International Journal of Molecular Medicine and Advance Sciences 2 (2) : 211-216, 2006

Impaired Biophysical Dynamics of Insulin Secretion Primarily Precipitate Transcription Failure and the Diabetic State

Lawrence M. Agius
Department of Pathology, St Luke's Hospital Gwardamangia,
University of Malta Medical School, Msida, Malta, Europe

Abstract: Evolving consequences in the genesis of failed secretory dynamics on the part of islet Beta cells indicate a full panorama of induced effects arising primarily from suppression of insulin transcription. In such an evolving scenario, the subsequent death of beta cells is a true reflection of cellular injury that redefines glucotoxicity as another aspect of the diabetic state that progresses in line with increased nonoxidative production of lipotoxins in the added context of a peripheral resistance to insulin action. Type 1 and type 2 diabetic states would constitute integral representations in evolution of a single pathogenetic pathway that directly implicates an eventual widespread death phenomenon that depletes the islet Beta cell pool as a final consequence of evolving transcription failure of the hormone. One might therefore link abnormal compensatory initial increases in insulin secretion as a marker of impaired transcription dynamics of insulin production arising largely as a direct consequence of progressive failure of insulin secretion and peripheral availability to tissues ranging from liver to skeletal muscle and heart and brain. It is the consequence of peripheral effective action of insulin that integrally converts impaired dynamics of insulin secretion to failed insulin transcription and subsequent widespread depletion of islet Beta cells

Key words: Transcription, insulin, biophysical dynmics, diabetic state

HYPERGLYCEMIA

Hyperglycemia arises independent of dynamics of turnover of the beta-cell mass or of beta-cell hypertrophy or beta-cell number. Beta-cell turnover constitutes an ongoing process of developing dynamics that promotes variability of response to hyperglycemia[1]. It is in terms of a continuous process in evolving dynamics of insulin secretory response to hyperglycemia that peripheral tissue sensitivity further determines how effective glucose homeostatic control is maintained.

A delineation of events in production of a maintained state of euglycemia appears to involve the contributing roles of a multitude of factors that converge on an interaction of insulin secretory rate and of peripheral sensitivity to insulin action.. Turnover of beta cells constitutes a functional attribute not related directly to any precise degree to blood glucose level. One might recognize dynamics of production and secretion of insulin related closely to evolving issues involving sensitivity of beta-cells to hyperglycemia.

A central concept of toxicity of action of glucose or lipids might prove at variance with an evolving progression of a type 2 diabetic state that is irreversibly linked to a diminished beta-cell islet pancreatic mass. Indeed, in terms of such turnover of beta-cells, it might be significant to recognize a full array of events related to an interactivity controlling hypertrophy of beta cells that is essentially unrelated to beta-cell number or responsiveness to glucose levels. It is in terms of an independence of any relative effect of beta-cell functional response to evolving fluctuations in glucose need of peripheral tissues that the type 2 diabetic state would both originate and progress subsequently as a hyperglycemia state.

INADEQUATE INSULIN AVAILABILITY AND ACTION

Beta-cell dysfunction represents a failed sensitivity of beta-cells to raised blood glucose levels that progressively rise even further[2]. One might recognize dynamics of evolution in terms of beta-cell dysfunction that translate in terms of glucose sensitivity of the beta-cells both in states of low and of high glucose levels.

One might consider the development of various pathways in the further increased destruction of the beta-cell mass in terms particularly of an interaction of both glucose tolerance and of glucose utilization.

The strict term of glucose tolerance has evolved particularly with regard to variably delineated action of insulin on different tissues in the body. Hence the

Corresponding Author: Lawrence M. Agius, 27 Ballarat Guzeppi Caruana Str., Tal-virtu, Rabat, Rbt09 Malta, Europe

diabetic state as a heterogeneous disease would constitute a spectrum of advancement of pathologic effect that incorporates not only adipose tissue but also muscle and brain, kidney and intestine.

One might view the full complexity of the diabetic state in terms not only of a heterogeneous pathology but also particularly in terms of interacting factors in onset and subsequent progression of insulin lack of action, insulin insufficiency and responsive secretion to glucose and nonglucose substrates. In various ways, a whole range of glucose molecular homologues in terms of equivalent or nonequivalent action on beta cells would include a variable parametric progression of a type 2 diabetic state that is functionally and anatomically interrelated pathologically and pathogenetically.

INADEQUATE GLUCOSE UTILIZATION

Inadequate glucose utilization of tissues represents a true inadequacy of insulin availability in type 2 diabetes.

The beta islet cell mass constitutes a correlate measure of insulin action in terms of various parameters of severity of possible type 2 diabetic state[3]. Insulin action represents in large measure a clearly delineated ability to utilize glucose in the face of a widely fluctuating blood glucose level that tends to subsequently progress with increasing duration of the diabetic state. One might view various forms of insulin insufficiency in terms not simply of inadequate amounts of secreted hormone but of a full panorama of interactive modes of influence including insulin resistance and fluctuation in blood glucose levels.

In terms of an overriding development of functional correlates in the overall schematic progression of the type 2 diabetic state, a relative state of insulin resistance is a central reflection of an inadequate insulin secretion. Indeed, insulin resistance would constitute an outcome of differences in development of various factors that progressively impair insulin availability.

In terms of such inadequacy of insulin action, it might be significant to consider how type 2 diabetes constitutes a formalization of ideal states of hyperglycemia progression beyond mode of action of any secreted insulin.

Beta-cell mass secretion constitutes progression of the type 2 diabetic state as a realization of different modes of development of glucose excess and of inadequate glucose availability to tissues. In terms of production of an inadequate amount of insulin, the type 2 diabetic state can progress pathologically beyond strict definition of any true state of existing insulin resistance.

INSULIN AS A CELLULAR TROPHIC FACTOR

Growth factor and hormonal regulation of survival and growth of beta cells appear to follow a unified scheme of promotion related inherently to insulin action peripherally[4]. In a real sense, insulin is itself a hormone that preserves beta-cell function in the face of a number of different types of possible cellular or islet insults. Indeed, all aspects of development of a diabetic profile would represent a deterioration in the survival of beta cells arising from loss of trophic actions of insulin.

INSULIN SECRETION FAILURE

A failure in the acute responsive increase in insulin secretion to a rise in serum glucose level would denote a primary defect in release of secretory vesicles[5]. In terms of other effects referable to insulin synthesis, it appears significant that production and release of active insulin would represent a constitutional attribute of islet beta cells in relation to both perfusion rate and action of factors such as growth hormone and prolactin.

One might recognize dynamics of development of the diabetic state that characterize not only decompensation of the beta-islet cells but more importantly constitute a biologic basis for hypertrophy of islet cells that set the stage for subsequent beta islet cell loss.

It is in terms of hypertrophy of islet beta cells as a response to initial hyperglycemia that subsequent deterioration in viability of beta cells leads to the diabetic state. The strict relevance of the concept of glucose toxicity as a prodiabetes might relate directly to nonresponsiveness of beta cells to high glucose levels as biophysical molecular interactions. A molecular characterization of events underlying an apparent glucose toxicity phenomenon might account for the development of beta cell injury that is primarily irreversible.

The prominent role of failed secretion rather than of failed synthesis of insulin might account for the further delineation of molecular events that are primarily interactive in terms of cellular membrane biofunction.

VIABILITY OF BETA-ISLET CELL FUNCTION

Insulin resistance constitutes an expression of how insufficient insulin action is translated to inadequate control of hyperglycemic states[6]. Hyperglycemia is an endstage list of factors that allows for progressive lack of insulin action at the level of the peripheral cell pool. It is in trying to understand inadequate insulin action as a prodiabetic factor that one would further recognize ongoing evolution of a prediabetic state.

Prediabetes constitutes a promotion of inadequate insulin action that particularly characterizes increased insulin resistance. One might also consider the evolving prediabetic state in terms particularly of modes of development of prodiabetic tendencies as exerted particularly by hyperglycemia.

Hyperglycemia develops as both the consequence of inadequate insulin action and also as a cause of a series of injuries to the beta islet cells. The lack of an acute release of insulin to a rise in serum glucose might constitute a mode of involvement that compromises both islet cells and the peripheral cell pool.

In a real sense, the hyperglycemic state constitutes a pathologic deterioration in viability of the beta-islet cells, beyond any considerations relative to the peripheral cell pool. Viability issues related to beta cell function and survival are the primary considerations relative to prediabetes and to significant action of a whole group of prodiabetic factors.

COMBINED PATHOGENESIS IN TYPE 2 DIABETES

Hyperglycemia and free fatty acids in plasma constitute mechanistic pathways of induced influence in prediabetic and early diabetic states[7]. Glucose and lipid toxicity appear to mutually promote the development of beta-cell injury largely in terms of apoptosis and as failed attempt at both neogenesis of islet cells and subsequent proliferation of beta-cells. One might recognize beta-cell islet plasticity largely in terms of different influencing factors that further promote degeneration of beta cells.

Longstanding or persistent states of hyperglycemia appear particularly significant in inducing progression of a prediabetic or early diabetic state. It is only in terms of induced promotion of plastic influence that diabetes might be delayed initially as a persistent hyperglycemia or as induced insulin resistance.

Pregnancy and obesity appear to constitute states of persistent compromise of beta cell islet function due to the development of insulin resistance. Indeed, a direct correlate of beta-cell impaired secretion of insulin and peripheral insulin resistance appears centrally operative in most patients with type 2 diabetes mellitus. Such a coupled impairment of insulin secretion and of peripheral insulin action would promote a progression of the hyperglycemia in terms of such injury as beta-cell toxicity; this may be due to free fatty acid in the presence of concomitant persistent hyperglycemia. Indeed, lipid toxicity appears largely a phenomenon arising within the context of progressively worsening hyperglycemia of some standing.

It is in terms of a combined approach to the pathophysiology of action of both free fatty acids in serum/plasma and of hyperglycemia that a dual pathogenesis of type 2 diabetes arises as impaired insulin secretion with attributes of peripheral insulin resistant state.

PRO-APOPTOSIS AS A PREDIABETIC STATE OR PROGRESSION

Apoptosis as an ongoing event of pathophysiologic cell death of pancreatic islets appears to constitute a developmental stage in the evolving plastic response to hyperglycemia[8].

Indeed, the diabetic state constitutes a complex constitutive outcome of various factors in response to such abnormally raised serum levels of glucose. One might interpret the full impact of hyperglycemia per se as purely pathophysiology of beta islet cells; this would prove important in relation to the possible subsequent development of apoptosis.

Calcium ion participation might further characterize events in the pathogenesis of diabetes in terms of various modes of involvement of pathways that subsequently implicate cell death. Indeed, islet beta cells are a constituent cell component in a survival-target axis constituted by growth hormone, prolactin and placental lactogen.

In such a setting, it is reasonable to recognize ongoing production and secretion of insulin as a fundamental index factor in evolution of different para-diabetic states of predisposition to glucose intolerance. Hyperglycemia would hence be a component system as evolving consequence to systems of injury to various influences as dictated by apoptosis of beta islet cells.

ISLET-BETA CELL DESENSITIZATION

Islet beta cell desensitization appears a dysregulatory secretory pattern primarily impairing insulin transcription and synthesis.

Overstimulation of beta islet cells as a general phenomenon results from the action of different potential agonists that induces increased influx of Ca2+ ions into the beta cells[9]. This process would activate intracellular proteases and result in apoptosis of cells or lead to an initial desensitization that impairs poststimulatory secretion of insulin by the affected beta cells. Whole panorama of changes in secretory activity on the part of beta islet cells appear central to a prodiabetic pathophysiology closely related to disturbed dynamics in secretory beta cell activity.

Understanding a process of initial overstimulation of compensatory insulin secretion in terms of injury of islet cells would comprise a phenomenon of reactivity that decompensates the actual mechanism of genetic transcription relative to secretion dynamics of insulin activity. An overall scheme of reproducible injury to beta islet cell function might implicate an inter-relative exchange of influence between dynamics of synthesis and secretion of insulin promoting peripheral action of this hormone. The stimulation or hyperstimulation of insulin secretion would represent an integral component of injury to beta islet cells that promotes progression of action of various agonists in further injuring the beta islet cells.

Overall dynamics of reproducible injury as represented by persistent states of hyperglycemia would constitute a fully representative form of dynamic injury that might be initially only a disturbed sensitivity of beta islet cell response. Indeed, responsive disturbances of secretory activity are reflected in a higher than normal ratio of proinsulin to insulin levels in cases of hyperglycemia.

Integral aspects of reproducible and repetitive injury to beta-islet cells might constitute a persistently impaired transcriptional mechanism resulting specifically from disturbed dynamics of secretion of insulin. Impaired or wide fluxes in insulin secretion would impair the subsequently evolving capability of beta-islet cells to synthesize further amounts of insulin.

Within such a scenario there would evolve a dual system of dysregulation whereby induced abnormal secretory patterns of insulin release from beta-islet cells would prove detrimental in the long term to synthesizing and transcriptional activity of insulin in these cells.

One might view the evolution particularly of the type 2 diabetic that overlaps with that of a type 1 diabetic subsequently resulting in permanent injury to beta islet cells.

The Ca2+ influx within these cells would form a biochemical substrate linking disturbed insulin secretory pattern to an inability to subsequently synthesize adequate amounts of insulin. One might view the relative importance in development of the diabetic state in terms of an ongoing series of events arising as abnormal exocytosis of insulin by beta-islet cells.

Such a reference framework in the biophysiologic damage to beta islet cells would constitute a valuable index of pathogenic activity of the diabetic state that relates to dysfunctional desensitization of beta cell activity.

A PARTIALLY DECOMPENSATED DIABETIC STATE IS SELF-PERPETUATING

Cytokine and nitric oxide mediated pathways leading to apoptosis of islet beta cells appear intrinsically inbuilt processes that deplete the responsive secretion of insulin to hyperglycemia[10]. Mitogen activated protein kinases and stress activated protein kinases appear to mediate a series of aberrant responses in cases of excessive activation that promote death of beta cells.

There would develop a series of inducing effects inherent to the establishment either of homeostatic control mechanisms or to the aberrant activation of apoptosis pathways in beta cells.

The diabetic state would appear to inherently arise as a phenomenon of production in eliciting abnormal metabolic responses on the part of beta islet cells. Strict concepts of functionality of beta islet cells would necessitate a redefinition of factors controlling homeostasis or else disturbed dynamics in insulin production and secretion. One might view dimensions of resolution of the diabetic state in terms particularly conducive to dysregulation or of otherwise disturbed functionality of beta islet cells that provoke compensatory insulin production.

Diabetic dysregulation of insulin production and secretion would underlie a pathophysiology distinguishing individual insulin resistant states as partly compensated and partly decompensated metabolic states of glucose utilization. One might further view essential dynamics as partly resolved pathways in the metabolic handling of glucose utilization that arise directly from injury to beta islet cells.

A partly compensated diabetic metabolic state would redefine the production of a glucose-resistant state that self-perpetuates onset and subsequent evolution of impaired insulin synthesis and release.

A PURELY DEPLETIVE EFFECT OF COOPERATIVE IMMUNE AND CYTOKINE ACTION IN TYPE I DIABETES

A complex, heterogeneously pathogenic series of pathways would operate in inducing beta cell death in type I diabetics that operates via cytokine and immune mechanisms[11]. Low glucose concentrations appear to potentiate susceptibility to beta cell necrosis or apoptosis. Release of Interleukin 1beta would induce iNOS and the production of nitric oxide that subsequently impairs viability of beta cells. Activated macrophages and antigen driven immune cells would mediate cytotoxic effects that co-operate with cytokine action.

An age-related decline of beta cells whereby early onset of beta-cell damage in the first few years of life would result in more widespread destruction of these cells appears a fundamental mechanistic operator in inducing type I diabetes. Intricate interstitial micro-environmental exposure of the beta cells to the ongoing action of cytokines such as nitric oxide would develop. Glucagon availability and particularly vascularity of the islet cells

would promote protection in terms of activation of protein synthetic pathways in beta cells. Duct epithelial cells found adjacent to the beta islet cells would appear a mechanistic pathway that cooperates in reactions of beta cells to various potentially damaging agonists.

Type 1 diabetics are prone to the immune and cytokine actions of various agents that converge on a final common pathway promoting beta cell depletion. In terms of such concerted action, it might be significant that beta cells are themselves foremost in inducing a diabetic state as a purely depletive pattern of immune and cytokine action.

CONFLICTING INJURIOUS AGENT ACTION IN PRO-DIABETES

A sufficient level of intracellular ATP within islet beta cells allows apoptosis to develop and this is a main criterion in distinguishing programmed cell death from cell necrosis[12]. In terms inherently arising from energy store availability to beta cells, there would evolve a substantial list of potential injurious agents that either deplete or maintain adequate ATP levels intracellularly. One might view the onset and development of beta islet cell loss largely as a phenomenon of combined cytokine and immune-mediated injury. Interleukin 1beta together with interferon gamma action would allow for the onset of injury that evolves either as cell apoptosis or as cell necrosis. Indeed, suppression of cell death pathways is either a stimulus for homeostatic maintenance of islet beta cell function or the initiation of various degrees of impaired secretion of insulin.

A whole range of effects either promote a participating role for beta-cells in inducing programmed cell death as apoptosis or else as directly induced necrosis of beta cells.

A balance between conflicting action of various transcription gene factors in evolution of injury to islet beta cells would allow for the delineation of potential pathways that progress either as zonal phenomena of beta cell necrosis or as individual beta cell loss through apoptosis. Type 1 and type 2 diabetes might conceivably evolve largely in terms of a quantitatively determined potential for increasing beta-cell death. Such a phenomenon might be quantifiably distinctive either as a permanent loss of significant insulin reserve and secretory production as in type 1 diabetes, or as an evolving insulin resistance state characterized by glucose toxicity and lipid toxicity to overstimulated residual islet beta cells.

PARACRINE MEDIATION OF BETA-CELL INDUCED APOPTOSIS

Disruption of ATP sensitive K+ channels on beta cells appears to consequentially disrupt paracrine interactions with alpha cells and other cell constituents of the pancreatic islets[13].

It appears relevant that architectural disorganization of islet cellular constituents implies a real disturbance in differentiation of the islet cells in a manner conducive to apoptosis of beta islet cells. Such a phenomenon might relate particularly to the onset of paracrine influences that promote progression of beta cell death in genetically engineered Kir 6.2 mice.

Pro-apoptosis of beta islet cells appears a propagated effect of combined cytokine action that is specifically dependent on nitric oxide[14]. It appears relevant to consider how modes of suppression of Bcl-2 and of Bax omega are correlated with persistence of action of Bax-x, a proapoptotic regulator. Indeed, in terms of such proapoptotic effects implicating inducing action of nitric oxide, cytokines as a combined action of interleukin 1beta and gamma-interferon might constitute an ongoing positive balance in promoting loss of beta-islet cells in diabetic subjects.

Molecular regulation of Fas expression in beta cells appears to promote a distinctive progression in apoptotic activity in terms particularly of a concomitant action of interleukin 1beta and gamma interferon[15]. It appears significant that dynamics of resolved onset of cell death pathways in beta cells constitute the result of induced expression of Fas on these cells beyond simple considerations of the diabetic state.

Lipotoxicity appears a significant promoting effect in inducing the diabetic state[16]. Nonoxidant action inducing the deposition of surplus long-chain fatty acids appears a promoting factor in further progression of beta-islet cell dysfunction in the diabetic state that develops concurrently with evolving ceramide deposition in non-adipose tissues and in a manner significantly correlated with reduced lipogenesis.

FAILED INSULIN TRANSCRIPTION SECONDARY TO FAILED DYNAMICS OF INSULIN SECRETION

Glucotoxicity induced by hyperglycemic levels appears a fundamentally operative mechanism that combines a failure to maintain sufficient levels of insulin secretion in the face of increased production of proinsulin[17]. In this regard, the evolving dynamics of the

injury to islet beta cells would implicate a direct toxic action that converts impaired insulin secretion to a progressive death process affecting the islet beta cell population. Indeed, one might further regard type 2 diabetes as a progressive impairment of transcription of insulin in the face of increasing peripheral insulin resistance borne out by a progressive failure of maintenance of normal glucose levels in blood

A central concept of initial compensatory but transient increase in insulin secretion might be contrary to a concept of evolving injury to beta cells as induced by glucotoxicity per se.

In realistic terms, it would appear significant that compensatory systems in the genesis of an initial high level of proinsulin production would allow for the establishment of impaired insulin secretion that is in turn conducive to transcription failure of insulin. Proinsulinemia is a protagonist in the genesis of failed insulin transcription and would arise as failed secretory dynamics of insulin release from the islet beta cells.

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