UNIVERSITY OF CALIFORNIA

Los Angeles

Alteration of Glucose Utilization in Rat Lungs After Exposure to Nitrogen Dioxide

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Public Health

by

Jean Joseph Ospital

1976

The dissertation of Jean Joseph Ospital is approved, and it is acceptable in quality for publication on microfilm.

Albert F. Bush

Albert F. Bush

Donald F. Tierney

Donald F. Tierney

James F. Mead

James F. Mead, Committee Chairman

University of California, Los Angeles

1976

TABLE OF CONTENTS

LIST OF TABLES

ACKNOWLEDGEMENTS

The dissertation is the culmination of many years of effort. There are several people who have made major contributions toward the completion of this work. I wish to extend my thanks to Nabil ElSayed, Paul Gundlach, Allen Hacker, Dr.P.H., and Alex Sevanian for their assistance, support, and advice. I also wish to thank Earl S. Flowers, Ph.D., and the members of my doctoral committee for their advice and guidance in conducting the research and in the preparation of the manuscript. I am especially indebted to Mohammad G. Mustafa, Ph.D., and Donald F. Tierney, M.D., for their advice, encouragement, and support, which contributed immeasurably to the completion of this dissertation. Finally, I wish to express my most heartfelt appreciation to Charlene Brax and to my parents, Mr. and Mrs. Joseph Ospital. Without their constant encouragement, this dissertation would never have been completed.

This work was supported in part by a grant from General Research Support Funds, U.C.L.A. School of Public Health, and by a grant from the U.C.L.A. Academic Senate.

VITA

June 30, 1947----Born, Madera, California

1969---B.S., University of California, Santa Barbara

1970---M.P.H., University of California, Los Angeles

ABSTRACT OF THE DISSERTATION

Alteration of Glucose Utilization in Rat Lungs

After Exposure to Nitrogen Dioxide

by

Jean Joseph Ospital

Doctor of Public Health

University of California, Los Angeles, 1976

Professor James F. Mead, Chairman

In order to assess the effects of low level nitrogen dioxide exposure on lung tissue metabolism, glucose utilization was studied in lung slices after exposure of rats to 5 ppm nitrogen dioxide for eight hours. The exposure resulted in increases in mean glucose utilization (28%) and mean lactate production (43%), with a small rise in mean pyruvate formation (6%). Rats were also exposed to 5 ppm nitrogen dioxide for longer periods of time, namely, one, two, and four days, and similar increases in glucose utilization and lactate and pyruvate production were found in lung slices from exposed rats relative to controls. The increase in glucose metabolism after an eight hour exposure was not due to an increased activity of the hexose monophosphate shunt as measured by the production of $^{14}CO_2$ by lung slices incubated with 1-^{14}C-glucose, nor was it associated with an increased activity of the citric acid cycle as measured by $^{14}CO_2$

production from 6-^{14}C-glucose. After incubation of lung slices with 6-^{14}C-glucose the incorporation of radioactive carbon into tissue components was analyzed, and an increase in mean incorporation was observed in total lipids (26%) total proteins (13%), and the nucleic acid fraction (12%), due to exposure. The mean tissue concentrations of lactate and pyruvate, as measured in freeze clamped lungs, were higher with the exposed animals than with controls (68% and 43%, respectively). In addition, the redox ratios of the pyridine nucleotides were judged to be in a more reduced state, as indicated by the mean ratios of the concentrations of substrates of several dehydrogenase systems, in the lungs from rats exposed to 5 ppm nitrogen dioxide for eight hours. The results demonstrate that cellular metabolism undergoes changes in response to nitrogen dioxide exposure. The alterations observed indicate an increased activity of the glycolytic pathway and may relate to the capacity of lung cells to augment the synthesis of cell constituents, presumably for tissue repair.

I. INTRODUCTION

A. Objective

Air pollution is widely recognized as a major problem in urban and industrial environments. However, the magnitude of hazard to human health posed by chemical air contaminants is yet to be adequately assessed. The highly oxidizing substance nitrogen dioxide has been identified as being among the major air-borne pollutants, and is of importance because of its prevalence in various environmental circumstances, notably in photochemical smog and in various occupational settings. Nitrogen dioxide is highly toxic, and its mechanism of action is likely to be related to the characteristic of being a strong oxidizing agent.

The measurement of biochemical parameters may offer sensitive indices of the effects of air pollutants on biologic systems. Because the lung is the main site of interaction with these agents, their biologic effects may be evaluated in large part in terms of alteration of lung metabolism.

The purpose of this study was to try to elucidate certain aspects of the metabolic response of animal lungs exposed to a relatively low level of an oxidant air pollutant. The physiologic and pathological effects of oxidant gases have been characterized, while the biochemical effects resulting from low level exposures have only

recently been studied, and are yet to be precisely defined. Glucose is an important substrate for lung tissue. It appears to be a major energy substrate in the lung and is involved in the synthesis of many substances, including lipids, amino acids and proteins. The investigation of alterations in glucose metabolism may provide insight concerning the metabolic response of lung tissue to the inhalation of noxious agents. As an approach to the problem, glucose utilization and its incorporation into various products of cellular metabolism was investigated in rat lungs after exposure to nitrogen dioxide.