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Review

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Synthalin: a lost lesson for glucagon suppression in diabetes therapeutics

Keith G. Thomas[1,*], Natalie J. Klempel[1], Peter R. Flatt[1], Clifford J. Bailey[1,2] and R. Charlotte Moffett[1]

[1]SAAD Centre for Pharmacy and Diabetes, Ulster University, Coleraine, Northern Ireland, UK,
[2]School of Life Sciences, Aston University, Birmingham, UK

[*]Correspondence: Keith G. Thomas, SAAD Centre for Pharmacy and Diabetes, Ulster University, Coleraine, BT52 1SA, Northern Ireland, UK. Email: kg.thomas@ulster.ac.uk

Abstract

Objectives Within mammalian pancreatic islets, there are two major endocrine cell types, beta-cells which secrete insulin and alpha-cells which secrete glucagon. Whereas, insulin acts to lower circulating glucose, glucagon counters this by increasing circulating glucose via the mobilisation of glycogen. Synthalin A (Syn A) was the subject of much research in the 1920s and 1930s as a potential pancreatic alpha-cell toxin to block glucagon secretion. However, with the discovery of insulin and its lifesaving use in patients with diabetes, research on Syn-A was discontinued.

Key findings This short review looks back on early studies performed with Syn A in animals and humans with diabetes. These are relevant today because both type 1 and type 2 diabetes are now recognised as states of not only insulin deficiency but also glucagon excess.

Summary Lessons learned from this largely forgotten portfolio of work and therapeutic strategy aimed at limiting the number or function of islet alpha-cells might be worthy of reconsideration.

Keywords: Synthalin (Syn); diabetes; alpha-cells; beta-cells; pancreatic islets; glucagon

Core tip: This review examines the history of synthalin A and its early evaluation as a potential diabetes treatment. The research was discontinued as insulin became available for the treatment of diabetes. However, re-evaluation of this early work may provide a useful perspective on alpha-cell function and therapeutic strategies to diminish glucagon secretion or action in diabetes.

Introduction

Fatal degenerative diabetes mellitus, now recognised as type 1 (insulin-dependent) diabetes, has been described in some of the earliest known medical texts, and before the discovery of insulin in 1921 the usual treatment was only palliative – starvation diets, sometimes supplemented with herbal medicines.[1] Among the herbal medicines, *Galega officinalis* has been described as a treatment for thirst and excess urination (early symptoms of diabetes) since the 1700s, and in 1850 (or thereabouts) this plant was shown to be rich in guanidine.[2] Some logic to the use of *G. officinalis* in diabetes was provided by the work of Watanabe who noted in 1918 that guanidine reduced blood glucose.[3] Unfortunately, effective amounts of guanidine (Figure 1) were not without toxicity, precluding use as a medicine. However, it was quickly noted that a monoguanidine derivative (galegine) and some diguanide derivatives [particularly synthalin A (Syn A) and synthalin B (Syn B)] retained the glucose-lowering effect with less toxicity.[4] Galegine was tried only briefly as a treatment for diabetes, but Syn A and Syn B were used widely as medicines by the late 1920s.[4] Surprisingly, the closely related biguanide molecules, phenformin and metformin, were identified at this time, but their antidiabetic properties were not appreciated and had to await rediscovery in the 1950s.[5]

Although Syn A and Syn B did not offer the life-saving effectiveness of insulin for type 1 diabetes, the limited supplies of insulin forced many patients in Europe to continue their use of alternative therapies into the 1930s. This article examines how the diguanide agents helped to control blood glucose for some patients, how animal studies revealed the mechanism, and what lessons are offered for supplementary approaches to manage the various types of diabetes we recognise today. This article examines how the diguanide agents helped to control blood glucose for some patients, how animal studies revealed the mechanism, and what important new lessons are offered by re-examining old literature for supplementary approaches to manage the various types of diabetes we recognise today.

Historical Aspects of Diabetes and Involvement of Glucagon

Most cases of diabetes reported 100 years ago described severe degenerative conditions typically associated with onset in early life, emaciation, ketonuria and premature death.[1] This was subsequently termed juvenile-onset diabetes and more latterly insulin-dependent or type 1 diabetes. The other

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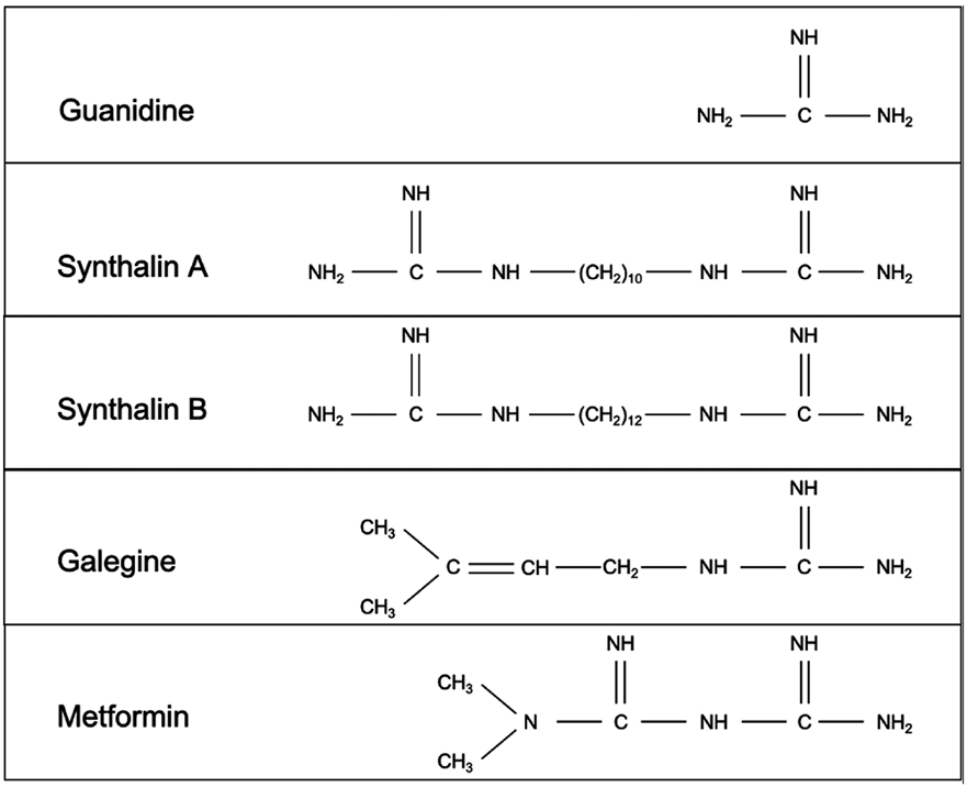

Figure 1 Chemical structures of guanidine, Syn A and B, galegine and metformin. (Adapted from Bailey and Day, 2004.)

main type of diabetes (non-insulin-dependent or maturity-onset diabetes), now known as type 2 diabetes, became increasingly recognised after the availability of insulin when patients with less severe symptoms were found to be insensitive to insulin and required excessive doses of insulin to control blood glucose.[6] This type of diabetes was designated as a separate disease in the 1950s[7]: it is often associated with obesity and currently represents about 90% of all cases of the disease worldwide.[8] Although advanced stages of type 2 diabetes may require insulin treatment to achieve adequate blood glucose control, treatments for the majority of type 2 patients offer scope for non-insulin medicines that lower blood glucose such as metformin, sulphonylureas, thiazolidenediones, sodium-glucose transporter-2 (SGLT2) inhibitors, dipeptidylpeptidase-IV (DPP-IV) inhibitors and glucagon-like peptide-1 (GLP-1) mimetic agents.[9]

Soon after the landmark discovery of insulin, it was noted (in 1922) that the pancreas was the source of a substance that raised blood glucose and was a contaminant of early insulin preparations.[1, 10] This substance was identified as glucagon in the 1950s[11] and was shown to be secreted by the alpha-cells of the islets of Langerhans. It was found to be the main counterregulatory hormone, promptly increasing blood glucose by simulating hepatic glycogenolysis and gluconeogenesis.[12] Since the mid-1970s, it has been appreciated that type 2 diabetes is associated with an absolute or relative hyperglucagonaemia (raised circulating concentration of glucagon relative to the blood glucose concentration) as well as disturbances of insulin action and insulin secretion.[12] Indeed, the current success of GLP-1 mimetic agents in the treatment of type 2 diabetes is attributed partly to their ability to inhibit glucagon release as well as increase insulin secretion. Interestingly, the guanidine derivatives introduced a century ago were helping to lower blood glucose by a toxic effect on the glucagon-secreting islet alpha-cells, and the search for new treatments for type 2 diabetes continues to investigate methods to suppress alpha-cells.[13]

The Synthalins

The diguanide Syn A (Figure 1) was first synthesised and proposed as an alpha-cell toxin in 1926 by Erich Frank and colleagues in Breslau.[14] Syn A was produced in several forms (tablets, injectables and a pure salt)[15] and oral administration was shown to reduce blood sugar in humans and animals. When injected into animals, Syn A had a biphasic action causing blood sugar to increase transiently before dropping into hypoglycaemia (excessively low blood sugar).[15] Studies were also conducted with the related diguanide Syn B,[14, 16, 17] but early publications did not always specify whether Syn A or Syn B was administered. Therefore, when describing the mechanism of action in the following paragraphs we sometimes refer to Syn (unspecified) unless the use of Syn A or Syn B was specified in the published works.

Morphological changes to pancreatic alpha-cells were observed with Syn A treatment, which caused these cells to become hydropic, and exhibit cytoplasmic vacuolation.[17, 18] It was unknown how Syn A brought about these changes, but an increase in functional activity causing cell exhaustion was suggested.[18, 19]

Concern about the safety of Syn in clinical studies was aroused by accounts of excess proteinuria, haematuria and urinary tract infections. There were also reports of digestive, hepatic and renal complications, although it was not clear

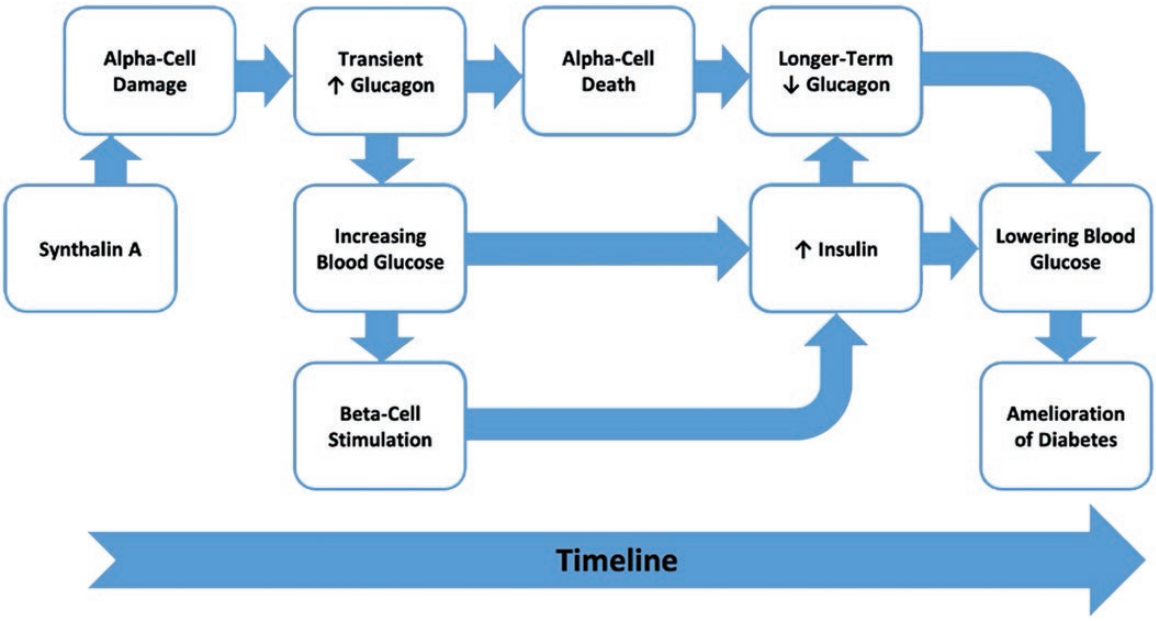

Figure 2 Simplified scheme of the envisaged effects of synthalin A on pancreatic islets leading to depletion of alpha-cells, reversal of hyperglucagonaemia and lowering of blood glucose based on observations in historical literature.

if these were related to the treatment or morbidities of diabetes.[4] However, safety concerns, limited durability of efficacy and increasing availability of insulin resulted in a decline of interest in using Syn as a treatment for diabetes, and the diguanides were little used by the end of the 1930s.[4, 20, 21]

Mode of Action of Synthalins

Several studies dating from the 1920s to the 1970s have examined the hypoglycaemic mechanism of Syn A, noting damage to alpha-cells, with little or no damage to beta-cells, thereby offering a means of decreasing blood glucose by reducing glucagon secretion in non-diabetic and diabetic states.[17, 20, 22–27] At high doses, Syn A produced more generalised organ toxicity as well as degeneration of alpha-cells,[3, 15, 20, 23, 25] and research in the 1950s and 1960s provided insights into the cellular mechanisms and species-specificity of this toxicity as summarised below.[19, 26, 28–31]

Human Studies

By the late 1920s, Syn was being tested in humans as an antidiabetic drug.[16, 32–35] In Boston (USA) in 1927 Elliot Joslin treated eight insulin-dependent (type 1) individuals with Syn and recorded positive effects with few side effects.[32] However, the efficacy varied greatly between individuals: for example, one individual required only 1 mg Syn to replace 1 unit of insulin while another individual needed 3 mg Syn to replace 1 unit of insulin for diabetes control. All but one of the patients noted reductions in glycosuria and one individual reduced their insulin dose from 28 to 16 units daily.[32] However, only one of the patients was followed for more than 3 months and only one became temporarily insulin free. In light of current knowledge, it is likely that the variable effects of Syn reflect the heterogeneity of type 1 diabetes in which some patients may retain some endogenous insulin secretion, especially during the early stages of the disease.

Similar small short-term studies by Frank et al. (1926)[14] and Graham (1928)[16] noted reductions in blood sugar levels and glycosuria during combination therapy of Syn and insulin. However, some patients reported gastrointestinal side effects, mostly vomiting but there was one case of a comatose state (possibly severe hypoglycaemia) which lead to cessation of the Syn.[16]

Thomson et al. (1932) conducted a long-term study (25–104 months) of Syn in combination with insulin in 64 diabetes patients and noted reductions in blood sugar levels in most patients at most times tested, with only mild adverse symptoms. The study concluded that an appropriate dose of Syn to optimise efficacy with minimal toxicity should usually be about 10 mg given three times daily following food intake for 3 consecutive days and no treatment on the fourth day.[35]

None of the foregoing studies recommended the use of Syn without insulin or in conjunction with another drug,[16, 32, 35] but a study by Rabinowitch (1927) found that Syn alone was able to replace insulin for 2–4 weeks in six of seven patients tested, but was not able to replace insulin long term.[34]

In these clinical studies, there was no opportunity to examine pancreatic histology and no discussion of the effects of Syn on pancreatic islets. In animal studies, however, the mechanism of action of Syn was examined in detail.

Animal Studies

A substantial number of early studies detailed the effects of enteral and parenteral administration of Syn on the morphology of pancreatic islets and other tissues, but it must be borne in mind that these studies pre-date reliable methods for direct measurement of insulin and glucagon. The species examined included rabbits,[15, 23, 36] guinea pigs,[17, 37] cats,[15] dogs,[15, 20] birds[22, 25, 26, 38] and rodents.[14, 39, 40] The results, summarised in Figure 2, revealed distinct species differences of sensitivity to the glycaemic effects of Syn A but consistent evidence of alpha-cell damage, although these effects were sometimes tempered by evidence of extra-pancreatic toxicity.

Particularly worthy of historical comment are the studies performed using birds and guinea pigs. Birds have a mixture of dark and light pancreatic islets, the former being composed almost entirely of alpha cells. The importance of glucagon in birds is illustrated by the effect of pancreatectomy which results in fatal hypoglycaemia (compared with fatal hyperglycaemia in mammals).[41] Consistent with this, injection of chickens with Syn A resulted in transient hyperglycaemia, possibly due to glucagon leakage associated with the destruction of alpha-cells, followed by glycogen depletion and severe hypoglycaemia, culminating in convulsions and death.[26, 38, 41] This accords with studies by Östenson et al. in 1983 using guinea pig islets which are rich in alpha-cells.[17] Brief exposure of guinea pig islets to Syn A increased glucagon release, accompanied by a concentration-dependent decrease in alpha-cell glucose oxidation, vacuolisation, necrosis and disintegration.

Although interesting from a mechanistic perspective the early experiments using non-diabetic models (with normal blood glucose levels) were not ideal for assessing the metabolic effects of agents intended to counter hyperglycaemia. While confirming the ability of Syn to suppress alpha-cell function, they provide limited insight for application in type 2 human diabetes which is now the main type of diabetes of interest for suppression of glucagon levels.

Based on the evidence summarised in Figure 2, it appears that an appropriate dose of Syn A can selectively disrupt islet alpha-cell function, leading to an initial release of glucagon which stimulates glycogenolysis and gluconeogenesis, which in turn promotes hyperglycaemia (Figure 3). More prolonged exposure to Syn A gives way to the gradual exhaustion of tissue glycogen stores and loss of functional alpha-cells, resulting in a lowering of blood glucose. Such an effect might proceed more rapidly in normal animals because glucagon will trigger insulin release by a direct stimulatory effect on beta-cells as well as by potentiating the positive effects mediated by increased glucose itself. However, similar beta-cell actions in man are less certain and will depend on the level of insulin secretory function in type 2 and the persistence of beta-cells in type 1 diabetes.

New Therapies and Approaches to Counter Hyperglucagonaemia

Although the studies with synthalins have become submerged in history, the quest to suppress glucagon secretion or action continues to be a therapeutic consideration for the control of hyperglycaemia in type 2 diabetes today, and it has been contemplated as a possible adjunct to insulin treatment for type 1 diabetes.[42, 43] Current experience with DPP-IV inhibitors and GLP-1 mimetic agents indicates that modest suppression of glucagon secretion can assist in the reduction of prandial glucose excursions. The mode of action of these agents on alpha-cell function does not appear to interrupt the increased secretion of glucagon at low glucose concentrations and does not, therefore, compromise the counter-regulatory response to protect against severe hypoglycaemia. Selective suppression of glucagon secretion or elimination of most or all pancreatic alpha-cells has been attempted in very few experimental studies, and as with Syn A it has proved difficult to avoid collateral toxicity, and as yet has not proceeded as a clinically viable therapeutic approach.[2]

An alternative strategy has focussed on the development of glucagon antagonists.[44, 45] Several of these agents have exhibited effective glucose lowering in type 2 diabetes patients, including glucagon antibodies, glucagon analogues

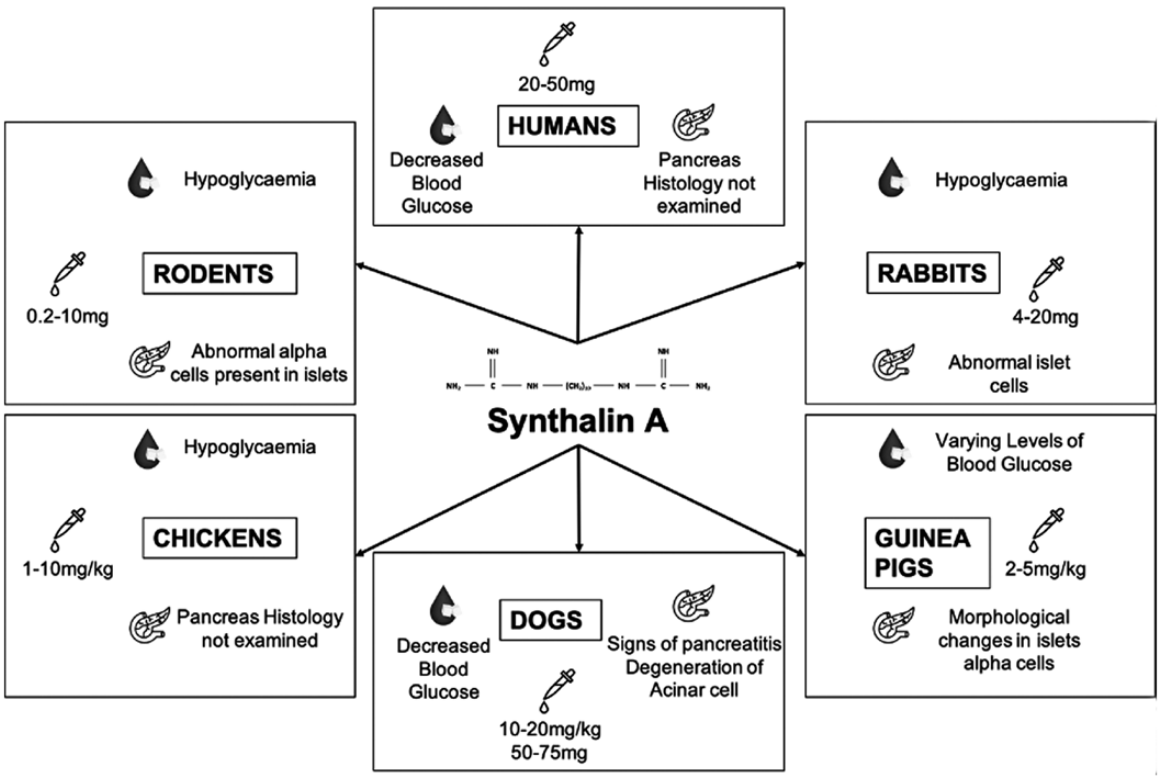

Figure 3 Overview of synthalin A studies across species with dose, blood glucose effects and pancreas toxicity.

and antibodies that inhibit glucagon binding to its receptor, antisense oligonucleotides against receptor mRNA, and small molecules that interrupt glucagon receptor binding or intracellular receptor signalling.[44, 45] Most of these approaches have been cautious to minimise the risk of severe hypoglycaemia, but they have exposed the requirement for glucagon to exert actions beyond blood glucose elevation. For example, glucagon antagonism has frequently increased circulating liver enzymes and given rise to alpha-cell hyperplasia with escalating circulating glucagon concentrations.[44, 45] This in turn causes a marked rebound hyperglycaemia if a treatment dose is missed. These side effects may challenge the ultimate use of glucagon antagonists. However, an emerging prospect for the future therapeutic manipulation of alpha-cells is their transdifferentiation into insulin-secreting beta-cells, and this might be achieved through pharmaceutical modification of the activity of key transcription factors such as Pax4.[13]

Conclusion

After its discovery in the 1920s, Syn A provided a new oral glucose-lowering medication to supplement the use of insulin and give temporary therapeutic benefits when insulin could not be obtained. While selective destruction of glucagon-secreting alpha-cells with Syn A was not without some collateral toxicity, the early studies suggest that careful dose titration could minimise adverse effects, possibly by reducing but not eliminating the alpha-cell population. Perhaps the lessons provided by the early studies on Syn A might stimulate a resurgence of interest in therapeutic approaches that reduce or repurpose the alpha-cell population, at least to reverse the hyperglucagonaemias of diabetic states, but without compromising the vital actions of glucagon that prevent severe hypoglycaemia and maintain other metabolic functions.

Author Contributions

P.R.F. and R.C.M. conceived the research. N.K. found/reviewed the literature and drafted the manuscript. P.R.F., C.J.B. and K.T. edited and added text, and all authors approved the final version.

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Conflict of Interest

The authors declare there are no conflicts of interest for this review article.

Data Availability

No data were used for the research described in the article.

Ethical Statement

No ethical approval applies to the review due to the review of published data.

References

1. Tattersall RB. The history of diabetes mellitus. In: Holt RIG, Cockram CS, Flyvbjerg A, and Goldstein BJ (eds.), *Textbook of Diabetes*. Chichester: John Wiley & Sons, Ltd, 2017, 1–22.
2. Bailey CJ. New pharmacological approaches to glycemic control. *Diabetes Rev* 1999; 7: 94–113.
3. Watanabe CK. Studies in the metabolism changes induced by administration of guanidine bases: I. influence of injected guanidine hydrochloride upon blood sugar content. *J Biol Chem* 1918; 33: 253–65. https://doi.org/10.1016/s0021-9258(18)86579-6
4. Sterne J. Pharmacology and mode of action of the hypoglycemic guanidine derivatives. In: Campbell GD (ed.), *Oral Hypoglycemic Agents*. New York: Academic Press, 1969, 193–245.
5. Bailey CJ. Metformin: historical overview. *Diabetologia* 2017; 60: 1566–76. https://doi.org/10.1007/s00125-017-4318-z
6. Himsworth HP. Diabetes mellitus: its differentiation into insulin-sensitive and insulin-insensitive types. *Lancet* 1936; 227: 127–30.
7. Lister J, Nash J, Ledingham U. Constitution and insulin sensitivity in diabetes mellitus. *Br Med J* 1951; 1: 376–9. https://doi.org/10.1136/bmj.1.4703.376
8. IDF Diabetes Atlas. *IDF Diabetes Atlas 2021. Report number: 10, 2021*. https://diabetesatlas.org/atlas/tenth-edition/?dlmodal=active (6 September 2022, date last accessed).
9. Bailey CJ, Day C. Treatment of type 2 diabetes: future approaches. *Br Med Bull* 2018; 126: 123–37. https://doi.org/10.1093/brimed/ldy013
10. Murlin JR, Clough HD, Gibbs CBF et al. Aqueous extracts of pancreas: I. influence on the carbohydrate metabolism of depancreatized animals. *J Biol Chem* 1923; 56: 253–96.
11. Staub A, Sinn L, Behrens OK. Purification and crystallization of glucagon. *J Biol Chem* 1955; 214: 619–32. https://doi.org/10.1016/s0021-9258(18)70910-1
12. Ahrén B. Glucagon – early breakthroughs and recent discoveries. *Peptides* 2015; 67: 74–81. https://doi.org/10.1016/j.peptides.2015.03.011
13. Klempel N, Thomas K, Conlon JM et al. Alpha-cells and therapy of diabetes: inhibition, antagonism or death? *Peptides* 2022; 157: 170877. https://doi.org/10.1016/j.peptides.2022.170877
14. Frank E, Nothmann M, Wagner A. Über synthetisch Dargestellte Körper mit insulinartiger Wirkung auf den Normalen und diabetischen organismus. *Klin Wochenschr* 1926; 5: 2100–7. https://doi.org/10.1007/bf01736560
15. Bodo R, Marks HP. The relation of synthalin to carbohydrate metabolism. *J Physiol* 1928; 65: 83–99. https://doi.org/10.1113/jphysiol.1928.sp002463
16. Graham G. Discussion on the action of synthalin. *Proc R Soc Med* 1928; 21: 527–36.
17. Östenson CG. Effects of the biguanide synthalin A on the pancreatic A2-cell of the guinea pig. *Exp Clin Endocrinol* 1983; 81: 255–62.
18. Gunnarsson R, Petersson B, Hellerstrom C. The two types of A-cells in the islets of Langerhans of normal and synthalin-treated guinea-pigs. *Acta Pathol Microbiol Scand* 1969; 76: 184–92.
19. Creutzfeldt W. Alpha cell cytotoxins; their influence on carbohydrate metabolism and the effect of the oral blood glucose reducing sulfonamides on the islet cells. *Diabetes* 1957; 6: 135–45. https://doi.org/10.2337/diab.6.2.135
20. Karr WG, Belk WP, Petty OH. The toxicity of synthalin. *J Pharmacol Exp Ther* 1929; 36: 611–8.
21. Kruger FA, Skillman TG, Hamwi GJ et al. The mechanism of action of hypoglycemic guanidine derivatives. *Diabetes* 1960; 9: 170–3. https://doi.org/10.2337/diab.9.3.170
22. Beekman BE. The effect of synthalin A on blood sugar and pancreatic alpha islet cells of the fowl. *Endocrinology* 1956; 59: 708–12. https://doi.org/10.1210/endo-59-6-708
23. Davis JC. Hydropic degeneration of the alpha cells of the pancreatic islets produced by synthalin A. *J Pathol Bacteriol* 1952; 64: 575–84.

24. Ferner H, Runge W. Synthalin A as selective mitotic poison acting on alpha-cells of the islets of Langerhans. *Science* 1955; 122: 420. https://doi.org/10.1126/science.122.3166.420
25. Fodden JH, Read WO. The activity of extracted pancreatic hyperglycemic-glycogenolytic factor after cobaltous chloride and synthalin A. *Endocrinology* 1954; 54: 303–10. https://doi.org/10.1210/endo-54-3-303
26. Langslow DR, Freeman BM, Buchanan KD. Responses of plasma glucose, free fatty acids, glucagon and insulin to synthalin A by Gallus domesticus. *Comp Biochem Physiol A Comp Physiol* 1973; 46: 437–45.
27. Martini FH, Nath JL, Bartholomew EF. The endocrine system. In: Serina Beauparlant (ed.), *Fundamentals of Anatomy & Physiology*, 11th edn. Harlow: Pearson Education, 2018.
28. Bailey C, Day C. Metformin: its botanical background. *Pract Diabetes Int* 2004; 21: 115–7. https://doi.org/10.1002/pdi.606
29. Dale HH. Discussion on the action of synthalin. *Proc R Soc Med* 1928; 21: 527–36.
30. Dey L, Attele AS, Yuan CS. Alternative therapies for type 2 diabetes. *Altern Med Rev* 2002; 7: 45–58.
31. Krishnarth N, Bisht A, Verma S et al. Design, synthesis of guanidine derivatives and their anti-hyperglycemic evaluation. *Der Pharma Chemica* 2013; 5: 59–66.
32. Joslin E. Synthalin: proceedings of the nineteenth annual meeting of the American Society for Clinical Investigation held in Atlantic City, New Jersey, May 2, 1927. *J Clin Investig* 1927; 4: 427–58.
33. Lawrence RD. Discussion on the action of synthalin. *Proc R Soc Med* 1928; 21: 527–36.
34. Rabinowitch IM. Observations on the use of synthalin in the treatment of diabetes mellitus. *Can Med Assoc J* 1927; 17: 901–4.
35. Thomson AP, Gittins RJ, Thomas G. Synthalin in the treatment of diabetes. *Br Med J* 1932; 1: 322–5.
36. Davis JC. Lesions in the rabbit liver produced by synthalin. *J Pathol Bacteriol* 1958; 76: 97–109.
37. Herbertson BM. The effects of synthalin on the liver of guinea-pigs. *J Pathol Bacteriol* 1958; 75: 183–8.
38. Langslow DR, Freeman BM. Investigations into the mode of action of synthalin A in *Gallus domesticus*. *Comp Biochem Physiol A Comp Physiol* 1973; 46: 447–62.
39. Hultquist GT. The effect of cobalt chloride and synthaline A on reduced glutathione in blood and tissues in rats with partial pancreatic duct ligation. *Br J Exp Pathol* 1956; 37: 357–60.
40. Lundbaek K, Nielsen K. A comparative study of the action of three hypoglycemic compounds on the blood sugar and the islet cells of the pancreas in the rat. *Acta Endocrinol (Copenh)* 1958; 27: 325–38.
41. Falkmer S, Marques M. Phylogeny and ontogeny of glucagon production. In: Lefebvre PJ, Unger RH (eds.), *Glucagon: Molecular Physiology, Clinical and Therapeutic Implications*. Oxford: Pergamon Press, 1973.
42. Mittermayer F, Caveney E, De Oliveira C et al. Addressing unmet medical needs in type 1 diabetes: a review of drugs under development. *Curr Diabetes Rev* 2017; 13: 300–14.
43. Van Name M, Sherr J. When insulin isn't enough: targeting glucagon in type 1 diabetes. *Nat Med* 2022; 28: 2007–8. https://doi.org/10.1038/s41591-022-02019-3
44. Scott RV, Bloom SR. Problem or solution: the strange story of glucagon. *Peptides* 2018; 100: 36–41. https://doi.org/10.1016/j.peptides.2017.11.013
45. Wewer Albrechtsen NJ. Glucagon receptor signaling in metabolic diseases. *Peptides* 2018; 100: 42–7. https://doi.org/10.1016/j.peptides.2017.11.016