MODIFICATION OF THE RESPIRATORY RESPONSE TO CARBON DIOXIDE BY SALICYLATE

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It is well known that CO_2 inhalation is associated with increased ventilation in normal man, and the sensitivity of the nervous regulatory mechanism to this physiological stimulus has been reasonably well defined (1–3). Likewise the clinical entity of hyperventilation associated with salicylate toxicity has long been recognized. The study reported here was designed to investigate one aspect of the effect of salicylate on respiration. Specifically an attempt has been made to determine whether salicylate might induce changes in the sensitivity of the nervous regulatory mechanism to the stimulus of CO_2 inhalation.

The approach has been essentially the same as that reported previously (3), namely, the correlation of arterial blood CO_2 tension and hydrogen ion concentration with effective alveolar ventilation when changes are induced by increased amounts of CO_2 in the inspired air.

MATERIAL AND METHODS

Three normal medical students were studied in the fasting state. Two studies each were made on two subjects and three on the third, each study extending over the period of one morning. Three sets of observations were made both before and after salicylate ingestion in order to determine three points on each of the stimulus response curves to be constructed. The observations were made while the subjects were breathing room air, 3 per cent CO_2 in air, and 5 per cent CO_2 in air in that order. The experimental procedure and apparatus used were the same as those previously employed in a larger group of normal subjects (3).

Single doses of 1.8 to 2.4 grams of acetyl salicylic acid were given orally in the form of "Bufferin®" [4] tablets approximately one and one-half to two hours before the second study was done, and blood for salicylate levels was drawn at the time the observations on ventilation and arterial blood were made.

In the normal subject a steady state as determined by consistency of respiratory quotient values, pulmonary ventilation, and respiratory frequency is obtained only after 25 to 30 minutes of uninterrupted breathing of a carbon dioxide gas mixture in the concentrations used (3, 4). Therefore, expired gas was collected during the last three minutes of 26 to 33-minute periods of continuous inhalation of the two CO_2 mixtures. During the middle minute of this three-minute period, arterial blood samples were steadily drawn from an indwelling needle in a brachial artery.

The analytical methods used have been described previously (3). Since the values for arterial CO_2 tension were partially derived from the blood pH, and the changes observed were relatively small, special attention was given to the determination of arterial blood pH in order to insure the greatest possible accuracy permitted by the technique employed. Duplicate determinations were carried out in every instance within five minutes after the blood had been removed from the vessel. Readings were made at 38° C. using a Cambridge glass electrode pH meter, transfer from vessel to electrode being accomplished anaerobically. Two standard phosphate buffer solutions of pH 7.18 and 7.58 at 38° C. (5) were used for reference, and duplicate blood determinations were required to check within ± .005 pH units. In this way changes in pH were measured accurately within .01 pH unit. Blood salicylate levels were determined colorimetrically (6). The usual 'alveolar' equation was utilized for the calculation of mean alveolar oxygen tension (7) when room air was inhaled, and in modified form (3) when CO_2 was added to the inspired air. Calculated values for whole blood buffer base were obtained from the Singer-Hastings nomogram (8).

If it can be assumed that in a steady state a consistent relationship or equilibrium exists between the concentration of certain chemical agents in the arterial blood and their intra-and/or extracellular concentrations acting at receptor or integrative levels on the nervous mechanism regulating respiration, then simultaneous measurement of arterial concentrations and pulmonary ventilation under varying conditions will permit the estimation of a stimulus response curve.

In analyzing the results of the study, the assumed physiological stimuli to respiration, *i.e.*, CO_2 tension and

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[4] Acetyl salicylic acid with aluminum glycinate and magnesium carbonate, Bristol Myers Co.

hydrogen ion concentration in the arterial blood, have been plotted against effective alveolar ventilation. Effective alveolar ventilation has been taken as the total pulmonary ventilation minus the physiological dead space ventilation (Bohr) to CO_2, assuming the arterial CO_2 tension to be equivalent to the mean alveolar tension. Alveolar ventilation has been utilized in constructing the stimulus response curves rather than the total pulmonary ventilation since it is the former which determines the tension of CO_2 in the arterial blood perfusing the receptor sites of the neural regulatory mechanism.

RESULTS

As indicated by the consistency of the respiratory exchange ratios,[5] a reasonably steady state was achieved in all three subjects during CO_2 inhalation in the control periods and following salicylate ingestion (Table I). In addition, relatively constant levels of salicylate ranging from 12 to 16 mg. per cent were obtained in the blood throughout the entire period of study in each subject (Table I). The latter findings were essentially the same as those of Smith, Gleason, Stoll, and Ogorzalek (6), who observed that after single 2 gram oral doses of acetyl salicylate the maximum plasma salicylate level was reached about one and one-half to two hours after ingestion and remained relatively constant for six hours thereafter.

The control observations (Tables I, II) on the ventilatory response to the increases in arterial CO_2 tension and hydrogen ion concentration associated with CO_2 inhalation were comparable to those made on a larger number of normal subjects. For a detailed discussion of the changes in pulmonary ventilation and arterial blood in normal subjects under these circumstances, the reader is referred to a previous report (3).

[5] Respiratory exchange ratio of expired air is used here as synonymous with respiratory quotient.

TABLE I

Physiologic data relative to pulmonary ventilation at rest and following salicylate ingestion *

Subject	State	Age	Sex	B.S.A.†	Dose, ASA‡	Blood salicylate level	Inspired gas mixture	Minutes on mixture	f	R_E	V_T	V_D§	$\dot{V}_E$	$\dot{V}_A$	PA_{O_2}
					grams	*mg. %*									
B. C.	Rest	23	M	2.06			Rm. air	—	13	0.75	528	200	6.87	4.27	95
							3% CO_2	27	15.3	0.85	738	257	11.32	7.38	121
							5% CO_2	30	26	0.85	1,075	564	27.95	13.28	130
	Post ASA				2.4	14.9	Rm. air	—	13	0.83	545	166	7.08	4.92	101
						16.4	3% CO_2	28	17	0.86	830	238	14.11	10.03	125
						16.4	5% CO_2	28	26	0.73	1,238	374	32.23	22.50	134
H. S.	Rest	24	M	1.90			Rm. air	—	8.3	0.86	788	269	6.57	4.33	102
							3% CO_2	26	12.3	0.83	951	300	11.72	8.02	118
							5% CO_2	26	23	0.75	1,433	745	33.0	15.84	129
	Post ASA				1.8	14.1	Rm. air	—	15	0.83	561	249	8.42	4.68	102
						13.0	3% CO_2	30	20.5	0.77	665	196	13.63	9.60	124
						13.3	5% CO_2	27	28	0.92	1,377	393	38.56	27.50	137
G. S.	Rest	23	M	1.92			Rm. air	—	9	0.75	646	211	5.81	3.92	93
							3% CO_2	33	11.3	0.75	1,024	338	11.61	7.78	117
							5% CO_2	26	13	0.65	1,843	935	23.96	11.81	125
	Post ASA				1.8	11.8	Rm. air	—	9.3	0.81	706	245	6.59	4.30	97
						12.8	3% CO_2	29	12	0.84	1,098	376	13.17	8.67	122
						11.8	5% CO_2	30	15.5	0.79	2,204	914	34.17	20.02	128
	Rest						Rm. air	—	7.7	0.77	693	211	5.33	3.71	95
							3% CO_2	28	9.3	0.70	1,000	218	9.30	7.27	114
							5% CO_2	28	11.3	0.79	2,070	839	23.42	13.94	127

* Symbols used are: f, respiratory frequency; R_E, respiratory exchange ratio, expired air; V_T, tidal volume, ml.; V_D, physiological (Bohr) dead space to CO_2 in ml., including both instrumental (60 ml.) and personal dead space; $\dot{V}_E$, total pulmonary ventilation, liters per minute at body temperature and pressure saturated with water vapor; $\dot{V}_A$, effective alveolar ventilation, liters per minute BTPS; PA_{O_2}, calculated mean alveolar oxygen tension, mm. Hg.

† Body surface area, square meters.

‡ Acetyl salicylic acid.

§ For a discussion of changes observed with CO_2 breathing in normal subjects, see a previous report (3).

TABLE II

Physiologic data relative to the arterial blood at rest and following salicylate ingestion *

Subject	State	Inspired gas mixture	pHs	$(H^+)a$	Cs_{CO_2}	Pa_{CO_2}‡	Sa_{O_2}	Vc	$(B_B^+)b$
B. C.	Rest	Rm. air	7.40	39.8	58.7	41.5	97	41	47.5
		3% CO_2	7.39	40.7	61.5	44.5	99	41	49
		5% CO_2	7.36	43.6	62.7	48.5	100	41	49
	Post ASA†	Rm. air	7.41	38.9	58.3	40	95	40	48
		3% CO_2	7.41	38.9	59	40.5	98	41	48
		5% CO_2	7.39	40.7	61.5	44	100	42	48.5
H. S.	Rest	Rm. air	7.40	39.8	58.7	41.5	95	45	48
		3% CO_2	7.39	40.7	60	43.5	95	46	49
		5% CO_2	7.36	43.6	62.4	48	97	46	48.5
	Post ASA	Rm. air	7.42	38.0	59.9	40	97	47	50
		3% CO_2	7.42	38.0	60.6	41	99	47	50.5
		5% CO_2	7.40	39.8	62	44	100	47	50
G. S.	Rest	Rm. air	7.40	39.8	63.1	44.5	98	47	50
		3% CO_2	7.38	41.7	61.8	46	97	46	50
		5% CO_2	7.34	45.7	63	51	100	47	49
	Post ASA	Rm. air	7.40	39.8	61.8	44	100	45	50
		3% CO_2	7.38	41.7	61.1	45	99	47	49
		5% CO_2	7.35	44.6	60.8	48	98	48	49
	Rest	Rm. air	7.40	39.8	60.4	42.5	96	48	49
		3% CO_2	7.39	40.7	61.2	44.5	97	48	50
		5% CO_2	7.36	43.7	61.5	48	99	49	50

* Symbols used are: pHs, serum pH; $(H^+)a$, hydrogen ion concentration, billionths of moles per liter; Cs_{CO_2}, serum CO_2 content, vol. per cent; Pa_{CO_2}, CO_2 tension, mm. Hg; Sa_{O_2}, oxygen saturation; Vc, hematocrit; $(B_B^+)b$, calculated whole blood buffer base, mEq./L.

† Acetyl salicylic acid.

‡ In calculating Pa_{CO_2} from the Henderson-Hasselbalch relationship, pK′ for carbonic acid in blood serum was taken as 6:10, and the solubility coefficient of CO_2 in serum as 0.510 at 38° centigrade.

After salicylate ingestion there was little change in the values obtained at rest relative either to pulmonary ventilation or to arterial blood. Particular attention is called to the alveolar ventilation and arterial CO_2 tension in this regard (Tables I, II). The constancy of arterial blood buffer base values both before and after salicylate is taken as evidence that little renal compensation occurred during the period of respiratory acidosis induced by CO_2. With CO_2 inhalation, the relation between effective alveolar ventilation and arterial CO_2 tension or hydrogen ion concentration was essentially linear both before and after salicylate ingestion. As indicated by the slopes of the stimulus response curves, an increased sensitivity to the chemical stimulus in terms of either arterial CO_2 tension or hydrogen ion concentration was found in all subjects following salicylate

TABLE III

Sensitivity to the carbon dioxide-hydrogen ion stimulus

	Subject	Control	After salicylate	Percentage increase in sensitivity
Increase in effective alveolar ventilation, liters per minute BTPS, associated with a rise of 1 mm. Hg in arterial CO_2 tension.	B. C.	1.37	4.0	192
	H. S.	1.75	5.75	228
	G. S.*	1.44	3.88	170
Increase in effective alveolar ventilation, liters per min. BTPS, associated with a rise in arterial hydrogen ion concentration of 1 billionth of a mole per liter.	B. C.	2.2	8.2	272
	H. S.	2.8	11.4	307
	G. S.*	1.9	3.5	84

* Control values represent average of two studies.

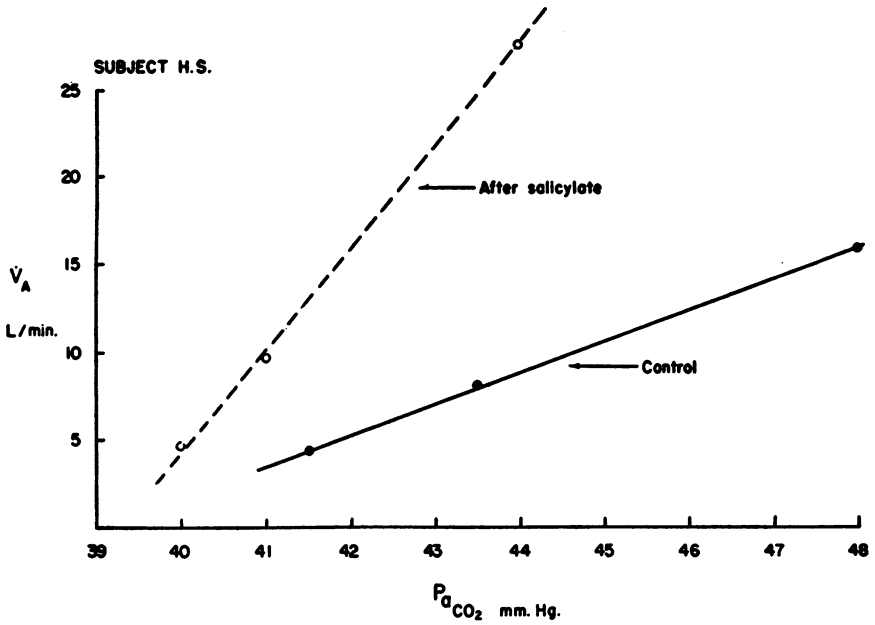

FIG. 1. RESPONSE TO THE CO_2 STIMULUS BEFORE AND AFTER SALICYLATE INGESTION

Effective alveolar ventilation in liters per minute (BTPS) on the ordinate is plotted against arterial CO_2 tension in mm. Hg on the abscissa to obtain the slopes of the stimulus-response or sensitivity curves.

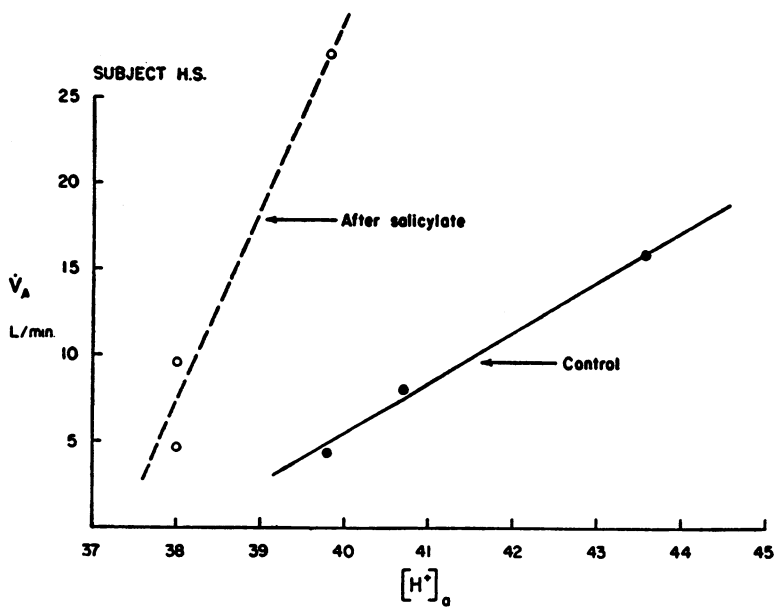

FIG. 2. RESPONSE TO THE HYDROGEN ION STIMULUS BEFORE AND AFTER SALICYLATE INGESTION

With arterial hydrogen ion concentration in billionths of moles per liter (see Table II) on the abscissa, sensitivity curves are constructed as indicated in Figure 1.

ingestion. The stimulus response curves of subject H. S. are shown in Figures 1 and 2. In Table III are shown the increments in effective alveolar ventilation associated with unit rise in arterial CO_2 tension and hydrogen ion concentration during the control observations and after salicylate, together with the percentage increase in sensitivity induced by salicylate in each subject. Even at the relatively low blood salicylate levels obtained, increases in sensitivity ranging from 84 per cent to 307 per cent occurred.

DISCUSSION

Possible mechanisms which have been suggested (9) to account for salicyl hyperpnea are (a) a direct stimulating effect upon the respiratory center, (b) a metabolic acidosis resulting from fixed acid degradation products of these compounds. In regard to the latter, recently reported studies by Singer (10) indicate that there may be accumulation of an as yet unidentified fixed acid in the blood with metabolic acidosis in the advanced phase of salicylate poisoning. However, it seems well established that the hyperpnea accompanying large therapeutic dosage or mild to moderate toxicity is associated with an uncomplicated respiratory alkalosis (9, 10).

The results of this study are interpreted as providing direct experimental evidence that an increase in the sensitivity of the nervous regulatory mechanism to normal chemical stimuli is at least one means whereby hyperventilation is induced by salicylates.

SUMMARY AND CONCLUSIONS

1. The sensitivity of the respiratory nervous regulatory mechanism to the CO_2 inhalation stimulus was determined in three normal subjects before and after salicylate ingestion, relating effective alveolar ventilation to arterial CO_2 tension and hydrogen ion concentration.

2. With blood salicylate levels of the order 12 to 16 mg. per cent, respiratory sensitivity to the carbon dioxide-hydrogen ion stimulus increased 84 to 307 per cent.

3. It is suggested that this increased sensitivity to a normal chemical stimulus is one mechanism whereby salicylates induce hyperventilation.

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