occur simultaneously during acute salicylate intoxication. The present experiments were designed to investigate the stimulatory effect of increased body temperature on respiration in this pathological state. Acute salicylate intoxication was produced in mongrel dogs by intravenous infusion of 200 mg sodium salicylate/kg body weight, and the effect of body temperature on salicylate-induced hyperventilation was studied by comparing the respiration of hyperthermic animals with the respiration of animals maintained normothermic during acute salicylate intoxication by bathing them in cold water. The minute volume of ventilation increased greatly over control levels in both normothermic and hyperthermic animals, but this increment was much larger in hyperthermic animals. The increase in ventilation of normothermic animals can be explained as a rise in alveolar ventilation which results in hypocapnia despite large increases in carbon dioxide production and oxygen consumption during acute salicylate intoxication. The further augmentation of ventilation in hyperthermic animals can be explained as a rise in deadspace ventilation in response to increased body temperature during acute salicylate intoxication.

Hyperventilation is one prominent feature of acute salicylate intoxication (1, 2) and occurs in this condition despite arterial hypocapnia, alkalemia, and normoxia. This salicylate-induced rise in ventilation has been attributed both to direct stimulation of intracranial receptors by salicylate ions (3) and to the mediation of intrathoracic receptors (4), but the relative roles of these and other mechanisms of salicylate-induced hyperventilation have not been completely elucidated.

Hyperpyrexia is another prominent feature of acute salicylate intoxication (1, 2). This increased body temperature stimulates respiration (5, 6), but the relative role of hyperthermia in the production of salicylate-induced hyperventilation is unknown. This report presents the results of a study specifically designed to determine the effect of increased body temperature on the hyperventilation associated with acute salicylate intoxication in dogs.

Materials and Methods. Mongrel dogs of either sex, weighing between 16 and 23 kg were divided into two groups and used as the experimental animals in this study. All of the dogs in each group were given 200 mg of sodium salicylate/kg body weight. Group A consisted of 15 animals whose body temperature was not controlled following sodium salicylate infusion. Group B was made up of 10 dogs whose rectal temperature was held within 0.2°C of the control value by bathing the animal in cold water following salicylate administration.

These animals were anesthetized with 30 mg sodium pentobarbital/kg body weight, administered intravenously, and supplemental doses were given as needed to maintain a constant level of anesthesia throughout both control and experimental periods. After anesthetization, an endotracheal tube was installed, a thermistor was placed in the rectum, and catheters were placed into the pulmonary artery via the right jugular vein and into the left common carotid artery. Control data were obtained 90 min after catheterization. Isotonic sodium salicylate (200 $mg \cdot kg^{-1}$) was then infused intravenously over a 15-min period. Experimental data were obtained 2 hr after the termination of the salicylate infusion.

An integrated pneumotachograph was used

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0037-9727/83 $1.50

to determine breathing rate and minute volume of ventilation. Minute volume of ventilation was corrected to body temperature, pressure saturated (BTPS). Tidal volume was calculated by dividing minute volume of ventilation by breathing frequency. Carbon dioxide production was determined by measuring the volume and carbon dioxide content of a timed collection of expired air. Oxygen consumption was determined by measuring the rate of decrease in the volume of an oxygen-filled rebreathing circuit containing a carbon dioxide absorber. Body temperature was measured with a rectal thermistor.

Mixed venous blood and arterial blood were drawn into heparinized glass syringes, and the pH, partial pressure of carbon dioxide (PCO_2) and partial pressure of oxygen (PO_2) of each blood sample were measured anaerobically with the appropriate electrodes maintained at 37°C. Reported values of pH, PCO_2 and PO_2 have been corrected to body temperature. Plasma salicylate concentrations were determined by the method of Trinder (7).

Each experimental animal served as its own control. The Student's t test was used to determine the statistical significance of salicylate-induced changes.

Results. Plasma salicylate concentrations were similar in the two groups of experimental animals (A, 45.5 ± 1.4; B, 46.9 ± 2.2 mg · dl^{-1}) immediately after the 15-min infusion of sodium salicylate (200 mg · kg^{-1}) and 2 hr after the end of salicylate loading (A, 37.4 ± 1.4; B, 38.7 ± 2.2 mg · dl^{-1}).

Following salicylate administration, rectal temperature increased 2.7°C in group A (hyperthermic) animals but was maintained within ±0.2°C of control values in group B (normothermic) dogs by bathing them in cold water throughout the 2 hr experimental period (Table I). Minute volume of ventilation increased greatly in both hyperthermic and normothermic animals following salicylate infusion, but the change in minute volume of ventilation which occurred in hyperthermic animals was much larger than that which occurred in normothermic dogs (Table I). Respiratory rate increased more than fourfold above control values in hyperthermic animals while their tidal volume decreased after salicylate administration (Table I). Respiratory rate rose only slightly in normothermic animals, while their tidal volume increased following salicylate administration (Table I).

Following salicylate administration, there were large increments of oxygen consumption and carbon dioxide production. These metabolic changes were of a similar magnitude in hyperthermic and normothermic animals (Table II). The ratio of carbon dioxide production to oxygen consumption was increased in both groups of dogs, following salicylate administration, but neither change was statistically significant (Table II).

Acute salicylate loading was associated with hypocapnia and respiratory alkalemia in the arterial and mixed venous bloods of both hyperthermic and normothermic animals (Table III). Arterial oxygen tension was elevated in

TABLE I. TEMPERATURE AND RESPIRATORY EFFECTS OF SALICYLATE INTOXICATION

	Group A (hyperthermic) (N = 15)		Group B (normothermic) (N = 10)	
	Control values	Experimental values	Control values	Experimental values
Rectal temperature (°C)	38.2 ± 0.3	40.9 ± 0.3[a]	38.0 ± 0.1[c]	37.9 ± 0.1[b]
Minute volume (liters · min^{-1})	5.9 ± 0.7	18.3 ± 2.5[a]	4.2 ± 0.3	9.7 ± 1.1[a,b]
Respiratory rate (min^{-1})	20.0 ± 3.4	87.5 ± 17.2[a]	15.6 ± 1.9	23.0 ± 2.6[a,b]
Tidal volume (ml)	352 ± 29	271 ± 39	302 ± 37	434 ± 24[a,b]

Note. Control values were obtained after a 90-min equilibration period; experimental values were obtained 2 hr after the administration of a sodium salicylate load. All values are listed as the mean ± SEM.

[a] These values are statistically different from the corresponding control values ($P < 0.05$).

[b] These experimental values are statistically different from the corresponding experimental values in group A ($P < 0.05$).

[c] None of the control values in group B was statistically different from the corresponding control value in group A ($P > 0.05$).

TABLE II. OXYGEN CONSUMPTION, CARBON DIOXIDE PRODUCTION, AND RESPIRATORY EXCHANGE RATIO BEFORE AND AFTER SALICYLATE LOADING

	Group A (hyperthermic) (N = 15)		Group B (normothermic) (N = 10)	
	Control values	Experimental values	Control values	Experimental values
Oxygen consumption ($ml \cdot min^{-1} \cdot kg^{-1}$)	7.0 ± 0.1	14.5 ± 0.5[a]	7.1 ± 0.2[b]	13.9 ± 0.8[a]
Carbon dioxide production ($ml \cdot min^{-1} \cdot kg^{-1}$)	5.2 ± 0.3	11.8 ± 0.9[a]	5.7 ± 0.1	13.8 ± 1.9[a]
Respiratory exchange ratio	0.74 ± 0.05	0.81 ± 0.05	0.80 ± 0.07	0.99 ± 0.08

Note. Control values were obtained after a 90 min equilibration period; experimental values were obtained 2 hr after the administration of a sodium salicylate load. All values are listed as the mean ± SEM.

[a] These values are statistically different from the corresponding control values ($P < 0.05$).

[b] None of the control values in group B was statistically different from the corresponding control value in group A ($P > 0.05$).

the hyperthermic dogs but exhibited no statistically significant change in normothermic dogs (Table III). The PO_2 of the mixed venous blood was reduced in both hyperthermic and normothermic animals (Table III).

Discussion. Intravenous infusion of 200 mg sodium salicylate/kg body weight resulted in plasma salicylate concentrations (37–47 $mg \cdot dl^{-1}$) which were toxic rather than therapeutic (8). This experimental salicylate intoxication was associated with a large rise in the minute volume of ventilation (Table I). Such salicylate-induced hyperventilation might have been caused by direct stimulation of intracranial receptors (3), but this effect has been shown to be minimal (4, 9). Ventilation might have also been stimulated by arterial hypercapnia, hypoxia, or acidosis caused by large increments in oxygen consumption and carbon dioxide production (Table II) resultant from uncoupling of oxidative phosphorylation during salicylate intoxication (1,2, 8). However, arterial hypocapnia, normoxia, and alkalemia occurred following salicylate admin-

TABLE III. ARTERIAL AND MIXED VENOUS BLOOD pH, PCO_2, PO_2, AND $[HCO_3]$ BEFORE AND AFTER SALICYLATE LOADING

	Group A (hyperthermi) (N = 15)		Group B (normothermic) (N = 10)	
	Control values	Experimental values	Control values	Experimental values
Arterial blood				
pH	7.37 ± 0.01	7.47 ± 0.02[a]	7.32 ± 0.01[c]	7.37 ± 0.01[a,b]
PCO_2 (Torr)	38.9 ± 1.3	27.6 ± 1.4[a]	40.6 ± 1.1	32.9 ± 1.8[a,b]
$[HCO_3^-]$ (meq/liter)	22.6 ± 0.6	19.8 ± 1.0[a]	20.6 ± 0.4[c]	18.7 ± 0.7[a,b]
PO_2 (Torr)	74.7 ± 2.5	85.3 ± 2.4[a]	75.9 ± 3.2	70.7 ± 3.4[b]
Mixed venous blood				
pH	7.35 ± 0.01	7.42 ± 0.02[a]	7.30 ± 0.01[c]	7.33 ± 0.01[a,b]
PCO_2 (Torr)	41.3 ± 1.1	33.0 ± 1.5[a]	41.3 ± 1.1	37.0 ± 1.6[a]
$[HCO_3^-]$ (meq/liter)	23.1 ± 0.7	21.3 ± 1.1	20.3 ± 0.4[c]	19.4 ± 0.6
PO_2 (Torr)	42.9 ± 2.1	34.0 ± 1.2[a]	45.1 ± 1.3	30.9 ± 1.4[a]

Note. Control values were obtained following a 90-min equilibration period; experimental values were obtained 2 hr after the administration of a sodium salicylate load. All values are listed as the mean ± SEM.

[a] These values are statistically different from the corresponding control values ($P < 0.05$).

[b] These experimental values are statistically different from the corresponding experimental values in group A ($P < 0.05$).

[c] These control values are statistically different from the corresponding control values in group A ($P < 0.05$).

istration (Table III). Moreover, hypocapnia and alkalemia also occurred in mixed venous blood during salicylate intoxication (Table III). There was, however, a fall in the oxygen tension of mixed venous blood following salicylate infusion (Table III), and this relative hypoxia may have stimulated ventilation by some undefined mechanism. Hyperpyrexia was another consequence of salicylate-induced uncoupling of oxidative phosphorylation which may have stimulated respiration. The purpose of this study was the determination of the effect of increased body temperature on salicylate-induced hyperventilation. The changes caused by salicylate intoxication were compared in two separate groups of mongrel dogs. Animals in group A became hyperthermic following salicylate administration whereas animals in group B were maintained normothermic by bathing them in cold water following salicylate administration.

The minute volume of ventilation increased greatly in both groups of experimental animals, but this salicylate-induced hyperventilation was much greater in hyperthermic than in normothermic dogs (Table I). Since the salicylate-induced changes in metabolism and blood gas composition were qualitatively similar in both hyperthermic and normothermic dogs (Tables II and III), it was unlikely that the disparity between ventilatory responses in the two groups of animals could have been accounted for by intergroup differences in oxygen consumption, carbon dioxide production, plasma pH, or blood gas tensions. Therefore, increased body temperature appeared to be one stimulus for hyperventilation during salicylate intoxication. However, the increment in the minute volume of ventilation of the normothermic animals indicated that hyperthermia was not the only stimulus for hyperventilation following salicylate loading.

The tidal volume of normothermic dogs increased greatly during salicylate intoxication, while the increment in respiratory frequency was quite small (Table I). Such a change in the pattern of respiration was consistent with an increase in alveolar ventilation. Respiratory alkalosis and arterial normoxia in the presence of elevated rates of oxygen consumption and carbon dioxide production were also suggestive of increased alveolar ventilation in response to salicylate loading. In fact, the moderate variations in plasma pH and arterial blood gas tensions suggested that the change in alveolar ventilation was well matched to the change in metabolism at the end of 2 hr of salicylate intoxication. Recently, Milhorn *et al.* (10) have presented evidence which suggested that salicylate-induced perturbations in metabolism occurred rapidly after salicylate administration whereas respiration changed more slowly but neared a steady state after 1 hr of salicylate intoxication. These data were consistent with the present observations that metabolic and respiratory changes were well matched after 2 hr of salicylate intoxication.

The effects of salicylate and temperature on the pattern of respiration can best be evaluated by consideration of the extensive work of vonEuler and others on this subject (11–13). Their evidence has indicated that the rate of lung expansion is governed by the rate of inspiratory activity generated with the brainstem, which activity increased with time during inspiration. The duration of inspiration was controlled by a neural center which switched off the centrally generated inspiratory activity. This off-switch also controlled the frequency of respiration, since the period of expiration was directly related to the period of inspiration. The off-switch was triggered when some combination of neural output from both the centrally generated inspiratory activity and the peripherally generated, lung-volume-dependent, vagal activity reached a certain threshold.

During salicylate intoxication, normothermic animals had greatly increased tidal volumes associated with only slight changes in respiratory frequency (Table I). These data were consistent with salicylate-induced elevations of both the centrally generated inspiratory activity and the threshold of the off-switch mechanism. These present data do not elucidate the manner in which salicylate alters the functioning of these respiratory centers, but past studies have suggested that salicylate ions did not directly stimulate these centers (4, 9).

During salicylate intoxication, hyperthermic animals had reduced tidal volumes associated with tremendously increased rates of respiration (Table I). These data are consistent with a temperature-induced elevation of centrally generated inspiratory activity accom-

panied by a much greater reduction in the off-switch threshold, which changes have been noted in hyperthermic animals under conditions other than salicylate intoxication (11–13). The present data indicated that the temperature effects outweighed the salicylate effects.

The administration and subsequent catabolism of the sodium salt of a weak acid (salicylic acid, $pK_a = 3$) might have had some effect on the acid–base state of the experimental animals. In the present study, 1.25 mmole of sodium salicylate/kg of body weight was administered. If the fractional decline (17.6%) in plasma salicylate concentration between the end of the salicylate infusion and the end of the 2-hr period of salicylate intoxication equalled the fraction of salicylate load metabolized, then 0.22 mmole of salicylate/kg of body weight would have combined with an equal amount of hydrogen ions during the catabolism of salicylate. Such a decline in hydrogen ion concentration would probably have resulted in a rise in the bicarbonate concentration of 0.22 mmole/kg body weight. If all of this bicarbonate were confined to the extracellular fluids, then the extracellular bicarbonate concentration would have increased approximately 0.9 mmole/liter. This small change in bicarbonate concentration represents a maximal estimate, since a portion of the salicylate load was no doubt excreted during the 2-hr experimental period and since any bicarbonate generated would have most likely not been entirely confined to the extracellular fluids.

The authors are indebted to Mrs. Wendy Lee, Mrs. Carol Super, and Mrs. Yoshiko Bettice for their excellent technical assistance.

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Received June 7, 1982. P.S.E.B.M. 1983, Vol. 174.