History and evolution of the concept of oral therapy in diabetes

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Summary

The object of diabetes treatment is to restore adequate carbohydrate, protein and lipid metabolism. The cornerstone of this treatment has been diet since the end of the 18th century, but true antidiabetic therapy started only with the identification and purification of insulin. Pressure for oral therapy then quickly built up. The hypoglycemic effect of guanidines was discovered in 1919, leading to their therapeutic use, but they were withdrawn in 1932 due to their hepatotoxic effects. The related biguanides appeared in the 1950s but have since diminished in importance so that metformin is practically the only representative still used today. Work in the 1940s and 1950s led to the discovery and development of hypoglycemic sulfonylureas (SU), a therapeutic class unique for its specificity and safety. These products were found to stimulate insulin secretion by the endocrine pancreas. In vitro studies have shown that they bind specifically to an ATP-dependent K\(^+\) channel of the \(\beta\) cell membrane. This binding closes the channel so that K\(^+\) outflow ceases, the \(\beta\) cell membrane depolarizes and voltage-dependent Ca\(^{2+}\) channels open to allow an influx of extracellular calcium. The result is migration and extrusion of insulin granules. Although this mechanism of action has been demonstrated in vitro, it cannot account for all the clinical actions of various SU. They thus appear to have extrapancreatic actions, probably potentiating the peripheral effects of insulin at a postreceptor site in target cells. Other effects involve fibrinolytic activity of the blood, platelet behavior and vascular reactivity. The future of oral diabetes therapy thus seems to lie with the sulfonylureas.

Introduction

Diabetes should logically date back to prehistory according to a genotype adapted to periods of food shortage which have become obsolete in our civilizations of abundance [1].

The history of diabetes and its treatment can be broken up into four periods: (1) the pre-Christian period, which gave it its name (from the Greek dia = through); (2) a second period, during which Thomas Willis (1674) gave it its full name (mellitus). This period also saw the first experimentally induced diabetes by pancreatectomy, performed by Bruner in 1682 [2]; (3) a third period, during which the most diverse empirical treatments were tried until Bouchardat established the basis for stringent dietary measures, an insufficient treatment but one which increased the life expectancy of these patients, especially those with maturity-onset diabetest. This was the period of the decisive studies by Claude Bernard, Kekulé, and Langerhans; (4) the fourth period is characterized by the experimental approach to treatment of the disease associated with
such distinguished names as Von Mering, Minkowski, Banting and Best, B. Houssay, A. Loubatières, etc.

The dawn of therapeutics

The objective of diabetes treatment is to restore normal carbohydrate, protein and lipid metabolism.

Since J. Rollo in 1796 and especially Bouchardat and Naunyn in 1870, diet is the cornerstone of diabetes treatment, but the true period of antidiabetic therapy only began with the identification and purification of insulin. Very rapidly, the wish for oral therapy developed, as evidenced by proprietary drugs listed in the French Vidal drug compendium of the 1930s:

- Diabetifuge
- Diabetosan
- Fornet oral insulin with its minute dosage (maximum 12 U tid) must have been hard to reconcile with its claim of being highly active!

Approach to oral therapy

Among the first approaches to oral therapy, I will only mention alcohol, used as a tranquilizer rather than a hypoglycemic, and hypoglycine, the poison from the breadfruit tree introduced in Jamaica at the end of the 18th century, the ‘forbidden fruit’ which is said to have caused the death of Captain Bligh left ashore by the mutineers of the Bounty.

The potential antidiabetic effect of salicylate derivatives has been listed in the Pharmacopoeia for over one hundred years. In 1918, the hypoglycemic effect of guanidines was discovered. These products were used as therapy approximately 10 years later (Synthalin A), but their toxic effects on the liver became rapidly apparent and led to the prohibition of their clinical use in 1932. Twenty years later, compounds with related structures were reintroduced in therapeutics. Phenformin and metformin are the main representatives of this class of biguanides, but phenformin has been practically out of use since 1978 and only metformin is still used, primarily in Europe.

Many other substances have been candidates for treatment of hyperglycemia such as quinines and other antimalarials (!), inhibitors of fatty acid oxidation, inhibitors of intestinal glycosidase, alpha2-adrenergic antagonists and ciglitazone derivatives, etc. In fact, it was the first observation in 1942 by Janbon et al. [3] of hypoglycemia induced by RP 2254 and the work by A. Loubatières which largely paved the way for oral treatment of non-insulin-dependent diabetes [4]. Soon after that, research in Germany led to the synthesis of carbutamide and then tolbutamide [5], the leaders of the hypoglycemic sulfonylurea (SU) drugs, a unique therapeutic class due to its specificity and safety.

Pharmacological and therapeutic action of sulfonylureas

Cause (sulfonylurea) and effect (hypoglycemia) relationship

Having observed that there was a lack of action of RP 2254 in animals from which the pancreas had been removed or which had been treated with alloxan, and that the effluent blood of the pancreas in a normal dog treated with RP 2254 was able to reduce hyperglycemia in a dog made diabetic by alloxan, A. Loubatières, after a few additional experiments, concluded that: the pancreas was essential to the drug’s action; the release of excess insulin by the pancreas was due to RP 2254; the concentration of RP 2254 in contact with the islets of Langerhans was the factor responsible for the insulin-secreting and hypoglycemic effect.

These mechanisms were confirmed in studies on the first SU. The evidence for stimulation of insulin secretion by SU was demonstrated by determining insulin levels (and, more recently, C peptide levels) in the peripheral blood following intravenous injection of tolbutamide [6]. Unfortunately, the same is not true of the β-cytotrophic effects observed in rats by A. Loubatières [7], effects by which the SU can increase the volume and weight of, and even induce the new formation of islets of Langerhans.
Unraveling the mechanism of action of SU on insulin secretion

The effect of SU in vitro or following single administration no longer needs to be demonstrated and the mechanisms by which SU stimulate insulin secretion have been the subject of many studies: (1) an increase in intracellular cAMP secondary to the activation of adenylate cyclase [8] or the inhibition of phosphodiesterase [9] has been suggested but should no longer be considered [10]; (2) the role of an increase in cytosol calcium [11,12] and its translocation by gliclazide, glipizide, or tobutamide [13] has been demonstrated. This role of Ca²⁺ was confirmed in vitro in studies demonstrating that verapamil and nifedipine counteract the secretory effect of SU [14,15]; (3) the existence of a specific binding site for SU at the surface of the β cells was demonstrated in 1979 [16]. The affinity for these binding sites is directly related to the biological activity of SU; (4) this site was later identified as an ATP-dependent K⁺ channel [17].

Taken together, these steps can be combined into a functional diagram: binding of SU to a site present on the β cell membrane and associated with an ATP-dependent K⁺ channel; inhibition-closure of this channel, hence decrease in K⁺ outflow causing membrane depolarization which leads to opening of voltage-dependent Ca²⁺ channels and influx of extracellular Ca²⁺; migration-extrusion of the insulin granules.

The increase in intracellular cAMP by pharmacological agents or nutrients is thought to act on this same channel at its cytoplasmic end. But this insulin-secreting effect does not necessarily lead to an increase in serum insulin levels with chronic administration of SU.

Insulin secretion, glucose tolerance and sulfonylureas

The in vitro mechanism of action on the pancreatic β cell does not clearly explain all the clinical actions of various SU. In particular, the time course of their action varies depending on the chemical structure [18]. At present, it seems difficult to state that the improved glycemic control with prolonged SU treatment is only due to an increase in insulin secretion in response to a stimulus. Increased insulin secretion in patients treated with glipizide for several years is an exception [19,20].

Apart from the quantitative effect of SU on stimulated insulin secretion, the improvement in glucose regulation may be the result of a qualitative effect such as restoration of the early insulin secretion peak observed with gliclazide treatment [21,22] with the second phase then remaining within normal limits: this effect is undoubtedly the reason for the absence of any induced hyperinsulinism [23].

This paradoxical reduction in hyperinsulinism may also result from direct peripheral effects, but the most likely hypothesis is that SU act by potentiating the effects of insulin without affecting the number of insulin binding sites on the cells. The mechanisms of this potentiation therefore concern a postreceptor site. In particular, in the liver [24–26] and skeletal muscles, SU are thought to act on insulin-dependent enzymes [27]. But one must also raise the question of the physiological role of SU binding sites in peripheral tissues [16] or the brain [28].

The parallel effects of sulfonylureas

Since Fearnley [29] demonstrated an increase in plasma fibrinolytic activity with tolbutamide, numerous studies, in particular with gliclazide [30], have confirmed this finding [31,32] and have also demonstrated an effect on parietal fibrinolytic activity [31,33,34], platelet behavior [31,35–37], microvascular [41] or macrovascular [42,43] reactivity, even in the absence of correct metabolic control [38], both in experimental studies [39] and in patients with insulin-dependent [32] or non-insulin-dependent [40] diabetes.

The scientific contribution of sulfonylureas

Despite the excessive conclusions of the UGDP [44], SU remain an exceptional therapeutic class
due to their specificity and safety. An effective drug is also a useful tool which furthers pharmacological and pathophysiological knowledge and opens new perspectives for reflection, research, and therapeutic strategy. Thus, we may measure the road covered since the 'severe hypoglycemic accidents by sulfa-midothiazol (RP 2254)' reported by Janbon [3].

References

29 Fearnley, G.R., Chakrabarti, R. and Avis, P.R.D. Blood fibrinolytic activity in diabetes mellitus and its bearing on


