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REVIEW ARTICLE

Regulation of amino acid metabolism and α-cell proliferation by glucagon

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ABSTRACT

Both glucagon and glucagon-like peptide-1 (GLP-1) are produced from proglucagon through proteolytic cleavage. Blocking glucagon action increases the circulating levels of glucagon and GLP-1, reduces the blood glucose level, and induces the proliferation of islet α-cells. Glucagon blockade also suppresses hepatic amino acid catabolism and increases the serum amino acid level. In animal models defective in both glucagon and GLP-1, the blood glucose level is not reduced, indicating that GLP-1 is required for glucagon blockade to reduce the blood glucose level. In contrast, hyperplasia of α-cells and hyperaminoacidemia are observed in such animal models, indicating that GLP-1 is not required for the regulation of α-cell proliferation or amino acid metabolism. These findings suggest that the regulation of amino acid metabolism is a more important specific physiological role of glucagon than the regulation of glucose metabolism. Although the effects of glucagon deficiency on glucose metabolism are compensated by the suppression of insulin secretion, the effects on amino acid metabolism are not. Recently, data showing a feedback regulatory mechanism between the liver and islet α-cells, which is mediated by glucagon and amino acids, are accumulating. However, a number of questions on the mechanism of this regulation remain to be addressed. The profile of glucagon as a regulator of amino acid metabolism must be carefully considered for glucagon blockade to be applied therapeutically in the treatment of patients with diabetes.

INTRODUCTION

Glucagon, a hyperglycemic substance present in aqueous pancreas extracts, was first discovered in 1923[1]. Nearly 60 years later, molecular cloning techniques were applied to identify glucagon precursors, and proglucagon and its derivative peptides, including glucagon-like peptide-1 (GLP-1), were identified[2]. Whereas glucagon is mainly produced in islet α-cells through the proteolytic cleavage of proglucagon by prohormone convertase 2 (Pcsk2), GLP-1 is mainly produced in the intestinal endocrine L-cells by Pcsk1. Both glucagon and GLP-1 are involved in the regulation of the glucose level; however, these peptides apparently work in opposite directions. Glucagon stimulates glycogenolysis and gluconeogenesis in the liver to increase the blood glucose level. In contrast, GLP-1, one of the major incretins, stimulates insulin secretion and β-cell proliferation to reduce the blood glucose level[3–5].

As both glucagon and GLP-1 are derived from proglucagon, it is difficult to produce isolated glucagon deficiency without affecting the production of GLP-1. The purpose of the present review was to provide an overview phenotype of animal models with glucagon deficiency, to underscore the regulation of amino acid metabolism as a specific physiological action of glucagon and to discuss recent advances in the understanding of the mechanisms that regulate islet α-cell proliferation.

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ANIMAL MODELS DEFECTIVE IN THE PRODUCTION OR ACTION OF GLUCAGON

The first animal model deficient in the production of glucagon was generated by the disruption of the *Pcsk2* gene. The *Pcsk2* knockout mice lacked active glucagon production, and showed lower blood glucose levels and islet α-cell hyperplasia[6]. The proteolytic processing of prosomatostatin and proinsulin is also attenuated in *Pcsk2* knockout mice; thus, it remained elusive whether their lower blood glucose levels and α-cell hyperplasia were simply attributable to the absence of active glucagon.

Several years later, animal models with glucagon receptor (Gcgr) deficiency were generated by two independent groups[7,8], and both groups reported lower blood glucose levels and marked

hyperglucagonemia in these animals. As Gelling *et al.*[8] also reported that *Gcgr* knockout mice showed islet α-cell hyperplasia, it was confirmed that the absence of glucagon induces α-cell proliferation. Gelling *et al.*[8] also reported that in addition to glucagon, the pancreatic tissue concentration of GLP-1 was increased in *Gcgr* knockout mice. Later, the plasma GLP-1 levels of *Pcsk2* knockout mice were also found to be increased[9].

An increase in the serum levels of glucagon and GLP-1, combined with islet α-cell hyperplasia, has also been observed in mice with liver-specific Gs α deficiency, in which glucagon-induced cyclic adenosine monophosphate production in the liver is markedly attenuated[10]. Liver-specific *Gcgr* knockout mice also showed a similar phenotype[11].

The data obtained through the analyses of these models clearly showed that impaired glucagon action causes an increase in GLP-1, a decrease in the blood glucose level and α-cell proliferation. However, the causal relationship among these characteristics in these animal models remained elusive until the establishment of animal models that lack both glucagon and GLP-1 action. The phenotypes of these animal models with deficient glucagon action are summarized in Table 1, together with those described in the following sections.

ANIMAL MODELS WITH DEFECTIVE GLUCAGON AND GLP-1 ACTION

Mice homozygous for glucagon-green fluorescent protein (GFP) knock-in allele ($Gcg^{gfp/gfp}$ [GCGKO]) lack all of the peptides derived from proglucagon, including glucagon and GLP-1 (Figure 1). GCGKO mice are virtually normoglycemic and develop GFP-positive α-like cell hyperplasia[12]. As the plasma insulin concentration of *ad libitum*-fed GCGKO mice is significantly lower than that of control littermates, the effects of glucagon deficiency on their blood glucose levels appear to be partially compensated by the suppression of insulin secretion[13]. Mice lacking both glucagon receptors and GLP-1 receptors ($Gcgr^{-/-} \times Glp1r^{-/-}$) also develop islet α-cell hyperplasia under normoglycemic conditions[14]. These data show the pivotal importance of GLP-1 in lowering the blood glucose level in the absence of glucagon action. In contrast, it is also clear that neither GLP-1 nor lower blood glucose levels are prerequisites for the α-cell proliferation induced by glucagon deficiency.

It is noteworthy that $Gcgr^{-/-} \times Glp1r^{-/-}$ mice develop hyperglycemia after streptozotocin-induced β-cell destruction, whereas $Gcgr^{-/-}$ mice with a similar degree of β-cell damage do not[15,16]. Based on the resistance to diabetes observed in $Gcgr^{-/-}$ mice, a glucagonocentric view of diabetes has been proposed, in which the hypersecretion of glucagon is as important as (if not more important than) insulin deprivation in the pathogenesis of diabetes[15,17]. However, it is clear that GLP-1 plays pivotally important roles in resistance to diabetes in $Gcgr^{-/-}$ mice, and that diabetes can develop in the absence of glucagon. Indeed, GCGKO mice that lack both glucagon and GLP-1 show hyperglycemia and/or glucose intolerance on the administration of streptozotocin, high-fat diet feeding or during pregnancy[18–20]. It has also been reported that $Gcgr^{-/-}$ mice develop diabetes after the near total ablation of β-cells[21]. Thus, glucagon is not an absolute prerequisite for hyperglycemia and diabetes.

GLUCAGON AS A REGULATOR OF α-CELL PROLIFERATION AND THE AMINO ACID METABOLISM

The proliferation of cells in various endocrine organs and/or tissues, such as the thyroid, adrenal cortex and gonadal glands,

Table 1 | Phenotype of animal models with deficient glucagon action

Gene	Defect	Glucagon	GLP-1	Blood glucose levels	Islet α-cell	References
Prohormone convertase 2 ($Pcsk2^{-/-}$)	Processing of proglucagon	Decreased	Increased	Lower	Hyperplasia	6, 9
Glucagon receptor (whole body) ($Gcgr^{-/-}$)	Glucagon action in whole body	Increased	Increased	Lower	Hyperplasia	7, 8
Gs α (liver specific) (Gs alpha-LKO, GNAS-LKO)	Hormone-induced cAMP production in liver	Increased	Increased	Lower	Hyperplasia	10
Glucagon receptor (liver specific) (Gcgr-LKO)	Glucagon action in liver	Increased	Increased	Lower	Hyperplasia	11
Glucagon ($Gcg^{gfp/gfp}$: GCGKO)	All the peptide derived from proglucagon	Absent	Absent	Normal	Hyperplasia (GFP-positive islet cell)	12
Glucagon receptor and GLP-1 receptor ($Gcgr^{-/-} \times Glp1r^{-/-}$)	Both glucagon action and GLP-1 action	Increased	Increased	Normal	Hyperplasia	14
NA (administration of glucagon receptor blocking antibody)	Glucagon action in tissues to which antibody accesses	Increased	Increased	Lower	Induction of proliferation	36, 37

cAMP, cyclic adenosine monophosphate; GCGKO, mice homozygous for glucagon-green fluorescent protein knock-in allele; Gcgr, glucagon receptor; GFP, green fluorescent protein; GLP-1, glucagon-like peptide-1; GNAS, guanine nucleotide binding protein, alpha stimulating; LKO, liver-specific knock out; NA, not applicable; Pcsk2, prohormone convertase 2.

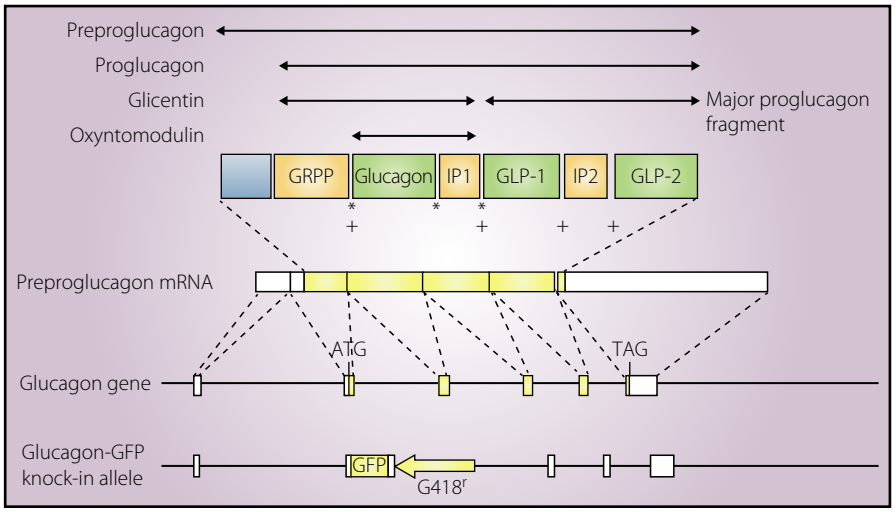

Figure 1 | Structure of proglucagon and proglucagon-derived peptides. Messenger ribonucleic acid (mRNA) transcribed from the glucagon gene encodes preproglucagon. The removal of the signal peptide from preproglucagon results in proglucagon, which serves as a precursor for multiple peptides, including glucagon and glucagon-like peptides (GLPs). *Cleavage sites for prohormone convertase 2; $^{+}$cleavage sites for prohormone convertase 1. The structure of the glucagon-green fluorescent protein (GFP) knock-in allele is also indicated at the bottom of the figure. ATG, initiation methionine codon; GRPP, glicentin-related pancreatic polypeptide; IP, intervening peptide; TAG, termination codon.

is strictly regulated by corresponding tropic hormones that are secreted from the hypothalamo–pituitary axes. In contrast, far less is understood about the mechanisms regulating the proliferation of islet endocrine cells. Animal models, in which the glucagon action in the liver is specifically impaired, develop α-cell hyperplasia[10,11]. Thus, signals to stimulate α-cell proliferation are considered to be derived from the liver. In addition, results from studies investigating the transplantation of islets or α-like cells into the subrenal capsule of glucagon-deficient animal models suggested that such signals are humoral rather than neural[11,22]. Accordingly, the expression of genes encoding stimulators of α-cell proliferation in the liver should be upregulated in animal models with glucagon deficiency, whereas the expression of suppressors should be downregulated. Thus, attempts were made to identify genes that were differentially expressed in animal models with glucagon deficiency; however, such attempts have not been able to identify the specific humoral factors that control α-cell proliferation[13] (and Y Hayashi unpublished data). In contrast, several genes involved in amino acid catabolism were found to be downregulated in GCGKO and *Gcgr*$^{-/-}$ mice[13,23]. These changes in the gene expression were accompanied by increased amino acid concentrations in plasma and liver extract, as summarized in Figure 2[13]. Thus, the absence of glucagon action results in the alteration of the amino acid metabolism in the liver and increased plasma amino acid levels, regardless of the presence or absence of GLP-1 action or lower blood glucose levels.

In the 1980s, it was reported that the serum amino acid levels increase in pancreatectomized patients with glucagon deficiency[24]. It has also been reported that the administration of glucagon reduces serum amino acid levels[25]. Human patients with glucagon receptor gene mutations show hyperglucagonemia and α-cell hyperplasia[26–29], and hyperaminoacidemia has been documented in one such case[29]. These reports clearly show that glucagon is also required to downregulate the serum amino acid levels in humans.

Glucagon increases the expression of genes encoding enzymes that convert amino acids into substrates available for gluconeogenesis, such as pyruvate and oxaloacetate (Figure 2)[13]. In contrast, insulin serves as a growth factor and promotes the utilization of amino acids as substrates for protein synthesis. A hypothetical schematic illustration of the underlying mechanism of hyperaminoacidemia under glucagon deficiency is shown in Figure 3. Glucagon and insulin regulate the blood glucose levels in opposite directions (Figure 3a); thus, the amount of insulin required to control the blood glucose level is decreased under the condition of glucagon deficiency. In animal models with glucagon deficiency, both the utilization of amino acids for protein synthesis and the consumption of amino acids for gluconeogenesis are decreased (Figure 3b); thus, such animal models develop hyperaminoacidemia (Figure 3c). In contrast, hyperaminoacidemia might partially compensate for the reduction in phosphoinositide 3-kinase–protein kinase B–mammalian target of rapamycin (mTOR) signaling activity, which is regulated by insulin, as amino acids directly activate mTOR complex 1 (mTORC1), which plays a critical role in the regulation of protein synthesis and cellular proliferation[30,31]. Indeed, an increased lean body mass and/or body size has been documented in glucagon-deficient models[8,12].

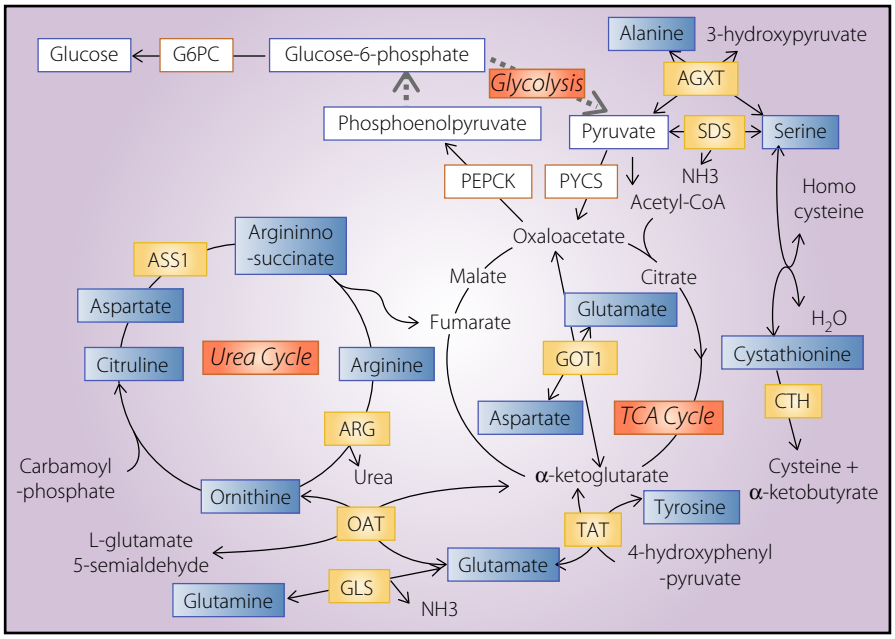

Figure 2 | Schematic representation of the metabolic pathways regulated by glucagon. The enzymes and metabolites involved in glycolysis, gluconeogenesis, the tricarboxylic acid (TCA) cycle and the urea cycle are summarized. The expression levels of genes encoding enzymes in letters with yellow boxes are decreased in the glucagon-green fluorescent protein knock-in allele liver, whereas the expression levels of metabolites in letters in blue boxes are increased. Other enzymes and metabolites with boxes were also analyzed; however, no significant differences were observed in their expression between the glucagon-green fluorescent protein knock-in allele and control liver. AGXT, alanine-glyoxylate aminotransferase; ARG, arginase; ASS1, arginosuccinate synthase 1; CTH, cystathionase; G6PC, glucose-6-phosphatase catalytic subunit; GLS, glutaminase; GOT1, glutamic-oxaloacetic transaminase; OAT, ornithine aminotranspherase; PEPCK, phosphoenolpyruvate creatine kinase; PYCS, pyruvate carboxylase; SDS, serine dehydratase; TAT, tyrosine aminotransferase.

TRANSIENT BLOCKADE OF GLUCAGON ACTION AND AMINO ACID METABOLISM

The blocking of glucagon action has been considered as a therapeutic approach to reduce the blood glucose level, and various approaches including antisense oligonucleotide for Gcgr messenger ribonucleic acid and small molecule glucagon antagonist, have been attempted[32–34]. Antisense oligonucleotide for Gcgr messenger ribonucleic acid successfully reduced blood glucose levels in rodent models of diabetes, including *ob*/*ob* mice and Zucker diabetic fatty rats[32]. Antisense oligonucleotide for Gcgr messenger ribonucleic acid also increased the plasma levels of glucagon and GLP-1, and induced α-cell hyperplasia; however, the data on the serum amino acid levels were not available in the study[32]. In contrast, an increase in the serum amino acid levels of rhesus monkeys treated with a small-molecule glucagon receptor antagonist has been reported[35].

The administration of REGN1193, a fully human monoclonal antibody that inhibits glucagon receptor signaling, has been shown to result in a threefold increase in the plasma total amino acid levels of diabetic cynomolgus monkeys[36]. An increase in the serum amino acid levels combined with the altered expression of genes encoding amino acid catabolism has also been shown in mice that were treated with mAb7, an allosteric antagonistic monoclonal antibody for glucagon receptor[37]. These studies clearly showed that the transient blockade of glucagon action is sufficient to remodel the hepatic amino acid metabolism in various mammalian species.

FEEDBACK REGULATION BETWEEN THE LIVER AND ISLET α-CELLS MEDIATED BY GLUCAGON AND AMINO ACIDS

Resistance to glucagon, either as a result of genetic defects or pharmaceutical intervention to inhibit glucagon signaling, causes hyperaminoacidemia and hyperplasia of α-cells. Attempts to identify genes that regulate α-cell proliferation have been unsuccessful or provided controversial results[38,39]. In contrast, amino acids themselves have emerged and attracted attention as candidate regulators of α-cell proliferation, and it has been hypothesized that a feedback regulatory mechanism between the liver and islet α-cells, which is mediated by glucagon and amino acids, exists[37,40,41].

Solloway *et al.*[37] cultured islets in media containing an amino acid concentration matched to *Gcgr*$^{-/-}$ serum or *Gcgr*$^{+/+}$ serum (high or low amino acid media, respectively). They observed a two- to threefold increase in the number of α-cells in islets cultured in high amino acid media in comparison to those in low amino acid media[37]. Dean *et al.*[42] showed expression of Ki67, a proliferation marker, in primary α-cells cultured

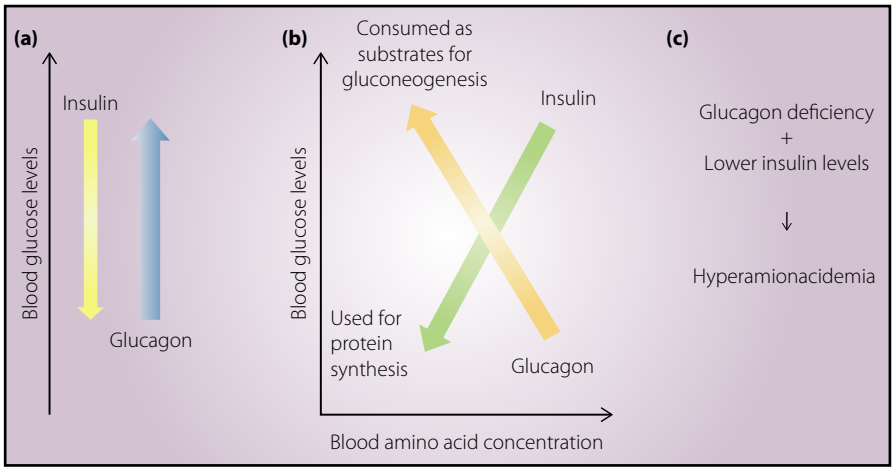

Figure 3 | Effect of glucagon deficiency on serum amino acid concentrations. (a) Schematic illustration showing that the blood glucose levels are lowered by insulin and increased by glucagon. (b) Schematic illustration showing that both glucagon and insulin lower the blood amino acid concentration. (c) Hyperaminoacidemia in glucagon deficiency (see main text).

in the presence of *Gcgr*$^{-/-}$ serum. Experiments involving size fractionated serum showed that molecules of <10 kDa in size have the potential to increase the Ki67 expression, and further experiments showed that amino acids, especially glutamine, play critical roles in promoting the proliferation of α-cells[42].

Kim *et al.*[43] analyzed the effect of antibody-mediated glucagon blockade on the gene expression in the liver and islets. They identified *slc38a5* – which encodes an amino acid transporter with preference for neutral amino acids including glutamine – as the most upregulated gene in the islets. They also showed that in mice deficient of the *slc38a5* gene, the proliferation of α-cells in response to glucagon blockade was attenuated[43].

The expression of the *slc38a5* gene is regulated by mTORC1, and the inhibition of mTORC1 by rapamycin inhibited the proliferation of α-cells and the induction of the *slc38a5* expression in these studies[42,43]. Thus, these studies clearly illustrated a feedback regulatory mechanism between the liver and islet α-cells, which was mediated by glucagon and amino acids (Figure 4). Glucagon increases the amino acid catabolism in the liver, as well as controlling serum amino acid levels. Glucagon blockade results in an increase in the serum amino acid levels, which in turn activates the mTORC1 complex in α-cells and promotes its proliferation. Among the various amino acid transporters, SLC38A5 is regulated by mTORC1 and plays a major role in the regulation of α-cell proliferation. In contrast, GLP-1 and lower blood glucose levels are not prerequisites for the proliferation of α-cells induced by glucagon deficiency, as discussed in the section entitled, 'Animal models defective in the action of both glucagon and GLP-1'.

REGULATION OF THE α-CELL MASS IN NORMAL DEVELOPMENT AND ARISTALESS-RELATED HOMEOBOX

Although SLC38A5 appears to play an important role in the proliferation of α-cells in response to glucagon blockade, the α-cell mass in mice with *slc38a5* gene deficiency was comparable with that in control mice. Thus, SLC38A5 is not required for the formation and maintenance of α-cell mass[43]. Alternatively, how the α-cell mass is controlled under normal development and/or physiological conditions remains largely elusive.

Mice with Aristaless-related homeobox (*Arx*) gene deficiency lack α-cells[44], and the mature β-cells acquire α- and PP cell-like phenotypes after the misexpression of *Arx*[45]. The expression of *Arx* is increased in the islets of GCGKO, which show α-like cell hyperplasia[12] (and Y Hayashi unpublished observation). While *Arx* null mice die shortly after birth, hypomorphic *Arx* mutants are viable[46]. Experiments using these hypomorphic *Arx* mutant and GCGKO mice showed that GFP-positive α-like cell hyperplasia in GCGKO mice with hypomorphic *Arx* was markedly attenuated[47]. Thus, *Arx* clearly plays important roles in the differentiation and proliferation of α-cells. Recently, the long-term administration of gamma amino butyric acid has been shown to reduce the expression of *Arx* in α-cells and promote the transdifferentiation of α-cells into β-cells[48].

Arx is also among the list of genes that are significantly upregulated in the islets of GCGR antibody-treated mice[43]. However, it is not clear whether the increase in the *Arx* expression reflects the increased expression in each α-cell or simply reflects an increase in the α-cell mass. Further analyses are required to elucidate the mechanism involved in the regulation of the *Arx* expression and to determine whether *Arx* plays a role in the α-cell proliferation induced by increased amino acid concentrations.

THE MECHANISM OF THE SELECTIVE PROMOTION OF α-CELL PROLIFERATION BY AMINO ACIDS

An increase in the serum amino acid levels can be expected to have various effects on organs that consist of numerous types of cells. The response of cells to the alteration of the amino acid concentration is thought to be determined by the repertoire of

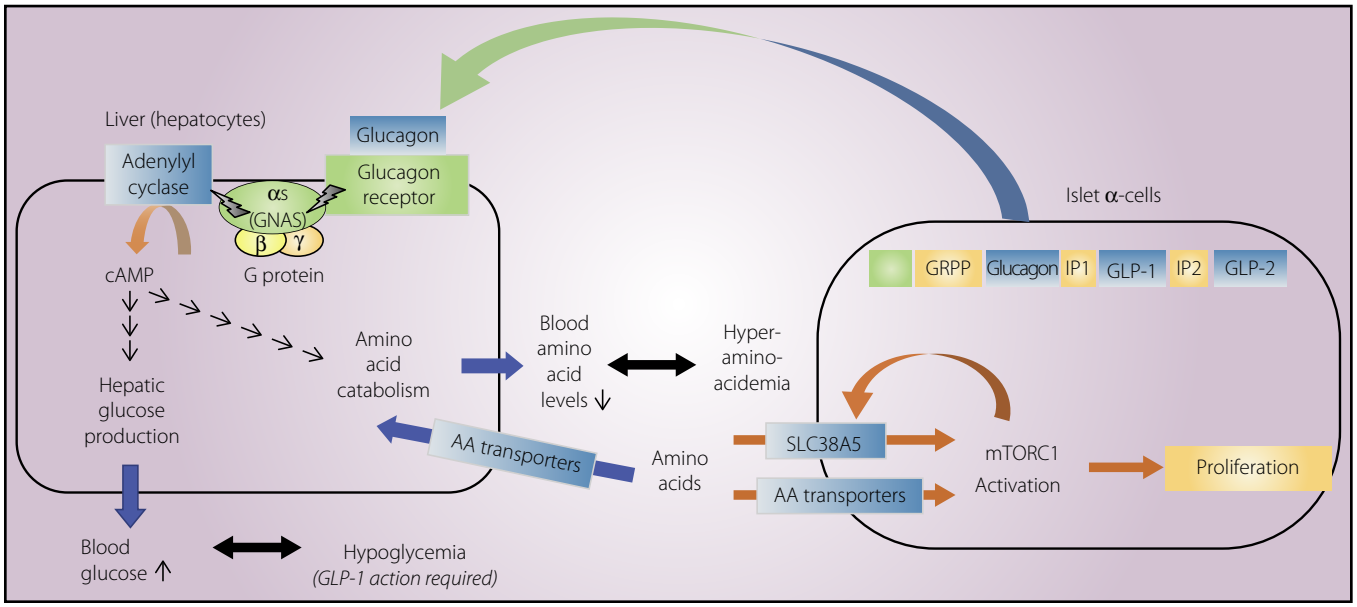

Figure 4 | Schematic representation of feedback regulation between the liver and the islet α-cells. Glucagon is produced in islet α-cells and the binding of glucagon-to-glucagon receptors in the liver increases the intracellular cyclic adenosine monophosphate level, which leads to an increase in hepatic glucose production and amino acid catabolism. Blockade of glucagon action results in an increase in the serum amino acid levels, and consequently promotes α-cell proliferation. cAMP, cyclic adenosine monophosphate; GLP-1, glucagon-like peptide 1; GLP-2, glucagon-like peptide 2; GNAS, guanine nucleotide binding protein, alpha stimulating; GRPP, glicentin-related pancreatic polypeptide; IP, intervening peptide.

amino acid transporters expressed in each cell[30] and intracellular amino acid sensors, including mTORC1[49]. The mechanisms involved in the selective proliferation of α-cells in response to hyperaminoacidemia as a result of glucagon blockade remains to be elucidated. Both islet α-cells and intestinal L-cells express the glucagon gene and *Arx*[50]. However, although α-cells show hyperplasia, the number of L-cells is not increased in glucagon-deficient animal models[12]. Thus, comparing a single-cell transcriptome profile of α-cells with that of L-cells might provide insights that can help to explore such mechanisms.

Among the amino acids, leucine and arginine play major roles in the activation of mTORC1 through interaction with intracellular amino acid sensor molecules[30,51]. Tan *et al.*[52] recently addressed the role of glutamine in the regulation of mTORC1 activity under the condition of amino acid starvation. During the preparation of the present review, a new mouse model with the specific deletion of *Raptor* (an mTOR regulator) in α-cells was reported[53]. In this model with the α-cell-specific loss of mTORC1 signaling, the α-cell mass is normal at birth; however, it is gradually decreased after weaning. The authors concluded that mTORC1 signaling is dispensable for α-cell development, but essential for α-cell maturation during the transition from a milk-based diet to a chow-based diet. They also showed that inhibition of mTORC1 reduces the expression of *FoxA2*, *Nkx2.2* and *Pou3f4*, but not the expression of *Arx*, in α-TC-1 cells[53]. These findings suggest that the mechanisms involved in the development of α-cells and those involved in the regulation of the α-cell mass in response to amino acid alterations are distinct.

DO ANY FACTORS OTHER THAN AMINO ACIDS REGULATE α-CELL PROLIFERATION?

Glucagon blockade results in a pleiotropic effect that affects most metabolic pathways, including those of amino acids, carbohydrates, fatty acids and nicotinamides. Although it has nearly been established that amino acids play a major role in regulating α-cell proliferation, the possibility that other factors might regulate α-cell proliferation has not been excluded.

The expression of FGF21 is regulated by glucagon, and it has been hypothesized that the physiological action of glucagon is partially mediated through an increase in the FGF21 level[54]. However, the proliferation of α-cells in response to glucagon blockade was not attenuated in FGF21-null mice. Thus, FGF21 is not required for the regulation[39]. In contrast, FGF21 serves as an endocrine signal for protein restriction[55]. Interestingly, a high-protein diet increases glucagon secretion and suppresses FGF21 levels, uncoupling the upregulation of FGF21 by glucagon (Hayashi *et al.*, manuscript in preparation).

Nicotinamide N-methyltransferase is one of the genes whose expression levels are markedly diminished in GCGKO and other glucagon-deficient models[13,41]. As nicotinamide N-methyltransferase has been reportedly involved in the regulation of the hepatic nutrient metabolism[56], the relationship among glucagon, nicotinamide N-methyltransferase, nutrient

metabolism (including that of amino acids) and α-cell proliferation should be further explored.

IS 'GLUCAGON' APPROPRIATE NOMENCLATURE?

Insulin and glucagon were discovered in the 1920s through exploratory research that aimed to treat diabetes by the administration of extracts from the pancreas; thus, the major physiological function of insulin and glucagon has been considered to be the regulation of the blood glucose level. Whereas insulin deficiency results in hyperglycemia and diabetes, glucagon deficiency results in hyperaminoacidemia rather than hypoglycemia. As discussed in the present review, data showing that the regulation of the amino acid metabolism is the most important specific physiological function of glucagon are accumulating. As a result, there might be questions as to whether 'glucagon' is the most appropriate nomenclature for the regulator of blood amino acid levels. As amino acids, especially glutamine, play a major role in the regulation of the α-cell mass, it might be interesting to imagine possible alternative names for glucagon, such as 'proteinon', 'aminoacidon' or 'glutaminon.' It is also noteworthy that the plasma concentration of glutamine increases to approximately 6 mmol/L, a molar concentration comparable with that of glucose, through glucagon blockade[43].

Protein-derived calories accounted for one-third of total caloric intake before the agricultural revolution, whereas they account for approximately 12% of the modern diet[57]. Glucagon appears to play a more important role as a regulator of the amino acid metabolism in protein-rich diets, such as those of the preagricultural or paleolithic era. Indeed, protein-rich food stimulates glucagon secretion, whereas carbohydrate-rich food suppresses the plasma glucagon level in humans[58].

PERSPECTIVE

Glucagon deficiency results in the alteration of the amino acid metabolism and hyperaminoacidemia. Among the amino acids, the plasma concentration of glutamine is the highest, and glutamine can serve as an energy source through glutaminolysis, especially in cells with rapid turnover, such as those in the intestinal mucosa[59]. Thus, an increase in the plasma glutamine concentration might affect the metabolism of various types of cells. The homeostasis of plasma amino acid levels is not as well understood as that of glucose, and the impact of hyperaminoacidemia on the whole body is not fully understood. Thus, although glucagon blockade might have powerful therapeutic effects with regard to the control of the blood glucose level, the effects of glucagon blockade on the amino acid metabolism should be carefully evaluated in clinical trials.

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DISCLOSURE

The authors declare no conflict of interest.

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