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Effect of hyperbaric-hyperoxic hyperventilation on blood, brain, and CSF lactate

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PLUM, FRED, JEROME B. POSNER, AND WIRT W. SMITH. *Effect of hyperbaric-hyperoxic hyperventilation on blood, brain, and CSF lactate.* Am. J. Physiol. 215(5): 1240–1244. 1968.—In previous experiments we found that lactate in CSF and brain rose substantially during hypocapnic hyperventilation with air at one atmosphere (1 atm) and even more if a 10% oxygen mixture was inhaled. The results suggested, but did not prove, that anoxia rather than alkalosis caused most of the lactate rise. To test this further, five dogs were hyperventilated for 5 hr in a hyperbaric chamber, with oxygen at 3 atm, to an arterial carbon dioxide tension (P_{aCO_2}) of about 12 mm Hg. Arterial and cerebral venous blood and cisternal CSF were sampled at 30, 90, 180, and 300 min and the brain was biopsied immediately after the last samples. Mean P_{aO_2} exceeded 2,000 mm Hg and mean cerebral venous P_{O_2} rose from a control of 39 mm Hg to 50 mm Hg. Blood lactate rose from a control of 1.12 to 2.72 mM at 300 min; CSF lactate rose from 2.20 to 4.29 mM. Brain lactate was 5.7 mM/kg wet wt. These values for CSF and brain lactate were significantly lower than those in the earlier experiments. The results reinforce the conclusion that severe hypocapnia at sea-level oxygen pressures induces substantial degrees of ischemic cerebral hypoxia.

lactate metabolism; brain acid-base; cerebral metabolism; hypocapnia; cerebral circulation; cerebrospinal fluid acid-base

WHEN EXPERIMENTAL ANIMALS are passively hyperventilated with air at one atmosphere (atm) of pressure so as to produce arterial carbon dioxide tensions (P_{aCO_2}) of about 10 mm Hg, the lactic acid concentration of the cerebrospinal fluid (CSF) and brain rises about threefold; concurrent increases in arterial and cerebral venous lactate are small and transient (13). If animals are hyperventilated to similar P_{aCO_2} levels while inhaling 10% O_2, the rise in brain and CSF lactate is nearly sixfold; the rise in blood lactate, while sustained, is less than twofold (13). One possible explanation for the large increases in brain and CSF lactate is that the hypocapnia causes sufficient cerebral vasoconstriction (5) to produce cerebral ischemia, thereby increasing anaerobic metabolism. If this hypothesis is correct, alleviation of cerebral hypoxia should curtail the brain's lactate production despite the same degree of hypocapnic hyperventilation. The present experiments test this hypothesis by hyperventilating dogs

MATERIALS AND METHODS

The experiments were conducted in a room-size hyperbaric chamber. Five dogs were anesthetized with pentobarbital sodium 30 mg/kg and paralyzed with gallamine. Supplementary anesthesia was given when necessary during the experiment. Cannulas were placed in the femoral artery and vein to record the blood pressure and to infuse fluids. The animals' calvaria were removed and cannulas were placed in the sagittal sinus to sample cerebral venous blood. A cannula was also placed in the cisterna magna to sample CSF and attached to a three-way stopcock so that the dead space of both the syringe and cannula could be washed out before each sampling. Expired CO_2 was sampled from the endotracheal tube and led to an infrared CO_2 analyzer outside the hyperbaric chamber. The animals were ventilated through cuffed endotracheal tubes by a respirator pump modified for hyperbaric chamber use. A bipolar electroencephalogram (EEG) was taken from leads placed on the dura in the frontal and parietal area of each side. Control samples of arterial blood, cerebral venous blood, and CSF were secured while the animals were ventilated on room air at 1 atm of pressure at P_{aCO_2} levels of approximately 40 mm Hg. Immediately after the control samples were taken, the chamber was pressurized to 3 atm absolute pressure and the animals were hyperventilated with oxygen to achieve P_{aCO_2} levels of approximately 10 mm Hg. Arterial, sagittal venous blood, and CSF samples were taken at 30 min, 90 min, 180 min, and 300 min after the onset of hyperventilation. Immediately after obtaining the 300-min sample, a cerebral biopsy was removed and promptly deproteinized by homogenizing in cold 6% perchloric acid. The biopsy could be removed and placed in the PCA in about 5 sec.

Blood and spinal fluid pH, P_{CO_2}, and P_{O_2} were meas-

TABLE 1. *Effect of hyperventilation on acid-base balance, oxygen tension and organic acid concentrations of blood and CSF*

	Hyperoxic Hyperventilation*						Eupoxic Hyperventilation†				
	pH	P_{CO_2}, mm Hg	HCO^-_3, mM	P_{O_2}, mm Hg	Lactate, mM	Pyruvate, (mM)	*pH*	P_{CO_2}, mm Hg	HCO^-_3, mM	P_{O_2}, mm Hg	Lactate, mM
			Resting						*Resting*		
Arterial	7.371 ±.014	40.4 ±1.4	22.8 ± .2	104 ±6.1	1.12 ±.15	.132 ±.014	7.264 ±.041	45.5 ±3.7	20.0 ±0.7		1.69 ±0.22
Sagittal	7.301 ±.012	50.5 ±1.6	24.3 ± .6	38.8 ±2.7	1.10 ±.15	.154 ±.024	7.204 ±.041	56.5 ±4.1	21.5 ±0.7	46.6 ±5.7	1.76 ±0.27
CSF	7.372 ±.018	40.5 ±1.5	22.8 ± .8	68.5 ±8.2	2.20 ±.15	.450 ±.038	7.316 ±.024	55.6 ±6.7	24.9 ±1.7		2.50 ±0.26
			30 Min						*60 Min*		
Arterial	7.790 ±.022	10.8* ±0.8	16.8 ±1.0	2177 ±26	1.82 ±.32		7.672 ±.056	11.8 ±2.3	12.9 ±0.6		4.25 ±0.70
Sagittal	7.507 ±.024	27.7 ±2.4	21.2 ±1.2	53.0 ±7.1	1.85 ±.27		7.534 ±.054	18.8 ±2.9	14.9 ±0.5	24.8 ±1.4	4.64 ±0.60
CSF	7.621 ±.026	20.6 ±1.8	20.7 ±1.5	575 ±19	2.70 ±.25		7.627 ±.022	15.1 ±1.3	14.6 ±1.8		6.09 ±0.64
			90 Min						*120 Min*		
Arterial	7.724 ±.029	10.2 ±0.9	13.3 ±1.2	2094 ±79	2.32 ±.57		7.741 ±.044	7.6 ±0.9	10.1 ±1.0		5.06 ±1.28
Sagittal	7.475 ±.224	27.6 ±1.9	20.1 ±1.7	49.2 ±8.3	2.39 ±.52		7.573 ±.036	14.3 ±2.1	12.9 ±1.5	21.6 ±1.0	5.76 ±1.31
CSF	7.593 ±.062	18.6 ±0.8	17.5 ±2.7	718 ±108	4.30 ±.35		7.673 ±.053	12.2 ±0.6	14.9 ±1.8		5.24 ±1.03
			180 Min						*180 Min*		
Arterial	7.669 ±.041	11.8 ±0.8	13.5 ±0.7	2162 ±39	2.58 ±.56		7.730 ±.025	9.1 ±0.6	12.6 ±1.2		3.61 ±1.00
Sagittal	7.425 ±.033	31.0 ±2.4	19.6 ±1.0	48.0 ±9.9	2.79 ±.53		7.614 ±.029	13.7 ±1.0	14.0 ±1.0	24.2 ±2.9	4.58 ±1.33
CSF	7.562 ±.027	21.5 ±2.6	18.6 ±1.4	608 ±51	4.07 ±.50		7.614 ±.034	13.7 ±1.7	13.3 ±0.6		7.41 ±0.54
			300 Min						*300 Min*		
Arterial	7.567 ±.056	11.6 ±0.6	10.9 ±1.3	2169 ±64	2.72 ±.55	.224 ±.034	7.762 ±.037	8.0 ±0.7	11.2 ±0.5		2.17 ±0.37
Sagittal	7.368 ±.044	32.2 ±3.6	17.7 ±1.3	55.8 ±2.9	2.91 ±.53	.228 ±.031	7.621 ±.031	13.8 ±0.7	13.7 ±0.7	24.1 ±0.8	2.50 ±0.53
CSF	7.495 ±.030	22.3 ±2.4	16.4 ±1.3	477 ±58	4.29 ±.94	.540 ±.078	7.520 ±.032	15.6 ±2.7	11.6 ±1.6		7.64 ±0.80

Values are means ± SE. * Since the P_{CO_2} electrode meter scale does not register values below 10 mm Hg, the P_{CO_2} value of arterial blood samples below 10 mm Hg was calculated from the measured arterial pH and the base excess of venous blood. Base excess of venous blood was assumed to be the same as that of the simultaneously drawn arterial sample. † Values for eupoxic hyperventilation are from a previous study (13) presented here for comparison with the hyperbaric data.

ured on an Instrumentation Laboratories (IL) blood-gas analyzer immediately after the samples were taken. A Radiometer pH microelectrode was attached to the IL amplifier to measure pH. These measurements were made at the atmospheric pressure at which they were drawn. Blood and spinal fluid samples were also drawn as rapidly as possible at each period and deproteinized in cold 6% perchloric acid. Lactate and pyruvate levels were determined by standard enzymatic methods.

RESULTS

During hyperoxic hypocapnia, oxygen tensions rose in both the arterial and cerebral venous blood. The mean value and standard error at each point in the experiment is summarized in Table 1. Arterial oxygen tension, which was about 100 mm Hg during the control period, rose to over 2,000 mm Hg when the animals were ventilated at 3 atm of oxygen and remained there throughout the experiment. Mean sagittal venous oxygen tension, which had a control level of 39 mm Hg, rose to 50 mm Hg during hyperbaric-hyperoxic hyperventilation and in only two individual samples in the entire experimental series did the tension fall below control values. This preservation of a high cerebral venous oxygen tension during hyperventilation contrasted with the consistent drop in sagittal blood oxygen tension noted in our previous animals hyperventilated with air at 1 atm pressure (Fig. 1).

The mean arterial, venous, and CSF pH and P_{CO_2} values at control levels and during hyperbaric-hyperoxic hyperventilation are presented in Fig. 2 and Table 1. The arterial P_{CO_2} decreased promptly to approximately 10 mm Hg (the P_{CO_2} electrode does not measure values below 10 mm Hg), and then increased slightly toward the

end of the experiment, reflecting a slight decrease in the rate of ventilation required to maintain the arterial blood pressure above hypotensive levels. The cerebral venous P_{CO_2} initially declined from a prehyperventilation value of 50.5 mm Hg to a mean of 27.7 mm Hg and rose slightly in parallel with the arterial P_{CO_2} toward the end of the experiment. Changes in the CSF P_{CO_2} were much the same. The pH values of the arterial blood, the venous blood, and the CSF initially rose with hyperventilation, then gradually decreased throughout the experiment. The diminishing pH values resulted in part from a slight rise in P_{CO_2} and in part from a rise in lactate concentrations (discussed below), but at no time did the pH in either the blood or CSF fall below the control level.

The mean arterial lactate rose during hyperbaric hyperventilation from a control value of 1.12 mM to 2.72 mM at 300 min ($P < .05$). The cerebral venous lactate values paralleled those of the arterial blood and there was no significant difference between the two at any point.

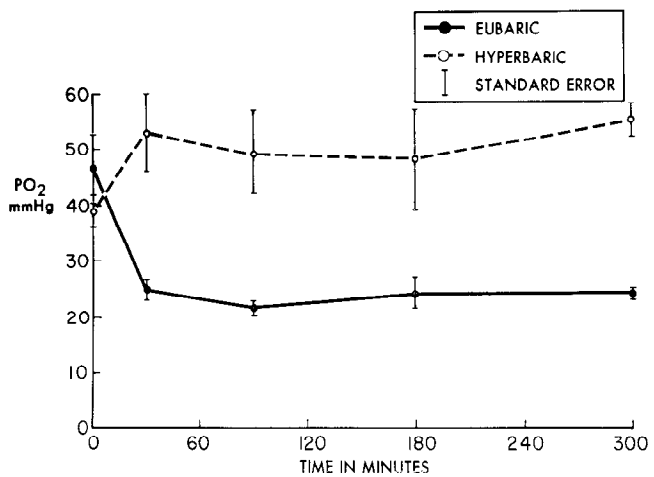

FIG. 1. Sagittal venous oxygen tension during eubaric and hyperbaric hyperventilation. At zero time the animals are breathing air at 1 atm pressure with P_{aCO_2} about 40 mm Hg. Hypocapnic hyperventilation at 1 atm pressure produced a prompt and sustained fall in P_{vO_2}. The same degree of hypocapnic hyperventilation under 3 atm of oxygen produced a rise in P_{vO_2}. The eupoxic data is from a previous study (13).

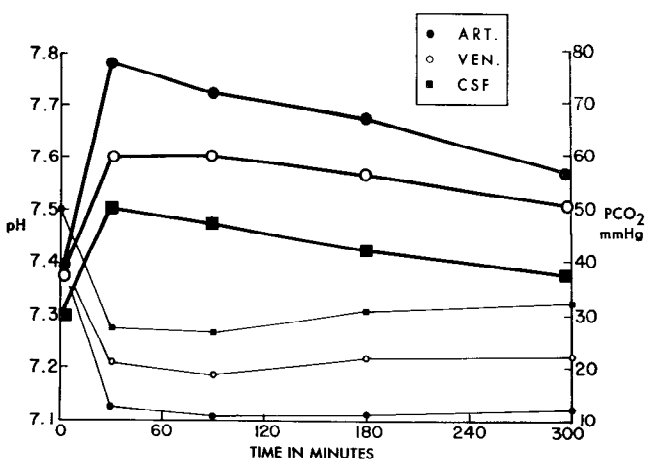

FIG. 2. Effect of hyperbaric hyperventilation on pH and P_{CO_2} of blood and CSF. The thick lines represent pH (*ordinate* on the left) and the thin lines P_{CO_2} (*ordinate* on the right).

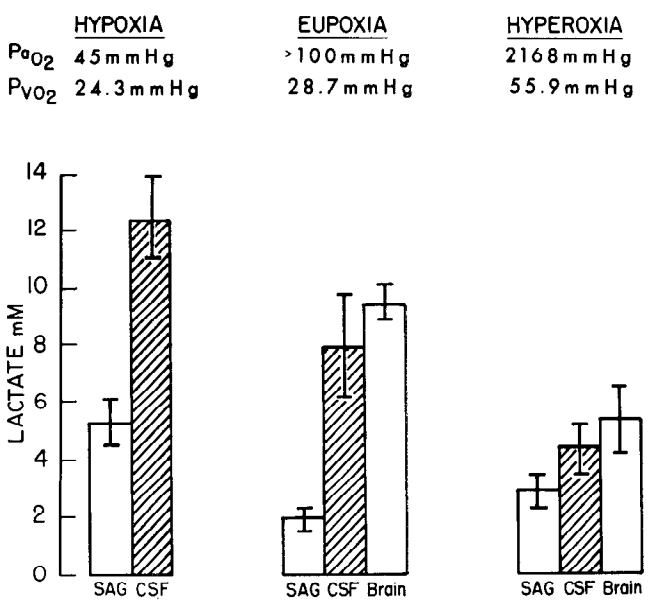

FIG. 3. Cerebral venous, CSF, and brain lactate concentrations during hypoxic, eupoxic, and hyperoxic hyperventilation. The values (mean ± SE) for blood and CSF are mM/liter and the values for brain mM/kg wet wt. Despite the higher cerebral venous lactate under hyperoxic conditions, both CSF and brain lactate concentrations were lower than under eupoxic conditions. The P_{O_2} values represent the mean values at the time the brain was sampled. In the eupoxic group, the mean P_{vO_2} had been lower than 28.7 mm Hg during most of the 6 hr of hyperventilation. The hypoxic and eupoxic values are from a previous study (13).

Figure 3 compares CSF and brain lactate values during hyperventilation with hyperoxia, eupoxia, and hypoxia. In the present experiments, the CSF lactate rose only 2 mM/liter (to a mean of 4.29 mM) during the 5 hr of hyperbaric-hypoxic hyperventilation. One of the five animals developed no increase in CSF lactate and in only one did the increase reach even the lowest level achieved by any animal in the previously studied series hyperventilated at 1 atm pressure (13). The mean lactate level in the brain was 5.7 mM/kg wet wt, a value higher than in either the blood or the CSF, although closer to the latter. The mean brain lactate level, like the CSF lactate level, was appreciably lower than had been observed in the previous experiments with animals hyperventilated at 1 atm (Fig. 3).

Pyruvate concentrations increased in both the blood and the CSF, but the pyruvate changes were relatively smaller than those of lactate, producing an increase in the lactate-pyruvate ratio between the control and final samples. The control ratios were: arterial blood 8.4, venous blood 7.1, and CSF 4.9. After hyperoxic hyperventilation, these ratios rose to 12.1, 12.7, and 7.9, respectively. The mean percent "excess lactate" (7) produced was arterial 45, venous 64, and CSF 36%.

Mean cisternal oxygen tensions during hyperbaric-hyperoxic hyperventilation rose to about 500 mm Hg and

lay between the arterial and sagittal venous blood oxygen tensions.

It was inexplicably more difficult in these experiments than in the previous ones to maintain an effective blood pressure in the face of the adverse circulatory effects of respirator-induced hyperventilation (13). The mean control blood pressure (BP) was 120/70 mm Hg; this dropped to 95/65 mm Hg as hyperventilation was begun, and in several instances tended to decline further unless the respirator pump was slightly slowed. The BP was not allowed to fall below 90/60 mm Hg but, as Table 1 indicates, this required accepting $Paco_2$ levels slightly above the desired goal of 10 mm Hg.

The EEG was monitored throughout the experiment. No seizure discharges were observed.

DISCUSSION

Effects of hyperoxia on cerebral oxygenation. Hypocapnic hyperventilation produces intense cerebral vasoconstriction and several investigators imply that this can lead to brain ischemia. Hyperventilation lowers cerebral venous oxygen tensions in both man (5) and animals (13) to values believed to be incapable of sustaining normal tissue oxygen tensions at a distance from the capillary (18). Also, cerebral oxygen uptake has been found in some experimental animals to decrease during profound hyperventilation (10). The EEG regularly slows during hypocapnic hyperventilation (11) and Reivich has reported (16) that cerebral ischemia probably is at fault since the slowing disappears with hyperbaric oxygenation at the same blood CO_2 tensions. In our previous series of animals, hyperventilated at 1 atm pressure, the oxygen tension of the sagittal venous blood fell to a mean level of 24 mm Hg.

Several things indicate that the brain was adequately oxygenated during hyperbaric-hyperoxic hypocapnia. Perhaps the best evidence is that the mean sagittal venous blood oxygen tension rose to 50 mm Hg. There are no arteriovenous shunts of significant size in cerebral tissue (6) so this high venous oxygen tension implies that the cerebral tissue being drained by the sagittal sinus was receiving sufficient oxygen to meet its metabolic demands. Further evidence that the brain was being sufficiently oxygenated comes from the high levels of cisternal oxygen tension. Several investigators (1, 8, 20) have found oxygen tensions in the CSF to be decreased during cerebral anoxic and ischemic states. Our data, however, cannot rule out the possibility that some areas of the brain were either marginally perfused or were actually ischemic when the remainder of the brain was receiving a sufficient oxygen supply.

Not only was the venous oxygen tension higher in the hyperoxic dogs but the cerebral venous CO_2 tension was also higher (mean 29.6 mm Hg for hyperoxic dogs and 15.1 mm Hg for eupoxic dogs). The higher venous P_{CO_2} value and the wider arterial-venous P_{CO_2} difference in the hyperoxic dogs suggests that the cerebral blood flow in these animals was less than in the eupoxic group. A lower cerebral blood flow in the hyperoxic group could have resulted from an inadequate blood pressure in these animals and, if so, might have led to cerebral ischemia and accounted for the small increases in lactate which we observed. However, if cerebral ischemia did result from inadequate cerebral perfusion, one would expect low, not high, venous and cisternal P_{O_2} levels. An alternate, and preferable, explanation is that the higher cerebral blood flow in the eupoxic group resulted from hypoxic cerebral vasodilatation which partially opposed the hypocapnic cerebral vasoconstriction. In the hyperoxic group, the absence of cerebral hypoxia allowed the unopposed cerebral vasoconstrictor effects of hypocapnia. If this explanation were correct, the lower cerebral blood flow in the hyperoxic animals would be additional evidence that adequate cerebral oxygenation existed.

The increased lactate-to-pyruvate ratios (L/P) and the resultant production of "excess lactate" are similar to our previous results (13) and those of others studying eupoxic hypocapnia (4, 19). The production of excess lactate has been viewed by Huckabee (7) to result from tissue hypoxia but the validity of this concept has been challenged on both experimental (4, 19) and theoretical (12) grounds.

Cause of increased cerebral lactate. Both alkalosis and anoxia can result in an increased tissue lactate production. Slices or minces of brain incubated in fully oxygenated alkaline fluids produce considerably more lactate than does tissue incubated at either physiologically normal or acid pH values (2, 9). The mechanism of increased lactate production is increased glycolysis probably resulting from stimulation of the enzyme, phosphofructokinase (17). Alkalosis increases lactate production in many tissues (19, 7). The lactate produced in systemic tissues diffuses rapidly into the bloodstream and is then removed and metabolized by the liver, thus accounting for the small rises seen in blood lactate. However, diffusion of lactate from brain and CSF is slow (15) and one would expect to see higher lactate levels in these organs even if the production rate were no greater than in systemic organs. If alkalosis were the sole cause of the rise in brain and CSF lactate during hypocapnia, there should be no difference in the increased lactate levels produced during eupoxic hypocapnia and hyperoxic hypocapnia provided the degree of alkalosis was the same.

This was, however, not the case: lactate increases were smaller in both the brain and the CSF during hyperoxic hypocapnia although there was no significant difference in the pH of the CSF between the eupoxic and hyperoxic animals. (Largely because of the greater lactate accumulation blood pH was 0.20 pH units lower in the hyperoxic animals at the end of the experiment.) Even if one speculates that interference with CO_2 transport produced by high-oxygen tensions may have resulted in less alkalosis in the brains of the hyperoxic animals at $Paco_2$ values comparable to those of the eupoxic animals, the resulting pH differences would be small, i.e., a few hundredths of a pH unit, as compared with the large alterations, several tenths of a pH unit, required to change lactate produc-

tion by in vitro methods. Therefore, the present experiments reinforce the conclusion that most of the increased lactate production by brain observed during eupoxic and hypoxic hypocapnia can be attributed to ischemic cerebral tissue anoxia. The explanation of the small rises in brain and CSF lactate produced by hyperoxia-hypocapnia remains a problem. There is no certainty that all of the brain was adequately oxygenated during these experiments and the lactate increases might represent anacrobic glycolysis from small areas of ischemic brain. If all areas of the brain were fully oxygenated, the increased brain and CSF lactate in these experiments probably represents the direct effects of alkalosis.

Relationships among blood, brain, and CSF lactate. These observations reaffirm (13) that measurement of lactic acid in the CSF produces a more reliable index of cerebral concentrations than does measurement of lactate in the arterial or cerebral venous blood. Prockop (15) has suggested that lactic acid leaves the brain to enter the bloodstream by passive diffusion. This mechanism may be sufficient to maintain cerebral and CSF lactate values close to those of serum when cerebral lactate production is normal, but we and others (14, 15) have demonstrated that acute alterations of cerebral metabolism can produce wide differences between blood and cerebral or cerebral spinal fluid lactate, so that large rises in CSF lactate are not reflected by abnormal values in either the arterial or cerebral venous blood.

Blood lactate values in these experiments changed somewhat differently from those in our earlier studies. Previously, after 6 hr of hypocapnic hyperventilation, there was no rise in the arterial or sagittal venous lactate from control levels despite a marked rise in both the CSF and brain lactate levels. In the present experiments there was a moderate but clear-cut and sustained rise in the arterial and sagittal venous blood lactate concentrations despite a rise in brain lactate that was significantly smaller than the rise in brain lactate that occurred at 1 atm pressure. The present rise in the arterial blood lactate perhaps suggests a reason for the disparity between our earlier data with cubaric hyperventilation and that of Eichenholz et al. (3). Eichenholz found large rises in blood lactate in dogs during hyperventilation at normal atmospheric pressure, often sufficient to cause the animals to become acidotic. We noted in the present animals considerable difficulty in maintaining BP when using the respirator pump and suspect that the greater blood lactate rise resulted from inadequate perfusion of peripheral tissues. If the same had happened to Eichenholz's animals, it would explain the rise in blood lactate and the fall of pH during his experiments.

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