

REVIEW ARTICLE

Glucocorticoid-Induced Death of Pancreatic Beta Cells: An Organized Chaos

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ABSTRACT

Glucocorticoids (GC) are renowned for their pleiotropic effects in all organ systems, their ubiquitous use in numerous clinical settings, and the abundant adverse effects they may exert, particularly in the endocrine-metabolic sphere. Although hyperglycemia and insulin resistance are well-defined GC-induced diabetogenic phenomena, an added component of direct injury to pancreatic β cells (PBC) may also participate in this scenario. Indeed, the apoptotic capacity of GC is widely recognized, and PBC do not escape this situation. No unified pathway has been characterized regarding GC-induced cell death; instead, it appears to depend on the specific machinery of each cell type, determining a great heterogeneity in GC-dependent apoptotic mechanisms among different tissues. In PBC, GC can induce the expression or activation of pro-apoptotic proteins (Bax, BAD, p38), repress anti-apoptotic proteins (Bcl-2), deactivate pro-survival mechanisms (cAMP-PKA signaling) and sensitize the cell to death induced by oxidative stress, fatty acids, hyperglycemia and cytokines. Although proliferative pathways (TGF- β , H-ras) are activated simultaneously –and an increase in PBC mass may be observed initially– pro-apoptotic and anti-proliferative mechanisms appear to eventually overcome their pro-survival counterparts, due to their synergic and aggregative action. Key molecules such as p38 and the cAMP-PKA system may be promising therapeutic targets in the prevention of GC-induced cell death.

INTRODUCTION

Glucocorticoids (GC) are steroid hormones essential to homeostasis of multiple organ systems, with glucocorticoid receptors (GR) present in virtually all human cells [1, 2]. In everyday clinical settings, their pharmacologic analogues are frequently used principally due to their powerful anti-inflammatory attributes, among other effects [3]. The tular ubiquity of GR conveys the main and most controversial disadvantage of their use: A well-known and extensive catalogue of adverse consequences in various spheres [4]. Their deleterious impact on energetic metabolism and glycemic status are particularly preoccupying, as they can not only directly induce hyperglycemia [5], but also potentiate this process by favoring development of insulin resistance [6]; and modulate proliferation and total mass of pancreatic β cells (PBC) [7]. These properties define the role of GC as potential inductors of secondary Diabetes Mellitus in certain scenarios [8]. The direct impact of GC in PBC is particularly concerning because –as with other effects of GC on carbohydrate and lipid metabolism– it may not be fully reversible [9].

Indeed, although the pro-apoptotic effects of GC have been profoundly studied in many tissues, and subsequently exploited in the management of GC-sensitive cancers such as small-cell lung carcinoma [10] osteosarcoma [11] and lymphoid malignancies [12]; yet their implications in the regulation of survival of other cell types may be overwhelmingly deleterious, especially in PBC, due to their paramount role in metabolism [13]. This review aims to offer an integrated vision of the main molecular hypotheses and findings underlying GC-induced cell death in PBC.

GLUCOCORTICOID SIGNALING – PHYSIOLOGIC ASPECTS

Much like other steroid hormones, GC act mainly through genetic induction and/or repression [14], and although novel non-genomic mechanisms have recently been described [15], these have not yet been described to be related to cell survival/death. In contrast, the genomic mechanisms of GC have been extensively studied (Figure 1), culminating in binding of GC-GR complexes to genomic sequences termed Glucocorticoid Response Elements, with association of co-activator and co-repressor proteins, resulting in facilitation or prevention of DNA transcription [16, 17]. In addition, GR may sequester various transcription factors through protein-protein interactions, including Nuclear Factor κ B (NF κ B) [18].

The properties of GR also determine cell sensitivity to GC. GR are codified in a single locus (5q31.3; OMIM: 138040), in 9 distinct exons [18]. Alternative splicing of exon 9 yields two transcription isoforms, GR α and GR β . While GR α is the

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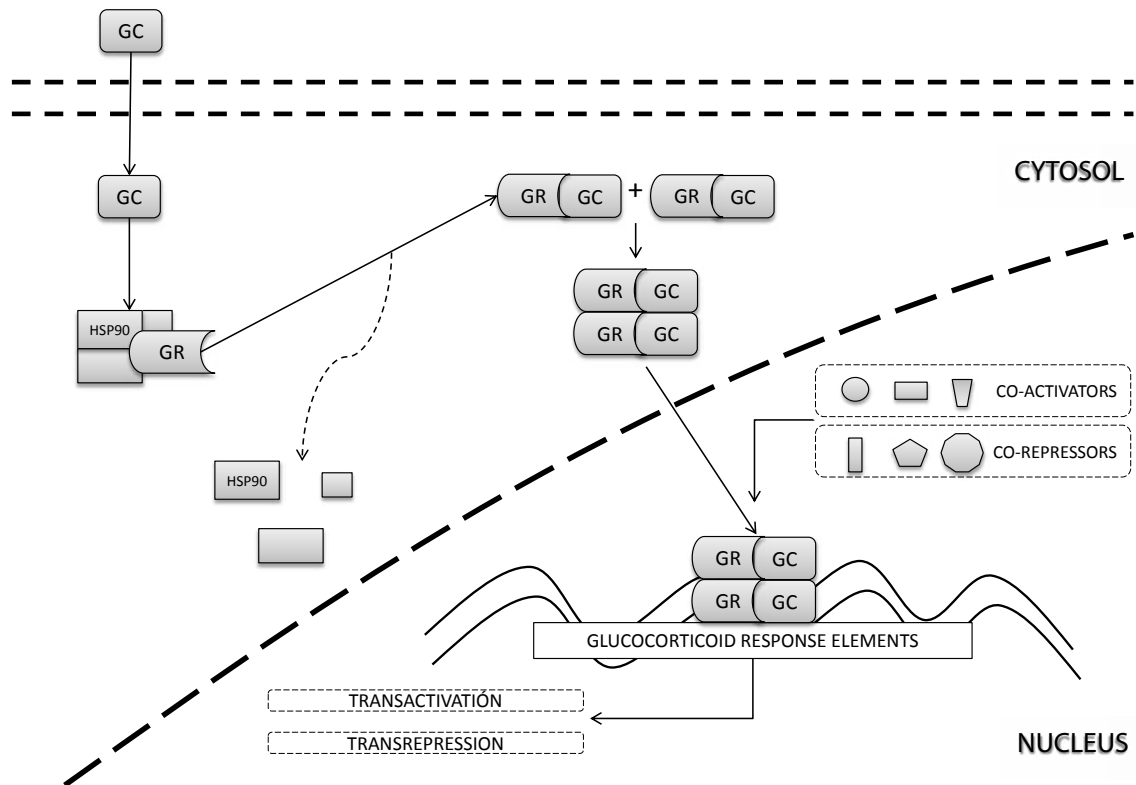
Abbreviations GC Glucocorticoids
PBC Pancreatic β cells

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GC: Glucocorticoid; HSP90: Heat Shock Protein 90; RG: Glucocorticoid Receptor. After entering the cytosol, GC bind to GR, which is held in its inactive form by chaperone proteins, notably HSP90. Formation of the GR-GC complex prompts conformational modifications in the structure of GR, leading to separation from chaperones and dimerization with other complexes. GR-GC dimers can then translocate to the nucleus, bind to Glucocorticoid Response Elements, and interact with nuclear co-activator and/or co-repressor proteins. This results in transactivation or transrepression of myriad of GC-modulated genes, variable in each cell type.

Figure 1. Genomic mechanism of action of glucocorticoids.

key mediator in the classical model of GC signaling, GR β is unable to initiate transcription, despite being able to homodimerize and bind to DNA [19]. Moreover, GR β may interfere with GR α activity through heterodimerization. Thus, GR β is an important modulator of GC sensitivity, with increased expression of this isoform linked to GC resistance [20]. On the other hand, initiation of translation the GR transcript may occur at four distinct sites (A-D) located in exon 2, yielding various translation isoforms (Figure 2). In consequence, although exon 1 remains untranslated, these variations heavily influence the behavior of GC intracellular signaling. Finally, in regards to induction of apoptosis, isoforms RG α -C and RG α -D appear to be the most and least powerful, respectively [21].

DIFFERENT STROKES FOR DIFFERENT CELLS

Impact of Glucocorticoids on Regulation of Cell Survival/Death

Glucocorticoids play a unique role in relation to regulation of cell survival, as they can act as both pro- and anti-apoptotic signals in different cell types. Indeed, they have been documented as inducers of cell death in various tissues [12], yet have also been observed to inhibit this process in select cells, such as neutrophils [22] and granulosa cells [23]. These steroids are also notable for lacking a distinct, universal apoptogenic mechanism; instead, GC appear to exploit each cell's autochthonous machinery, originating highly cell-specific pro-apoptotic molecular cascades [12].

In this aspect, GC are thought to predominantly utilize the intrinsic apoptotic pathway, as they appear inoffensive to this cascade, as seen in pre-B leukemic cells exposed to GC, which have been observed to undergo apoptosis even after treatment with Cytokine Response Modifier A (crmA), a caspase-8 inhibitor, a key mediator in the extrinsic pathway [24]. Moreover, they may in fact prevent apoptosis by interfering with the extrinsic counterpart, as they have been proved to inhibit expression of Fas-L in T cell hybridomas [25].

In contrast, the impact of GC on the intrinsic pathway is better understood, and relies mainly on the differential induction or repression of pro-apoptotic (Bid, Bax, Bim, Bad, Puma, Noxa) and anti-apoptotic (Bcl-2, Bcl-xL) proteins, modifying a cellular "rheostat" which may favor cell survival or death [26]. Predominance of pro-apoptotic proteins leads to cell death primarily through mitochondrial mechanisms, especially the release of cytochrome c, which activates caspase-9 and thus renders cell death imminent [27]. However, the molecular events modifying this balance are widely variable amongst cell types [12].

Activation of GR appears to be a fundamental event for GC-induced apoptosis, as cell lineages with mutated GR seem resistant to this fate [28]. Likewise, downregulation of 11 β -hydroxysteroid dehydrogenase –which converts cortisol to inactive cortisone – sensitizes cells to GC-induced apoptosis [29]. Furthermore, the susceptibility to

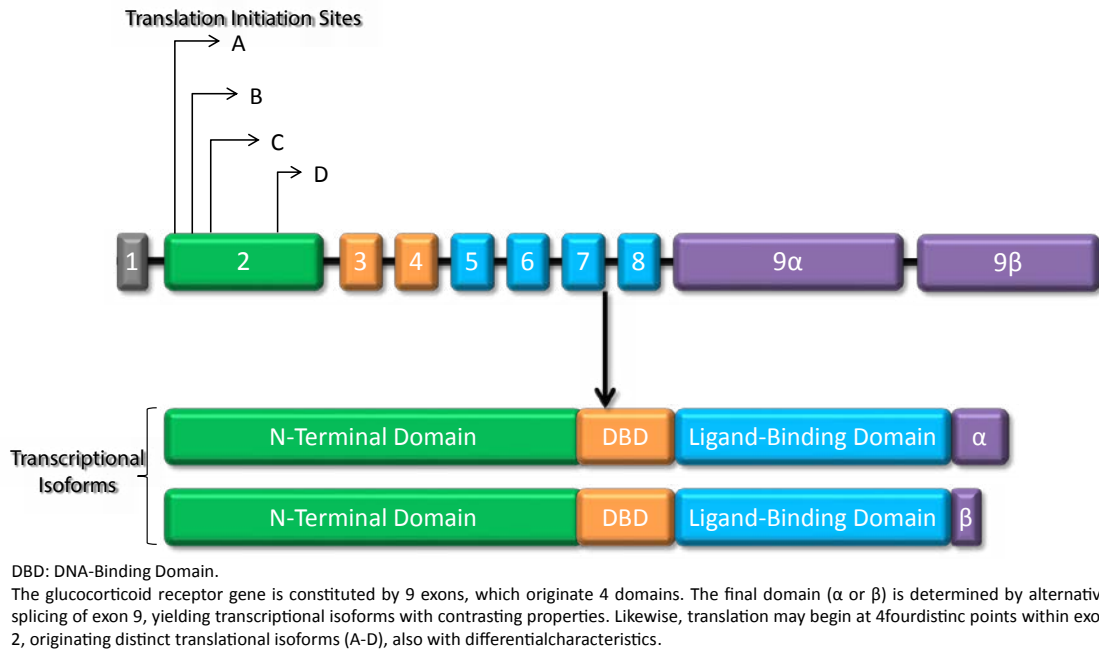


Figure 2. Structure of the glucocorticoid receptor gene.

GC-induced apoptosis is correlated to both the degree of GR expression and the isoform most abundant in each cell, as has been demonstrated in transgenic murine models [30, 31]. Although quantitative regulation of GR expression is generally subject to negative feedback [32], in certain especially susceptible cells – such as leukemia cells – auto-induction of GR expression may be an important amplifier of GC-dependent apoptosis, although the mechanisms underlying this positive feedback remain unelucidated [33]. Upregulation of specific GR isoforms has also been observed, as in T cells, which appear to favor synthesis of RGα-C [34]. Failure to accomplish this auto-induction has been associated with glucocorticoid resistance in leukemia cells [29].

Hundreds of genes have been proposed to be involved in GC-dependent apoptosis, yet their participation appears extremely heterogeneous, with very few GC-modulated genes coinciding across different tissues, leading to broadly variable molecular cascades [35]. Alongside those coding proteins within the cell rheostat, expression of other genes may also modulate cell survival, such as RAFTK activity in myeloma cultures [36]; inhibition of NFκB [37, 38]; expression of anti-apoptotic mediators, such as IL-7 and TGF-β [39, 40]. Furthermore, protein-protein interactions of GR with NFκB, AP-1 and p53 also participate, not only as rheostat regulators, but also contributing to the anti-inflammatory effects of GC [41].

Another group of implicated genes are those that indirectly favor cell death by conditioning a hostile cell milieu, such as disruption of carbohydrate, lipid and protein metabolism [42], and alterations in gene transcription and translation [43]. Likewise, GC-dependent disruption of reactive oxygen species (ROS) management has been reported [44]. Other GC-inducible alterations are involved with calcium ion traffic [45] regulation of pH [46] and cell volume [47]. These disorders in the cytosolic environment entail a dynamic

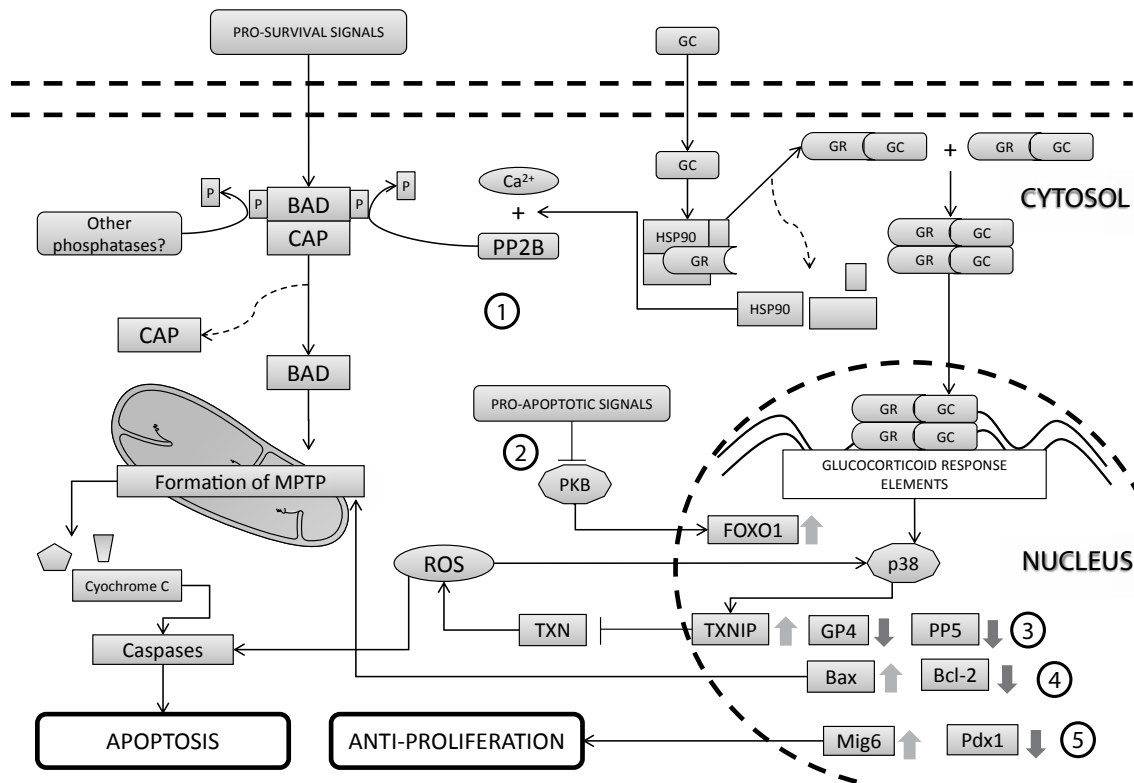
role in cell death: Although they may induce apoptosis, concurrent blocking of this pathway –potentially through upregulation of anti-apoptotic rheostat components– may eventually lead to necrosis. This phenomenon highlights the continuous nature of apoptosis and necrosis, especially in the context of GC-induced cell death [33].

ALL ROADS LEAD TO DEATH

Mechanisms of Glucocorticoid-Induced Cell Death in Pancreatic β Cells

In PBC, GC can prompt a myriad of molecular pathways, all of which lead to the same fate –death– amidst a chaotic, yet organized milieu where several pro-apoptotic mechanisms coexist (Figure 3). As in other tissues, GC-induced cell death strictly requires GR activation, as demonstrated through *in vitro* inhibition of GC-induced apoptosis in INS-1 cells treated with mifepristone, a GC antagonist [48]. Likewise, this process seems to substantially rely in rheostat modulation, mainly through upregulation of Bax, downregulation of Bcl-2, and dephosphorylation of BAD [49]. Diminished Bcl-2 activity may be especially relevant in PBC, as various studies have underlined its remarkable role as an inhibitor of cytokine-mediated apoptosis in these cells [50, 51].

On the other hand, dephosphorylation of BAD activates this cytosolic protein, unleashing its pro-apoptotic effects. In its phosphorylated, inactive state, BAD is bound to Cytoplasmic Adaptor Protein 14-3-3 (CAP) [52]. BAD may be phosphorylated in 5 different sites (Ser112, Ser128, Ser136, Ser155 and Ser170) by a myriad of kinases activated by pro-survival signals, although only Ser112, Ser136, and especially Ser155 appear required for binding to CAP [53]. These pro-phosphorylation cues include PKA [54], PI3K and PKB [55, 56]. Dephosphorylation separates BAD from CAP, allowing BAD to bind to Bcl-2 in the mitochondrial membrane, leading to formation of a mitochondrial permeability transition pore and finalizing



GC: Glucocorticoids; HSP90: Heat Shock Protein90; GR: Glucocorticoid Receptor; Ca²⁺: Calcium Ions. PP2B: Protein Phosphatase 2B; P: Phosphate; PCA: Cytoplasmic Adaptor Protein 14-3-3; MPTP: Mitochondrial Permeability Transition Pore; PKB: Protein Kinase B; GP4: Glutathione Peroxidase-4; TXNIP: Thioredoxin-Interacting Protein; TXN: Thioredoxin; ROS: Reactive Oxygen Species.

GC may induce death in pancreatic β cells through several mechanisms: 1) Binding of GC to GR entails release of HSP90, which can then activate PP2B in presence of Ca²⁺. PP2B can dephosphorylate BAD, leading to its separation from CAP. Other undetermined phosphatases may partake in this process. Dephosphorylated BAD participates in formation of a MPTP, leading to influx of cytochrome c and other caspase-activating proteins into the cytosol, triggering apoptotic cascades. 2) Various pro-apoptotic signals can inhibit PKB activity, which is associated with increased FOXO1 signaling. 3) GC can repress expression of GP4, which –with p38 as a co-activator – can induce expression of TXNIP, a TXN inhibitor, leading to a increase in ROS, cellular stress and death. 4) GC can also directly upregulate Bax and downregulate Bcl-2, which are pro- and anti-apoptotic, respectively. 5) GC exert anti-proliferative effects by promoting expression of Mig6.

Figure 3. Mechanisms of glucocorticoid-induced death in pancreatic β cells.

in exit of cytochrome c and other pro-apoptotic proteins from the intermembrane space into the cytosol [57].

This dephosphorylation has been proposed to be mediated by HSP90 and Protein-Phosphatase 2B (PP2B): Once HSP90 is free – after the GC-GR complexes have dimerized – it can bind to and activate PP2B, which can then dephosphorylate BAD, triggering downstream pro-apoptotic mechanisms [49]. Activation of PP2B requires increased intracellular calcium concentration and calmodulin signaling [58], and appears to be independent of calpain activity [59]. Because PBC tend to attenuate fluctuations in concentration of this ion, an important influx is required. The augmented intracellular glucose traffic caused by systemic GC-induced hyperglycemia may be a potential source [49]. Although PP2B is the only BAD phosphatase with well-characterized GC-prompted activity, it can only dephosphorylate P-Ser112 and P-Ser136, and not P-Ser155 [60], suggesting other serine-phosphatases with activity over BAD, such as PP1A, PP2A and PP2C [60-62] may also be implicated. Likewise, because GC appears to repress HSP transcription in PBC [48], other proteins or triggering mechanisms may parallel the role of HSP90.

Inhibition of PKB may also be an important component in GC-induced death, as it is associated with increased transcription, dephosphorylation, and nuclear localization of

FOXO1, with pro-apoptotic properties [63]. However, because inhibition of all PKB isoforms, as well as serum/glucocorticoid-regulated kinase 1 is required to achieve these effects, FOXO1 activity is unlikely to be the main mediator in GC-induced death [63], although it may gain relevance when several signals for PKB inhibition converge.

Such signals notoriously include the JNK pathway, which in turn may be activated by glucolipotoxicity, oxidative stress [64], proinflammatory cytokines [65], and interestingly, glucocorticoids [66], by binding to activated GR [67]. It should be noted that JNK isoforms have been observed to exhibit differential behavior regarding cell survival, depending on the triggering stimuli: Regarding cytokine-induced apoptosis, JNK1 and JNK2 appear pro-apoptotic, and JNK3 is anti-apoptotic [68]. In contrast, in relation to glucolipotoxicity, JNK1 serves anti-apoptotic functions, JNK2 does not appear to participate, and JNK3 is associated with increased cleaved caspase-9 and caspase-3, but not apoptosis [69]. Lastly, the distinct behavior of JNK isoforms in response to GC remains unknown, although treatment of MIN6 β -cells with JNK inhibitors has been reported to increase DNA fragmentation and caspase-3 cleavage [70]. Further research is required to clarify the role of JNK regarding GC and PBC death/survival.

Glucocorticoids may also lead to PBC death by inducing cellular stress, particularly by increasing ROS levels. To this end, in PBC, GC can directly repress Glutathione Per-

oxidase-4 [48], and inhibit thioredoxin by upregulating Thioredoxin-Interacting Protein –two ROS-scavenging enzymes–, possibly through MAPK and p38 signaling [71]. Repression of Protein-Phosphatase 5 further potentiates this pathway [66], which may also be started ROS, constituting a positive feedback circuit which potentiates oxidative stress in PBC [72]. Additionally, p38 overexpression also sensitizes PBC to apoptosis induced by free fatty acids [73], hyperglycemia and cytokines [74], all aspects variably compromised during exposure to GC.

Nonetheless, GC exert an ambivalent effect on PBC survival/death, as activation of pro-apoptotic pathways and induction of proliferative factors such as TGF- β and oncogenes such as H-ras have been reported to occur simultaneously [48]. Indeed, *in vivo*, the initial effect of GC on PBC appears to be proliferative [7], possibly in synergy with other stimuli, such as hyperglycemia and insulin [75]. Towards the fifth day of treatment with GC, pro-apoptotic mechanisms are activated, in coexistence with PBC proliferation [7]. It may be hypothesized that the eventual overcoming of apoptotic over proliferative activity is due to early activation of rheostat-dependent pathways [48], along with the anti-proliferative impact of downregulated Pdx1 [63] and upregulated Mig6, which rises progressively in time [76]. Other deleterious elements also accumulate over time, including cellular stress due to ROS [77], hyperglycemia and hyperlipidemia [78], enhancing the shift towards loss of PBC.

Remarkably, some of the effects of GC on PBC may begin as early as *in utero*: Dexamethasone has been described to reduce expression of Pdx1, Pax-6 and Nkx6.1, favoring acinar differentiation [79]. GC also promote expression of PGC-1 α , a GR co-activator, which is associated with Pdx1 repression due to binding of GR/PGC-1 α to the Pdx1 promoter region [80], resulting in decreased PBC mass and glucose intolerance [81]. These mechanisms may be important factors underlying the role of GC exposure in fetal programming related to Diabetes Mellitus, obesity and hypertension [82, 83].

NO CELL IS AN ISLAND

Effects of Glucocorticoids on other aspects of Pancreatic Islet Dysfunction

In addition to disruption of PBC and insulin physiology, GC also trigger variable consequences on other pancreatic islet cells and hormones. Glucagon-secreting pancreatic α cells (PAC) respond differently to acute and chronic GC exposure [84]. In the former scenario, opposing data have been reported, both supporting and denying GC-stimulated glucagon activity [85, 86], depending on specific conditions of each experimental model. On the other hand, PAC response to chronic GC stimulation is better characterized. Regarding PAC mass, the impact of GC is opposite depending on the period of time they act: Whereas *in utero* exposure has been described to reduce PAC mass, GC exposure in adults is associated with greater mass, in rat models [86, 87]. Furthermore, GC have been demonstrated to potentiate glucagon secretion in both

animal and human models, promoting hyperglucagonemia and further boosting its hyperglycemic effects [84].

Amylin, a polypeptide co-secreted with insulin in PBC, has anti-hyperglycemic effects, by inhibiting gastric emptying and glucagon secretion in response to food intake [88]. Nevertheless, aggregation of amylin into toxic amyloid substances has been linked to induction of PBC apoptosis [89]. Amylin hypersecretion is a major promoter of this deleterious aggregation; as has been seen in rats and humans in response to dexamethasone administration, contributing to islet dysfunction [90].

The role of other pancreatic endocrine messengers is less clear. Although somatostatin – which opposes both insulin and glucagon secretion and is released by δ cells [91] – appears to be upregulated by GC [92], this does not match the overall profile of GC-induced pancreatic dysfunction: Hyperinsulinemia and hyperglucagonemia. Further research may uncover a missing link in this pathophysiologic link. Lastly, ghrelin is secreted by both gastric P/D1 cells and pancreatic ϵ cells, inhibiting insulin and somatostatin release, increasing glucagon and growth hormone secretion, and stimulating appetite [93]. Reports of GC effects on this hormone are contradictory, and fail to differentiate between pancreatic and gastric ghrelin release [84]. Future studies should attempt to unravel the role of this peptide in relation to GC signaling.

PUTTING DEATH INTO PERSPECTIVE

Clinical Aspects of Glucocorticoid-Induced Pancreatic Islet Dysfunction

Animal models have shown that chronic GC treatment induces stress, weight gain and decreased insulin sensitivity [94], increased lipolysis and visceral adipogenesis [95], modulates mood centers related to depression [96], and favors overeating behavior [97]. Although animal protocols using GC vary broadly in regards to strain of mice or rat, GC molecule, dosage, duration of treatment and route of administration [98]; the general consensus is that GC treatment induces insulin resistance and hyperinsulinemia in a dose-dependent manner [99]. Likewise, induction of PBC death varies according to dosage and duration of exposure, and for example, can be observed in rat islets incubated with 100 nM of dexamethasone for 2-4 days [100, 101]. However, different dosages of different GC have variable effects on PBC, from glucose-induced insulin secretion to cell death, as seen with 1-100 nM of dexamethasone and 0.02-20 mg/L of cortisone [98], associated with inhibition of AS160 activity [102] and oxidative stress [103].

In healthy human subjects, low doses of prednisone have been associated with diminished insulin sensitivity, including elevated levels of insulin and C-Peptide at day 7 after exposure [104]. This phenomenon appears to be dose-dependent [105]: Whereas with prednisone 15 mg *b.i.d.* these effects are seen after 5-7 days of exposure, with dexamethasone 3-4 mg *b.i.d.* these are achieved

after only 2-3 days [98]. In contrast, acute administration of methylprednisolone has been linked with short-term hyperinsulinemia, inhibition of Pyruvate Dehydrogenase and glucose intolerance, all of which tend to last for less than 24 hours; suggesting this particular mode of use may be safe [106].

Regarding chronic administration of GC, González-González *et al.* [107] showed subjects on prolonged, high-dose prednisone use tended to display hyperglycemia towards the second to fourth weeks, yet two-thirds of these cases spontaneously normalized by the eighth week. This pattern may be a reflection of the previously discussed interplay of pro- and anti-survival signals triggered in PBC by GC. Continuous use schemes proved more detrimental than cyclic regimes [107], while age, body mass index [108], and family history of Diabetes Mellitus [109] have also been described as risk factors for GC-induced hyperglycemia.

In this context, various drugs have been studied in relation to GC-associated dysglycemia. GLP-1 analogues have proven helpful in controlling GC-induced PBC death. For example, exendin-4 has been seen to antagonize GC-induced cell death, by promoting cAMP synthesis, with subsequent activation of PKA [49], JNK3 [110] and possibly PKB [111], improving glucose control [112]. Moreover, van Raalte *et al.* [113] conducted a randomized, placebo-controlled, double-blind, crossover study, evaluating exenatide in a GC-induced glucose intolerance model, reporting this drug to be able to prevent dysglycemia and GC-induced pancreatic islet dysfunction in healthy humans. Another GLP-1 analogue, liraglutide, has also been proposed as a possible therapeutic alternative for improvement of insulin sensitivity in corticosterone animal models, improving beta cell mass [114]; yet studies on this aspect remains scarce.

CONCLUSION

Future research should assess the relative importance of GC-induced PBC death in comparison to other GC-dependent diabetogenic mechanisms, as it remains unclear. In the face of this prospect, key mediators such as p38 [73] and PKA [49] have been outlined as potential therapeutic targets regarding GC-induced PBC death. Incretins appear outstandingly promising by virtue of the central role they play as survival promoters through PKA [115]. Further studies are required in order to characterize the clinical extrapolation of the molecular interplay of GC modulation of PBC survival/death, and value the true impact of GC-induced PBC death in metabolism. Nevertheless, metabolic surveillance and management should remain a fundamental aspect when utilizing GC and assessing subjects with hypercortisolism in the clinical setting.

Conflict of Interest

Authors declare to have no conflict of interest.

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