THE ROLE OF THE ADRENAL MEDULLA AND CORTEX IN PREVENTING INSULIN CONVULSION

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It is well established that adrenalectomized animals are extremely sensitive to insulin and easily seized with hypoglycemic convulsion. That the adrenal cortex may be more intimately involved in antagonizing insulin effect was first suggested by Swann and Fitzgerald (1938). The significance of the cortex was also stressed by Arnett et al. (1942). Based upon their experiments on adreno-demedullated and adrenalectomized rats, they reached to a conclusion that in the absence of the cortex the central nervous system become highly sensitive to hypoglycemia and that coma and convolution together with the characteristic EEG changes appear at much higher level of blood sugar than in the adreno-demedullated animals. This seemed to be supported by a clinical observation that in patient with Addison's disease symptoms of hypoglycemia may develop at much higher level of blood sugar than in normal persons (Thorn et al., 1940). However, as has been noticed by Arnett et al. themselves, adrenalectomized rats frequently fail to recover from insulin convolution or coma on injection of glucose and there exists a possibility that concomitant circulatory disturbances may participate in the sensitization of the central nervous system.

In the present study it has been shown that in adrenalectomized rabbits of which no fatal outcome occurs after insulin the significance of glucocorticoids can only be evaluated in preventing the appearance of extreme hypoglycemia. The absence of epinephrine secretion after insulin seemed to be the main cause for the increased susceptibility to insulin after adrenalectomy. However, the secretion of epinephrine in intact animals was found not solely dependent on the degree of hypoglycemia. This was discussed with the puzzling problem of sensitive and non-sensitive groups to insulin in this animal species.

METHOD

Albino rabbits of about 2.8 kg body weight were used. They were fed "Okara" (soy-bean curd's waste 300 g with 0.5 g NaCl, daily). After adrenalectomy no special
treatment was done and the completeness of adrenalectomy was checked by water diuresis test. Food was withheld 24 hours before experiments. Insulin was administered subcutaneously and blood samples were taken from the ear vein. Blood sugar level was determined by the Somogyi method. Plasma catecholamine (epinephrine) was determined after Weil-Malherb & Bone with additional purification of the samples through a column of Dowex 50 at pH 3.0. Bipolar electrocorticogram was obtained from the motor area, blood pressure recorded by catheterizing the carotid artery and ear temperature measured by a thermo-junction. All the observations were made in the state without tying. For this purpose each animal was accustomed to sit quietly in a lightly restraining open box, putting his head out of a hole of the front plate.

RESULTS

Insulin convulsions of adrenalectomized and intact rabbits. The effect of insulin (1 U/kg, s. c.) was observed in five animals before and 10 day after adrenalectomy. As shown in Fig. 1, the fall of blood sugar level especially in the later phase was accelerated after adrenalectomy, but the threshold level at which convulsion occurred was not altered (about 20 mg %). The general behaviours after insulin also remained much the same. The most characteristic feature was that animals became excitable just before the onset of convulsion. With the appearance of alertness, marked exophthalmos and midriasis a sudden rise in blood pressure occurred, which had been tended to decline after insulin (Fig. 2). This was followed immediately by a reflex bradycardia which could be abolished by section of carotid sinus and aortic nerves (Fig. 3).
Despite repeated convulsions circulatory disturbances did not ensue and the animals could recover by intravenous glucose administration. Inspite of the generalized signs of sympathetic activation the delta wave became prominent in EEG (delta shift) (Fig. 3). Therefore, the dissociation of electroencephalographic and behaviour pattern was apparent.
Protection of insulin convulsion by glucocorticoid. The above mentioned course of the blood sugar fall and the appearance of convulsion of adrenalectomized animals could not be influenced even by a massive dose of glucocorticoid (dexamethasone-21-phosphate; Decadron, 4 mg), when it was given intravenously within one hour before insulin. Thus no direct antagonism between glucocorticoid and insulin was observed. Protective effect of glucocorticoid against insulin convulsion could only be noticed when the same dose of Decadron was administered intramuscularly 24 hours before insulin. Thereby as shown in Fig. 1 the fasting blood sugar level was considerably elevated and its fall especially in the later phase was markedly inhibited. In order to induce convulsion another dose of insulin was necessary. However, the blood sugar level at which convulsion occurred was not altered. Also changes in behaviour and EEG in extreme hypoglycemia remained much the same. Thus it is probable that glucocorticoid can not have any appreciable effect upon the susceptibility of the central nervous system to hypoglycemia. The effectiveness of Decadron in counteracting the insulin effect was merely the result of sufficient glucose supply in the later phase of insulin hypoglycemia.

Sensitive and non-sensitive groups in intact rabbits. Rabbit is a special animal species in which insulin convulsion can easily be induced. However, some of the animals resist even large dose of insulin, as has been noticed in case of the insulin bioassay on rabbits. Since in non-starved condition the significance of glucocorticoids seemed to be rather minor, the medullary secretion was examined in relation to the insulin sensitivity in intact rabbits. The plasma epinephrine level after insulin (2 U/kg, s. c.) was compared in convulsive and non-convulsive groups. As shown in Fig. 4, in the convulsive cases the level was lower than 1.1 µg/l, while in the non-convulsive cases it was higher than 1.8 µg/l, when examined 80 minutes after insulin. It is quite noteworthy that despite the signs of generalized sympathetic activation and

![Fig. 4. Plasma epinephrine level after insulin in rabbits. Examined 80 minutes after insulin (2 U/kg s.c.).](image-url)
repeated convulsions the epinephrine level remained low in the convulsive cases. Estimated from the relation of the plasma epinephrine level to the rate of epinephrine infusion (Fig. 5), the critical epinephrine level for the prevention of insulin convulsion roughly corresponded to the epinephrine infusion

![Graph](image-url)

**Fig. 5.** Plasma epinephrine level in relation to the rate of intravenous epinephrine infusion. Determined 10-15 minutes after beginning the infusion.

![Graph](image-url)

**Fig. 6.** Plasma epinephrine level in relation to insulin dose in dogs. Determined 80 minutes after insulin.
rate of 0.5µg/kg/min. This was just sufficient for preventing the extreme lowering of blood sugar level. In this animal species there was no definite relation between the rise in plasma epinephrine level and the dose of insulin administered. In sensitive animals even larger dose of insulin (10 U/kg) failed to elevate the epinephrine level further. These circumstances were quite different from that observed in dogs. As shown in Fig. 6 the plasma epinephrine level of dogs rose progressively with the dose of insulin administered up to 10 U/kg, beyond which further rise was hardly possible. This would explain why dogs, contrary to rabbits, are resistant to insulin and do not easily convulse with insulin dose of less than 10 U/kg. The maximal level of plasma epinephrine after insulin corresponded to the epinephrine infusion rate of about 1.0µg/kg/min (refer Fig. 5). This is well in accord with the maximal epinephrine secretion rate after insulin observed directly by cannulating the adrenal vein.

The mechanism of sufficient secretion of epinephrine after insulin. It was quite remarkable that in the convulsive cases of intact animals marked elevation of plasma epinephrine level could not be observed despite extreme fall of blood sugar level. In these cases progressive “delta shift” in EEG was prominent, whereas in the non-convulsive cases in which sufficient secretion of epinephrine occurred the “delta shift” was temporary and not progressive even with massive dose of insulin (Fig. 7). It seemed as if the sufficient secretion of epinephrine could not occur in the state of “delta shift”. In other words some other central factors might be necessary for the induction.

Fig. 7. Comparison of insulin-sensitive and non-sensitive rabbits.
of epinephrine secretion. In this connection the following observation might give some light on this problem. As shown in Fig. 7 a marked rise in ear temperature due to vasodilatation was constantly observed in the non-convulsive cases relatively shortly after insulin, whereas in the convulsive cases no such vasodilatation occurred. The rise in the ear temperature here observed was always preceded by an alert behaviour or "flight reaction". It is well known that in this animal species dilatation of the ear vessels can readily be induced together with tachypnea in emotional excitement which is invariably accompanied by a rise in blood sugar level due to epinephrine secretion. Thus it would appear that unless the central nervous system is not in a state to induce the "flight reaction" in the face of falling blood sugar level, the sufficient secretion of epinephrine will not occur. The above mentioned differences in the EEG pattern in the convulsive and non-convulsive groups might reflect these circumstances.

**DISCUSSION**

The findings of the present study on rabbits have demonstrated that glucocorticoid does not have any appreciable effects upon the susceptibility of central nervous system to hypoglycemia. The prevailing conception concerning the significance of glucocorticoid based on experiments on adrenalectomized rats may not be acceptable. The experiments on small sized animals may be easily complicated with the attendant hypothermia which often reaches a lethal level in adrenalectomized animals. Glucocorticoid which protects this hypothermia and the accompanying respiratory and circulatory disturbances would be beneficial for the central deterioration in hypoglycemia.

The principal protection against insulin hypoglycemia and convulsion was found to be afforded by epinephrine secretion. However, its degree in rabbits seemed to be rather determined by an emotional reactivity than the dose of insulin given. Sufficient epinephrine secretion for the homeostasis of blood sugar level could not be observed, unless "flight reaction" occurred in the face of falling blood sugar level. This might be the reason why rabbits, in contrast to dogs, are extremely sensitive to insulin and have been used for the insulin bioassay. The puzzling problem thereby experienced that some rabbits easily convulse and the others not, might be due to the individual difference in the emotional reactivity. In this respect it may be noted here that even sensitive rabbits when excited by tying to an animal board would not convulse even with large dose of insulin.

It was quite remarkable that in the convulsive stage of insulin hypoglycemia which is characterized by a marked generalized sympathetic activation and the dissociation of behaviour and EEG pattern, enough secretion of epinephrine could not occur. This was at variance with the well documented
doctrine of "sympathetico-adrenomedullary system" (Cannon) or the concept of orthosympathetic system. In this respect the observation of GRANT et al.\(^4\) that the release of epinephrine from the adrenal medulla occurs on activation of the sympathetic vasodilator nerve to the skeletal muscles in the cat by hypothalamic stimulation, seems to deserve special attention. Their speculation that both might constitute an integrative part of the autonomic reaction pattern associated with emergency reaction or "flight reaction" seems to be applicable here.

In passing it may be mentioned here that the epinephrine secretion after insulin is most prominent when the decrease in the blood sugar occurs rapidly\(^5\) and that the early clinical symptoms of hypoglycemia are attributable to the epinephrine response and are identical, in several respects, with those produced by the administration of epinephrine\(^6\). Occasional discrepancy between the clinical manifestation and the blood sugar level is marked when there is a marked secretion of epinephrine\(^6\). These points should be considered in interpreting hypoglycemic susceptibility in clinical cases.

**SUMMARY**

It was shown that the increased susceptibility to insulin after adrenalectomy in rabbits was mainly due to the absence of epinephrine secretion. Protective effect of glucocorticoids against insulin convulsion, when observed, was due to their hyperglycemic effect. They did not show any appreciable effects upon the susceptibility of central nervous system to hypoglycemia.

The degree of epinephrine secretion after insulin seemed to be determined rather by emotional reactivity than the dose of insulin given. The marked generalized sympathetic activation in insulin convulsion did not enhance epinephrine secretion. Thus the concept of "sympathetico-adrenomedullary system" could not be appreciated here.

**REFERENCES**


