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Metabolic control in a state of decreased activation: modulation of red cell metabolism

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JEVNING, R., A. F. WILSON, H. PIRKLE, J. P. O'HALLORAN, AND R. N. WALSH. *Metabolic control in a state of decreased activation: modulation of red cell metabolism*. *Am. J. Physiol.* 245 (Cell Physiol. 14): C457-C461, 1983.—Very little is known in depth of the biochemical and physiological changes induced at the cellular level by human behavioral states. For study of the physiology of behavior at this level, the erythrocyte may be useful, because it is readily available and its metabolism and metabolic control are comparatively well understood. In this report we describe a marked decline of red cell glycolytic rate induced by the transcendental meditation technique (TM). This decline was significantly correlated with decreased plasma lactate concentration and with relaxation as indicated by electrodermal response. The occurrence of sleep was not correlated with the metabolic changes. The observed lack of variation of blood pH, blood gases, glucose, and hematocrit in this behavior implies that the decrease of erythrocyte metabolism is not an epiphenomenon of respiratory change or substrate availability. Based upon further measurements indicating persisting alteration of the red blood cell, we suggest the possibility of attachment of a humoral agent(s) to the cell in the mechanism of this effect. This behavioral effect is unique, and the effector(s) responsible may increase our understanding of metabolic control of the erythrocyte and of TM.

consciousness; behavior; meditation; blood glycolysis; lactate

GLYCOLYSIS accounts for approximately 90% of human red cell metabolism, and the detailed mechanisms of glycolysis in this cell are comparatively well understood (1, 2, 18, 26). Possible effectors range in size and complexity from small inorganic ions such as phosphate and magnesium to hormones such as epinephrine and growth hormone. However, it remains to be shown that modulation of red cell glycolytic rate, and, in particular, human red cell glycolytic rate, by these or other agents occurs *in vivo* and is significant under physiological conditions.

In this report we describe a unique response of human red cell metabolism to a physiological state of reduced activation induced by the stylized procedure known as the "transcendental meditation technique" (TM) (7-11, 25). Possible change of red cell metabolism in this state was suggested by previous observations of rapid decline of plasma lactate concentration during TM (9, 25) and the fact of a major contribution by the red cell-to-whole blood lactate content in normal resting humans (14). Several relevant physiological variables have been well characterized during this behavior, including hormonal, circulatory, and blood gas changes (7-11, 25). Because practitioners are a relatively numerous and homogenous

group in terms of induction of a modified state of physiology (11, 25), the study of this phenomenon and the mechanism(s) responsible may contribute to better understanding of red cell metabolic control and its significance under normal circumstances.

METHODS

Subjects and experimental protocol. We studied 32 normal male subjects with at least 6 yr of experience in this technique, all of whom are instructors of TM. These individuals regularly elicit this behavior twice daily for 20-40 min. As far as possible, subjects were observed at the same time between 10:30 and 12 A.M. in a comfortably seated arrangement. Subjects were fasted since midnight. Uniform conditions of reasonable quiet, low-level lighting and a constant comfortable room temperature were maintained; these conditions approximate normal circumstances of TM practice. Previous to the day of the experiment, there were at least two accommodation periods (leads for electrophysiological monitoring were attached) and the subject was asked to rest or practice TM in the laboratory situation. Signed consent was also obtained at this time.

To minimize effect of testing and interaction of testing with practice, an experimental time series design similar to one recommended by Campbell and Stanley (3) was used; this design does not employ a pretest period. Subjects were studied on two occasions, 1 wk apart. On one occasion, the subjects were asked to close their eyes and practice TM for 45 min, followed by a recovery eyes-open period of 30 min. On the other (control) occasion, subjects were asked to read a "relaxing" selection of their own choice for 45 min followed by a 30-min period without reading. The sequence of practice and reading occasions was randomized. All subjects were told that it was acceptable to sleep during practice if that was the tendency.

Blood sampling was performed twice: once during TM and once during the control occasion. Prior to the beginning measurements, an arterial catheter (1.5 in. 20-gauge Longdwell) was placed percutaneously into a brachial artery. Subjects were not able to see insertion of the catheter, because their arms were placed through a slit curtain and the actual insertion was painless after local anesthesia was achieved with 1% lidocaine. After insertion, there was a 2.5-h wait period during which subjects were free to move; this period was necessary, because venipuncture is associated with large alterations in blood constituents such as plasma-free amino and free fatty

acid, with return to basal levels generally assured after 1 h (21). Before starting the experiment, subjects were comfortably seated in a quiet enclosure 6 × 6 × 8 ft, which permitted blood drawing outside the area without disturbing the subject.

To monitor occurrence of sleep, a unipolar electroencephalogram (EEG), electromyogram (EMG), and electrooculogram (EOG) were recorded during practice periods. As a marker of cognitive relaxation, phasic electrodermal response (EDR) was also measured (12).

Preparation of blood and metabolic measurements. Eighteen-milliliter arterial blood samples were taken every 15 min into heparinized syringes throughout practice and after-practice periods at 0, 15, 30, 45, 60, and 75 min. Two milliliters of blood were used for determination of blood gases (Radiometer ABL Blood Gas Laboratory, Radiometer, Copenhagen, Denmark), glucose, and hematocrit.

The remaining 16 ml of blood were immediately placed in ice water and subsequently divided into two equal volumes (all preparations were open to air unless otherwise noted). One was used for determining rate of total whole blood aerobic lactate generation and concentration of whole blood lactate, and the second was used for measuring the lactate generation rate by red blood cells resuspended in "isologous" plasma (i.e., red blood cells from *times 0, 15, ... 75 min* were resuspended in plasma from the corresponding *times 0, 15, ... 75 min*). Red blood cells were separated from this second volume by centrifugation at 2,000 *g* followed by aspiration of the buffy coat and upper layer of red blood cells. Cells were then washed two times by alternate resuspension and centrifugation in isotonic ice-cold saline. The red blood cells were then resuspended in their isologous plasma with amounts of remaining cells and plasma adjusted to give the same hematocrit as the original volume of whole blood. Both aliquots were kept at 4°C during this preparatory period to ensure minimal lactate generation. Subsequently, both whole blood and red cell-plasma volumes were incubated at 37°C in an atmosphere of 5% CO₂-95% air (Fisher Isotemp Series 400, Fisher Scientific, Pittsburgh, PA) for 20 min to replace CO₂ lost during preparation (5), to restore approximately the pH of the sampled blood. To check this, pH was remeasured. Both volumes were then each divided into two equal portions for aerobic incubation at 37 and 25°C for 90 min. Lactate generation rate was then determined from slopes of best-fit lines through lactate concentrations measured at 0, 30, 60, and 90 min. The incubation at 25°C was for possible enhancement of the putative effect on red cell metabolism at a different temperature. Measurements of lactate concentration were performed in duplicate (utilizing a Technicon autoanalyzer (Technicon Instrument, Tarrytown, NY) by use of an enzymatic method (6), except that the supernate for analysis was prepared by delivery of 0.45 ml of sample into 0.90 ml of 5 N ice-cold perchloric acid followed by neutralization with 5.63 N K₂CO₃ according to the methods of Beutler (2), with modifications of McManus (personal communication). Mean difference (±SE) between the known values and determined standard lactate concentrations in the assays was 2.1 ± 1.7% with correlations 0.95 ≤ *r*

≤ 0.99.

In addition to these aerobic incubations, anaerobic whole blood glycolytic rate at 25°C was measured in 20 subjects in the same manner, except that blood was incubated in capped syringes by the drawing of 8 ml of extra blood. The purpose of the anaerobic measurement was evaluation of the sensitivity of the possible metabolic effect to pH, because anaerobic pH differs markedly from pH during aerobic incubation (5; and Fig. 3).

Finally, measurements called the "plasma exchange experiment" were performed in 14 subjects restudied in the same manner, except that in the red cell measurements, to the separated erythrocytes of each sample (*times 0, 15, 30, ... min*) was added plasma from the *time 0* sample, instead of their own sample, and glycolytic rate was again measured. The time course of glycolytic rate in this exchange series was then compared with the normal time series plasma-red cell preparations. The rationale for this procedure was that unless a persisting change of the erythrocyte occurs [possibly by attachment of inhibitory agent(s)], a significant trend in the normal series would be eliminated by this separation of red blood cells from their isologous plasma.

Metabolic data consisted of rates of aerobic lactate generation every 15 min at 37 and 25°C by whole blood samples, by red blood cells suspended in their own and in *time 0* plasma, and of anaerobic lactate generation at 25°C by whole blood samples. Similarity of trends of metabolic rate in whole blood and red cell preparations would be attributed to primary contribution by red blood cells to the behavior-associated decline of blood metabolism. Data were analyzed in an analysis of variance with groups and time as classification variables (24).

RESULTS

Figure 1 describes marked decline of aerobic blood

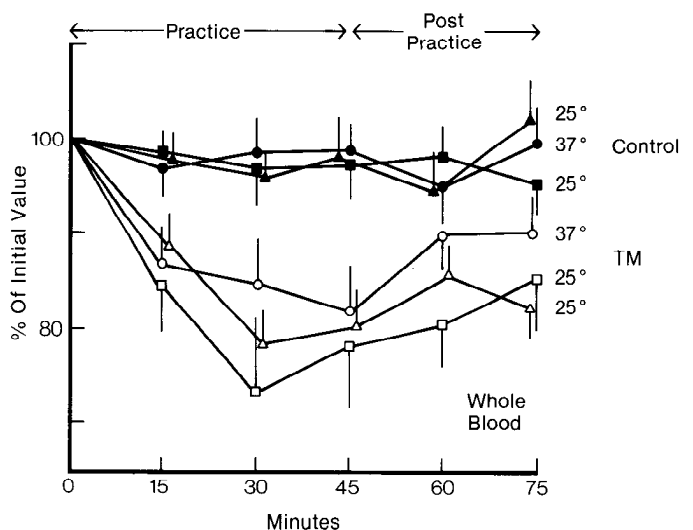


FIG. 1. Change of either aerobic or anaerobic (capped syringes) lactate generation rate by whole blood during and after transcendental meditation (TM) practice or reading control periods. Values displayed for each 15-min interval are means ± SE for 32 subjects of rates expressed as percentages of the *time 0* generation rate. Practice aerobic incubations were at 37°C (○) and 25°C (□); control aerobic were at 37°C (●) and 25°C (■). Practice (△) and control (▲) anaerobic measurements were at 25°C only.

glycolytic rate at 37 and 25°C during TM compared with either *time 0* or control samples; the decline was larger at 25°C, although the difference between the two trends was not significant. Also shown is the similar decline of anaerobic blood glycolytic rate at 25°C. The practice trends were significant ($P < 0.001$) and differed significantly ($P < 0.01$) from the control measurements with insignificant time variations. Figure 2 illustrates corresponding trends of aerobic glycolytic rate by the separated red cell preparations incubated in their own plasma. These patterns were not significantly different from the whole blood measurements, consistent with primary contribution of the red cell to decline of whole blood lactate generation. Approximately 80% of TM subjects showed decline of glycolytic rate; Table 1 shows the data at 0 and 30 min from which mean glycolytic rate changes were calculated for TM and control occasions. Table 2 shows initial values (*time 0*) of glycolytic rate for the different conditions; the data agree with those reported previously (1, 2, 18, 26).

Gourley and Matschiner (5) reported a marked increase in blood pH upon exposure to air, due to loss of CO₂. In this study, pH during the 90-min aerobic incubations increased to approximately 8.1 for whole blood and the red cell preparations at 37°C, while increasing to approximately 7.8 at 25°C (Fig. 3). These conditions were much more basic than the pH of the anaerobic 25°C series, which decreased to 7.0. The initial pH values of all incubations series were very similar and comparable to the originally sampled blood values of Table 3, with no significant difference of trends of pH change between TM and corresponding control blood incubations.

Results of the plasma exchange experiment are shown in Fig. 4; there was no significant difference between trends of glycolytic rate at 25 and 37°C during this experiment and the trends of the normal time series experiment in either the whole blood or red cell meas-

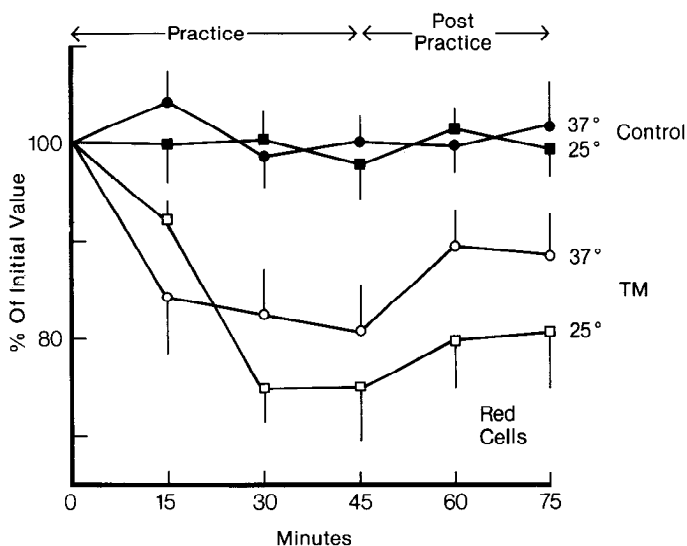


FIG. 2. Change of aerobic lactate generation rate by separated erythrocytes resuspended in their own plasma during and after transcendental meditation (TM) practice or reading control periods. Practice incubations at 37°C (○) and 25°C (□). Control incubations at 37°C (●) and 25°C (■). Means \pm SE of percentages of initial value for the same subjects as in Fig. 1.

TABLE 1. Initial and 30-min lactate generation rate values at 37°C

	TM		Control	
	0 min	30 min	0 min	30 min
	3.7	2.3	2.9	1.7
	2.6	1.0	3.1	2.5
	3.1	2.8		2.1
	2.7	2.4	2.6	2.6
	3.2	3.7	2.8	3.1
	3.4	1.3	3.1	2.8
	3.9	2.9	4.2	3.6
	2.0	2.8	2.9	2.9
	4.9	1.2	2.9	3.0
	1.8	0.7	4.7	3.8
	4.8	3.8	2.1	1.8
	2.7	1.6	4.7	3.9
	3.6	2.2	1.0	
	1.9	1.6	2.8	2.3
	5.0	3.8	3.4	3.1
	1.8	0.8	2.0	2.4
	1.9	1.2	2.1	2.4
	3.7	2.8	4.8	6.0
	2.7	1.9	2.9	3.2
	2.5	1.6	3.9	4.5
	2.2	1.6	2.9	2.9
	4.1	2.8	2.6	2.9
	1.7	1.7	4.2	3.8
	3.6	1.8	2.1	2.0
	3.0	3.0	2.7	2.9
	2.7	1.0	3.8	3.6
	2.6	2.3	3.0	2.9
	2.4	1.8	2.9	1.9
	1.9	1.5	3.6	4.7
	2.1	2.7	2.1	2.5
			1.7	1.4
Mean	2.9	2.1	3.0	2.9
\pm SE	± 0.2	± 0.1	± 0.2	± 0.2

Values are given in μ moles per milliliter cells per hour.

TABLE 2. Initial lactate generation rate

	37°C	25°C
Whole blood aerobic	3.2 \pm 0.3	1.5 \pm 0.2
Whole blood anaerobic		1.2 \pm 0.1
Red cell aerobic	2.9 \pm 0.2	1.7 \pm 0.1

Values are means \pm SE in μ moles per milliliter cells per hour.

urements (Figs. 1 and 2).

Concentration of arterial lactate declined during TM; initial lactate concentration did not differ between TM and control occasions (Table 3). Table 3 also shows that no significant variation in any group was noted of arterial O₂ and CO₂ tensions (P_{O₂} and P_{CO₂}, respectively), pH, base excess, hematocrit, or glucose.

On the average, 85% of meditation time in these subjects was spent in wakefulness and 15% in *stage 1 sleep* in general agreement with previous findings (7, 8, 10). Standard correlation analysis (24) did not reveal a relationship between total sleep time or sleep stage percentage and change of generation rate. Significant decrease of EDR occurred during the TM period. Partial correlation analysis (24) among blood glycolytic rate, lactate content, and EDR showed a significant relationship between glycolytic rate and both lactate content and EDR (36 and 40% of variance of glycolytic rate, respectively).

DISCUSSION

In summary, these results indicate decreased whole blood metabolism during TM; this was accounted for mostly by decline of red cell glycolysis [according to Bartlett and Marlow (1), 90–95% of human blood lactate generation is due to red cells]. This effect was correlated with relaxation as indicated by both electrodermal response and decline of plasma lactate concentration. Because rate of muscle and skin lactate generation does not change during TM (7), red cell glycolysis supplies a major proportion of total blood lactate (14), and decline of blood lactate concentration in this experiment correlates with decline of red cell metabolism, the decrease of red cell metabolism is almost certainly the major contributor to the plasma lactate decline (Table 3; Refs. 7, 9, 25).

Although we do not know the cause of this effect from

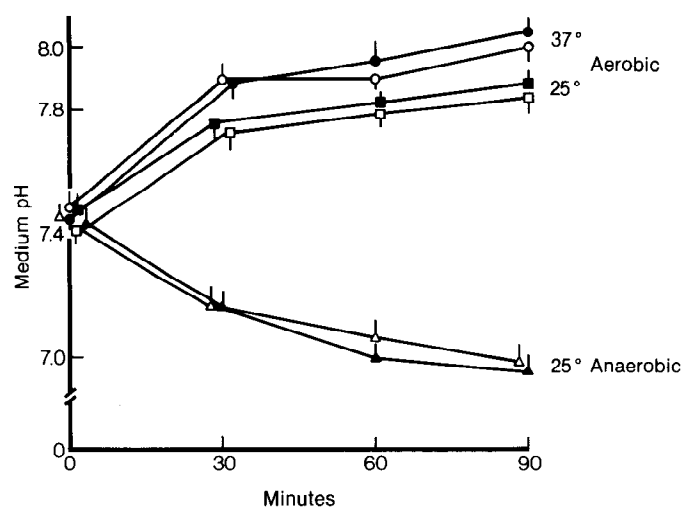


FIG. 3. pH (means \pm SE) during whole blood incubations of transcendental meditation (TM) group. Data is displayed from aerobic incubations of blood drawn during TM at 37°C (○) and 25°C (□); it was also drawn from the same subjects during control reading at the same temperatures: 37°C (●) and 25°C (■). Anaerobic incubation at 25°C—blood in capped syringes—is also shown during TM (Δ) and control (\blacktriangle). These results are averages of 30- and 45-min sample incubations in 10 subjects.

this study, several mechanisms can be reduced in likelihood based upon the biochemistry of the red blood cell and the physiology of TM. Reduction of metabolism due to decreased glucose transport is unlikely; whereas glucose is the predominant substrate of red cell glycolysis, and metabolism in some tissue is regulated by substrate permeability, facilitated glucose transport in the mammalian red blood cell is 2- to 250-times greater than rate of glucose phosphorylation (17, 25). Also, mean blood glucose levels were unaltered during TM (Table 3). The possibility that a decrease in the number of red blood cells is responsible for the noted decline of whole blood metabolism can also be eliminated, because hematocrit was virtually constant throughout the experiment (Table 3).

The agency of several possible red cell effectors in plasma that may act at glycolytic control steps may be eliminated, including the powerful effector, pH, because arterial blood pH was unaltered (Table 3) and pH of

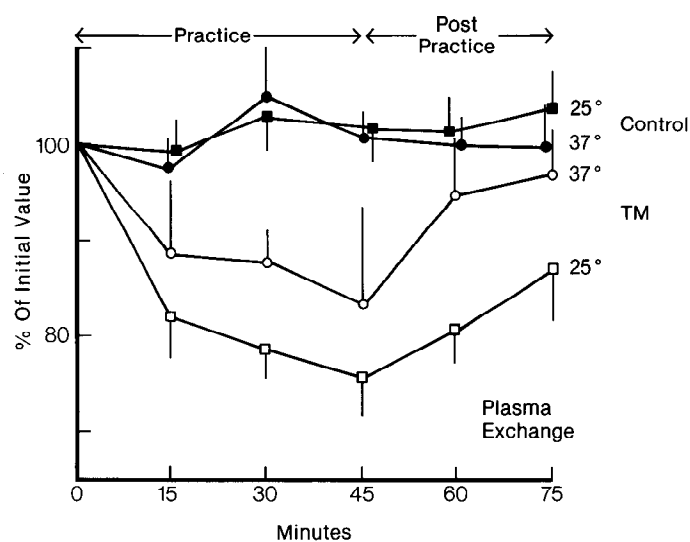


FIG. 4. Plasma exchange study: cells separated from each of times 0, 15, 30, 45, 60, and 75 min were resuspended in time 0 plasma (instead of their own plasma as in Fig. 2). Means \pm SE of percentages of initial value for 14 subjects.

TABLE 3. Mean arterial blood gas and lactate concentration values

	0 Min	15 Min	30 Min	45 Min	60 Min	75 Min
<i>TM</i>						
pH	7.41 \pm 0.02	7.40 \pm 0.04	7.40 \pm 0.04	7.42 \pm 0.04	7.42 \pm 0.02	7.42 \pm 0.05
PCO ₂ , mmHg	38.6 \pm 2.9	39.4 \pm 3.4	39.8 \pm 2.4	38.6 \pm 7.2	39.3 \pm 2.9	40.5 \pm 2.4
PO ₂ , mmHg	102.0 \pm 8.0	99.0 \pm 9.5	99.0 \pm 10.0	102.0 \pm 8.0	106.0 \pm 7.4	106.0 \pm 4.8
Base excess, meq/l	-0.56 \pm 0.3	-0.48 \pm 0.6	-0.65 \pm 0.4	-0.64 \pm 0.3	-0.80 \pm 0.7	-0.44 \pm 0.2
Lactate, μ mol/ml*	0.72 \pm 0.05	0.57 \pm 0.07	0.55 \pm 0.03	0.52 \pm 0.03	0.62 \pm 0.09	0.63 \pm 0.05
Glucose, mg/100 ml	69.0 \pm 7.0	71.0 \pm 10.0	65.0 \pm 7.4	70.0 \pm 8.3	72.0 \pm 9.1	68.0 \pm 10.0
Hematocrit, %	45.6 \pm 10.0	46.0 \pm 8.0	45.9 \pm 13.0	45.7 \pm 8.0	46.0 \pm 9.0	45.7 \pm 11.0
<i>Control</i>						
pH	7.44 \pm 0.01	7.43 \pm 0.04	7.42 \pm 0.03	7.43 \pm 0.04	7.47 \pm 0.04	7.42 \pm 0.03
PCO ₂ , mmHg	39.6 \pm 3.4	37.5 \pm 4.4	39.8 \pm 9.0	40.7 \pm 5.2	37.1 \pm 3.6	38.7 \pm 4.2
PO ₂ , mmHg	101.0 \pm 10.0	102.0 \pm 6.4	99.0 \pm 8.9	103.0 \pm 8.9	98.0 \pm 8.7	99.0 \pm 9.6
Base excess, meq/l	-0.71 \pm 0.8	-0.56 \pm 0.4	-0.72 \pm 0.5	-0.67 \pm 0.7	-0.71 \pm 0.4	-0.61 \pm 0.4
Lactate, μ mol/ml	0.79 \pm 0.08	0.72 \pm 0.09	0.76 \pm 0.07	0.74 \pm 0.06	0.72 \pm 0.01	0.76 \pm 0.6
Glucose, mg/100 ml	67.0 \pm 10.0	69.0 \pm 4.0	71.0 \pm 8.0	73.0 \pm 9.0	72.0 \pm 4.0	71.4 \pm 5.6
Hematocrit, %	47.3 \pm 9.0	48.0 \pm 11.0	47.6 \pm 9.0	48.0 \pm 10.0	48.2 \pm 13.0	47.6 \pm 12.7

Values are means \pm SD. PCO₂ and PO₂, CO₂ and O₂ tensions, respectively. * $P < 0.05$, significance of trend.

incubation of TM samples differed little from pH of corresponding control incubations (Fig. 3). [This does not completely rule out the possibility of altered cell pH in the mechanism, but such alteration is probably unlikely because hydrogen ions are believed to be passively distributed across the red cell membrane in most circumstances according to Gibbs-Donnan equilibrium (4).] Weaker red cell effectors in blood such as PO_2 and PCO_2 can be similarly eliminated, because they also did not vary. Although we cannot absolutely rule out change of glycolysis associated with variation of small plasma inorganic ions, such as phosphate and magnesium that are acknowledged red cell effectors, certain facts decrease the likelihood of significant role for them: both absolute and relative control strengths of phosphofructokinase and hexokinase are sensitive functions of pH (18, 26); yet, as shown in Fig. 1, in vitro decline of glycolytic rate was similar under both anaerobic and aerobic incubation conditions that differed considerably in pH (Fig. 3).

The data in Fig. 4 indicate that red blood cells during TM still exhibited decreased metabolic rate when they were separated from their own plasma and were resuspended in the plasma of the initial (*time 0*) sample. This observation is consistent with the possible role of a humoral effector that binds to the red blood cell. Hormone-receptor interaction has been established for the red blood cell for insulin (20) and has been reported by

several investigators for other hormones (13). However, while known hormones have been reported to affect red cell 2,3-diphosphoglycerate levels, deformability, osmotic fragility, membrane structure, and size (15, 19), their significance for physiological modulation of red cell metabolism, and specifically human red cell metabolism, is not established.

In conclusion, specific, acute modulation of human red cell glycolytic rate under physiological conditions has not been previously demonstrated, and demonstration of specific change of glycolytic rate in connection with a behavioral state is previously unknown. Therefore the effector(s) responsible may be significant for increased understanding of red cell metabolic control under physiological conditions. Also, because modulation of red cell metabolism may directly participate in control of O_2 transport (18, 19, 26) and in determination of total body oxidation-reduction potential (16), this phenomenon may be significant for increased understanding of the basis of the hypometabolism induced by TM.

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