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Effect of chronic hypercapnia on body temperature regulation

K. E. SCHAEFER, A. A. MESSIER, C. MORGAN, AND G. T. BAKER III
Naval Submarine Medical Research Laboratory, Naval Submarine Base, Groton, Connecticut 06340

SCHAEFER, K. E., A. A. MESSIER, C. MORGAN AND G. T. BAKER III. *Effect of chronic hypercapnia on body temperature regulation.* J. Appl. Physiol. 38(5): 900–906. 1975.—Guinea pigs and rats exposed to 15% CO_2 for 7 days showed a parallel time course of changes in pH, body temperature (T_b), and oxygen consumption ($\dot{V}O_2$). Between 1 and 6 h of exposure the maximal drop in actual pH occurred in guinea pigs simultaneously with the maximal fall in T_b and $\dot{V}O_2$. During the subsequent period pH, T_b, and $\dot{V}O_2$ rose again. Skin blood content (heat loss) also exhibited a biphasic pH-dependent time course. Animals showing no partial compensation of respiratory acidosis during 3 days exposure also failed in raising their T_b back to normal in this time. The behavior of T_b was found to be a good indicator of the acid-base status and adaptive potential of the animals to hypercapnia. Similar results were obtained in rats. Thermoregulatory processes in the hypothalamus were affected during exposure to 15% CO_2. Both guinea pigs and rats showed a decrease in norepinephrine content of the hypothalamus during the first part of exposure reaching a maximal fall at the end of 24 h. The serotonin content increased slightly during this period. During prolonged exposure to 3% CO_2 for 7 days, T_b showed a transient rise, and $\dot{V}O_2$ was slightly elevated.

epinephrine; neurochemical transmitters; oxygen consumption; respiratory acidosis; serotonin; skin blood content

THE ACUTE EFFECTS of exposure to increased CO_2 on temperature regulation have been studied extensively in different animal species. It has been demonstrated that acute exposure to concentrations above 8% CO_2 causes a fall in body temperature in rats at ambient room temperature of 24–28°C (1, 5, 31). Similar effects have been observed in cats, mice, dogs, and rabbits (6, 7, 13, 26).

The fall in body temperature is usually associated with a fall in oxygen consumption (1, 5, 32). Exposure to lower concentrations of CO_2 causes a rise in body temperature. The difference between the acute effects of lower and higher concentration of CO_2 is according to Stupfel (33) based on stimulatory and depressive effects on metabolism.

There are no reports in the literature on chronic effects of CO_2 on temperature regulation. This report deals with studies of guinea pigs and rats exposed for prolonged periods to 15% CO_2 and 3% CO_2.

The concentration of 15% CO_2 was chosen, for these studies, because it is below the level of narcotic effects, and it is high enough during the acute phase to cause a sufficiently large fall in pH (7.40 to 7.0) thus affecting pH-dependent enzymes (27). During the subsequent adaptation to respiratory acidosis, the pH rises again above the level at which most of the pH-dependent enzymes are inhibited (27). Under these conditions we observed biphasic changes, an initial transitory depression of functions followed by a recovery and a return to control levels associated with the biphasic changes in pH. A lower concentration, 3% CO_2, which does not have an inhibitory effect on metabolic functions, was used in a comparative study.

METHODS

Within the framework of a larger project on CO_2 toxicity, different series of experiments were carried out. Data which had a bearing on temperature regulation and acid base balance during chronic hypercapnia were compiled in this paper. The results of the following series of experiments were utilized in this report. *1*) Data on acid base balance and temperature regulation were obtained in guinea pigs exposed to 15% CO_2 for various time periods. This series comprised 126 animals, which included 37 control animals. *2*) Data on the time course of mortality of guinea pig were collected in 89 animals exposed for 7 days to 15% CO_2 in a study of body weight (30). *3*) Eighty-one rats (14 controls were studied under the same experimental conditions. *4*) A separate investigation of oxygen consumption was performed on 14 guinea pigs during exposure to 15% CO_2 using an open-circuit method. *5*) Blood distribution in organs of guinea pigs exposed to 15% CO_2 was measured in 47 animals. *6*) Data on acid-base balance and body temperature of guinea pigs exposed to 3% CO_2 were collected in 140 animals (38 controls). A separate study on oxygen consumption during exposure to 3% CO_2 was undertaken in 10 animals using an open-circuit method.

Male guinea pigs of the Hartley strain weighing between 400 and 600 g and Sprague-Dawley rats weighing between 200 and 300 g were exposed to 15% CO_2 and 3% CO_2 in 21% O_2, with the balance of the gas mixture being nitrogen, for prolonged periods of time in environmental chambers with temperature and humidity control (Sherer-Gilette). The environmental temperature was kept at 25.6 ± 1.1°C and the humidity between 65 and 75%. The gas mixtures were prepared by mixing proportional amounts of CO_2 to air; oxygen was added from a high-pressure cylinder. The air within the chamber was recirculated 12 times a minute. With this fast and large turnover of chamber air, mixing of CO_2 and air was nearly instantaneous. The carbon dioxide concentration

in the chamber was continuously monitored with a Beckman infrared CO_2 analyzer and the oxygen content was sampled intermittently with a Beckman O_2 analyzer. The CO_2 concentrations were kept at 15% within limits of $\pm 0.5\%$ and $3\% \pm 0.2\%$ and the oxygen concentrations at $21\% \pm 0.5\%$. Ammonia vapor was absorbed by boric acid placed in the chamber. The chamber was opened each morning for a period of 3–5 min to fill the water and food containers and to remove the urine and feces.

Prior to blood sampling, the animals received 40 mg pentobarbital/kg body wt subcutaneously and were returned to the CO_2 exposure chamber. The body temperature was measured using a thermistor probe placed 7 cm deep into the colon. The reading was taken 1 min after the thermistor was in place. It took about 40 s for the thermistor to reach an equilibrium. The anesthesia was usually effective after approximately 5 min, at which time the animals were taken out of the exposure chamber and immediately placed under a mask through which they breathed the same CO_2 gas mixture to which they had been exposed. Blood samples were drawn from the abdominal aorta. Blood pH and P_{CO_2} was determined with an Instrumentation Laboratory blood gas and pH analyzing system.

The animals were decapitated and the brain removed as rapidly as possible, dissected and stored at $-10°C$ until time of assay.

Measurements of serotonin and norephinephrine of hypothalamic and cortical areas of the brain were carried out, using the method of Maikel et al. (16).

Oxygen consumption ($\dot{V}_{O_2}$) of guinea pigs exposed to 15% CO_2 for 7 days was measured in 14 individual animals throughout control and exposure periods using a Beckman 1_3 paramagnetic oxygen analyzer with a span of 20–21% O_2 and an all glass metabolic chamber which was submerged in a water bath at 25°C. $\dot{V}_{O_2}$ was not measured in rats.

Included in this report are the results of a separate series of studies on blood distribution in the skin during 7 days' exposure to 15% CO_2. The blood volume of the skin and other organs were measured by a modification of the technique of Dewey (9). The animals were injected intravenously via the jugular vein with reconstituted blood tagged with ^{51}Cr and ^{125}I as previously described by Baker and Schaefer (2). Whole blood samples were taken after 15 min and assayed as previously described. All tissue samples were taken as soon as the blood sampling was completed. The skin was obtained from the abdominal region. Care was taken to remove all adhering muscle and adipose tissue. The skin tissue was then blotted with surgical gauze and placed in preweighed glass test tubes. Tissue samples were weighed in preweighed test tubes with a Torbal top loading balance to ± 2 mg. Tissue samples were digested for 24 h with an equal volume by weight of KOH (38%) as described by Martin et al. (17). The tissue samples were then counted three times for a minimum of 15 min of 10,000 counts with a Picker Spectroscaler II for ^{51}Cr and ^{125}I.

Calculations.

$$a)\ \text{Red cell wt/g tissue} = \frac{\text{cpm } ^{51}\text{Cr/g RBC (circulating)}}{\text{cmp } ^{51}\text{Cr/g tissue}}$$

$$b)\ \text{Plasma wt/g tissue} = \frac{\text{cpm } ^{125}\text{I/g plasma (circulating)}}{\text{cpm } ^{125}\text{I/g tissue}}$$

$$c)\ \text{Blood volume/g tissue} = (\text{plasma volume/g tissue} + \text{red cell volume/g tissue}) \times \text{total wt of tissue}$$

$$d)\ \text{Tissue hematocrit} = \frac{\text{red cell volume/g tissue}}{\text{red cell} + \text{plasma volume/g tissue}} \times 100$$

The weight of 1 ml of whole blood, as determined in duplicate on 12 guinea pigs to be $1.0271 + 0.004$ g, was used to convert the weight values to volume. Since the net amount of blood removed by sampling was less than five percent of the initial blood volume no correction was made for this loss in determination of the tissue blood volumes, Gibson et al. (12). All blood tissue sampling was done at the same time of day (between 11 AM and 12 noon) to avoid any possible errors due to circadian oscillations in the parameters studied.

Statistical analysis was carried out in each series of experiments by comparing data obtained under control conditions with those collected during different time periods of exposure to increased carbon dioxide concentrations. In one case two experimental groups were compared with each other (Table 1). The level of significance for all tests was selected such that any comparison where $P \leq 0.05$ was considered to be statistically significant, using a two-tailed table.

RESULTS

As shown in Fig. 1 exposure of guinea pigs to 15% CO_2 causes initially a fall in body temperature; but with adaptation to CO_2, the body temperature returns to control levels after 3 days. The time courses of body temperature and pH parallel each other. Mortality of guinea pigs exposed to 15% CO_2 ranged between 25 and 50%. It was observed that animals which are unable to adapt to CO_2 by achieving a partial compensation of the acidosis and rise of the pH after 3 days will die. It was also noted that their body temperature failed to rise.

Body temperaure and pH data from such a group of animals were obtained at the third day of exposure (dotted line) and were found to be significantly lower, as compared with those animals which had adapted to chronic hypercapnia at the third day of exposure. Table 1 presents additional data on the acid base status of these two groups of animals, who reacted in different ways to exposure to 15% CO_2. Moreover corresponding data are included from controls and from guinea pigs exposed to 15% for 6 h. At this time the highest degree of acidosis and the greatest drop of body temperature occurred. The time course of mortality is listed in Table 2. It shows a sudden rise in mortality at 3 and 4 days and a subsequent decline to zero at 6 and 7 days. The time course of mortality shows that it was not possible to separate prior to the third day of exposure to 15% CO_2 two groups consisting of surviving (adapting) and nonsurviving (nonadapting) animals. *Group A* represents the surviving guinea pigs which have accomplished partial compensation of the

TABLE 1. *Acid-base status and body temperature in controls and two groups of guinea pigs exposed to 15% CO_2, 21% O_2, balance N_2 for 3 days*

		pH	P_{CO_2}, mmHg	HCO_3^-, meq/l	Standard HCO_3^-, meq/l	Base Excess, meq/l	Body Temp, °C
Controls (N = 37)	Mean	7.408	39.1	23.9	22.6	−1.7	40.4
	±SE	±0.013	±0.7	±0.5	±0.2	±0.3	±0.8
15% CO_2, 6 h (N = 14)	Mean	7.085	119.4	33.5	20.9	−4.0	33.5
	±SE	±0.011	±1.1	±1.2	±0.4	±0.5	±0.6
	P	0.001	0.001	0.001	0.001	0.001	0.001
3 Days							
Group A, partial compensation of acidosis (N = 16)	Mean	7.191	116.4	42.0	30.6	+7.7	38.5
	±SE	±0.014	±3.9	±1.3	±1.0	±1.1	±0.2
	P	0.010	0.001	0.001	0.001	0.001	0.02
Group B, no compensation of respiratory acidosis (N = 6)	Mean	6.926	136.6	26.1	17.0	−3.0	34.8
	±SE	±0.011	±6.0	±2.7	±1.5	±2.2	±0.5
	P	0.001	0.001	NS	0.001	0.001	0.001
	P*	0.001	0.001	0.001	0.001	0.001	0.001

P, differences between controls and experimental groups. * Differences between *groups A* and *B*.

acidosis after 3 days. Their pH has markedly risen above the lowest point at 6 h, and the associated large increase in bicarbonate and base excess demonstrates the capability of this group to make sufficient bicarbonate buffer available to cope with the CO_2-induced acidosis. *Group B* comprises the nonsurviving animals, which are unable to compensate the acidosis. The pH of this group is even lower than that measured after 6 h of exposure, so are standard bicarbonate and base excess concentrations. The fall of standard bicarbonate below the level found during acute CO_2 exposure of 6 h is an indication of a "metabolic acidosis" superimposed on the respiratory acidosis. In these experiments, body temperature proved to be a good noninvasive technique to give an indirect indication of the acid-base status of the animals. Oxygen consumption followed the pH changes, decreasing significantly during the first day and slowly rising during the subsequent days, during which adaptation developed.

Rats are much more resistant to CO_2 and do not exhibit any mortality during exposure to 15% CO_2. This is apparently related to their higher buffer capacity (30). The time courses of pH and body temperature of rats exposed to 15% CO_2 (Fig. 2) shows the same pattern as that observed in guinea pigs. A transitory fall of body temperature was found during the acute state of acidosis and a return to control values by 3 days after a partial compensation has been reached.

Significant increase of both red cell volume and plasma volume of the skin was found after 1-h exposure, which was followed by a significant decrease of both functions at 7 days and plasma volume at 3 days. Since the measured red cell and plasma volume were both statistically significantly elevated at 1 h and decreased after 7 days, the calculated total blood volume also showed significant differences from controls at these time periods. To indicate the magnitude of the changes in skin blood content during exposure to 15% CO_2, percent changes in blood content are listed in the lower part of Fig. 3. A rise of nearly 60% occurred at 1 h followed by a fall to 20% below control values by the third day and 40% by 7 days.

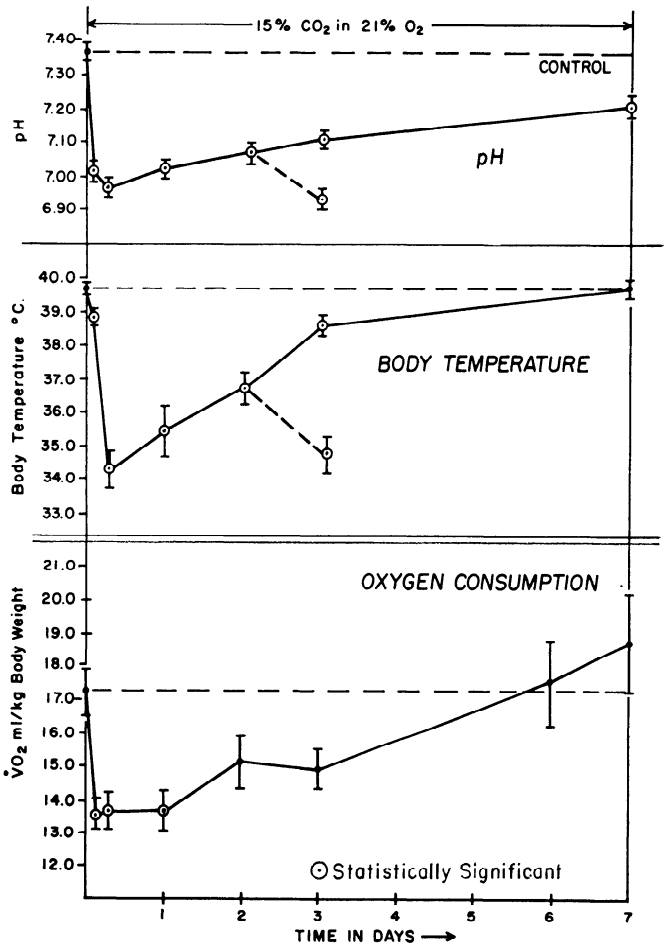

FIG. 1. Effect of prolonged exposure of guinea pigs to 15% CO_2 in 21% O_2 on pH, body temperature, and oxygen consumption. No. of animals: control, 20; experimental group, 14–21. Means and SEM. Oxygen consumption was measured separately on a group of 14 animals, of which 9 continued through the whole 7-day period.

TABLE 2. *Time course of mortality in guinea pigs (Hartley strain) exposed to 15% CO_2*

15% CO_2 in 21% O_2, Time of Exposure	Mortality, No. of Animals Died	% Mortality
1 h	0	0
6 h	0	0
1 day	1	1.1
2 days	2	2.2
3 days	8	9.0
4 days	10	13.5
5 days	2	2.2
6 days	0	0
7 days	0	0

Eighty-nine guinea pigs exposed to 15% CO_2 for a period of 7 days.

Since both red cell volume and plasma volume exhibited these biphasic changes, the hematocrit remained practically unchanged.

Measurements of norepinephrine and serotonin content of the hypothalamus of guinea pigs exposed to 15%

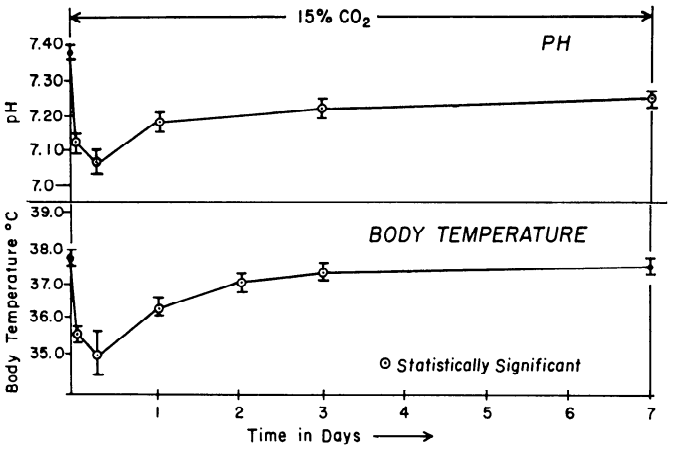

FIG. 2. Effects of exposure of rats to 15% CO_2 in 21% O_2 on pH and body temperature. No. of animals: control, 10; experimental, 10–12. Means and SEM.

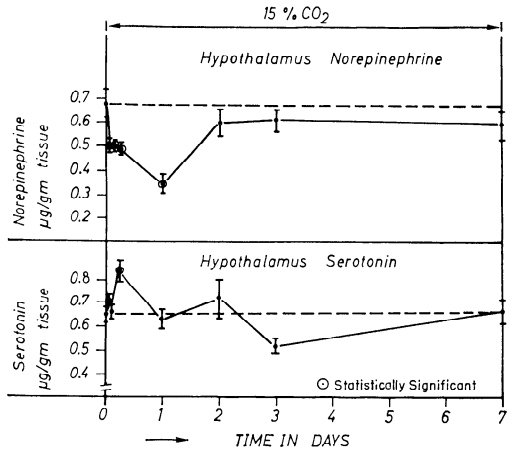

FIG. 4. Effect of prolonged exposure to 15% CO_2 in 21% O_2 on norepinephrine and serotonin content of the hypothalamus in guinea pigs. No. of animals: control, 10; experimental, 11–20. Means and SEM.

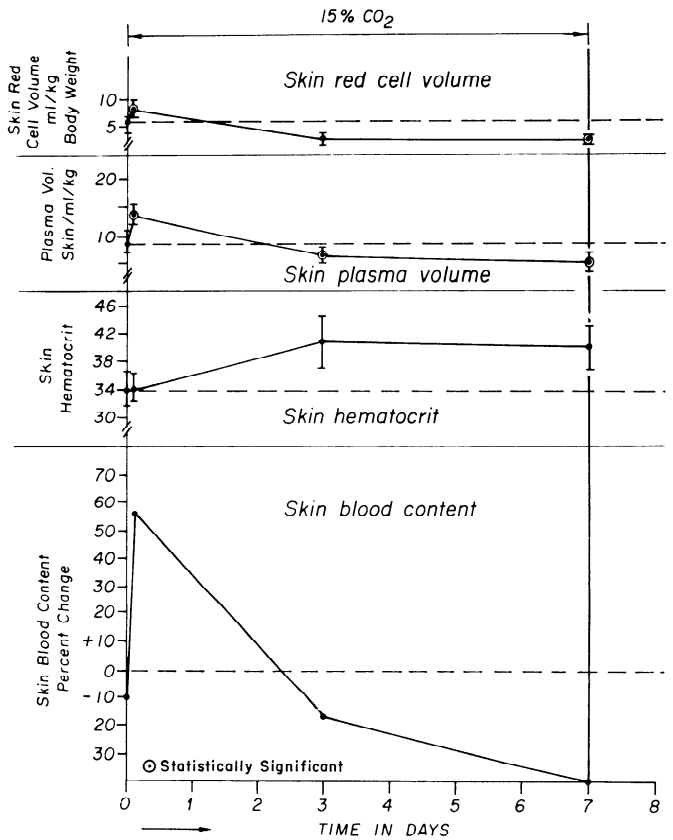

FIG. 3. Effect of prolonged exposure to 15% CO_2 in 21% O_2 on red cell volume (^{51}Cr), plasma volume (^{125}I), hematocrit and total blood volume of the skin of guinea pigs. No. of animals: control, 13; experimental, 4–8. Means and SEM.

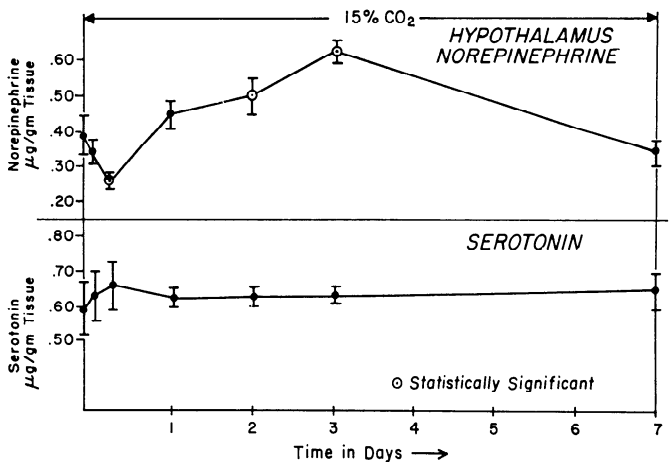

FIG. 5. Effect of prolonged exposure to 15% CO_2 in 21% O_2 on norepinephrine and serotonin content of the hypothalamus in rats. No. of animals: control, 10; experimental, 6–9. Means and SEM.

CO_2 for prolonged periods are exhibited in Fig. 4. The norepinephrine concentration showed a fall and rise while the serotonin levels did not change significantly except for a transient increase at 6 h. In rats similar biphasic changes in the norepinephrine content of the hypothalamus were observed. However, norepinephrine concentration increased significantly above control values during the second and third day, while the serotonin concentration did not change (Fig. 5).

During exposure to 3% CO_2 guinea pigs did not show a fall in body temperature; in fact there is a small but significant rise of body temperature after 1 h and 1 day amounting to 0.7 and 0.5°C, respectively (Fig. 6). Oxygen consumption is slightly elevated.

DISCUSSION

The anesthesia used in these experiments has a small effect on acid base balance. Potén and Siesjö (24) determined pH, bicarbonate, and arterial CO_2 tension prior to injection of barbiturate and after attainment of surgical anesthesia. The pH was found to decrease by 0.07 pH units, the bicarbonate level decreased 2–3 meq/l, and the Pa_{CO_2} rose by 4.7 mmHg. The large alterations in pH produced by exposure to 15% CO_2 in guinea pigs would not be influenced significantly by the effects of anesthesia. Since the changes are superimposed in both control and experimental animals, all the measured blood pH values are a little too low, but the time course of the uncompensated and compensated respiratory acidosis is not altered by the anesthesia effects.

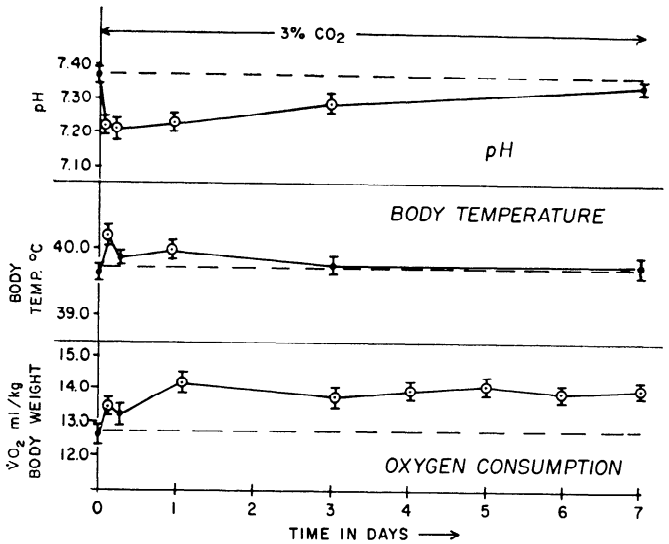

FIG. 6. Effect of prolonged exposure to 3% CO_2 in 21% O_2 on pH, body temperature, and oxygen consumption of guinea pigs. No. of animals: control, 38; experimental, 12–39. Oxygen consumption separately measured on a group of 10 animals and which were exposed for the full period of 7 days. Means and SEM.

In chronic hypercapnia induced by prolonged exposure to 15% CO_2, guinea pigs and rats show changes in body temperature which clearly depend on the acid-base status of the animals. The maximal fall in arterial pH in guinea pigs exposed to 15% CO_2 occurs at 6 h of exposure simultaneously with the maximal fall in body temperature. During the subsequent period, both pH and body temperature rise again. Similar results were obtained in rats.

Guinea pigs have a lower resistance to CO_2 than rats due to their lower buffer capacity and develop, in contrast to rats during exposure to 15% CO_2, a superimposed metabolic acidosis for 3 days as indicated in the fall of standard bicarbonate (Table 1) (30). As a consequence, guinea pigs exhibit 25–50% mortality during prolonged exposure to 15% CO_2, while rats have no mortality under these experimental conditions.

The guinea pigs which did not survive were unable to compensate the respiratory acidosis by three days or to elevate the pH above the low level attained at 6 h. They also were unable to raise their body temperature after the initial fall of 6–7°C.

The behavior of the body temperature turned out to be a good indicator of the acid-base status of the animals and their potential to adapt to chronic CO_2 exposure. These findings clearly prove the dependence of body temperature on pH in chronic respiratory acidosis.

Because of the many sided effects of CO_2 on physiological functions, it is difficult to identify the exact mechanism of action of CO_2 in regard to body temperature regulation. However, the results of these studies shed light on some of the effects of CO_2 involved in body temperature regulation.

CO_2 effects on heat production. Heat production is inhibited in guinea pigs during the first day of exposure to 15% CO_2, as indicated in a 30% fall of O_2 consumption below basal metabolic rate. During the subsequent period in which pH and body temperature increase, oxygen consumption returns to control levels after 3 days. This means that with the achievement of partial compensation of the acidosis, heat production returns to normal. This dependence of heat production on the level of acidosis is underscored by the behavior of body temperature in noncompensating animals after 3 days of exposure and points to a direct action of CO_2 or pH on metabolism, via pH-dependent enzymes (27). More specifically, an impairment of glucose and fat utilization for heat production must be considered when pH changes of the range (7.40 to 7.00) are encountered during exposure to 15% CO_2.

Other studies demonstrated that during exposure to 15% CO_2, a transient pH-dependent inhibition and subsequent recovery of glucose utilization occurs, as indicated in the elevation of blood sugar and decline of lactate and pyruvate during the acute phase of respiratory acidosis (14).

Phosphofructokinase activty which regulates glycolysis was found to be reduced 55% during maximal extracellular acidosis and showed a partial recovery during the later phase of exposure to 15% CO_2 without returning to control values (15).

These findings indicate that glucose energy sources cannot be sufficiently utilized for heat production during the acute phase of respiratory acidosis induced by exposure to 15% CO_2.

Acidosis also inhibits lipolysis and impairs fat utilization as demonstrated by Nahas and Poyart (21). In subsequent in vitro experiments using rat epididymal tissue, Triner and Nahas (34) demonstrated that acidosis in the medium inhibited the lipolytic activity induced by norepinephrine and ACTH, which suggest an inhibiting effect of H^+ on cyclic 3′,5′-AMP formation.

We obtained more evidence of inhibition of lipolytic activity during exposure of guinea pigs to 15% CO_2. No significant increase in free glycerol and triglycerides were observed, although there was a marked stress response during the first 2 days of exposure as indicated in an increase in blood corticosterone, decrease in adrenal catecholamines, and increase in free fatty acids (29). Moreover, the fat content of organs such as liver, muscle, and heart increased markedly during the first 3 days of exposure to 15% CO_2 in guinea pigs, which gives further support for the existence of an inhibition of lipolysis (30). Changes in fat metabolism seem to be of particular significance in chronic hypercapnia and require a more detailed investigation to elucidate the mechanisms involved.

CO_2 effects of heat loss. The well-known vasodilatory effects of inhalation of increased CO_2 concentrations on the skin blood vessels was also observed in guinea pigs exposed to 15% CO_2 for 1 h. The increase in the blood volume of the skin by nearly 60% must result in an increased heat loss. During the subsequent period in which pH and body temperature rose again, blood volume of the skin fell significantly below initial values. This means that with the achievement of partial compensation of the acidosis heat loss is reduced due to the vasoconstriction of skin blood vessels.

In this connection, it would be interesting to know whether an inhibitory action of CO_2 inhalation on the

cold thermoreceptors, as suggested by the experiments of Dodt (10) and Bowman, Hensel, and Witt (3), persists throughout the period of chronic hypercapnia, or whether it changes in association with the biphasic alterations of skin blood volume.

The biphasic changes in the skin blood content are most likely produced by the opening and closing of the extensive arteriovenous anastomoses, since the hematocrit did not change significantly during the large variations of blood volume associated with the two phases of respiratory acidosis. The opening of the arteriovenous anastomoses has been found to be associated with excessive blood flow resulting in heat dissipation (18). During the first 2 days of exposure to 15% CO_2, guinea pigs in particular hyperventilate strongly accompanied by a high degree of panting, which must result in an increased heat loss via the respiratory system and increased water loss. Stupfel (32) measured increased water loss in rats exposed to 10% CO_2.

CO_2 effects on endocrine control of temperature regulation. In the endocrine control of heat production, the adrenal medulla plays a major role by releasing epinephrine and norepinephrine and increasing metabolism. Evidence has been cited above showing an inhibitory effect of acidosis on the metabolic activity of catecholamines. On the other hand, numerous studies in guinea pigs (29), rats (22), and man (25) have demonstrated that acidosis produced by CO_2 inhalation causes a marked elevation of blood epinephrine and norepinephrine levels. In addition to the increased release of catecholamines, an increased synthesis of catecholamines was demonstrated in rats exposed to 20% CO_2 (22). We are dealing, therefore, with a dissociation or normally correlated functions. Acidosis stimulates enzymes that control catecholamine synthesis, and inhibits enzymes that regulate intermediary metabolism and are activated by catecholamines.

CO_2 effects on neurochemical control of temperature regulation. The pH-dependent fall in body temperature found in guinea pigs and rats could also have been caused by pH-dependent changes in the neurochemical transmitters of the hypothalamus affecting thermoregulation.

Epinephrine injections in the hypothalamic areas of guinea pigs and rats have been found to cause a rise in body temperature while injections of serotonin produce a fall in body temperature. According to Feldberg and Myers (11), norepinephrine and serotonin levels in the hypothalamus affect thermoregulation by stimulation or inhibition of the heat production and heat-loss pathways and influence the setpoint serving as a reference for the thermoregulatory system. The neurochemical theory of thermoregulation advanced by Feldberg and Myers (11) and Myers (19) has found further support by Cranston et al. (8) providing evidence concerning the effects of endogenous norepinephrine changes upon body temperature in cats and dogs. The findings reported here give additional support showing that the pH-dependent alterations in body temperature produced in chronic hypercapnia in guinea pigs are related to the changes in the concentrations of the endogenous epinephrine and serotonin in the hypothalamus. There is some evidence that the set point of body temperature regulation is changed by different internal stimuli and in particular by acidosis. Injections of norepinephrine in the anterior hypothalamus of unanesthetized guinea pigs increased O_2 uptake and body temperature and led to an upward shift of the threshold temperature for the onset of shivering (35). In a separate study carried out jointly with Dr. Wuennenberg, at the J. B. Pierce Foundation, the response of hypercapnic guinea pigs exposed for various time periods to 15% CO_2 in a cold environment (1 h at 15°C) was investigated (unpublished observations). During control conditions, oxygen consumption and electrical activity increased upon exposure to cold, but were suppressed following 1-h exposure to 15% CO_2. In animals which had reached partial compensation of the acidosis after 3 days of exposure to 15% CO_2, both energy production and muscle activity were restored to normal in response to cold. These findings demonstrate that during the acute respiratory acidosis induced by exposure to 15% CO_2 the threshold response to shivering is shifted to lower temperatures but returns to control levels following adaptation to CO_2. Moreover, the hypothalamic set point for shivering in conscious dogs breathing 5% CO_2 was found to be decreased by more than 2°C. (23).

The increase in oxygen consumption and the transient rise in body temperature found in guinea pigs during exposure to 3% CO_2 is in line with findings of Stupfel (33) who established that in most mammals O_2 consumption is increased during acute exposure to CO_2 concentrations between 3 and 10%. The increased oxygen consumption under these conditions is most likely caused by the CO_2 induced hyperventilation and the increased amount of respiratory work.

The multiple and complex effects of 15% CO_2 on physiological functions participating in thermoregulation observed in the present investigations can be summarized as follows. CO_2 effects on temperature regulation involve *1)* a direct inhibition of metabolism (oxygen consumption decreased 30% during the first day of exposure, resulting in a decreased heat production); *2)* increased heat loss through the skin due to vasodilation of skin blood vessels; *3)* a dissociation of adrenal function consisting of a stimulation of the adrenal medulla resulting in an increased catecholamine release and an inhibition of the action of catechol amines e.g., on fat metabolism; *4)* biphasic changes in the neurochemical transmitters controlling thermoregulation—a decrease and subsequent increase in norepinephrine content of the hypothalamus and opposite changes in the serotonin content were found to be associated with the decrease and subsequent increase in body temperature. Exposure to lower levels of CO_2 (3%) stimulated the metabolism and led to a transient rise in body temperature.

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