Review

Metabolic Role of GABA in the Secretory Function of Pancreatic β-Cells. Its Hypothetical Implication in β-Cell Degradation in Type 2 Diabetes

Jorge Tamarit-Rodriguez *

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Review

Metabolic Role of GABA in the Secretory Function of Pancreatic β-Cells. Its Hypothetical Implication in β-Cell Degradation in Type 2 Diabetes

Jorge Tamarit-Rodriguez

Emeritus Professor, Biohemistry Department,Medical School, Complutense University, Madrid , Spain, tamarit@ucm.es

Abstract: The stimulus-secretion coupling of glucose-induced release is generally attributed to the metabolism of the hexose in the β-cells in the glycolytic pathway and the citric acid cycle. Glucose metabolism generates an increased cytosolic concentration of ATP and of the ATP/ADP ratio that closes the ATP-dependent K+-channel at the plasma membrane by the interaction of ATP with the regulatory Kir6.2 channel subunit The resultant depolarization of the β-cells opens voltage-dependent Ca2+-channels at the plasma membrane that allow an increase of the cytosolic cation concentration that triggers the exocytosis of insulin secretory granules. The resultant secretory response evolves in time as a biphasic secretion with a first and transient peak of approximately 10 minutes duration followed by a sustained phase of secretion lasting as long as the stimulus. Whereas the first transient peak can be reproduced by a simple depolarization of β-cells with high extracellular KCl maintaining the KATP-channels open with diazoxide, the sustained phase is agreed to depend on the participation of some metabolic signal that remains to be determined Our group has been investigating for several years the participation of β-cell GABA metabolism, together with that of glucose (the β-cell "specific" nutrient secretagogue) and some other "metabolic" secretagogues (branched-chain alpha-ketoacids and a mixture of L-Leucine + L-glutamine, at supraphysiological concentrations) in their mechanism of stimulation of insulin secretion. All three types of stimuli promote the flux in the GABA shunt of rat islets by different metabolic pathways that end in the production of α-ketoglutarate. This citric acid cycle intermediary is preferentially derived to the GABA shunt instead of its continuous oxidation in the citric acid cycle. Islet content of GABA is significantly suppressed by all the stimuli and blocking the GABA shunt with gabaculine, or Ɣ-vinyl-GABA (GABAT inhibitors), diminish the insulin secretory responses as well as total ATP and the ATP/ADP ratio. It is concluded that GABA metabolism is increased in parallel to glucose metabolism and is significantly contributing to the magnitude of the insulin secretory response. Its possible implication in β-cells degradation in type-2 (perhaps also in type 1) diabetes is suggested.

Keywords: GABA; GABA metabolism; GABA and stimulus secretion-coupling of glucose-induced insulin secretion; β-cells; pancreatic islets; insulin secretagogues; branched-chain alpha-ketoacids and insulin secretion; alpha-amino acids; and insulin secretion

I. Metabolic role of GABA on the mechanism of stimulation of insulin secretion.

1. Introduction

The stimulus-secretion coupling of glucose-induced release is generally attributed to the metabolism of the hexose in the β-cells in the glycolytic pathway and the citric acid cycle. Glucose metabolism generates an increased cytosolic concentration of ATP and of the ATP/ADP ratio that closes the ATP-dependent K^+-channel at the plasma membrane by the interaction of ATP with the regulatory Kir6.2 channel subunit (1). The resultant depolarization of the β-cells opens voltage-dependent Ca^{2+}-channels at the plasma membrane that allow an increase of the cytosolic cation concentration that triggers the exocytosis of insulin secretory granules (1). The resultant secretory response evolves in time as a biphasic secretion with a first and transient peak of approximately 10 minutes duration (in rat perifused islets) followed by a sustained phase of secretion lasting as long as the stimulus. Whereas the first transient peak can be reproduced by a simple depolarization of β-

cells with high extracellular KCl maintaining the K_{ATP}-channels open with diazoxide (2), the sustained phase is agreed to depend on the participation of some metabolic signal that remains to be determined (3,4). Given that extracellular ATP alone (10 mM) triggers a biphasic insulin secretion in KCl-permeabilized islets (5), the metabolic signal responsible for the sustained phase may be any enzymatic pathway capable of leading to ATP synthesis. Our group has been investigating for several years the participation of β-cell GABA metabolism, together with that of glucose (the β-cell "specific" nutrient secretagogue) and some other "metabolic" secretagogues (physiological metabolites at supraphysiological concentrations) in their mechanism of simulation of insulin secretion.

ϒ-Aminobutyric acid (GABA) is abundant exclusively in the β-cells of pancreatic islets that are equipped with all the enzymes required to synthesize and metabolize it in the GABA shunt (6): 1. Glutamic acid decarboxylase isoenzymes (cytosolic GAD65 and GAD67) generating GABA by L-glutamate decarboxylation. 2. GABA transaminase (GABAT), a mitochondrial enzyme exchanging an amino group between GABA and α-ketoglutarate (αKG or 2-oxoglutarate, 2-OG) to give succinic acid semialdehyde (SSA) and L-glutamate. 3. NAD^+-dependent SSA dehydrogenase oxidizing SSA to succinic acid that is further metabolized in the Krebs cycle. 4. NAPH-dependent SSA-reductase reduces SSA to ϒ-hydroxybutyric acid, competes with the previous enzyme for the same substrate.

Its functional role in β-cells has been discussed for many years (7) but there is not yet any conceptual consensus on its participation on the mechanism of biphasic insulin secretion triggered by glucose and some other known metabolic stimuli (fundamentally L-leucine + L-glutamine and some branched-chain 2-oxoacids (BCKAs)). So far, the most accepted hypothesis seems to be the autocrine regulation by the released (or co-secreted with insulin?) of GABA through the stimulation of either GABA-A or -B receptors (8,9). Also, a possible mechanism of paracrine regulation of glucagon secretion by GABA, co-secreted with insulin, through the activation of $GABA_A$ receptors of α-cells has been postulated (10). However, we will limit our review to experimental data dealing with the participation of intracellular GABA in islet metabolism.

2. Effect of glucose stimulation of insulin secretion on islet GABA content

Since the pioneering work of M. Erecinska (11) suggesting an energetic role for GABA in β-cells contributing to the maintenance of islet ATP/ADP ratio, some progress has been achieved. A first important finding was the demonstration that islet GABA synthesis *in vitro* was dependent on the extracellular concentration of L-glutamine (12): it reached a maximum between 0.5 to 1 mM, the physiological value of plasma L-glutamine concentration (13). That means that rat islet GABA content is regularly maintained at relatively high values, together with L-glutamate and L-aspartate, in comparison with other L-amino acids (13). A detailed study of the effect of 20 mM glucose on the spectrum of islet plasma L-amino acids showed strong, specific, and significant decreases of islet GABA-content with respect to the values at 0 mM glucose in a range of L-glutamine concentrations (0.0,0.5 and 10.0 mM). The simultaneous measurements of GABA release at either 0.5 or 10.0-mM L-glutamine were also strongly reduced (14). It was concluded that the suppression of islet GABA content did not depend on an increased rate of release, but it was produced by an increase of its metabolic rate. This was supported by the finding that inhibition of glucose metabolism by D-mannoheptulose blocked sugar capacity to suppress islet GABA content (Figure S1 in 14 and 15). A significantly positive, linear correlation was found between islet content and GABA release among all the values obtained at both 0- and 20-mM glucose: the averaged GABA release at 0 mM glucose was higher than at 20 mM glucose at 0.5- and 10.0-mM L-glutamine: the lower the GABA content the lower the rate of release (12,14). The linear correlation obtained between GABA content and release has been confirmed by other authors that have supplied experimental evidence of the mediation of GABA release and uptake by the membrane anion transporters VRAC and TauT, respectively (8). Like the previous authors, our data speak against the co-secretion of insulin and GABA under glucose stimulation. By contrast, our data do not predict an increase of GABA release by high glucose but a decrease (14). Notwithstanding the remaining release of GABA through the postulated specific anion transporters might contribute to the pulsatility of the contemporarily stimulated insulin secretion (8).

3. Effects of branched-chain 2-oxoacids (BCKAs) stimulation of insulin release on islet GABA content

Besides glucose, branched-chain 2-oxo acids (α-ketoisocaproic acid or KIC, α-keto-β-methyl-valeric acid or KMV), deaminated products of L-leucine and L-norleucine, respectively; and other branched-chain α-keto acids) are potent "metabolic" stimuli of islet insulin secretion at supraphysiological concentrations, in the absence of glucose. They induce a biphasic secretion of insulin like that of glucose but of variable magnitude and strongly decreased the islet content of GABA, similarly to glucose (16). The mentioned branched-chain 2-oxo acids (KIC and KMV) were aminated back to their corresponding amino acids (L-leu and L-norLeu, respectively) that diffused and accumulated in the incubation medium without increasing their islet content (16). These results suggested the hypothesis that the amination of the branched-chain 2-oxo acids was coupled to the deamination of L-glutamate to αKG by α-branched-chain amino acid transaminases (BCATs: cytosolic or mitochondrial). This hypothesis was supported by the suppression of BCKAs-stimulated insulin secretion with generic or more specific inhibitors of BCKATs (17). Moreover, a contemporary publication demonstrated that a general knockout of BCKATm (mitochondrial isoform) in mice led to a block of insulin secretion stimulation of the majority of regularly used BCKAs without affecting glucose stimulation (18). These results further support the contention of the important role of BCKAs-amination in their stimulation of secretion. However, the authors did not investigate the effects of BCKAs on islet GABA metabolism.

4. Effects of L-leucine plus -L-glutamine stimulation of insulin release on islet GABA content

Another example of a long known, strong "metabolic" secretagogue mixture is the combination of L-glutamine plus L-leucine, the latter at supraphysiological concentrations. L-leucine has been shown to be an allosteric activator of mitochondrial L-glutamate dehydrogenase (GDH) catalyzing the conversion between L-glutamate and α-KG (19). L-leucine alone (10 mM) stimulated a predominantly first phase of insulin secretion in comparison with glucose (20 mM) but in combination with 10 mM-glutamine, it triggered a stronger biphasic secretion (13,20). L-leucine (10 mM) did not modify islet GABA content in the absence of extracellular L-glutamine but significantly stimulated the islet concentrations of L-glutamate and L-aspartate. At 5 and 10 mM-glutamine, the islet content of all recorded amino acids increased several folds and that of GABA was significantly decreased by L-leucine (-38%), 10 mM BCH (GDH activator). (-56%) and 10 mM allylglycine (GAD inhibitor) (-42%) (13).

5. Conclusions and prospects

In these three main examples of nutrient and metabolic secretagogues, their metabolism shares a common metabolic step: the diversion of αKG to the GABA shunt where it would be first transaminated with GABA by GABAT to render L-glutamate and semialdehyde succinic acid (SSA). SSA will be oxidized by semialdehyde succinic acid dehydrogenase (SSAdh) to succinic acid that will in turn enter the Krebs cycle for its further oxidation. The resulting ATP synthesis would lead to elevated ATP/ADP ratios and the closure of K^+_{ATP} channels that initiates the stimulation of insulin secretion.

Confirmation of these hypothetical mechanisms presupposes that interference with GABA shunt may alter Insulin responses to nutrient and metabolic secretagogues as well as their capacity to increase their mitochondrial production of ATP. For that purpose, gabaculine and allylglycine have been used as GABAT- and GAD65-inhibitors, respectively, to check their effects on insulin secretion, adenine nucleotides concentrations and GABA metabolism.

6. Postulated metabolic pathway leading to the stimulation of BCKAs-induced insulin secretion (Figure 1)

10mM KIC induced a biphasic insulin secretion in the absence of glucose and its magnitude was not modified by either 0.5- or 10.0-mM L-glutamine. Gabaculine (0.25mM) diminished the height of

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the first peak of secretion and suppressed significantly by 33% the second phase of sustained release (16). KIC increased $^{14}CO_2$-production from 0.5- and 10.0-mM L-(U-^{14}C) glutamine by 27% and 66%, respectively (16). Considering that the rate of L-(U-^{14}C) glutamine-oxidation is stoichiometric with the amount of GABA synthesized (13), this would facilitate the replenishment of the intracellular pool of GABA. On the other hand, 0.25 mM gabaculine did not modify the rate of L-glutamine oxidation in the presence of KIC whereas 40 μM gabaculine strongly suppressed GABAT activity in rat islet homogenates (16). Gabaculine (0.25mM) also blocked within 59% the abrupt decreased of intra-islet oxygen tension caused by 10mM KIC reflecting that the contribution to islet oxygen consumption promoted by the α-keto acid is partially attributable to an increased flux in the GABA shunt and part of the Krebs cycle (16).

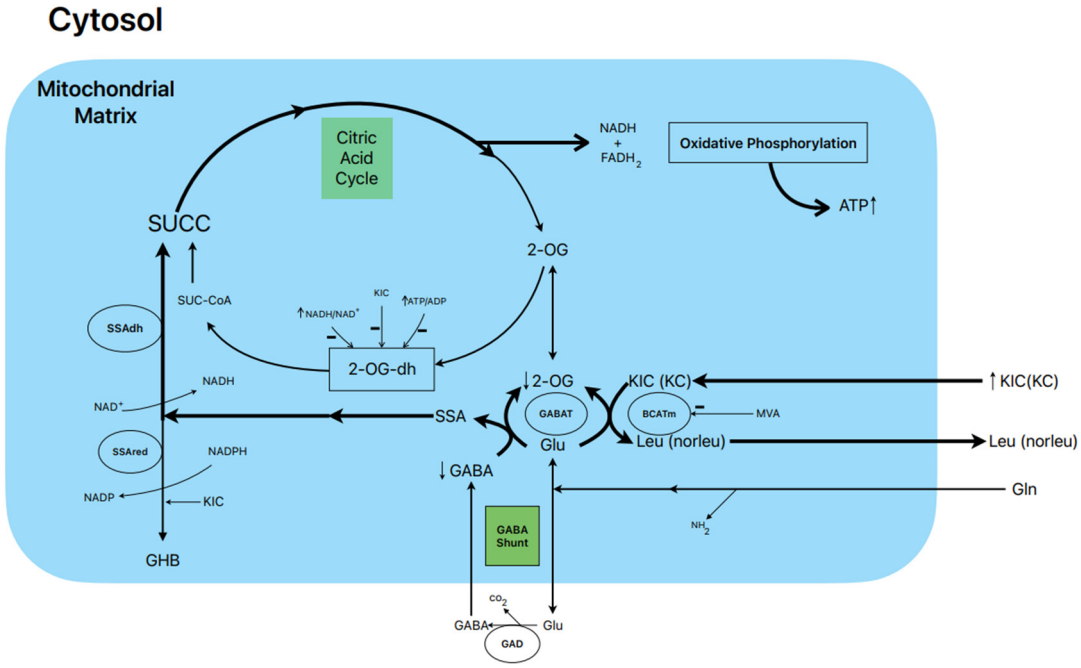

Figure1. Postulated metabolic pathway leading to the stimulation of BCKAs-induced insulin secretion.

7. Postulated metabolic pathway leading to the stimulation of insulin secretion by L-Leucine plus L-glutamine (Figure 2)

L-leucine (10 mM) alone does not stimulate the oxidation of $^{14}CO_2$-production from 0.5- and 10.0-mM L-(U-^{14}C) glutamine (13). However, other authors have shown that BCH (GDH activator) and some amino acids (L-isoleucine and L-norvaline, at 20 mM) stimulate $^{14}CO_2$-production from islets pre-labelled with 1 mM L-(U-^{14}C) glutamine (19). Notwithstanding, 10 mM L-leucine strongly suppressed islet GABA content in the presence of 0.5- and 10.0-mM L-glutamine (13). L-glutamine potentiation of L-Leucine stimulated insulin secretion is generally assumed to be due to the production of αKG secondary to GDH stimulation. According to our own data, the equilibrium of GDH activity in islet homogenates favors the amination (A) versus the deamination (D) reaction (A/D= 8.2) (13). L-leucine (10 mM) increases the ratio more in favor of the amination (A/D= 10.1; $p<0.05$ versus the absence of Leu) (13). This condition would not facilitate an optimal αKG concentration to increase the net flux trough GABAT. Therefore, possibly GABAT requires a higher supply of GABA (higher medium L-glutamine concentration) than KIC. In fact, KIC induces a strong decrease of cellular GABA in the absence of extracellular L-glutamine whereas L-leucine failed to do it (13). Moreover, the dimethyl ester of α-ketoglutarate (dmKG), a membrane permeable analogue of αKG, increased the islet GABA content at 5 mM but decreased it significantly at higher concentrations in the absence and presence of L-leucine (13).

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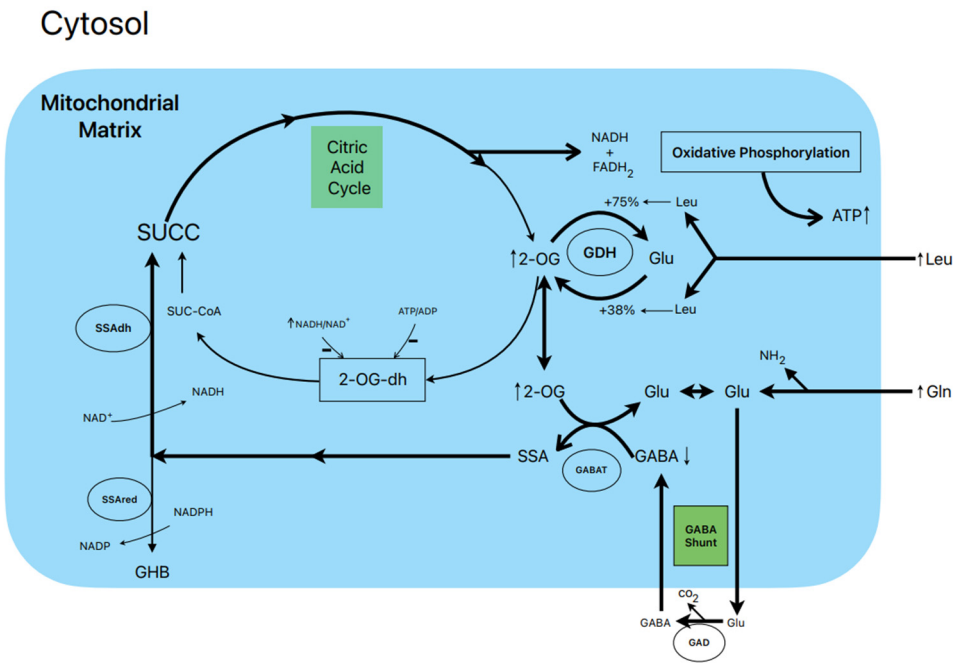

Figure 2. Postulated metabolic pathway leading to the stimulation of insulin secretion by L-Leucine plus L-glutamine.

8. Postulated metabolic pathway leading to the stimulation of insulin secretion by glucose (Figure 3)

The biphasic stimulation of insulin secretion by 20 mM glucose in rat islets was partially suppressed by 1 mM gabaculine in the presence of 10 mM L-glutamine and it was also decreased by 20 mM allylglycine (14, Figure 3C and Figure 2S, respectively). These experimental data support that the metabolic flux in the GABA shunt also contributes to the stimulated secretion. This is also supported by the reduction of islet ATP contents and the ATP/ADP ratios at 20 mM glucose induced by 1 mM gabaculine in the absence and presence of 1- and 10-mM L-glutamine (14).

An important argument to support what might be named as the **"GABA metabolic hypothesis"** for the stimulation of insulin secretion by glucose and other non-physiological secretagogues is why the GABA shunt might be required to participate in the metabolic stimulation of insulin secretion. We have proposed that, at least in islet β-cells, the flux in the Krebs cycle is limited by the lower expression of the 2-oxo-glutarate (αKG) dehydrogenase gene compared with the gene of its competitor enzyme in the GABA shunt, GABAT, for their common substrate 2-oxo-glutarate (αKG) (see supplementary Figure S4 in 14). In a model of "KCl-permeabilized islets" (5) we have demonstrated that 5 mM αKG stimulates a sustained phase of insulin secretion after the peak of release induced by 70 mM KCl (21). It was reversible and returned to basal levels after withdrawing αKG and was suppressed within 47% by 1 mM gabaculine. In parallel experiments in incubated and permeabilized islets, the ATP content and ATP/ADP ratio of islets and the amount of ATP diffused and accumulated in the extracellular medium were measured (21). The islet ATP content was decreased by 1 mM gabaculine ($p<0.05$) and the medium ATP severely reduced within 37% ($p<0.0005$). Neither the islet ATP content nor the amount of medium ATP due to metabolism of any other Krebs cycle intermediary metabolites tested were significantly modified by gabaculine. 10 mM SSA alone, surprisingly permeable trough the plasma membrane, stimulated a biphasic secretion of insulin of less magnitude than 20 mM glucose and whose second phase was partially suppressed by 1mM gabaculine (14). It also significantly increased islet ATP content (+93.5 %) and the ATP/ADP ratio (+84%). At 1mM glucose, 10 mM SSA depolarized the membrane potential of isolated β-cells and diminished membrane currents through K_{ATP}-channels. The depolarization capacity of glucose was not altered after pre-incubating the β-cells for 1-2 h with1 mM gabaculine (results not shown).

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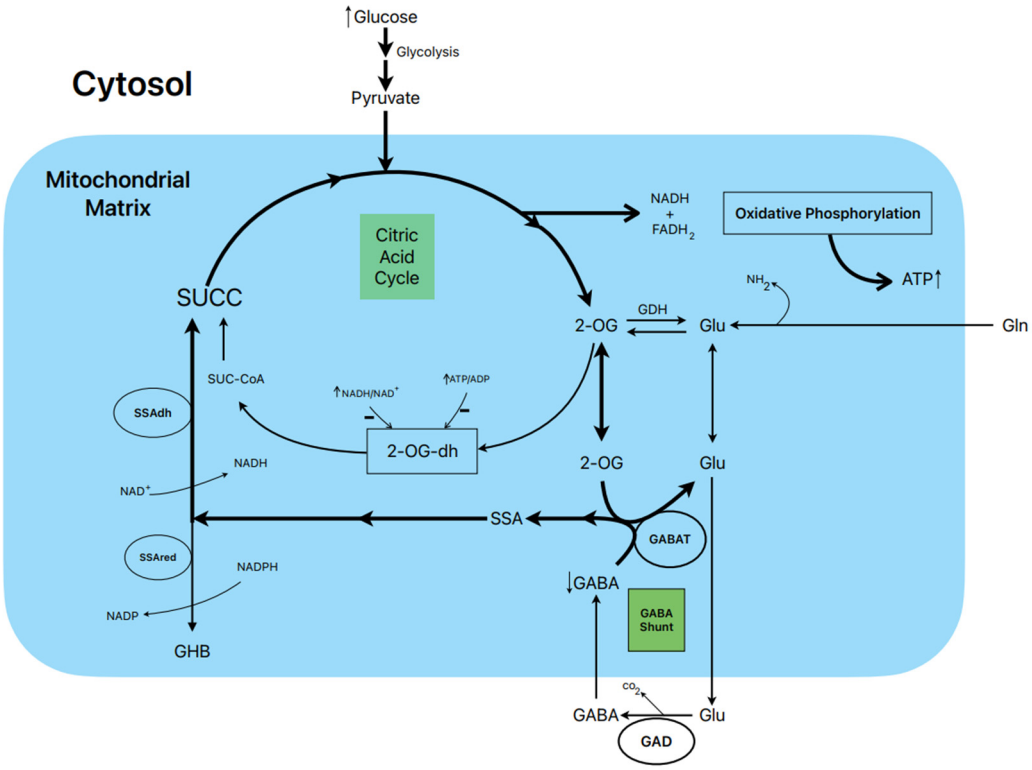

Figure 3. Postulated metabolic pathway leading to the stimulation of insulin secretion by glucose.

9. Conclusion

The GABA shunt in islet β-cells seems to contribute to the metabolic energy required for a sustained stimulation of insulin secretion by nutrient and metabolic secretagogues. As judged by the documented dependence of the metabolic oxidation of αKG and its ATP production on the functioning of the GABA shunt, its contribution might be significant.

II. Possible implication of the GABA-shunt on β-cell degradation in type 2 diabetes.

1. Introduction

Type 1 diabetes is an autoimmune disease caused by the activation of CD8+ and CD4+ T cells targeted to a group of autoantigens released from the β-cells: (Pre)proinsulin, glutamic acid decarboxylase of 65 KD (GAD65), tyrosine phosphatase IA2 and the zinc transporter ZnT8. GAD 65 is one of the most prevalent autoantigens found in patients with type 1 diabetes (22).

2. Intracellular versus extracellular effects of GABA.

GABA is released in a pulsatile manner by non-diabetic human islets, and it is not modified by a range of glucose concentrations (1, 3 and 11 mM), as "detected by cytosolic Ca2+ flux in GABAB receptor-expressing biosensor cells or on total GABA secretion measured by HPLC" (8). The lack of sensitivity of GABA release to glucose makes it difficult to understand how it might be synchronized with glucose-induced insulin secretion. Inhibition of GABA biosynthesis with allylglycine decreased GABA release and stimulated basal serotonin/insulin secretion that "failed to display regular secretory pulses" (8). By contrast, blocking islet GABA metabolism with 10 μM Ƴ-vinyl-GABA (GABAT inhibitor) increased GABA release and decreased basal serotonin/insulin secretion at 3 mM glucose (8). These results are coherent with the assumption that GABA release is governed by the intracellular content of the Ƴ-amino acid. However, these inhibitors do not mimic the effect of insulin secretagogues that increase GABA metabolism and consequently decrease islet GABA content and

its release as commented before. Otherwise, as islet GABA content depends on the extracellular L-glutamine concentration, addition of a physiological (0.5-1.0 mM) or higher (10 mM) concentration of the α-amino acid would increase islet GABA content, and therefore its release, resulting in the inhibition of high glucose-induced insulin secretion against accumulated experimental evidence. In fact, it might be considered that a physiological L-glutamine concentration should be always used to study the function of non-cultured islets in *in vitro* experiments. However, it cannot be denied that both functions of islet GABA, intra- and extra-cellular, might be concordant, mainly in the inhibitory side of the context.

Importantly, Islets from type 1 and 2 diabetic patients' donors were shown by immunostainings to be depleted of GABA in β-cells spite the presence of GAD65 (8). No pulsatile GABA secretion could be observed in type 2 diabetic islets, and it could be rescued by 10 μM Ɣ-vinyl-GABA (GABAT inhibitor). However, the periodicity of serotonin/insulin release was diminished (<0.01) by 10 μM Ɣ-vinyl-GABA (8). It might be interesting to check whether there is any alteration of the gene expression or the activity of GABA shunt enzymes that might contribute to the derangement of diabetic islets 'function.

3. Metabolic changes contributing to Islet degradation in type 2 diabetes

In a recent and exhaustive publication, the metabolic mechanism(s) that might be implicated in the degradation of β-cells of type2 diabetic islets due to persistent hyperglycemia were studied (23). The authors found an elevated expression of most of the genes codifying glycolytic enzymes and a very strong suppression of glyceraldehyde phosphate dehydrogenase (GAPDH) activity Hyperglycemia-induced consequences were prevented by D-mannoheptulose. They checked the hypothesis that an increase of a glycolytic metabolite between glucokinase and GAPDH mediates the effects of hyperglycemia trough inhibition of AMPK and activation of mTORC1 activities, respectively. Most of the consequences of hyperglycemia could be prevented by an inhibitor of one of the effectors activated by mTORC1, ribosomal protein S6 kinase (70S6K-Pi), that promotes the translation of mRNAs exhibiting specific sequences in their 5'-terminus. Besides glycolysis, hyperglycemia suppressed the expression of some of the genes of the Krebs cycle enzymes and of the mitochondrial electron chain transporters (23), leading to a suppression of ATP-linked respiration. However, this down-regulation of mitochondrial gene expression could not be prevented, like in the case of glycolysis, by S6K inhibitors. It is unknown whether GAPDH enzymatic activity may be restored by S6K inhibitors in diabetic islets or INS-1 cells cultured at 25 mM glucose for 48 hours.

Islets and INS-1 cells are characterized by a "reverse" Pasteur effect when subject to anoxia (under N_2): their glucose utilization rate at high glucose levels is almost completely depressed instead of being stimulated (24). This "anomalous" feature of β-cells has been attributed to their low lactic acid dehydrogenase activity that cannot cope with the re-oxidation of cytosolic NADH at high rates of glycolysis (25). This function is taken over by the glycerol phosphate shuttle coupled to the respiratory chain. One might conclude that most of the islet glucose utilization rate is performed as aerobic glycolysis that depends on the integrity of mitochondrial respiration. This suggests that a mitochondrial respiratory defect might be the primary cause of islet degradation in diabetic islets. This might produce a block of GAPDH and of the reoxidation of glycolytically produced NADH followed by the upregulation of the gene expression of some glycolytic genes and the already described consequences (23).

4. Conclusions and perspectives

To our opinion, there is yet no consensus about the priority of an autoimmune attack against GAD65 versus a pre-existing metabolic derangement of the β-cells in the development of type-1 diabetes. Studies made in type-1 diabetes patients suggest that "a 2-component causal model for T1D comprising constitutional metabolic impairments that act in concert with autoimmunity "might be responsible for the development of the sickness (26). Moreover, studies in non-inbred BB rats (BB/Hagedorn, a model of spontaneous autoimmune type 1 diabetes) suggest that "beta cells may have an inherent sensitivity that possibly makes them susceptible to autoimmune attack" (27). In

contrast, in type-2 diabetic patients, one has identified several risk factors that might primarily provoke a functional derangement of the β-cells (26).

In conclusion, many experimental data support a role for GABA shunt metabolism in the stimulation of insulin secretion. The fact that GAD65 is one of the most prevalent autoantigens in type 1 diabetic patients that is immunologically destroyed in the development of the sickness may indicate that a block of the GABA shunt might be co-responsible of β-cell degradation. Therefore, any of the enzymes of GABA shunt might be considered as a risk factor for the triggering of β-cell malfunction: GAD65, GABAT, SSA-dehydrogenase (NADH-dependent, generating succinic acid) and, perhaps, SSA-reductase ($NADP^+$-dependent, producing ϒ-hydroxybutyric acid, GHB). The latter enzyme is, surprisingly, strongly inhibited (-98%) by 10 mM KIC without affecting its competitor enzyme (SSA dehydrogenase) for their common substrate SSA (14).

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Abbreviations

Gamma-hydroxybutyric acid (GABA), Semialdehyde succinic acid (SSA), Succinic acid (SUCC), (α-ketoisocaproic acid (KIC), α-keto-β-methyl-valeric acid (KMV), 2-oxoglutarate or α-ketoglutarate (2-OG or α-KG), gamma-hydroxybutiric acid (GHB), 2-OG-dehydogenase (2-OG-dh), SSA-dehydrogenase (SSA-dh), SSA-reductase (SSA-red), GABA-transaminase (GABAT),glutamate dehydrogenase (GDH), 4-methyl valeric acid (MVA).

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