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Mechanism of Insulin Convulsions. I. Serum Electrolytes and Blood Sugar in Relation to Occurrence of Convulsions.

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The increasing evidence that potassium plays an essential rôle in carbohydrate metabolism,^{1, 2} as well as in nervous activity,³ suggests the possibility that the decrease of this element in the blood plasma following administration of insulin^{4, 5} might be involved in the mechanism of insulin convulsions. The following is a brief report of experiments undertaken to explore this possibility.

The method used was to determine the level of K in the plasma immediately before and at various intervals after the administration of convulsive doses of insulin. Preparatory to their being subjected to the various experiments, dogs were kept on a standard diet for a fore period of several days, after which they were fasted for either 24 or 48 hours. Control blood specimens were obtained before each experiment was begun. Only those animals which had definite generalized insulin convulsions during preliminary tests were used for subsequent studies. The blood sugar, hemoglobin and plasma inorganic phosphorus were also determined. In a few instances changes in the serum calcium, lactic acid and sodium were likewise followed. The dosage of insulin varied somewhat from animal to animal, but in most of the experiments comparatively large doses (10 to 25 units per kg of body weight) were given because the results were found to be more regular with these than they were with smaller doses. The effect of insulin alone was determined 80 times in 43 dogs. In addition 8 experiments were carried out with continuous administration of K salts (chloride and citrate) in amounts sufficiently large to maintain the plasma K at normal levels while the blood sugar and inorganic phosphorus were reduced by the insulin. In other experiments phosphate, as well as K, was adminis-

¹ McQuarrie, I., Thompson, W. H., and Anderson, J. A., *J. Nutrition*, 1936, **11**, 77.

² Silvette, H., and Britton, S. W., *Proc. Soc. Exp. Biol. and Med.*, 1937, **37**, 252.

³ Holmes, E. G., *Annual Review of Biochemistry*, Stanford University Press, 1934, **4**, 435.

⁴ Briggs, A. P. Koechig, I., Doisy, E. A., and Weber, C. J., *J. Biol. Chem.*, 1923, **58**, 721.

⁵ Harrop, G. A., and Benedict, E. M., *J. Biol. Chem.*, 1924, **59**, 683.

tered to prevent decrease in both of these inorganic ions during the period of hypoglycemia. Because administration of Na salts appears to accentuate the excretion of K and to have an effect on carbohydrate metabolism antagonistic to that of K, Na was administered in the form of chloride, lactate and citrate in different experiments. In order to elevate the plasma inorganic P without preventing the usual reduction in K and glucose, animals receiving insulin were made to breath atmospheres high in CO₂ in 11 experiments. The methods used for determination of the various blood constituents were as follows: glucose, Folin;⁶ potassium, Shohl and Bennet;⁷ inorganic phosphorus, Kuttner and Lichtenstein.⁸

The results may be summarized as follows: Although the plasma K and inorganic P values were decreased in all experiments following administration of insulin alone, there was no definite relationship between the absolute level of either substance and the occurrence of convulsions. In contrast with the findings in relationship to the hypoglycemic curve, there was no evidence of a tendency for convulsions to occur at the lowest point on either the K or the P curve. Administration of glucose caused a prompt return of the plasma K to normal without raising the inorganic P. Administration of K salts to prevent decrease in the plasma K did not prevent insulin convulsions so long as it did not prevent a fall in the blood sugar to the previously determined convulsive level. In 2 such experiments convulsions did not occur, but in neither of these did the blood glucose fall below 30 mg per 100 cc. When the plasma inorganic P was elevated or was maintained at normal levels by administration of PO₄ salts or by having the animal breath an atmosphere containing between 5% and 10% CO₂ plus 20% to 80% O₂, convulsions still occurred as in control experiments soon after the blood sugar had fallen to between 15 and 25 mg per 100 cc. Administration of NaCl appeared to hasten the onset of convulsions in one animal but in three others had no effect on their occurrence. Sodium lactate appeared to prevent the occurrence of a convulsion in one experiment in spite of a decrease in the blood sugar to a level slightly below that found just prior to a convulsion in the control experiment. In 2 other essentially identical experiments, however, this organic salt of sodium had no inhibiting effect. The effects of sodium citrate were almost identical with those of sodium lactate. The *conclusion* drawn from these experiments is that there is no direct relationship

⁶ Folin, O., *J. Biol. Chem.*, 1929, **82**, 91.

⁷ Shohl, A. T., and Bennet, H. B., *J. Biol. Chem.*, 1928, **78**, 643.

⁸ Kuttner, T., and Lichtenstein, L., *J. Biol. Chem.*, 1930, **86**, 671.

between the level of plasma K or inorganic P and the occurrence of insulin convulsions. Glucose was the only blood constituent that appeared to be of significance in this connection.

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Mechanism of Insulin Convulsions. II. Effects of Varying Partial Pressures of Atmospheric O₂, N₂ and CO₂.

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In connection with a study on the relationship between the levels of potassium, inorganic phosphorus and glucose in the blood and the occurrence of insulin convulsions¹ dogs were subjected to atmospheres varying greatly in their partial pressures of O₂, N₂ and CO₂. The finding by Glickman and Gellhorn² that rats subjected to lowered O₂ tension (air in low pressure chamber at 460 mm Hg) became more sensitive to insulin and had convulsions sooner than they did in ordinary air, suggested the use of induced anoxic anoxia as an additional means of modifying our experimental conditions. The fact that the convulsions of epilepsy³ and those of hypoparathyroidism can not infrequently be prevented or aborted by the subject's breathing a gaseous mixture containing 10% CO₂ and 90% O₂ further suggested the desirability of investigating the influence of such alterations in the air breathed on the various constituents of the blood and on the occurrence of convulsions following the administration of insulin.

The method used was that of determining the effects of insulin administration, first, when the experimental animal was allowed to breath room air, and again, one week later when the same animal was kept in an ordinary oxygen tent containing O₂, N₂ and CO₂ at different partial pressures. The insulin was given subcutaneously in large single doses (10 to 25 units per kilo of body weight). In addition to the preliminary control experiments performed on all animals, the following studies were carried out: 17 experiments with low O₂ percentages; 4 with high O₂; 4 with high O₂ plus high CO₂; 4 with low O₂ plus high CO₂, and 10 with high CO₂ plus 20% O₂.

¹ Ziegler, M. R., and McQuarrie, Irvine, *PROC. SOC. EXP. BIOL. AND MED.*, 1938, **39**, 142.

² Glickman, N., and Gellhorn, E., *Am. J. Physiol.*, 1938, **121**, 358.

³ Lennox, W. G., and Cobb, S., *Med.*, 1928, **7**, 105.