THE HISTOLOGICAL CHANGES IN THE DIABETIC ADRENAL GLAND AFTER BIGUANIDE INDUCED LACTIC ACIDOSIS

N N Y Nawar
I Kamel
N A Schoukri

Faculty of Medicine
Ein Shams University
Cairo, Egypt

SYNPOSIS

The adrenal gland of normal rats receiving biguanide therapy, diabetic rats without lactic acidosis and diabetic rats with induced biguanide lactic acidosis were studied by haematoxylin and eosin, Holme's technique and modified Gros-Bielschowsky stain. No histological changes were noticed in the normal rats that received biguanide therapy. Degenerative changes in the nerve fibres of the cortex and those reaching the medulla together with chromatolysis of the chromaffin cells were noticed more accentuated in diabetic rats with induced lactic acidosis than in the diabetic rats with normal lactate/pyruvate (L : P) ratio. Moreover, haemorrhagic destruction throughout the whole gland was met with in the diabetic rats with induced lactic acidosis. These histological changes were correlated with the bio-chemical data and clinical picture met with in such cases.

INTRODUCTION

Recently lactic acidosis has been in the news as a dangerous and preventable association of treatment of diabetes with biguanides (Alberti and Nattrass, 1977). The biochemical and metabolic aspects together with the histological changes occuring in the liver, gastrointestinal mucosa and some other tissues in such condition were reviewed (Williams and Porte 1974). However, histological changes taking place in the adrenal gland received little attention. Therefore, it became the aim of the present work to study the histological changes occuring in the diabetic adrenal gland in biguanide induced lactic acidosis especially when Williams and Porte (1974) emphasized the importance of glucocorticoids and fludrocortisone in correcting the shock encountered in some of such conditions.

MATERIAL AND METHODS

Male albino rats weighing about 120 g were used in this study. Biguanide (metformin hydrochloride 2.5 mg per 100 g daily in two divided doses) was given by a stomach tube to six normal rats (Group I). Out of 25 rats that were rendered diabetic as described by Nawar et al (1975) twelve animals were chosen. These had permanent glycosuria and a blood glucose level (estimated by the Nelson — Somogi methods; 1944) between 250 — 320 mg %. These constituted group II and III. Group II consisting of four animals, received no treatment. Group III consisting of eight animals received the same dose of biguanide as in group I. After six weeks, the lactate/pyruvate (L : P)

ratio was determined in all animals as described by Gutmann and Wahlefeld (1974) and Czok and Lamprecht (1974). Animals of Group I and II showed no appreciable change in their L : P ratio. From Group III five animals were chosen with L : P ratios ranging from 9/1 to 13/1. The animals of the 3 groups were sacrificed, their adrenal glands extracted and fixed in Bouin's solution. Dehydration, clearing and embedding were carried out in the usual manner. Serial sections were cut 12μ in thickness and stained with Haematoxylin and eosin and by the Holme's and modified Gros-Bielschowsky silver methods.

RESULTS

The normal rats that received biguanide therapy manifested no histological changes in their adrenal gland. However, in the adrenal gland of the diabetic group with normal lactate/pyruvate ratio (Group II), beading was observed in some of the nerve fibres terminating in the cortex and those reaching the medulla. Moreover, the cytoplasm of some of the nerve cells contained coarse Nissl granules, their nuclei were pale and eccentric in position (fig. 1 and 2).

In the diabetic group showing lactic acidosis, more accentuated degenerative changes were met with in the intrinsic nerves of the adrenal gland as manifested by their beading and vacuolation (Fig. 3). At the same time a good proportion of medullary nerve cells underwent chromatolytic changes (Fig. 4). Moreover, areas of haemorrhages were noticed throughout the adrenal gland. These were more numerous in the medulla than in the cortex (Fig. 5). In some cases, haemorrhages extended beneath the capsule while in other cases the haemorrhage extended throughout the whole thickness of the cortex and reached the medulla (Fig. 6).Throughout the cortex and medulla no inflammatory reaction could be detected in the material studied.

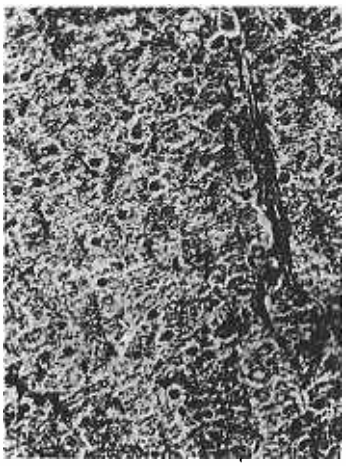

Fig. 1 Vacuolation and beading of nerve fibres in cortex Holme's stain X 120.

Fig. 2 Beading of some of nerve fibres in medulla and some nerve cells showed pale eccentric nucleus. Modified Gros — Bielschowsky Stain X 120.

Fig. 3. Degenerative changes in the nerve fibres in cortex manifested by their beading and vacuolation. Holme's Stain X 120.

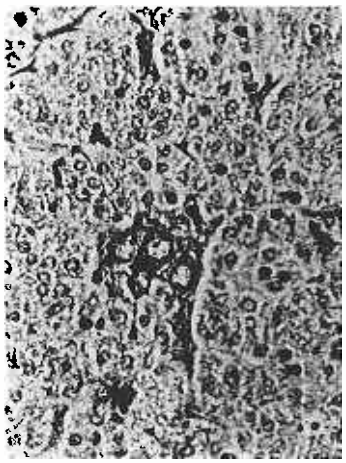

Fig. 4. Aggregation of chromatolysed nerve cells in medulla. Modified Gros — Bielschowsky stain X 120.

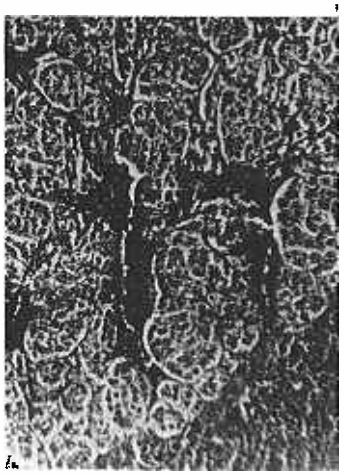

Fig. 5. Medullary haemorrhages. Haematoxylin and Eosin X 420.

Fig. 6. A subcapsular haemorrhage extending throughout the whole thickness of cortex and reaching the medulla. Haematoxylin and Eosin X 60.

DISCUSSION

Williams and Porte (1974) mentioned that biguanides do not increase lactic acid much in normal persons. Moreover, the body is normally capable of removing a large quantity of lactate very rapidly. This might explain the absence of histopathological changes in the adrenal gland in the normal animals receiving biguanide therapy. Nawar et al (1975) reported autonomic neuropathy of the adrenal gland in the form of chromatolysis of the chromaffin cells and degenerative changes in the nerve fibres ending in the cortex and medulla in long standing diabetics. In the present study not only similar but also exaggerated chromatolytic and degenerative changes were encountered in the diabetic adrenal gland after biguanide-induced lactic acidosis. An explanation for such morbidity might be due to the action of biguanide as Williams and Porte stated that biguanides are toxic to many tissues. Another probability might be that (in lactic acidosis) the lactate was increased to a greater extent than the pyruvate (Nattrass et al 1977) thus enhancing the degenerative and chromatolytic processes taking place in the adrenal gland in such cases.

Another finding in the present study was the haemorrhagic destruction occuring in the gland. These haemorrhages seemed to occur in the medulla in mild cases but extensive haemorrhages were met with in severe cases. In the literature, there was a proven association between lactic acidosis and biguanide therapy. Cohen and Woods (1976) divided lactic acidosis into type A and B. Type B was further subdivided into B1, B2 and B3. Diabetes and biguanide therapy were implicated in precipating type A, B1 and B2. The contributing factors for lactic acidosis occuring in diabetic patient receiving biguanide therapy were the inhibition of intestinal absorption of glucose (Larner and Haynes 1975), the anoerobic glycolysis (Williams and Porte, 1974), and decreased gluconeogenesis (Gordon and De Hartago, 1973); Haeckel 1973). However, from the present study it could be postulated that under such circumstances a condition of acute cortical hypofunction might develop. This might explain the electrolyte imbalance, plasma pH disturbances, together with the hypotension and shock encountered in such conditions (Williams and Porte 1974). In support of that hypothesis was that, no benefit was found in giving glucose and insulin in experimental phenformin lactic acidosis (Iversen et al 1976). Moreover, Williams and Porte (1974) mentioned that some of these patients responded to the administration of corticosteroid and fludrocortisone.

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