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HYPOGLYCAEMIC AND ANTIDIABETIC SULPHONAMIDES

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In 1942 Janbon and his colleagues at Montpellier, in the course of treating typhoid fever patients with *p*-aminobenzenesulphonamidoisopropylthiodiazole (=I.P.T.D., 2254RP, P.A.S.I.T., see formula I), observed that hypoglycaemia sometimes developed and that this could be fatal under the dietary conditions obtaining in France at that time. Professor Auguste Loubatières was able to follow up these interesting chemical observations by laboratory experiments at Montpellier despite the difficult conditions which then prevailed. He has recently summarized his findings concerning the action of I.P.T.D. (Loubatières, 1955). He finds that the administration of the drug by oral or by intravenous means can induce substantial hypoglycaemia in numerous species of animal under conditions of fasting, and in a dog from which the pituitary gland, or the adrenal glands, or the thyroid plus parathyroid glands, together with the gonads, have been removed. Nevertheless, he states that complete removal of the pancreas prevents the hypoglycaemic action of I.P.T.D., although the drug is capable of augmenting the utilization of glucose in the partially depancreatized dog. In the alloxan-diabetic rabbit the daily administration of I.P.T.D. was found by Loubatières to reduce or abolish the diabetic symptoms. Similar but less striking and consistent results were seen in the alloxan-diabetic dog. No evidence was found that the drug could oppose the diabetogenic action in the dog of a crude extract of anterior pituitary tissue.

Cross-circulation experiments with a donor dog treated with the drug, and an alloxan-diabetic recipient animal, led Loubatières to deduce that I.P.T.D. stimulates the secretion of insulin by the β -cells of the pancreatic islets. On the basis of these and other experiments he concludes that the drug may have a dual action on the islets—that of stimulating the secretion of insulin by β -cells and depressing the secretion of glucagon by the α -cells.

In 1952 Davis made the interesting observation that the administration of "synthalin" (decamethylenediguanidine, see formula II) induces degenerative changes in the α -cells of the pancreatic islets of the normal rabbit. This substance was developed many years ago as a synthetic hypoglycaemic and antidiabetic agent, active by mouth (Frank, 1927), and when von Holt and his colleagues at Hamburg (1954, 1955) found that I.P.T.D. also exerts a toxic action on the α -cells of the pancreatic islets it seemed possible that the effects of these two substances might be related. von Holt has

in fact ascribed the hypoglycaemic action of I.P.T.D. to its destructive action on the α -cells of the pancreatic islets. (For recent reviews see Ferner, 1956; von Holt *et al.*, 1956.)

Mechanism of Action

On October 7, 1955, a series of publications appeared in the *Deutsche medizinische Wochenschrift* (Franke and Fuchs, 1955; Achelis and Hardebeck, 1955; Bertram

I. *p*-Aminobenzenesulphonamidoisopropylthiodiazole (=I.P.T.D., 2254RP, P.A.S.I.T.)

II. Decamethylenediguanidine (synthalin)

III. *N*₁-Sulphanilyl-*N*₂-*n*-butylcarbamide (=BZ 55, Nadisan, U 6987)

IV. *N*₁-*p*-Tolylsulphonyl-*N*₂-*n*-butylcarbamide (=D 860, U 2043, Orinase)

et al., 1955) describing the hypoglycaemic and antidiabetic action of *N*₁-sulphanilyl-*N*₂-*n*-butylcarbamide (*N*-butyl-*N'*-sulphanilylurea, BZ 55, "nadisan," U 6987, see formula III), the substance being active when administered by mouth or parenterally. Apparently, as with I.P.T.D., this sulphonamide derivative was found to possess an important effect on carbohydrate metabolism as the result of chance clinical observation. The first suggestion about the mechanism of its action was that it might inhibit the activity of the α -cells of the pancreatic islets, in line with the views of von Holt and Ferner about the action of I.P.T.D. Subsequently Mirsky and his colleagues (1956) found that BZ 55 and related substances are non-competitive inhibitors of the enzyme found in the liver which destroys insulin (insulinase), and that a diminution in insulinase activity is associated with the hypoglycaemia induced by these substances. The natural suggestion was therefore made that these substances act on carbohydrate metabolism,

at least in part, by preventing destruction of insulin. The fact that these drugs were capable of controlling the symptoms of diabetes in a proportion of patients suffering from this disease might indicate that in some diabetic patients abnormally vigorous destruction of insulin could be a significant factor in the maintenance of the condition (Mirsky *et al.*, 1956).

In addition to its action on insulin BZ 55, like I.P.T.D., appears to stimulate the secretion of insulin by the β -cells of the pancreatic islets (Kracht and Rausch-Stroomann, 1956).

Animal Experiments

In our own laboratory we have given BZ 55 orally to a cat with a diabetic condition which had persisted for about a year after a short period of treatment with growth hormone (metahypophyseal diabetes). In the cat, untreated metahypophyseal diabetes usually shows spontaneous remission after six to twelve months (Young, 1948), but in this particular animal (No. 286) the diabetes had become mild (5–10 g. of glucose excreted daily) with no sign of complete remission over a period of many months. After two daily oral doses of 20 mg. of BZ 55 the diabetic condition disappeared, and during the following ten days the blood sugar averaged about 50 mg. per 100 ml., as compared with 250 mg. per 100 ml. before treatment with the BZ 55. The animal was killed ten days after the diabetic condition had disappeared, and histological examination of the islets kindly carried out by Mr. K. C. Richardson showed extensive hydropic changes in both α - and β -cells of all the pancreatic islets examined. In cats which show spontaneous recovery from metahypophyseal diabetes the α -cells are usually normal in appearance while the β -cells are intensely hydropic (Young, 1948).

Among the chemical relatives of BZ 55 that have been shown to be hypoglycaemic and antidiabetic, the most highly active appears to be N_1 -*p*-tolylsulphonyl- N_2 -*n*-butylcarbamide (D 860, U 2043, "orinase," see formula IV). This substance is not an obviously active antibacterial agent.

It is of interest to recall that for long it has been known that acridine derivatives possess hypoglycaemic activity (Nielsen, 1929; Monasterio, 1931), while more recently Mendes-Alves (1952) and Mendes-Alves and Gomes (1954) have demonstrated an antidiabetic action of penicillin in partially depancreatized dogs and in alloxan-diabetic rats. The studies of Mendes-Alves were undertaken as the result of the observation that the administration of penicillin to certain diabetic patients induced an alleviation of the diabetic condition, which could not obviously be attributed to the suppression of an infective state. In some instances the amelioration of the diabetic condition persisted after cessation of the treatment with penicillin, and the possibility of an action of penicillin on the cells which produce insulin was suspected (Mendes-Alves and Gomes, 1954).

When one considers the range of substances which exert some degree of hypoglycaemic and antidiabetic action—guanidine derivatives, acridines, sulphonamides, and penicillin—one is struck by the fact that all possess some antimicrobial action. Can these two actions reasonably be related?

At this point I should like to recall the fact that Markowitz, Rappaport, and Scott (see Markowitz and Rappaport, 1951) observed that, although dogs usually die if the hepatic artery is ligated, they survive the operation when given large amounts of penicillin to facilitate post-operative recovery. This unexpected finding led Markowitz and Rappaport (1951) to survey the literature concerning the bacteriology of normal liver. It appears from this that the livers of many species of animal normally contain spore-bearing anaerobic bacteria, and in numerous instances *Cl. welchii* can be isolated. Moreover, tissues of normal animals other than the liver are frequently found to contain bacteria, often anaerobic organisms. But as Markowitz and Rappaport strikingly comment, "It is logical that the liver, situated

at the head of the portal system which drains a cesspool, should have bacteria in it more consistently than other tissue." They conclude that penicillin prevents death in the dog, when the hepatic artery is ligated, by inhibiting the growth of anaerobic organisms which otherwise might flourish and produce lethal enzymes such as lecithinase.

Two Pertinent Questions

Although there is evidence that bacteria can lurk in normal tissues and might therefore play a part in the economy of the normal animal, such an idea is foreign to modern thought and is usually ignored. Nevertheless it is not possible that the breakdown of insulin in the normal or in the diabetic animal or patient might result in part from the activity of bacteria present in normal tissues? Is it possible that insulinase might be in part at least of bacterial origin? Certainly proteolytic enzymes are known to be present in many bacteria, including *Cl. welchii*, while the exacerbating effect of infection on clinical diabetes is well recognized. Although no conclusive answer can be given to these questions, the possibility can reasonably be envisaged that the antidiabetic sulphonamides might exert a significant effect by diminishing the number of bacteria, and therefore the amount of proteolytic enzymes, in the tissues, particularly those of the liver. An objection that might at once be raised to this view is that the antidiabetic action and the antibacterial effectiveness of the sulphonamides are not quantitatively related. In particular D 860, which is effective in many diabetic patients, is not obviously antibacterial.

However, when we are dealing with bacteria surviving in normal tissues under presumably special conditions, the question of the accession of the drug to the microbe may well be of paramount importance. A substance with a hydrocarbon non-polar grouping at both ends might have special advantage in this respect and be enabled to bring weak antibacterial action to bear with vigorous effect at the needed site of action. Furthermore, the possibility that the substance which is effective in the tissues is a metabolite of that which we have given to the patient or animal, and not the administered drug itself, should not be ignored in such an instance.

There is evidence that the antidiabetic sulphonamides not only depress the catabolism of insulin but also stimulate the secretion of insulin by the β -cells of the pancreatic islets. Such an action might depend on the stimulation of the secretion of glucagon or other hyperglycaemic substances by the α -cells of the pancreatic islets (cf. Young, 1955), and if such an action occurred the changes in the α -cells observed by some investigators to follow the administration of sulphonamides might be accounted for.

There is at present no simple solution to hand of the problem of the mechanism of action of the antidiabetic sulphonamides. But clearly the observations made in Montpellier in 1942 foreshadowed much that is of growing interest and importance to-day.

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