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Rôle of Adrenals in Blood Pressure Reaction to Anoxia During Insulin Hypoglycemia.

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Gellhorn, Ingraham and Moldavsky[1] reported recently that on inhalation of 6% oxygen for brief periods (1-3 minutes) the blood

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1 Gellhorn, E., Ingraham, R., and Moldavsky, L., *J. Neurophysiol.*, 1938, **1**, 301.

pressure rises greatly during insulin hypoglycemia whereas at normal blood sugar level the blood pressure is either unchanged or rises only a few millimeters. The reaction is reversible when the original blood sugar level is restored by the injection of glucose. Kraines and Gellhorn[2] showed that this reaction is observed under similar conditions in the human. This phenomenon was interpreted as an indication of a synergistic action between the effects of anoxia and those of hypoglycemia on the central nervous system. Since the latter seems to depend almost exclusively on the consumption of carbohydrates as indicated by the fact that the R.Q. of the brain approaches unity (Lennox,[3] Dickens and Simer[4]) a reduction in the glucose level of the blood is apt to curtail the oxidative metabolism of the central nervous system and to make it more susceptible to the effects of a diminished oxygen supply induced by the inhalation of gas mixtures low in oxygen. It is assumed that this diminution in the oxygenation of nervous tissues is the cause of the excitation of the sympathico-adrenal system which commonly accompanies states of anoxia. The question, therefore, presents itself to what extent the greatly increased blood pressure reaction to low oxygen in the hypoglycemic state is due to purely nervous impulses over the sympathetic and to humoral effects due to an increase in the liberation of adrenin. The following experiments were devised to decide this question.

Methods. Experiments were carried out on 7 dogs under chloralosane or amytal anesthesia. Insulin was injected intravenously (3 to 12 units per kilo); 6.2% oxygen was inhaled from Douglas bags for periods of 3 minutes before the injection of insulin and at various intervals during the hypoglycemia. As soon as a greatly increased blood pressure reaction occurred the adrenal veins were ligated bilaterally and the test was repeated.

Results. The results were uniform in all experiments and seem to indicate that the adrenal glands do not play any significant part in the increased blood pressure reaction to low oxygen observed in the hypoglycemic state. In the first curve of Fig. 1 the blood pressure response to 6.2% oxygen is practically the same before and after the ligation of the adrenals, the blood sugar values being 66 and 63 mg % respectively. The second curve of Fig. 1 shows an experiment in which during the time which elapsed between the last test carried out before and the first test carried out after elimination of the adrenals the blood sugar fell from 75 mg % to 68 mg %. In spite of

2 Kraines, S., and Gellhorn, E., in press.

3 Lennox, W. G., *Arch. Neurol.-Psychiat.*, 1931, **20**, 719.

4 Dickens, F., and Simer, F., *Biochem. J.*, 1931, **25**, 985.

the elimination of the adrenal glands the blood pressure reaction to the inhalation of 6.2% oxygen increased greatly. Similar was the result in other experiments. The blood pressure reaction was dependent on the blood sugar level but not on the presence of the adrenal glands. When the former fell the reaction increased; when the blood sugar rose the blood pressure response was diminished.

An interesting experiment is reproduced in the third curve of Fig. 1. The blood sugar level before and after ligation of the adrenals was practically identical (39 and 38 mg % respectively) but much lower than in the experiment shown in the top curve of Fig. 1. It is seen from the graph that the reaction was greatly increased after elimination of the adrenals. This result is in harmony

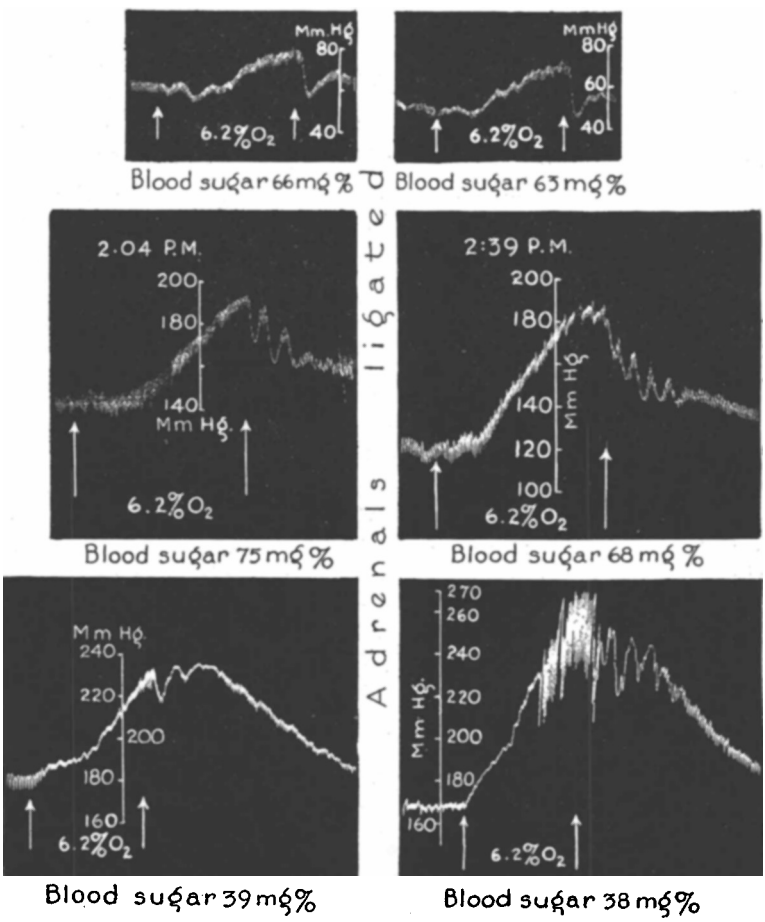

FIG. 1.

Experiments on narcotized dogs showing the blood pressure response to the inhalation of 6.2 % oxygen before and after ligation of both adrenals.

with the earlier experiments of Gellhorn, Ingraham and Moldavsky,[1] who observed that at low blood sugar levels the blood pressure response to 6.2% oxygen increased with increasing duration of the hypoglycemic state. It may, therefore, be said that the two conditions, *i. e.*, the blood sugar level and the duration of the hypoglycemic state at a given blood sugar concentration which were found to determine the blood pressure reaction to low oxygen in the normal animal also determine this reaction after elimination of the adrenals. The latter do not seem to play any part in the blood pressure reaction.

It still remains to be decided if an anoxia of the extent and duration employed in these experiments is a sufficient stimulus to cause the liberation of significant quantities of adrenalin. An approach to this problem has been made by causing unnarcotized rabbits to inhale 6.2% oxygen for 3 minutes and following the blood sugar level over a period of 30 minutes. It was found that at the end of the 3-minute period of anoxia the blood sugar level was raised by an average of 12.8% and showed a maximum (average rise of 24%) 13 minutes later. Therefore, under these conditions, this period of anoxia is a sufficient stimulus for adrenalin liberation but because of the species difference and lack of narcosis, these results cannot be applied directly in interpreting the experiments described here. But if we take into account the fact that according to unpublished observations of one of us (Gellhorn) the effectiveness of anoxia to increase adrenin secretion as measured by the blood sugar response is greatly augmented during insulin hypoglycemia it seems to be probable that adrenin is secreted to an increased extent during the anoxia period in our experiments on dogs. But the amount liberated is insufficient to account for the observed blood pressure reaction.

Studies on the blood pressure reaction produced by the intravenous injections of adrenalin compared with the response to 6.2% oxygen during insulin hypoglycemia throws further light on this problem. It was found that the injection of 0.05 mg adrenalin produces a blood pressure rise similar to that seen in the last graph of Fig. 1. The reaction, however, was of much shorter duration than that observed during inhalation of 6.2% oxygen at a low blood sugar level. It is, therefore, necessary to assume that a multiple of this amount of adrenin must be secreted in order to account for the blood pressure changes. This may not appear impossible in the light of the investigations of Cannon and Rapport,[5] who found the adrenin output greatly increased under stress. But the experiments reported in this paper show clearly that the amount of adrenin which may be se-

[5] Cannon, W. B., and Rapport, D., *Am. J. Physiol.*, 1921, **58**, 308.

creted during such a brief anoxia period is insufficient to account for the greatly increased blood pressure response to anoxia. This reaction is, therefore, under the conditions of our experiments exclusively or almost completely due to increased sympathetic discharges and not to humoral factors.

It is interesting to note that our results as to the relation of sympathetic discharges to the secretion of adrenin are similar to those of Heymans[6] and Nowak[7] who studied the significance of adrenin secretion for the blood pressure response in carotid sinus reflexes. They found that the rise of blood pressure following a decrease of the pressure in the carotid sinus was quantitatively unaltered by the elimination of the adrenals although it is known that under these conditions the adrenin secretion increases (Heymans,[8] and others).

Summary. The blood pressure rise which increases in response to the inhalation of 6% oxygen when the blood sugar falls during the course of insulin hypoglycemia is not influenced by bilateral ligation of the adrenals. It is, therefore, concluded that under the conditions of our experiments an increased secretion of adrenin does not account for the greatly increased blood pressure response. The latter seems to be due to increased sympathetic discharges only.

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Concentration and Possible Significance of Histaminase in the Human Placenta.

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Occasional reports have appeared which indicate the presence of histamine and its precursors in the placenta.[1-4] This seems logical because of the amount of degenerating tissue present in the placenta during the later months of pregnancy. Since histamine may be

6 Heymans, C., *Compt. Rend. Soc. Biol.*, 1933, **114**, 148.

7 Nowak, St., *Compt. Rend.*, 1934, **115**, 1731.

8 Heymans, C., *Arch. internat. Pharm. Therap.*, 1929, **35**, 269.

1 Harding, V. J., and Fort, C. A., *J. Biol. Chem.*, 1918, **35**, 29.

2 Bartholomew, R. A., and Kracke, R. R., *Am. J. Obst. and Gynec.*, 1932, **24**, 797.

3 Bartholomew, R. A., and Parker, F., *Am. J. Obst. and Gynec.*, 1934, **27**, 67.

4 Hofbauer, J., *Am. J. Obst. and Gynec.*, 1926, **12**, 159.