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Alpha-cells and therapy of diabetes: Inhibition, antagonism or death?

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ABSTRACT

Absolute or relative hyperglucagonaemia is a characteristic of both Type 1 and Type 2 diabetes, resulting in fasting hyperglycaemia due in part to increased hepatic glucose production and lack of postprandial suppression of circulating glucagon concentrations. Consequently, therapeutics that target glucagon secretion or biological action may be effective antidiabetic agents. In this regard, specific glucagon receptor (GCGR) antagonists have been developed that exhibit impressive glucose-lowering actions, but unfortunately may cause off-target adverse effects in humans. Further to this, several currently approved antidiabetic agents, including GLP-1 mimetics, DPP-4 inhibitors, metformin, sulphonylureas and pramlintide likely exert part of their glucose homeostatic actions through direct or indirect inhibition of GCGR signalling. In addition to agents that inhibit the release of glucagon, compounds that enhance the transdifferentiation of glucagon secreting alpha-cells towards an insulin positive beta-cell phenotype could also help curb excess glucagon secretion in diabetes. Use of alpha-cell toxins represents another possible strategy to address hyperglucagonaemia in diabetes. In that respect, research from the 1920 s with diguanides such as synthalin A demonstrated effective glucose-lowering with alpha-cell ablation in both animal models and humans with diabetes. However, further clinical use of synthalin A was curtailed due its adverse effects and the increased availability of insulin. Overall, these observations with therapeutics that directly target alpha-cells, or GCGR signaling, highlight a largely untapped potential for diabetes therapy that merits further detailed consideration.

1. Introduction

It is now 100 years since the discovery of glucagon but the role of this hormone in the maintenance of normoglycemia in healthy subjects and in the pathophysiology of diabetes is complex and still incompletely understood [77]. The primary action of glucagon is to stimulate glycogenolysis and gluconeogenesis thereby counteracting the glucose-lowering activity of insulin. Consequently, the idea that glucagon, or derivatives based upon its primary structure, may find application in diabetes therapy appears paradoxical. Indeed, glucagon preparations are an established and effective means to counter severe hypoglycaemia following excess insulin administration in type 1 diabetes mellitus (T1DM) [59]. However, administration of glucagon promotes weight loss, an important factor in reversing insulin resistance, by increasing energy expenditure and lipid catabolism, suggesting a possible therapeutic role in the management of obesity-related type 2 diabetes mellitus (T2DM) [12]. Unimolecular dual-agonist peptides based upon the primary structures of glucagon-like peptide-1 (GLP-1) and glucagon, that regulate multiple metabolic pathways through targeting both the GLP-1 receptor (GLP1R) and the glucagon receptor (GCGR), are currently in clinical development [81].

On the other hand, the possibility that glucagon excess may make an important, if not essential, contribution to the pathogenesis of diabetes was proposed by Unger and Orci [88] in their rather sweeping bihormonal-abnormality hypothesis, which held that absolute or relative glucagon excess is the principal factor in the over-production of glucose in diabetes. The authors suggested that therapy directed at correcting the pancreatic alpha-cell abnormality through control of glucagon secretion would improve existing methods of glucoregulation. In this light, the possibility of diminishing glucagon action or release, either via glucagon receptor (GCGR) antagonism or selective reduction of islet α-cell mass, seems attractive. On the negative side, since glucagon plays a key role in the counter-response to hypoglycaemia, as well as in protein and lipid metabolism, diminution in its release and/or action could lead to adverse off-target side-effects. In addition to this, hyperglucagonaemia is also apparent in other metabolic diseases beyond diabetes, such as obesity and non-alcoholic fatty liver disease (NAFLD) [71]. This may suggest importance of the liver-alpha cell axis

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for development of hyperglucagonaemia, where potential glucagon resistance due to excess hepatic fat accumulation leads to decreased amino acid and fat uptake by the liver, and subsequent increased stimulation of glucagon secretion from pancreatic alpha-cells [71]. However, methods to improve hepatic glucagon sensitivity are outside the scope of the current review.

2. Targeting the alpha-cell in diabetes

The hyperglycaemic action of glucagon has been documented since its initial discovery, with the very name of the hormone reflecting this; glucagon – "the glucose agonist" [60]. The GCGR is widely expressed, particularly in the liver where it is the primary regulator of hepatic glucose production, with glucose elevating actions are mediated via intracellular cyclic AMP and phospholipase C/inositol triphosphate signalling cascades [77]. Although the GCGR is primarily expressed in liver, it is also expressed in varying amounts within the central nervous system, kidney, heart and adipose [77]. In these tissues glucagon is known to regulate energy expenditure, electrolyte handling, heart rate and contractility as well as lipolysis, respectively [77]. However, given that hyperglucagonaemia, and resultant glucose-elevating actions, are a pathophysiological feature of diabetes the current review will focus on the practicality of attenuation of GCGR signalling and inhibition of glucagon production and release, through various mechanisms, as treatment options for this disease. We will also consider how selected current antidiabetic therapies affect GCGR action as part of their inherent biological action profile [Table 1].

3. GCGR antagonists

Early studies employed glucagon antisera produced in rabbits to neutralise circulating glucagon and although impact of this approach on glycaemic control was limited to non-diabetic rodents [36], significant reductions in plasma glucose concentrations were observed in obese diabetic (*ob/ob*) mice [21]. Treatment with human monoclonal glucagon antibodies might be worthy of consideration [63] but more recently, experimental methods to target directly the GCGR as a treatment option for T2DM have been developed and include use of antisense oligonucleotides, low molecular weight and peptide-based GCGR antagonists as well as GCGR antibodies [11]. Of these, the peptide-based GCGR antagonists are still under the early development phase, with only preclinical observations generated to date. However, such compounds may ultimately prove to exert the most favourable efficacy vs. side-effect profile within this drug class. Thus, antisense oligonucleotides, low molecular GCGR antagonists and GCGR antibodies all promote significant reductions of circulating glucose in T2DM [67], but therapeutic application is limited in humans due to the increased occurrence of hypoglycaemia, elevations in plasma LDL cholesterol levels, fatty liver disease, alpha-cell hyperplasia and more recent observations of hyperaminoacidaemia linked to the newly recognised liver-alpha-cell axis [71] [Table 1]. Indeed, there appears to be an overall decline in discovery efforts toward novel non-peptidic GCGR antagonists [11], with a more recent focus on peptide entities [94].

As might be expected, design of peptide-based GCGR antagonists was largely founded on the sequence of native glucagon, with appropriate incorporation of current structure/function knowledge to generate peptides that bind, but do not activate, the GCGR through amino acid modification/substitution/deletion [37,89,90]. In this regard, desHis^{1}-Pro^{4}Glu^{9}(Lys^{12}PAL)-glucagon and desHis^{1}Pro^{4}Glu^{9}(Lys^{30}PAL)-glucagon (PAL = palmitate) employed deletion of the His^{1} residue as well as Gly^{4} to Pro^{4} and Asp^{9} to Glu^{9} substitutions to create effective GCGR antagonists, alongside fatty acid derivation that extended the pharmacokinetic profile of the peptides [62]. Encouragingly, both compounds effectively countered the actions of glucagon in vitro and in vivo [62], and possessed an excellent safety profile in lean mice following twice daily injection for 10 days [25]. More importantly, these fatty acid-derivatised GCGR peptide antagonists exerted prominent metabolic improvements in high fat fed mice that exhibit obesity, impaired glucose tolerance and insulin resistance with no obvious adverse effects [55,61]. Interestingly, these GCGR antagonists also augmented the antidiabetic efficacy of the incretin hormone, glucose-dependent insulinotropic polypeptide (GIP) [56], but not GLP-1 [24]. This being despite a suggestion that GCGR antagonism upregulates the secretion and action of GLP-1 by promoting intestinal L-cell proliferation and inhibiting apoptosis [29,46,47]. A similar molecule, namely desHis^{1}Glu^{9}-glucagon-[mPEG] (PEG = polyethylene glycol), employed C-terminal pegylation rather than acylation to extend peptide pharmacodynamic profile [40], but was not progressed to efficacy studies in diabetic rodents despite possessing clear and protracted GCGR antagonist properties. Additional studies have identified N-terminally truncated glucagon fragments as effective GCGR antagonists, with a Lys^{10} fatty-acid derived Pla^{6}Asp^{28}-glucagon(6−29) peptide analogue displaying notable efficacy [94]. Intriguingly, the Phe^{6} to L-3-phenyllactic acid (Pla) substitution was established to be of critical importance for GCGR antagonism, but the specific reasons behind this remain to be elucidated [94].

Table 1
Overview of different methods to target the alpha-cell in diabetes, alongside positive and possible negative effects of each approach.

Specific approach	Positive effects	Negative effects
Glucagon antagonism (small molecules or peptide analogues)	Improved glycaemic control	Increased incidence of hypoglycaemia Occurrence of alpha-cell hyperplasia Potential to disrupt liver-alpha cell axis leading to excess circulating lipids and amino acids
Inhibition of glucagon secretion (established antidiabetic drugs)	Increased insulin action Already clinically employed Improved glycaemic control	Adverse effects as already established for each drug
Promotion of alpha- to beta-cell transdifferentiation (experimental and some established antidiabetic drugs)	Increased beta/alpha-cell mass Some agents already clinically approved Improved glycaemic control	Adverse effects as already established for each drug Some debate as to whether circulating glucagon is decreased Magnitude of effect may differ between agents
Alpha-cell ablation (Synthalin A, cobalt or other toxins)	Decreased alpha-cell mass Decreased glucagon secretion Improved glycaemic control	Species specific side-effects Drugs will require high specificity Potential of systemic toxicity of non-specific agents

4. Approved antidiabetic therapies involving inhibition of glucagon release and GCGR signalling

4.1. GLP-1 mimetics

The most commonly ascribed antidiabetic actions of GLP-1 centre around potent glucose-dependent insulin secretion as well as induction of appetite suppression [83]. However, there can be no doubt that another important aspect in terms of the notable antidiabetic efficacy of GLP-1 mimetics in T2DM relates to their glucagonostatic actions [83]. Indeed, early observations from the University of Copenhagen suggested that the glucagonostatic and insulinotropic effects of GLP-1 contribute

equally to its glucose-lowering action in patients with T2DM [33]. The mechanism(s) behind this action is debated, with strong evidence to advocate that it is mediated indirectly through increased insulin or somatostatin secretion [64,87], while others promote more direct effects of GLP-1 on the alpha-cell [17], despite relatively low expression (~10%) of GLP-1R on the human alpha-cell [70]. Interestingly, one report also proposes that the DPP-4 degradation product of GLP-1, namely GLP-1(9−36), may antagonise GCGR on alpha-cells to influence the overall glucagonostatic effects of GLP-1 [30] but this action still needs to be confirmed.

4.2. DPP-4 inhibitors

DPP-4 inhibitors augment the bioactivity, and related antidiabetic actions, of the incretin hormones GIP and GLP-1 [18]. In this respect, the aforementioned glucagonostatic effects of GLP-1 might be expected to be offset by the glucagonotropic action of GIP [10]. However, the glucagon elevating actions of GIP are only evident under hypoglycaemic conditions [10], likely as an inherent safety mechanism. Taken together, DPP-4 inhibitors combine two beneficial GCGR signalling effects, namely GLP-1 induced glucagonostatic actions during hyperglycaemia and glucagonotropic effects of GIP during hypoglycaemia. Thus, DPP-4 inhibitors are generally regarded to increase insulin secretion and lower glucagon concentrations through enhancement of the incretin effect in T2DM [18].

4.3. Metformin

The global first choice treatment option for T2DM, barring contraindications, is metformin. Metformin is well known to inhibit the mitochondrial respiratory chain in the liver leading to activation of AMP–activated protein kinase (AMPK) that mediates an array of its antidiabetic actions [3]. Moreover, there is also a suggestion that metformin can suppress GCGR hepatic signalling to inhibit glucose production by the liver [57]. In agreement, metformin has been demonstrated to counter directly glucagon-induced hepatic gluconeogenesis [95]. However, this action has been contested, and it is believed that the clinical relevance on metformin's effect of GCGR signalling may be negligible in human T2DM [43]. To add to the complexity of metformin action, the drug has also been shown to induce significant GLP-1 secretion [2], as well as potentially inhibit dipeptidyl peptidase-4 (DPP-4) activity [52], that would further enhance antidiabetic actions through alternative pathways indirectly linked to inhibition of GCGR signalling. As such, one of the key actions of GLP-1 is to inhibit glucagon release from islet alpha-cells [35].

4.4. Sulphonylureas

The classic pharmacological action of sulphonylurea drugs in diabetes is stimulation of insulin secretion in a glucose-independent manner through closure of beta-cell K_{ATP} channels and subsequent cellular depolarisation [69]. However, some agents within this class of drugs have been documented to suppress glucagon secretion in vivo, including glibenclamide [45]. Such an effect could not be replicated in the perfused rat pancreas [28], suggesting indirect effects on glucagon release. This could be linked to somatostatin secretion or through sulphonylureas acting on K_{ATP} channel-expressing neurons in the brain [26]. Although, K_{ATP} channel regulated glucagon secretion from alpha-cells has also been documented [72].

4.5. Amylin

Amylin is a peptide hormone secreted from beta-cells with insulin, and is clinically approved for both T1DM and T2DM treatment as pramlintide. Amylin is recognised to inhibit glucagon secretion, alongside slowing gastric emptying and promoting satiety [9]. Notably, amylin suppresses glucagon release in a glucose-dependent manner that is thought to be centrally mediated and may function to safeguard against unwanted hypoglycaemia [78]. However, the overall importance of inhibition of glucagon secretion for the therapeutic benefits of pramlintide in diabetes still needs to be fully elucidated.

5. Agents that promote alpha- to beta-cell transdifferentiation

An understanding that adult mammalian cells possess inherent plasticity is not new, but the importance of such cell lineage alterations have only recently been identified in terms of the endocrine pancreas and development of diabetes. Thus, the alpha-cell represents a viable target for replenishment of beta-cell mass in diabetes [5]. Indeed, there had been a suggestion that the antimalarial drug artemether could induce alpha- to beta-cell transdifferentiation, enhancing beta-cell mass and improving overall glycaemic control potentially through modulation of islet γ-aminobutyric acid (GABA) signalling [51]. However, subsequent advanced lineage-tracing studies from our and other laboratories refute this claim [1,74,92]. Nevertheless, it is now accepted that islet cell transdifferentiation is a naturally occurring phenomenon [32,86], and that cell lineage fate can be influenced by numerous therapeutic agents. For example, incretin enhancer drugs have been demonstrated to both promote alpha- to beta-cell lineage changes as well as counter beta- to alpha-cell transdifferentiation in diabetes [27,50,66,82]. In addition, other approved diabetes therapies such as metformin and rosiglitazone have also been shown to target alpha-cells and prevent cellular dedifferentiation [75]. Moreover, preclinical experimental antidiabetic agents that possess established biological actions on pancreatic islet cells such as apelin, GIP, PYY and vasopressin are likewise reported to exert positive effects on alpha- to beta-cell transdifferentiation events [44,58,73,84]. It follows that appropriate targeting of the glucagon secreting alpha-cell and promotion of transdifferentiation towards an insulin-positive islet cell phenotype could help to limit excess glucagon secretion in diabetes [Table 1]. However, whilst there is a strong indication that, as expected, alpha- to beta-cell transdifferentiation can reduce circulating glucagon concentrations in diabetes, this observation is not consistent across all studies [44,58]. Such discrepancies could be related to the impact of each individual drug intervention on glucagon secretion as well as the extent of alpha- to beta-cell transdifferentiation induced.

6. Specific ablation of pancreatic alpha-cells

Prior to the availability of insulin in meaningful quantities, the prognosis of diabetic patients and particularly those with T1DM, was extremely poor. Thus, the antidiabetic properties of numerous pharmaceutical agents that demonstrated hypoglycaemic action in animals were evaluated in both human T1DM and T2DM generally with only limited success [Table 1]. Out of the possible therapeutic agents, synthalin A (SynA; 1,1'-decamethyleneguanidinium dichloride) and synthalin B (SynB; 1,1'-dodecamethylenediguanidinium dichloride) demonstrated the greatest promise and were subsequently shown to act as selective alpha-cell toxins. Cobaltous chloride was also revealed to be an effective alpha-cell toxin in animal models of diabetes but to date has been employed at concentrations likely to cause toxicity in humans. However, reports of species- and disease-specific toxicity of cobalt may suggest further investigation of the alpha-cell toxicity capacity of cobalt is required [19,38,39,54,91]. Certainly, as the renowned Swiss alchemist Paracelsus (1493–1541) once remarked: "The right dose differentiates a poison from a useful medicine". Initial claims that some organic compounds such as sodium diethyldithiocarbamate, p-aminobenzolsulfonamidisopropylthiodiazol (IPTD) and N-[4-methyl--benzolsulfonyl] -N^1butylcarbamide (D 860) functioned as alpha-cell toxins were not subsequently substantiated [13]. On a separate note, agents that augment alpha-cell secretion could also be of some therapeutic interest, linked to the reported metabolic benefits of dual GCGR

and GLP-1R in obesity-driven forms of diabetes [81]. This aspect is discussed in detail elsewhere [27,32,44,58,73–76,82–84,86,92] and the following section concentrates on methods to ablate alpha-cell secretions and the antidiabetic efficacy of such approaches.

6.1. Synthalins and other guanidine-based agents

The origins of the synthalins date back to medieval times when an extract of the herb *Galega officinalis* (French lilac) was widely used in folkloric medicine to treat a range of diseases including symptoms of what is now described as T2DM [4]. In the late 19th century, it was shown that the extract contained high concentrations of guanidine and subsequently lead to hypoglycaemia when administered to animals, but unfortunately toxicity prevented clinical use [93]. However, in the 1920 s a range of less toxic derivatives of guanidine which included SynA and SynB, together with phenformin and the now clinically established antidiabetic agent, metformin, were synthesised [7,80] [Fig. 1].

6. .2. Synthalin A administration in humans

The synthalins were initially considered as potential treatment options for diabetic patients since they reduced blood glucose levels [23, 41,68,85]. SynA was a particularly attractive proposition due to its efficacy in tablet form. Administration of SynA appeared to produce a biphasic effect causing blood sugar to increase transiently before a sustained reduction. These effects were attributed to a toxic effect of SynA on alpha-cells to ultimately decrease hyperglucagonemia [8]. Morphological changes were observed following SynA treatment, which resulted in cells becoming hydropic and exhibiting cytoplasmic vacuolation [15,22,31,42]. While SynA was reported to primarily damage alpha-cells, it has also been suggested to negatively affect islet beta-cell integrity to some degree [14,15,20]. Additionally, in clinical trials, some individuals undergoing SynA treatment excreted urine containing protein and red blood cells. These toxic effects, in conjunction with the timely success of insulin therapy, resulted in a sharp decline of interest drugs such as SynA as therapeutics for diabetes. However, proof-of-principle for the glucose-lowering actions of SynA is clear within the literature and this approach of targeting alpha-cells in diabetes perhaps merits reconsideration.

6.2. .1. SynA administration in animals and mechanisms underlying actions

Studies in a range of animal models confirmed glucose-lowering

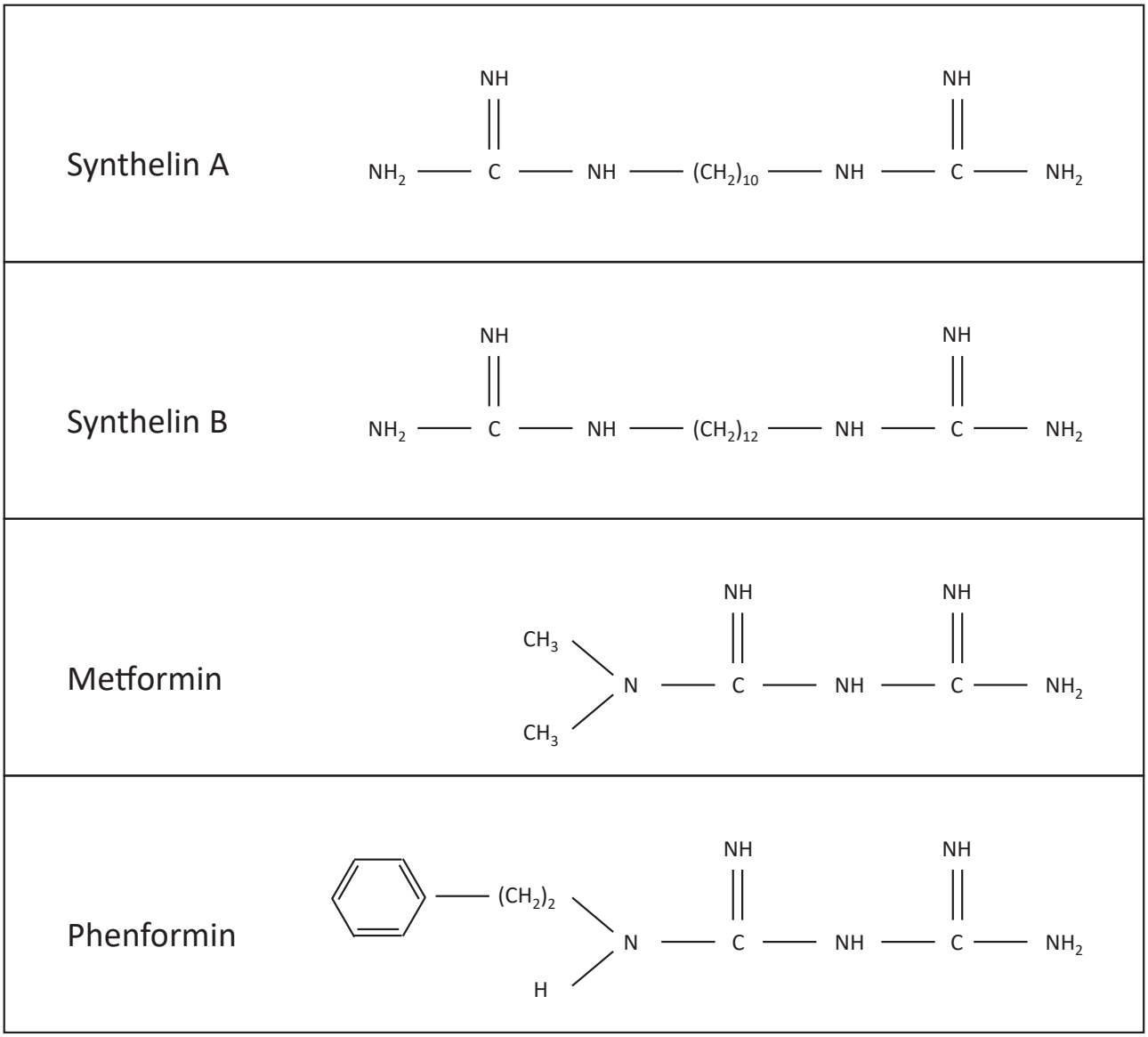

Fig. 1. Chemical structures of synthalin A, synthalin B, metformin, and phenformin.

action of SynA and allowed histological evaluation of effects at level of the pancreatic islets. However, there appeared to be species-dependent effects and toxicity likely linked to altered drug pharmacokinetics in each animal [13]. Species investigated include the rabbit [8,14,16], rat [20,38,53], guinea-pig [34,65], dog [42] and chicken [6,48,49]. A simple overview of these studies is presented in Fig. 2 and reviewed in detail by Creutzfeldt [13]. The rat appears to be less sensitive to the effects of SynA when compared to rabbits and guinea-pigs, and the agent was described as a very selective mitotic poisoning agent for alpha-cells in this species [20]. Administration of SynA to dogs was demonstrated to induce a particularly harmful phenotype, although only 4 dogs were examined in this report suggesting further study of SynA effects may be necessary in this species [42]. Glucagon rather than insulin is the major regulator of basal blood glucose concentrations in birds [79] and it is interesting that administration of SynA to chickens produced a transient hyperglycaemia followed by a profound hypoglycaemia, concomitant with a pronounced rise in circulating free fatty acids and substantial drop in glucagon concentrations [48,49]. As such, the chicken appears to be particularly susceptible to the alpha-cell toxic effects of SynA, and fatal convulsions, probably linked to hypoglycaemia, were commonly observed [6].

Despite these somewhat limited observations in a variety of species, it is possible to devise a scheme for the pharmacological actions of SynA. This considers that SynA, at an appropriate dose, results in selective destruction of islet alpha-cells leading to a sharp and relatively sustained release of glucagon. Stimulation of glycogenolysis (and longer-term gluconeogenesis) ensues, which in fed state leads to a protracted hyperglycaemia despite accompanying hyperinsulinaemia. Together with loss of functional alpha-cells, decline of circulating glucagon and possible depletion of hepatic glycogen stores, this then results in normalisation of blood glucose levels. However, many important mechanistic and bioactivity questions remain to help understand the claimed specificity and cellular mechanism of action of SynA on alpha-cells. Such knowledge might reveal molecular targets for development of more effective and therapeutically useful alpha-cell toxins.

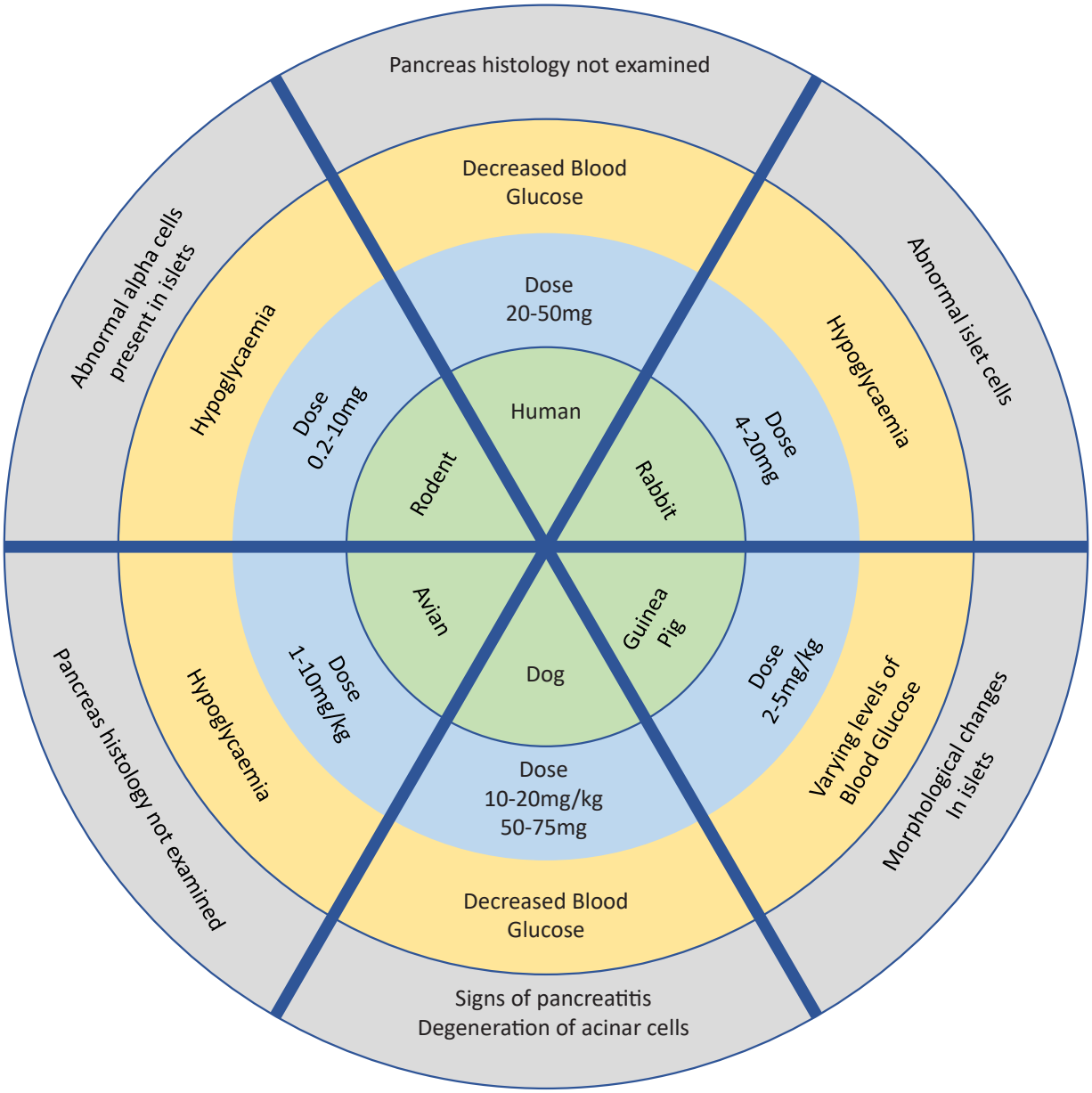

Fig. 2. Overview of Synthalin A studies across species with dose, blood glucose effects and actions on pancreatic islets documented.

7. Future perspectives

Effective clinical use and approval of various formulations of insulin over the past century, alongside more recent adoption of injectable and oral GLP-1 compounds, highlights the therapeutic capabilities of endogenous peptides that exert direct effects on glucose metabolism. In that respect, it is perhaps surprising that the only application for glucagon preparations within the diabetes clinic is to counter hypoglycaemia [59]. To date, various clinical trials with low molecular weight GCGR antagonists confirm potent glucose-lowering efficacy of diminished glucagon action, despite a somewhat troublesome side-effect profile [Table 1]. In that regard, peptide-based GCGR antagonists may provide a more secure route towards the clinic and warrant further investigation in the human setting, since negative side effects such as alpha-cell hyperplasia, increased hypoglycaemic episodes or altered lipid profiles have not been observed in preclinical trials [25,40,55,61]. It is also evident that numerous currently prescribed and highly effective antidiabetic agents exert part of their benefits in diabetes through annulment of GCGR signalling. In addition, some of these agents, alongside other less established glucose-lowering compounds, may also impact upon the lineage fate of alpha-cells promoting conversion to insulin-positive islet cells [Table 1].

Further to this, specific ablation of pancreatic alpha-cells represents another conceivable method to annul GCGR signalling in diabetes [Table 1]. In this regard, SynA was researched quite extensively in the 1920 s in the hope to provide a new effective oral antidiabetic medication. Glucose lowering actions of SynA were observed in patients and a range of animal models [Fig. 2], probably linked to destruction of glucagon-secreting alpha-cells. Although interest in SynA was eclipsed by the emergence of insulin therapies, as well as off-target side effects and possible increased hypoglycaemia, it may still be worth recalling some of the early lessons with SynA. Taken together, there can be no doubt that targeting the alpha-cell in diabetes has unquestionable glucose homeostatic efficacy. In terms of patient subgroups most likely to benefit from inhibition of glucagon action, the obvious target would be those displaying clear signs of hyperglucagonaemia. In that respect people with T2DM who are already prescribed an incretin enhancer, metformin or sulphonylurea drug may already be benefiting from inhibition of GCGR signalling to some extent as part of their therapeutic regimen, and augmentation of this by alpha-cell ablation could improve overall disease management. However, in T1DM, effective management of blood glucose levels with insulin tends to reverse the hyperglucagonaemia present at diagnosis [71], and may indicate that such therapies could be less beneficial in this setting. It is also interesting that recent studies have demonstrated that insulin promotes alpha- to beta-cell transdifferentiation in mice [76].

Finally, in contrast to the above but not the focus of the current review, the ability of upregulated GCGR signalling to induce satiety and increase energy expenditure, leading to benefits in obesity and consequently insulin action, presents an alternative and unexpected therapeutic avenue. Thus, despite a hyperglycaemic effect of glucagon, dual modulation of GCGR and GLP-1R demonstrates impressive metabolic benefits in obesity-diabetes [81]. Such therapies can exert benefits in diabetes owing to the ability of GCGR signaling to reduce body weight, with GLP-1 acting similarly to control of body weight while concomitantly able to effectively offset or reverse any potential detrimental effect of GCGR signalling on blood glucose concentrations. However, the current review focuses exclusively on methods to annul glucagon activity, and aspects of the positive effects of upregulated GCGR signalling for diabetes and obesity have been recently reviewed in detail elsewhere [81]. Indeed, at the present time it appears therapies to enhance GCGR signalling, albeit only in combination with other glucose-lowering medications, may be closer to clinical realisation for diabetes than those aimed at curbing glucagon action. That said, it is clear that, in the correct setting, moderating glucagon action or release can exert important glucose-lowering actions that should not be ignored.

8. Conclusion

Glucagon stands at a crossroads between being confounding factor in diabetes or a potential saviour in helping to treat the disease. Thus, targeting the alpha-cell has obvious therapeutic potential for diabetes, given that hyperglucagonaemia is a recognised presenting feature contributing to the prevailing hyperglycaemia, whereas upregulation of GCGR signalling may actually be beneficial in obesity-driven forms of diabetes. In terms of annulling glucagon activity, compounds that can inhibit glucagon secretion and/or GCGR signalling, or encourage lineage switch of an alpha-cell towards a beta-cell like phenotype, possess antidiabetic potential that has been recently highlighted within the literature. On the other hand, use of specific toxins to ablate alpha-cell mass and exert glucose lowering actions has been largely overlooked since the 1930 s. In this regard, the chemical structure and narrative of one such toxin, namely SynA, has clear parallels with the biguanide, metformin, and whilst the remarkable comeback story for metformin is unlikely to be replicated for SynA, the rationale and effectiveness of partial alpha-cell ablation in T1DM and T2DM should not be discounted.

Data Availability

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

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