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Review

The [pre-] history of the incretin concept

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Abstract

The discoverers of secretin already thought of the existence of a chemical excitant for the internal secretion of the pancreas. Numerous experiments have been performed and published between 1906 and 1935 testing the effect of injected or ingested duodenal ("secretin") extracts on fasting or elevated blood glucose levels of normal or diabetic animals and humans with contradictory results. In 1940, after a series of negative dog experiments performed by an opinion leader, the existence of an incretin was considered questionable and further research stopped for more than 20 years. However, after the development of the radio-immunoassay, the incretin-concept has been revived in 1964, showing that significantly more insulin was released after ingestion of glucose than after intravenous injection. The possibility that nerves or one of the known gut hormones were responsible for the incretin effect could be ruled out. In 1970, glucose dependent insulinotropic polypeptide (GIP), and finally, in 1985 glucagon-like peptide 1 (GLP-1) and its truncated form GLP-1(7-36) were recognized as true incretins. Thereafter, multiple antidiabetic qualities and the therapeutic perspectives of GLP-1(7-36) and its analogues and mimetics have been demonstratred.

Keywords: Secretin; Gut extracts for treatment of diabetes; Incretin; Duodenin; Incretin concept; Insulin release by gut hormones; Insulin RIA; Entero-insular axis; GIP; GLP-1(1-36); GLP-1(7-36); History of incretin hormones

1. "Chemical control of the functions of the body" (1902–1906)

In 1902, William M. Bayliss and Ernest H. Starling [1] published their paper "The mechanism of pancreatic secretion". This was the birth hour of gastrointestinal endocrinology. The authors had shown that acid extracts of intestinal mucosa contained a factor which stimulated via the blood stream the exocrine secretion of the pancreas and named this factor secretin. Their finding revolutionized physiology because at this time (especially under the influence of Iwan P. Pawlow), it was believed that the functions of the body were controlled solely by nerves. In his famous four "Cronian Lectures" on the chemical correlation of the functions of the body, Starling introduced the word "hormone" for chemical factors which influenced via the blood stream the function of a distant organ [2]. He exemplified this with his experiments on the effect of secretin on pancreatic exocrine secretion.

According to Moore et al. [3], Starling had already considered the possibility that the duodenum does also supply a chemical excitant for the internal secretion of the pancreas. They wrote: "This line of argument appears to have occurred to the discoverers of secretin themselves, for Starling mentions a case of diabetes which was tested by Spriggs by injections of secretin solutions but with negative results. It would, however, be illogical to rule out the hypothesis outlined above upon the evidence of one negative case or even a number of negative cases of treatment of diabetes with secretin" (Ref. [3], p. 30).

Moore et al. [3] studied the effect of extracts of duodenal mucosa given by mouth (!), 3×15 g daily, in three freshly discovered juvenile diabetics, "for testing the hypothesis that the internal secretion of the pancreas might be stimulated and initiated (similarly to the

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external secretion) by a substance of the nature of a hormone or secretin yielded by the duodenal mucous membrane; and that in certain cases of diabetes the appearance of sugar in the urine might be due to functional disturbance occasioned by the absence of such an intestinal excitant of the internal secretion" (Ref. [3], p. 28).

The first patient (a man, aged 25 years) showed decreasing glucosuria 6 weeks after starting treatment with acid extract of duodenal mucosa by mouth. He was urine sugar free 3 months later, increased in weight and stopped taking the extract. Two months later, he contracted a cold, lost weight and had again glucosuria of 120 g daily; he died 2 months later of tuberculosis of the lung.

The second patient (a boy aged 7 years) had at diagnosis 179 g/day sugar in his urine and was treated with diet and acid extract of duodenal mucosa by mouth. The urinary sugar excretion decreased, became zero after 6 weeks and remained negative 4 months further, i.e., up to the time of writing the manuscript.

In the third patient (a girl aged 9 years) with daily sugar excretion of 23 g, the sugar fell 3 1/2 weeks after initiating treatment with the acid extract of duodenal mucosa by mouth to zero and remained negative until publication of the paper, i.e., for another week.

Two other patients of the authors were treated with the extract with negative results, but the observation period was short. Moore et al. ended their paper with the words: "no sweeping conclusions can be drawn from such a small number of cases, and they are here given as preliminary, and in order to excite further work upon the subject". Retrospectively, this may be commented as follows: First, gut hormones with insulin-releasing potency are peptides and will be destroyed if given by mouth. Bayliss and Starling injected their secretin extracts intravenously. Second, the authors have tested their hypothesis in freshly diagnosed juvenile (type 1) diabetic patients. Such patients often experience after initiating diet or insulin therapy a long-lasting remission of their diabetes. This phenomenon has been named the honeymoon phase. It may well be, that the three observations of Moore et al. are such examples.

2. Search for an intestinal chemical excitant of the pancreatic islets in secretin extracts (1923–1940)

Not until the discovery of insulin by Banting and Best in 1921, a systematic search for a gut hormone influencing carbohydrate metabolism took place. Meanwhile, reliable methods for estimating blood glucose levels had been established. Different groups published the results of animal experiments, in which the effect of extracts of duodenal mucosa (prepared according to the methods for secretin extraction) on fasting blood glucose levels or on hyperglycemia induced by glucose ingestion or injection had been investigated. The extracts were intravenously or subcutaneously injected or given by mouth or per rectum to rabbits or dogs. The results were not uniform. The Belgian physiologists Edgar Zunz and Jean La Barre [4] listed in the introduction to their 1929 landmark paper 10 publications in which the effect of secretin on the blood glucose level has been investigated: two found no changes, three observed hyperglycemia, followed by mild hypoglycemia and only five were found to have a consistent blood glucose decrease, mostly lasting several hours, i.e., much longer than after the injection of insulin.

Oehme and Wimmers [5], examples of the last group, observed only a weak glucose lowering effect of their secretin extracts in rabbits in the fasting state, but a strong effect after intravenous glucose injection. The findings of the Hungarian Ladislaus Takacs [6] were in two aspects remarkable: his secretin extracts lowered the blood glucose level of rabbits after intravenous, subcutaneous and oral application for 8 h and even in pancreatectomized dogs. Takacs [7] also confirmed his animal experiences in healthy and diabetic humans after one intravenous, oral or rectal application of impure secretin without defining the type or severity of the diabetes.

Zunz and La Barre [4] explained the contradicting results by the different quality of the secretin extracts. They presented sophisticated cross-circulation experiments in dogs by connecting the pancreatic vein of a dog (donor) with the jugular vein of a second dog (recipient). Injection of secretin extracts into the donor dog only slightly lowered its blood glucose level but significantly more the glucose level of the recipient. Zunz and La Barre concluded from their experiments that secretin extracts lowered blood glucose levels by stimulating the endocrine pancreas to secrete insulin.

In 1930, La Barre and Still [8] reported from Chicago that they had purified crude secretin into a fraction which is only secretagogue (stimulating the exocrine pancreas) and another which lowers the blood sugar. They also claimed that the latter effect is mediated via stimulation of insulin secretion (most important) and in addition by an effect of the preparation per se, because it also lowers the blood glucose of pancreatectomized dogs.

In 1932, La Barre [9] introduced for the first time the name "incrétine" (incretin) for a substance extracted from the upper gut mucosa, which produces hypoglycemia and does not stimulate pancreatic exocrine secretion. He claimed that incretin lowers the blood glucose level of normal rabbits and dogs if given intravenously, subcutaneously and by mouth, not however in pancreatectomized dogs (withdrawing in this point his own publication with Still [8]). He also considered the use of incretin for the treatment of human diabetes for the years to come.