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GLUCOSE CATABOLISM FOLLOWING CARBON MONOXIDE OR HYPOXIC HYPOXIA EXPOSURE

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It has been reported that at high altitude metabolism proceeds through the pentose phosphate pathway rather than the Embden-Meyerhof pathway (1). Isom et al. (2) have shown that sublethal doses of cyanide result in an increase in catabolism of carbohydrates by the pentose pathway. Previous work from this laboratory has demonstrated that pre-exposure of mice to nonlethal levels of carbon monoxide (CO) or hypoxic hypoxia affords protection against subsequent exposure to lethal levels of CO. This protective effect was not associated with alterations in carboxyhemoglobin levels or hemoglobin affinity for oxygen (3). Protected pre-exposed animals did have significantly lower lactate/pyruvate ratios in blood than controls after exposure to lethal levels of CO suggesting that the pre-exposed animals were less dependent on anaerobic metabolism than controls.

The present studies were designed to explore the possibility that pre-exposure of mice to CO or hypoxic hypoxia produces either an increase in the overall oxidative utilization of glucose or a preferential shift of metabolism to the pentose phosphate pathway. Administration of specifically labeled ^{14}C-glucose and subsequent analysis of the respiratory excretion of $^{14}CO_2$ were employed to assess the utilization of glucose by the various pathways (2).

All experiments employed Sutter derived Swiss-Webster mice weighing between 30-40 g. Animals had free access to Purina laboratory chow and water prior to the initiation of experiments.

The mice were first exposed for 4 hours to room air (control), 1000 ppm CO or 10% O_2 in glass exposure chambers of 6 liter volume maintained with a gas flow rate of 1200 ml/min. The CO concentrations were monitored by a Bendix Series 2500 gas chromatograph equipped with a hydrogen-nickel catalyst column and an automatic sampling device (Bendix Process Instruments, Roncoverte, W. Va.). Oxygen concentrations were monitored using a Beckman OM-11 oxygen analyzer (Beckman Instruments, Fullerton, Calif.).

After the termination of the first exposure (room air, CO or 10% O_2), the mice were

maintained (fasted) in room air for 24 hours. Except for a room air control group all mice were then exposed to 2500 ppm CO. After 20 minutes of exposure to 2500 ppm CO the mice were removed briefly from the chambers and quickly injected i.v. with the appropriately labeled glucose. ^{14}C-1-glucose or ^{14}C-6-glucose (New England Nuclear Corp., Boston, Mass.) was mixed with non-radioactive glucose so that each mouse received 100 mg of glucose containing 1-2 μCi of the desired ^{14}C-glucose. The glucose was administered in a distilled water solution (5%) in a volume of 0.5 ml via the tail vein. Following return to the exposure chambers, expired $^{14}CO_2$ was collected at 15 minute intervals for a period of one hour by directing the effluent gas flow from the exposure chambers through a bubble trap containing 5.3 N sodium hydroxide. The $^{14}CO_2$ content was determined according to the method of Yeh *et al.* (4) using a Beckman LS-230 liquid scintillation system (Beckman Instruments, Fullerton, Calif.). Quench correction was accomplished by the external standard method. Data were compared statistically by the student t test utilizing a significance level of $p<0.05$ for rejection of the null hypothesis (5).

Experiments using glucose labeled in position one or six were conducted to determine whether there was a preferential shift occurring in the pentose phosphate pathway. The amount of $^{14}CO_2$ collected after administration of ^{14}C-1-glucose was significantly greater in the 1000 ppm CO pre-exposed mice than air pre-exposed controls. The 10% O_2 pre-exposed mice showed a slight but non-significant increase in $^{14}CO_2$ production (Figure 1). The 1000 ppm CO pre-exposed mice also showed a significant increase compared to air pre-exposed controls in $^{14}CO_2$ production after administration of ^{14}C-6-glucose (Figure 2). The 10% O_2 pre-exposed mice also showed a slight increase in $^{14}CO_2$ production compared to the air pretreated controls but the difference was not statistically significant.

Although the total percent of $^{14}CO_2$ recovered from the C-1 and C-6 labeled glucose was increased in the CO and 10% O_2 pre-exposed mice, the ratio of $^{14}CO_2$ recovered from the C-1 and C-6 labels was not different from air pre-exposed control values. This suggests that there was no preferential shift to the pentose phosphate pathway, since an increase in the C-1/C-6 ratio of $^{14}CO_2$ production would have been anticipated (6). However, more extensive studies are needed to confirm this possibility.

In conclusion, the data obtained in this study indicate that the mice pre-exposed to 1000 ppm CO showed a significantly greater utilization of C-1 and C-6 labeled glucose by oxidative pathways (Figures 1 and 2). This is supported by the data showing a greater percentage of the administered glucose being recovered as $^{14}CO_2$ in expired air. There is no evidence to suggest a preferential shift to the pentose phosphate pathway. An increased aerobic utilization of glucose in the CO pre-exposed mice is consistent with previous studies demonstrating a protective effect of CO pre-exposure on CO lethality (3). This increased aerobic utilization of glucose may be due to an overall increase in utilization of oxidative metabo-

ism although an alternation of other aspects of glucose disposition must be considered such as a redistribution of blood flow to critical tissues which is reflected as an increased aerobic utilization of glucose (7). Since previous studies have shown no change in oxygen consumption in animals pre-exposed to CO or hypoxic hypoxia (3), a selective redistribution of blood flow would have to be considered as a reasonable possibility.

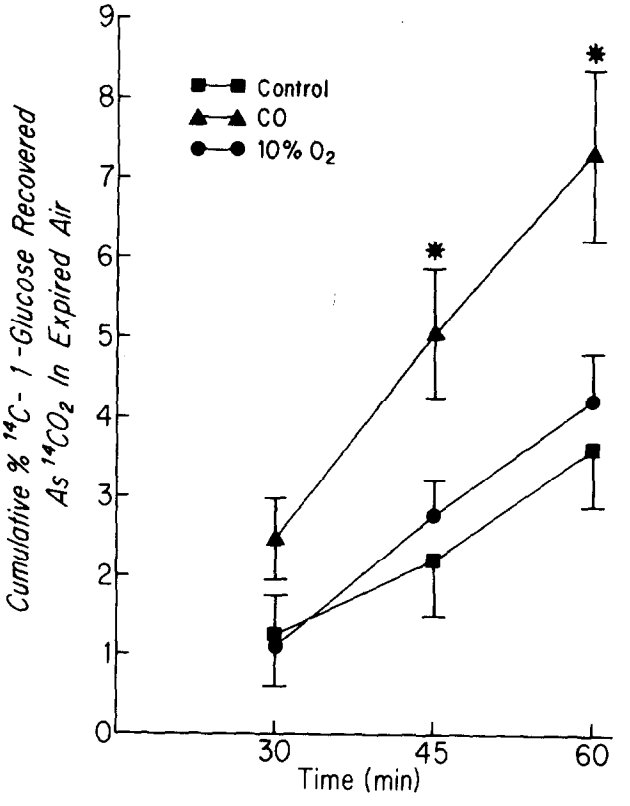

Figure 1

Figure 1. Effect of pre-exposure to room air (■—■ Control), 1000 ppm CO (▲—▲ CO), or 10% O_2 (●—● 10% O_2) on $^{14}CO_2$ production from ^{14}C-1-glucose during exposure to 2500 ppm CO. Data are expressed as mean ± S.E. of 3-5 mice. Asterisk indicates values significantly different from control ($p<0.05$).

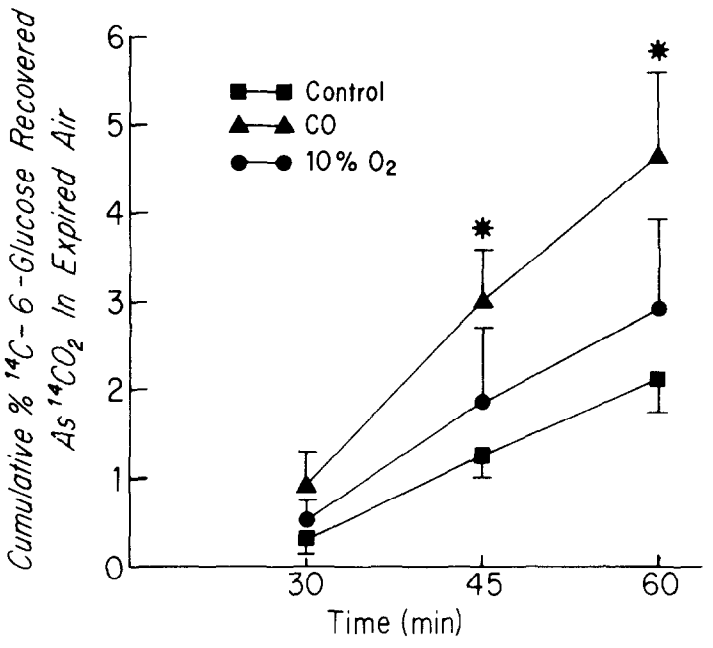

Figure 2

Figure 2. Effect of pre-exposure to room air (■—■ Control), 1000 ppm CO (▲—▲ CO), or 10% O_2 (●—● 10% O_2) on $^{14}CO_2$ production from ^{14}C-6-glucose during exposure to 2500 ppm CO. Asterisk indicates values significantly different from control ($p<0.05$).

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