SOME FACTORS INFLUENCING THE EFFECTS OF ANOXIC ANOXIA • †

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Received for publication August 31, 1950

A summary of the reports of patients who have had persistent symptoms following an anoxic experience indicates that all of the pertinent signs and symptoms, as well as the lesions observed on post-mortem examination, are directly referable to the central nervous system (1, 2). The usual picture in the fatal case in which the patient does not expire immediately, is one of a history of an anoxic episode: continuous coma, convulsions and decerebrate rigidity, hyperthermia and ultimate death. Of those patients who recover following an anoxic experience most show no subsequent symptoms. A few, however, may exhibit delirium with personality regression, alteration in the visual fields, aphasia, eighth nerve imbalance, amnesia, paralysis and occasionally hemiplegia. Most of these residuals clear up and many patients show no obvious alterations from their anoxic accident, but there are some whose changes are apparently irreversible. The treatment of post-anoxic sequelae has not been very satisfactory.

Although all patients who have suffered from anoxic experiences have at the same time suffered from other or associated conditions such as various diseases, surgical operations, anesthesia, drugs, poisoning, asphyxia, circulatory arrest or depression, the common factor of anoxia makes it appear certain that anoxia is the major factor in the production of the disturbance of the central nervous system. Animal experiments with anoxia, however, indicate that serious symptoms seldom persist after periods of anoxia of either short or long duration and that those animals not dying from acute oxygen deprivation recover rapidly when adequate respiratory oxygenation is resumed.

For this reason a study of several factors which are known to exert some influence on the ability of rats to withstand the acute effects of

• Read at the meeting of the American Medical Association, San Francisco, California, June 26 to 30, 1950.
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anoxia was made. It was considered that these factors might be varied experimentally so that postanoxic symptoms and cerebral changes could be produced with sufficient regularity to provide means of further study of this condition. A factor which would make animals more susceptible to oxygen deprivation might produce cerebral changes during exposure to sublethal concentrations of oxygen. The following conditions were investigated for their ability to alter the resistance of the white rat to the effects of exposure to atmospheres containing low concentrations of oxygen. Comparisons were made between simultaneously exposed standard and experimental animals. The experimental conditions investigated were hyperglycemia, hypoglycemia, hyperthyroidism, hypothyroidism, hemorrhagic anemia and the resistance of the newborn. From these experiments we concluded that hyperglycemia (glucose injection) did not alter the resistance of the rat to the effects of anoxia. Hypoglycemia (insulin), hyperthyroidism (thyroxine) and hemorrhagic anemia lowered the resistance, but hypothyroid (thiouracil) rats and the newborn were more resistant than normal adult rats to the effects of oxygen deprivation. These changes, however, did not provide a means for the experimental production of postanoxic cerebral changes or persistent symptoms.

**Experimental Procedure**

Rats were exposed to an atmosphere of reduced oxygen content in a closed chamber system of 83 liters' capacity with an offset balanced gasometer of 10 liters' capacity (fig. 1). The observation lucite hood of the apparatus provided space for eight small lucite cages each holding one rat. When the hood was in place leakage was prevented by a mercury seal. The other parts of the apparatus provided for circulation of the enclosed air and the maintenance of constant conditions of temperature, humidity, carbon dioxide and oxygen concentration and other factors. Circulation was provided by a sealed air pump forcing the air through the observation chamber and withdrawing the air from the opposite side of the chamber. The withdrawn air then passed successively through a soda lime carbon dioxide absorber, a water-cooled temperature regulator and a glass wool filter, and returned to the pump. An offset spirometer added oxygen to replace the volume of carbon dioxide removed by the absorber during the course of the experiment. The procedure followed in all of these experiments was similar. After the rats (4 control animals and 4 experimental animals) had been placed in their cages and the observation hood had been set in place, the apparatus was checked for leaks. The oxygen content of the system was then reduced by flushing with nitrogen at a rate which reduced the oxygen contents, measured by small sampling with a Beckman model D oxygen analyzer, to the desired concentration.

Male white rats of the Sprague-Dawley strain which weighed between 185 and 215 Gm. were selected for these experiments. In order
to maintain as much uniformity as possible all rats were placed on a
definite feeding schedule five to ten days before being used. At 1:00
p.m. they were placed in feeding cages with free access to a commercial
food and water. At 5:00 p.m. they were removed to cages free of food
with water accessible. Most rats lost weight the first day or two but
subsequently maintained a gradual increase in weight. All animals
subsequently used in experiments had eaten a full meal sufficient for
their daily requirements eighteen hours previously. Rats exposed
daily in the apparatus four to five hours with oxygen content of 18.8 to
21.5 per cent showed a slight loss of weight for several days but re-
gained their original weight within a week and showed no untoward
effects.

![Diagram](image)

Fig. 1. Diagram of apparatus used to maintain constant oxygen
concentration desired in exposure chamber.

A series of preliminary experiments indicated that a uniform satis-
factory procedure could be adopted. The oxygen content of the cham-
ber was reduced in about seven minutes to between 4.5 and 6.0 per cent
oxygen. This produced a degree of anoxia which did not produce im-
mediate or too rapid death. The exposure was terminated at two
hours because it was found that all the animals either died within this
time or survived continued exposure at the same oxygen concentration
for many hours with no subsequent effects. During the period of
lowering of the oxygen content of the contained air almost all animals
were observed to increase their respiration rate and become restless
when the oxygen content of the air was reduced slightly below 10 per
cent. With further reduction of the oxygen content the animals be-
came quiet and remained so for the period of two hours. Those that
died went suddenly into extension and a convulsive seizure, followed immediately by relaxation and death.

Results

Of 50 rats that were exposed to oxygen concentrations of 4.5 to 6 per cent 21 died in the first half hour, 27 in the first hour and 29 in two hours. The 21 which survived regained their original weight in sixteen days and showed no other ill effects from the exposure (fig. 2).

Hyperglycemia was produced in 49 rats by the intraperitoneal injection of a 10 per cent solution of glucose thirty minutes before the onset of anoxia (4.4 to 5.6 per cent oxygen); 27 rats received 250 mg. for each 100 Gm. of body weight and 22 received 500 mg. for each 100 Gm. of body weight. Of these, 24 died of the acute effects of anoxia, and the 25 survivors showed no residual effects after the two-hour exposure. Of the 48 control animals which received similar treatment except for the administration of glucose and which were exposed to anoxia with the hyperglycemic rats, 22 died and the 26 survivors showed no subsequent prolonged effects of the anoxia. The administration of glucose in the amounts used did not appear to alter the susceptibility of the rat to the effects of anoxia (figs. 3 and 4).

Hypoglycemia was produced by the injection of insulin into rats of nutritional status similar to that of the experimental animals. After subcutaneous injection of insulin (0.5, 1.0 or 1.5 units for each 100 Gm. of body weight) the animals were lethargic within one hour; convulsions occurred in almost all animals only after three hours. All animals survived more than five hours, but two-thirds of those receiving the larger dosage succumbed within the following few hours. For the
Fig. 3. The survival time, on exposure to low concentration of oxygen, of 27 rats which had received 250 mg. of glucose for each 100 Gm. of body weight, and of 25 control rats.

Experiments with anoxia, 0.5 unit of insulin for each 100 Gm. of body weight was injected subcutaneously into each of 25 rats. One hour later, when the animals were lethargic, they were exposed to oxygen concentrations of 5.2 to 6.0 per cent. All of these animals died within thirty-two minutes. Fourteen simultaneously exposed control animals survived the two-hour exposure and showed no subsequent effects, and 11 control rats died during the exposure (fig. 5).

Sixteen additional rats were given 0.5 units of insulin for each 100 Gm. of body weight and exposed to 7.0 to 8.0 per cent oxygen one hour later. Five died within the two-hour period, and 11 survived and showed no subsequent ill effects. Fifteen simultaneously exposed control rats survived and showed no subsequent effects (fig. 6).

Fig. 4. The survival time, on exposure to low concentration of oxygen, of 22 rats which had received 500 mg. of glucose for each 100 Gm. of body weight, and of 23 control rats.
Factors in the Effects of Anoxic Anoxia

Fig. 5. The survival time, on exposure to 5.2 to 6.0 per cent of oxygen, of 25 rats which had received 0.5 unit of insulin for each 100 Gm. of body weight, and of 25 control rats.

Rats into which 0.1 mg. of thyroxine for each 100 Gm. of body weight was injected daily lost from 7 to 10 per cent of their body weight in three to five days. Twenty-four such rats were exposed to oxygen concentrations of 4.8 to 6.0 per cent. Twenty-three died within two hours, and the single survivor recovered completely. Of the control animals 14 died and 7 survived with no subsequent symptoms (fig. 7).

Hypothyroidism was produced in rats by supplying them with 0.1 per cent thionouricil in water as their only supply of drinking water for from thirteen to twenty-two days. Seven of 27 of these animals exposed to 4.8 to 6.0 per cent oxygen died, while 14 of 21 control animals

Fig. 6. The survival time, on exposure to 7.0 to 8.0 per cent of oxygen, of 16 rats which had received 0.5 unit of insulin for each 100 Gm. of body weight, and of 15 control rats.
died during the same exposure. All of the survivors showed no subsequent symptoms (fig. 8).

The effect of anemia produced by bleeding on the tolerance of the rat to the effects of anoxic anoxia was studied in the following manner. Rats were bled by cardiac puncture while under ether anesthesia. 1.75 cc. of blood for each 100 Gm. of body weight being removed. The animals recovered in a few minutes from the effects of the ether, and one hour later a second small sample of blood was taken from 8 rats so treated. The number of erythrocytes in the blood was found to be reduced 28 per cent (average), and the hemoglobin content was reduced 21 per cent (average). All of these animals survived. Morrison (3)
found that rats survived bleeding up to 3.5 cc. of blood for each 100 Gm. of body weight. Twenty-four rats were bled in a similar manner, 1.75 cc. of blood for each 100 Gm. of body weight, and one hour later were exposed to oxygen concentrations of from 4.5 to 5.6 per cent. Nineteen died and 5 survived, while 5 control animals died and 19 survived. None of the surviving animals showed any residual effect from the exposure (fig. 9).

Infant rats were exposed to oxygen concentrations of from 5 to 6 per cent along with adult control animals for two-hour periods. Litters of one-day-old rats and others of increased age up to nine days weighing from 4 to 15 Gm. were removed from their mothers a few minutes prior to exposure. A total of 134 infant rats were exposed; all survived and showed no subsequent symptoms which could be attributed to anoxia. Nine of the 11 adult control rats died during their simultaneous exposure.

![Oxygen concentration graph](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931704/)

**Fig. 9.** The survival time, on exposure to low concentration of oxygen, of 24 rats which had been bled 1.75 cc. for each 100 Gm. of body weight, and of 24 control rats.

In the entire series 200 standard control animals were exposed to 4.2 to 6.0 per cent oxygen for two hours and 96 survived. In the experimental series of similar exposure with comparable rats which had received additional treatment 149 rats were used and there were 51 which survived. Of the total 147 rats which survived a two-hour exposure to 4.2 to 6.0 per cent oxygen, none showed any prolonged symptoms or effects of the anoxic exposure other than a delay of a few days in regaining their original weight. Three of these survivors died during their third week after anoxic exposure but had remained active for two weeks without displaying any symptoms other than continued loss of weight. No cerebral lesions were observed in these animals, and no immediate cause of death was determined at necropsy.
Comment

In all experiments a constant response to the lowering of the oxygen tension was present. As the oxygen concentration fell there appeared an increase in the depth of respiration. When the oxygen concentration was reduced to 9.5 to 10.0 per cent the animals began to struggle violently and gasp for breath. At lower concentrations the animals became semicomatose and moved or reacted only occasionally. At this point some degree of cyanosis was observable in the tail, nose and feet. The animals that survived the first half hour appeared to respire with greater ease than at the beginning of low oxygen concentration which was subsequently maintained at the same level. The infant rats showed air hunger at about the same point as the controls, but they showed less tendency to become comatose at the lower levels of oxygen when cyanosis was very evident in them. The hyperthyroid, hypoglycemic or anemic rats displayed air hunger at slightly higher oxygen concentrations than did the controls.

The effect of anoxia on weight, although not a newly described one is nevertheless interesting. Loss of weight has been commonly reported among those persons who sojourn at high altitudes for periods of time and occurs early in their stay, after which their weights become stabilized as they become acclimatized. Atland (4) reported a marked weight growth deficiency, more marked in male than in female rats exposed four hours daily to a simulated altitude of 25,000 feet.

The loss of weight which follows exposure to anoxia is probably not related to the ability of the rat to digest and absorb food. Northup and Van Liere (5) and MacLachlan and Thacker (6) have shown that anoxia interferes very little with the ability to digest and absorb food. The behavior of the rats which had recently recovered from an anoxic exposure appeared to be only a lack of interest in the food available when they were placed in feeding cages. This was in marked contrast to the normal rats, which immediately rushed to the food and began to eat. It is possible that the lack of interest in food may indicate a cerebral imbalance which has lessened the stimulus of hunger.

Hyperglycemia prior to anoxic exposure did not seem to affect the outcome of the experiments in any way. This is at variance with the findings of Selle (7), who found that the injection of glucose increased the survival of respiratory activity approximately 30 per cent. The hypoglycemic animals demonstrated early in the exposure to anoxia the interaction between anoxia and hypoglycemia. This is seen both in the early occurrence of death and in the total increased mortality rate of these animals. It was also observed that the insulin convulsions under anoxia occurred only just prior to the death of the animal and were less severe and less prolonged than when anoxia was not present. This is similar to the observations of McQuarrie and Ziegler (8).
The additive effect of increased oxygen demand and decreased oxygen supply is clearly seen in the increased mortality to oxygen deprivation in the thyroxine-treated rats. Loss of thyroid activity had the reverse of this effect, since the thiouracil-treated rats were definitely more resistant to the effects of anoxia than normal rats. Blood and associates (9) and Hughes and Astwood (10) have reported similar findings.

The increased susceptibility of the acutely anemic rats to anoxia would be expected. Whether this is due solely to the lower oxygen-carrying capacity in addition to the anoxia or whether the loss of blood volume was also a factor is problematical. These experiments did differ from those involving hypoglycemia or hyperthyroidism in that the anemic rats survived longer in each experiment while the hypoglycemic or hyperthyroid rats died soon after the induction of anoxia. However, there were no cerebral lesions of permanent nature produced in the animals that survived. Many cases of anoxic anesthetic accidents occur in association with hemorrhage (1).

The marked increase in the resistance of infant rats to the effects of anoxia is in agreement with the results of Avery and Johlin (11), Kabat (12), and Himwich, Fazekas and Alexander (13).

Summary

The ability of rats to withstand the acute effects of exposure to an atmosphere containing 4.5 to 6.0 per cent oxygen is definitely diminished by acute anemia, hypoglycemia or hyperthyroidism. Hypothyroid rats and infant rats are more resistant than normal adult rats to the acute effects of anoxic anoxia. The administration of glucose did not appear to alter the susceptibility of rats to the effects of anoxia.

Rats which survived exposure to atmospheres containing 4.5 to 6.0 per cent oxygen for a period of two hours appeared to show no residual effects and were normal in appearance and behavior after a few days. These animals, however, did lose their desire for food and required about twice as long to regain their pre-experimental body weight as did rats exposed in a similar fashion to 20 per cent oxygen. Measures which altered the susceptibility of rats to the acute effects of anoxic anoxia did not produce residual effects in the animals that survived a two-hour exposure.

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