STUDIES DEFINING INTERACTIONS BETWEEN HYPERTENSION AND AIR POLLUTANTS

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INTRODUCTION

MASTER

In the 1960's when the word "relevance" was not so important, one very interesting project at Brookhaven National Laboratory concerned the investigation of the causes of hypertension. By developing an animal model of hypertension the late Dr. Lewis K. Dahl proved that both genetic and environmental factors were involved in the development of hypertension. Over the ensuing fifteen years or so at Brookhaven we have refined this model, selectively breeding two lines of rats from the same initial breeding stock. One of the lines is susceptible (S) to salt-induced hypertension, and the other is resistant (R) to salt-induced hypertension (figure 1). We have used this model to investigate interactions between commonly encountered air pollutants and the development of hypertension. Since the experiment is loaded in favor of producing a positive effect, a negative finding, i.e. one in which no increased effects occur subsequent to a significant challenge by the pollutant in question, can be interpreted favorably. This paper summarizes our studies investigating the interaction of two air pollutants, sulfur dioxide (SO₂) and ozone (O₂) with the hypertensive models.

Both studies were designed as 2 X 2 X 2 matrix studies with three variables; air vs. the pollutant, high dietary salt vs. low dietary salt, and (S) vs. (R) lines of rats. This design requires eight groups of ten rats each. For studies with SO₂, the high salt diet consisted of 4% salt and the low salt diet, 0.4% salt. Forty male (S) rats and 40 male (R) rats were weaned at 21 days, arranged in groups of ten animals each, and immediately established on either high or low salt diets.

Exposures to SO₂ started the following week. All exposures were done in

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27 x 27 inch stainless steel and glass chambers. The animals were exposed to SO_2 at 50 ppm for six hours per day, five days per week for 31 weeks. Control animals were exposed to air for the same six hour regimen as that of the SO_2 exposed animals.

Blood pressures were measured under ether anaesthesia using a tail cuff method after the fourth week of exposure and on alternate weeks thereafter. Animals were allowed food and water ad lib, except during exposure and were housed with a 12 hour on/off light cycle. The measurements were made immediately after an exposure to SO_2 on Thursday or Friday.

Ozone exposures were carried out in similar chambers at a concentration of 2 ppm, six hours per day, five days per week for 20 weeks. In this study, however, female rather than male rats were used. They were allowed one week from the time of weaning until being established on the low or high salt diets. In this case, the high salt diet was 8% salt rather than the 4% salt diet used in the SO_2 experiment. In addition, each group was divided into sub-groups of five animals because of the limited availability of sibling animals. Thus, twenty (S) females and twenty (R) females were weaned on two consecutive weeks prior to random assignment to one of the eight experimental groups. Exposures of the first sibling group (half of the animals) began one week prior to the exposures of the second group. All of the animals were subsequently exposed simultaneously. Blood pressure was measured after the fourth exposure week and on alternate weeks thereafter. The data have been accumulated on the basis of exposure duration.

RESULTS

Figures 2 and 3 show blood pressure as a function of time for SO_2 animals on low and high dietary salt, respectively. It is clear from the figures that the initial blood pressures in (S) animals were markedly higher

than in (R) animals. It is also clear from figure 2 that over the course of the experiment there are minimal differences between SO_2 and air-exposed rats fed low salt diets. In figure 3 the mean blood pressure in the (S) animals maintained on high salt diets does increase as expected. In this case, the SO_2 exposed animals have blood pressures that are higher than their air-exposed counterparts. This difference is statistically significant at certain time points while not significant at others. However, any differences disappear after the last exposure to SO_2 .

In these studies the percentage of salt in the diet and the concentration of SO_2 were chosen in order to severely challenge the animals. Based on previous studies it was anticipated that the (S) animals given high dietary salt would succumb to hypertension in four to six months. This did not happen. Only four (S) rats on high salt, two from the exposed and two from the control group, died during the SO_2 study. Furthermore, no differences were observed in the growth rates between any of the groups in question. Although the exposed (S) rats on high salt diets always had a slightly higher blood pressure, any apparent relationship between SO_2 and hypertension is tenuous. Thus, we conclude from these studies that exposure to 50 ppm SO_2 does not alter the development of salt-induced hypertension.

The results of our ozone studies can be seen in figures 4 and 5, which show blood pressure as a function of time for the animals on low and high dietary salt, respectively. It is apparent from these figures that the ozone exposed animals in both diet groups have lower blood pressures than their air-exposed counterparts. This difference is significant at the probability level of .05.

Of greater interest is the effect of ozone on mortality as shown in figure 6. The level of salt in a diet was sufficient to cause a 50%

mortality in the (S) animals exposed to air on high dietary salt; no other air exposed animals died. The ozone challenge (2 ppm for six hours per day, five days per week) was sufficient to cause three and two deaths in the (R) rats on either high or low salt, respectively. In contrast, the (S) animals all died within 16 weeks of exposure to ozone, regardless of the presence or absence of salt in the diet. These deaths do not appear to be related to hypertension.

What we may have observed is a susceptibility to ozone that is independent of the dietary salt and of the blood pressure. We are excited about these results since this difference in ozone susceptibility with regard to (S) vs. (R) animals may be very useful in understanding how the lung interacts with ozone from a biochemical/physiological standpoint. There is, however, the possibility that there is a general difference in terms of susceptibility to all stresses. If the susceptibility is unique to ozone, this model will allow us to evaluate the biochemical changes resulting from ozone exposure and may also allow us to intervene with various treatment regimes to ameliorate the response to ozone.

This is the end of my formal presentation. Do we have time for questions?

Figure Captions

Figure 1. Blood pressure of (S) and (R) male rats on high and low salt diets as a function of time.

Figure 2. Blood pressure of (S) and (R) male rats exposed to air or SO_2 and maintained on low dietary salt.

Figure 3. Blood pressure of (S) and (R) male rats exposed to air or SO_2 and maintained on high dietary salt.

Figure 4. Blood pressure of (S) and (R) female rats exposed to air or to ozone and maintained on low dietary salt.

Figure 5. Blood pressure of (S) and (R) female rats exposed to air or to ozone and maintained on high dietary salt.

Figure 6. Mortality of (S) and (R) female rats exposed to air or ozone and maintained on high or low dietary salt.

MALE RATS ON 4% SALT