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''Targeting Cellular Hypoxia in βcells and Autophagy in Prevention and Propagation of Type 2 Diabetes-A narrative review''

Kulvinder Kochar Kaur* , **Gautam Nand Allahbadia** , **Mandeep Singh**

Obstt & Gynae, specialist reproductive endocrinology & Infertility specialist, India

***Corresponding Author:** Kulvinder Kochar Kaur, Obstt & Gynae, specialist reproductive endocrinology & Infertility specialist, India

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Abstract

portrays a chronic disease possessing considerable hyperglycemia; dysfunctional insulin liberation by pancreatic βcells is an emblem of such disease. Recent studies have illustrated that hypoxia takes place in the pancreatic βcells of patients having T2D with hypoxia as a result leading to abnormalities of insulin liberation in addition to elimination of βcell mass via mechanistic modes inclusive of activation of hypoxia inducible factor alpha(HIF 1-α), induction of transcriptional suppressors along with activation of 5' AMP-activated protein kinase(AMPK) . Earlier we had reviewed on the aetiopathogenesis of Type 2 diabetes mellitus(T2D) along with role of gutmicrobiota(GM),diabesity,oral health AGEs stimulated & ERand Inflammatory Stress- modulated control of the GLUT4 expression (SLC2A4) promoted genes,;details of epigenetics, mitochondrial melatonergic pathwaysand different methods of use of various plant products ,role of extracellular vesicles ,iron&mineral metabolism and umpteen other articles Here our concentration is on insight into βcell hypoxia that might result in dysfunctional insulin liberation in T2DM .An understanding of βcell hypoxia might aid in generation of innovative strategies for the treatment of T2DM . Further with emerging evidence of how autophagy might be implicated in propagation of Type 2 Diabetes,thereby targeting both hypoxia and autophagy might bethe mechanistic modes of how separate plant products are contributing in T2D avoidance as well as propagation.Here we have attempted to give insight regarding how βcells hypoxia aids in generation of βcells impairment in T2D. Achieving greater insight of βcell hypoxia might aid in generating innovative approaches for T2D treatment.

Key words: Type 2 Diabetes(T2D); hypoxia; hypoxia inducible factor alpha(HIF 1-α); pancreatic βcells; transcriptional suppressors

Introduction:

Diabetes mellitus(DM) represents a chronic disorder associated with considerable hyperglycemia and portrays one of the commonest etiological factor of mortality along with morbidity globally .It has been determined that 529 million people have been living with DM worldover of which Type2 Diabetes mellitus(T2DM) was implicated in 96% of full patients, in addition to proportion of the patients with DM have been estimated to escalate greater than double of 1.3 billion individuals globally by year 2050[1]. Etiological factors

responsible for T2DM are complicated crosstalking amongst numerous genetic as well as environmental factors. The genetic makeup results in insulin resistance (IR) along with pancreatic ßcells, whereas escalated weight along with sedentary life aggravates such metabolic abnormalities[2]. Dysfunctional insulin liberation in addition to IR specialized properties of T2DM[2]. In case of IR pancreatic ßcells escalate insulin liberation regarding sustenance of normal glucose tolerance; nevertheless, once ßcells lose their capability of escalating insulin liberation the plasma quantities of glucose get escalated. Continued exposure to hyperglycemia possess inimical sequelae over ßcell numbers along with working;a postulate referred to as gluotoxicity which results in the generation as well as propagation of T2DM[3,4]. Hyperglycemia has a negative impacts via plethora of mechanistic modes toxic actions inclusive of Oxidative stress(OS) along with endoplasmic reticulum (ER) stress in addition to inflammation[5]. Nevertheless, recent studies have pointed that hyperglycemia further stimulates hypoxia in ßcells[6,7]. Hypoxia in turn aids in ßcell impairment through various mechanistic modes inclusive of hypoxia inducible factor alpha(HIF 1-α) [8]. Earlier we had reviewed on the aetiopathogenesis of Type 2 diabetes mellitus(T2D) along with role of gutmicrobiota(GM),diabesity,oral health AGEs Stimulated & ERand Inflammatory Stress- Modulated Control of the GLUT4 expression (SLC2A4 promotedgenes,;details of epigenetics, mitochondrial melatonergic pathwaysand different methods of use of various plant products ,role of ecv,iron&mineral metabolismand umpteen other articles [9-25].Here our concentration is on insight into ßcell hypoxia that might result in dysfunctional insulin liberation in T2DM .Aninsight of ßcell hypoxia might aid in generation of innovative strategies for the treatment of T2DM .

Methods

Thus a narrative review was carried out using the pubmed, Web of Science , Medline, Embase, Cochrane reviews, and Google Scholar, Search engine with the MeSH Terms; Type 2 diabetes mellitus(T2D); Hypoxia; the mitochondrial melatonergic pathways; oxidative phosphorylation (OXPHOS); adenosine triphosphate(ATP); insulin exocytosis; hyperglycemia; Pancreatic ßcells; prolyl hydroxylase domain(PHD) proteins ; HIFs from 1995 till date in 2024.

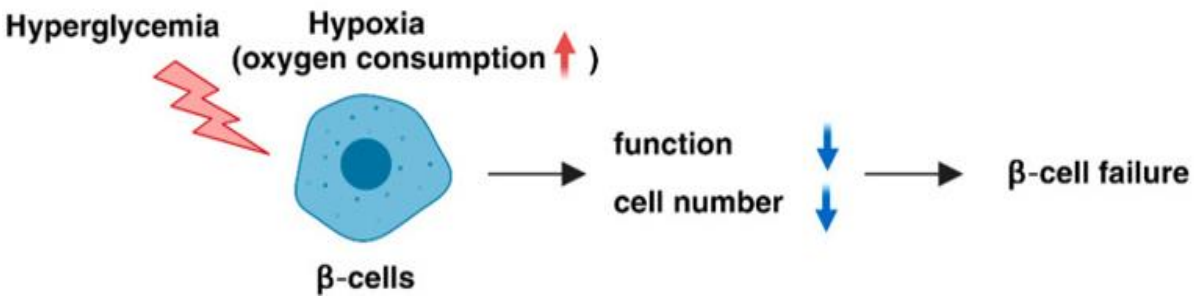
Results

We found a total of 250 articles ,out of which we selected 68 articles for this review.No meta-analysis was done.

2. Stimulation of Hypoxia in pancreatic ßcells by hyperglycemia

In case of normoxic IR pancreatic ßcells, glucose gets metabolized into pyruvate through glycolysis in addition to its further oxidation takes place for generation of adenosine triphosphate(ATP) through oxidative phosphorylation (OXPHOS).An escalation of ATP results in the closing of ATP sensitive potassium (KATP) channels In pancreatic ßcells resulting in membrane depolarization, Calcium(Ca2+) influx as well as insulin vesicle exocytosis[26]. Cellular oxygen quantities are controlled by the harmony amongst supply along with requirement of oxygen in addition to once hypoxia takes place oxygen utilization is greater than its supply . Acknowledged the considerable requirement of mitochondrial OXPHOS at the time of insulin liberation, ßcells utilize considerable oxygen quantities . Actually it has been revealed by the group of Yamagata et al.[[6,7,27], along with others that pancreatic islets of Langerhans as well as ßcells lines become hypoxic [6,7], with ease under escalated glucose situation [6,7,27]. Such studies have further illustrated that islets in animal models of T2DM are hypoxic[28]. Thereby inadequate oxygen supply might further be implicated in ßcells hypoxia in vivo.

The oxygen tension in maximum mammalian cells is varying amongst the values of 20-65 mmHg(parallel to 3-9%O2) [29], as well as the average tissue oxygen tension at the surface of the normal mouse islets varying amongst the values of44.7-45.7mmHg (parallel to 6.3-6.4%O2) [30]. Hypoxic reactions have been illustrated to take place in culture situations in vitro [31]. Continuous exposure of MIN6 ßcells to 5%O2 tension result in cellular hypoxia with dysfunctional insulin liberation along with hampers ßcells growth ; 3%O2 tension resulted in apoptosis with ease in addition to diminished ßcells numbers as well as working [32,33]. Thereby hypoxic stress represents the mechanistic mode behind ßcells failure in case of T2DM[32,34]., [32reviewed in ref 35].(Figure1)

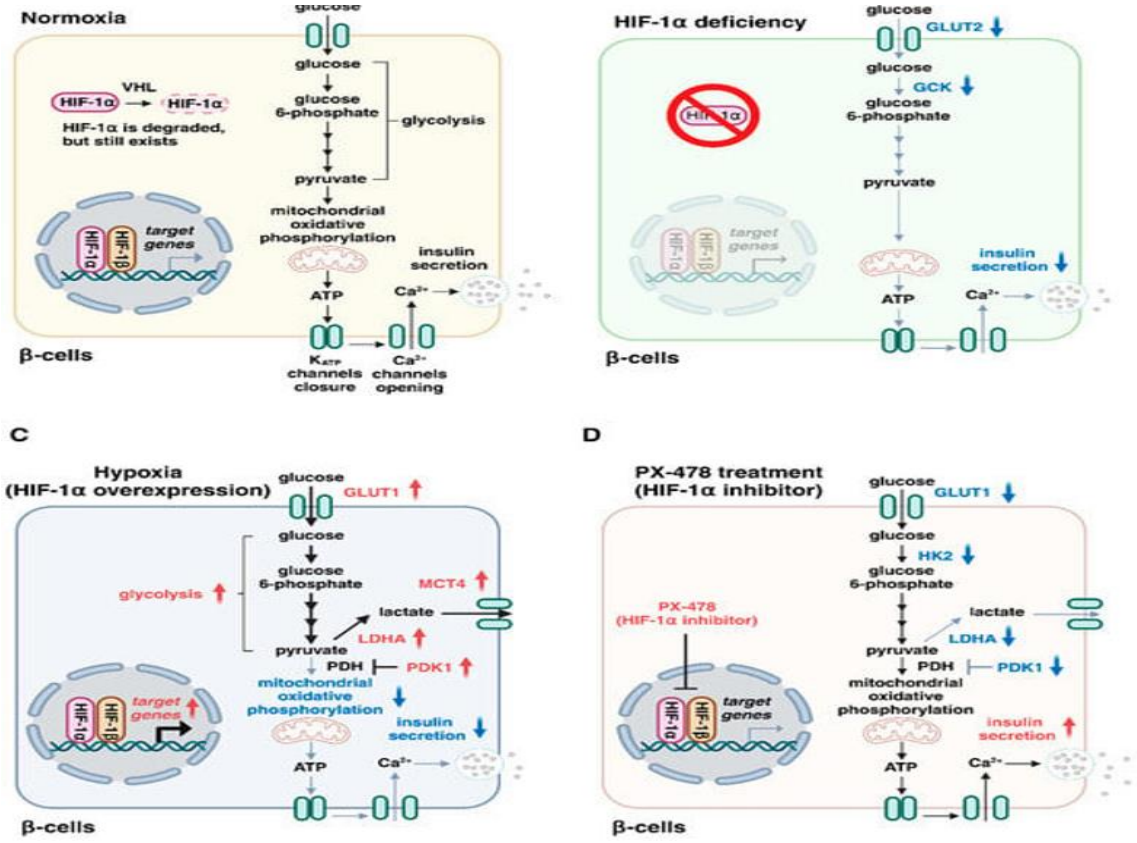


Courtesy ref no-35-Role of hypoxic stress in pancreatic β-cells. Hyperglycemia induces hypoxia in β-cells, mostly due to the high levels of oxygen consumption required for insulin secretion. Hypoxia, in turn, exerts deleterious effects on β-cell function and number, leading to progressive β-cell failure in type 2 diabetes.

3. Part of HIFs in Pancreatic ßcells

The sustenance of oxygen homeostasis is significant in reference to ATP generation in addition to energy accessiblity in cells .Thereby all mammals possess the capacity of sensing, reacting to as well as rectifyingy hypoxia .HIFs portray crucial members of the basic-loop-helix PerArntSim transcription factor family along with are comprised of oxygen sensitive HIF 1-α subunit in addition to a HIF 1ß/ aryl hydrocarbon receptor nuclear translocator (ARNT) subunit which gets constitutively expressed [31,36,].Three kinds of HIFs are existent (HIF 1-α, HIF 2-α, in addition to HIF 3-α); nevertheless, maximum of the transcriptional reactions are apparently secondary to HIF 1-α, along with HIF 2-α[37].At the time of normoxic situations, HIF 1-α undergoes hydroxylation at the 2proline residues amongst the oxygen based breakdown domain by the prolyl hydroxylase domain(PHD) proteins in the existence of oxygen,2 oxoglutarate as well as iron . Hydroxylated, HIF 1-α subunits get poly ubiquitinated by the vonHippel-Lindau protein in addition to are targeted for proteasomal breakdown. Hydroxylation by the PHD proteins gets avoided along with following breakdown in case of hypoxic situations . In view of this stabilized HIF 1-α undergoes dimerization with HIF 1ß along with activation of a substantially greater quantities of target genes inclusive of those implicated in glycolysis ,erythropoiesis , in addition to angiogenesis by binding to the hypoxia response element in their promoter areas.

Three kinds of PHD proteins(PHD1, PHD2 in addition to PHD 3)get expressed in ßcells[38], as well as HIF 1-α gets brokendown pacily in case of normal oxygen situations .Nevertheless, HIF 1-α is existent in normoxic ßcells[39]. Glucose transporter 2 (GLUT2) portrays a lesser affinity glucose transporter whose requirement is for sustenance of normal glucose stimulated insulin liberation in ßcells[40]. Glucokinase,that is a rate restricting glycolytic enzyme, works in the form of a sensor for the physiological insulin liberation in ßcells[41]. Intriguingly elimination of Hif-α gene in ßcells results in dysfunctional insulin liberation in addition to glucose intolerance in mice having a diminished expression of soluble carrier family 2 member 2 (Slc2a2)gene that encodes GLUT2 along with Gck gene(that encoded glucokinase) [39]. Frequently HIF 1-α knockout (KO) diminished expression quantities of Slc2a2 in addition to Gck are considerably repressedin case of insulin liberation in MIN6 ßcells at the time of normoxic situations [39]. Thereby HIF 1 expression at basal quantities for insulin liberation is necessary, despite mechanistic modes behind this diminished expression quantities of Slc2a2 in addition to GckbyHIF1-αinsufficiencyareuncharted(Figure2A,B).



Legend for Figure 2.

Courtesy ref no-35-Roles of hypoxia-inducible factor (HIF)-1 in insulin secretion by ß-cells. (A) Glucose is metabolized via the glycolytic pathway and mitochondrial oxidative phosphorylation, resulting in the generation of adenosine triphosphate (ATP), KATP channel closure, Ca2+ entry, and insulin exocytosis. Under normoxic conditions, HIF-1α is degraded by von Hippel–Lindau (VHL) proteins. (B) HIF-1α is degraded under normal oxygen conditions, but remains present in normoxic ß-cells. HIF-1α deficiency causes impaired insulin secretion with a decreased expression of glucose transporter type 2 (GLUT2) and glucokinase (GCK). (C) HIF-1α overexpression switches glucose metabolism from mitochondrial oxidation to glycolysis, thereby leading to the attenuation of mitochondrial activity and impaired insulin secretion. (D) Treatment with the HIF-1α inhibitor PX-478 prevents the upregulation of HIF-1α targets (GLUT1, HK2, LDHA, and PDK1) and restores insulin secretion in metabolic workload. HK2, hexokinase 2; LDHA, lactate dehydrogenase A; MCT4, monocarboxylate transporter 4; PDH, pyruvate dehydrogenase; PDK1, pyruvate dehydrogenase kinase 1.

Additionally, HIF 1-α confers protection against ßcells damage in type 1 diabetes mellitus(the autoimmune kinds of diabetes) [42]. Furthermore HIF 1-α/ ARNT insufficiency further repressed insulin liberation in ßcells[43]. Interestingly, declined HIF 1-α in addition to ARNT /HIF1ß have been found in T2DM patients [39,43]. Moreover HIF 1-α signaling gets repressed in a complicated manner by hyperglycemia via PHD) proteins based mechanistic modes[8,44]. Such findings robustly portray that HIF 1-α proteins possess a significant part in sustenance of ßcells working as well as the manner dysfunctional HIF 1 signaling is responsible for ßcells impairment in type2 diabetics .

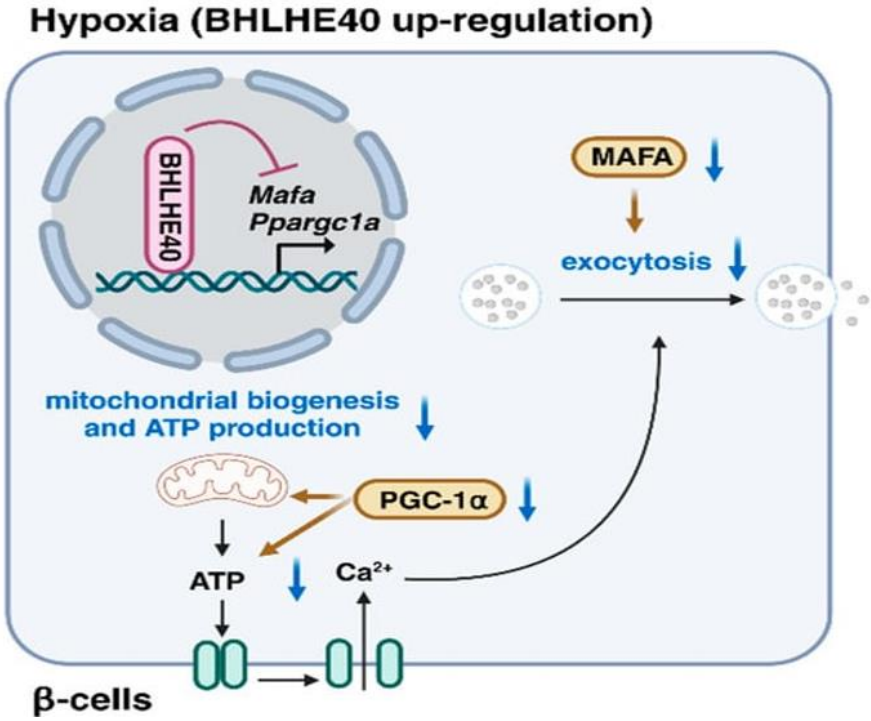
Compared to that it have further been illustrated that HIF 1-α expression is escalated in the ßcells of various diabetic animals, inclusive of ob/ob mice, mice which received high fat diet(HFD), in addition to db/db mice [7,45]. Maintainance of HIF 1-α overexpression by the elimination of Vhl gene(implicated in encoding vonHippel-Lindau protein) results in dysfunctional insulin liberation along with glucose intolerance in mice[46], pointing that the upregulation of HIF 1-α is inimical for the working of ßcells as well as aids in T2DM generation. HIF 1-α results in the activation of the transcription of the genes encoding GLUT 1, glycolytic enzymes(glucose-6- phosphatase isomerase, and phosphoglycerate mutase)ii) pyruvate dehydrogenase kinase (PDK) iii) lactate dehydrogenase A(LDHA) in addition to iv) monocarboxylase transporter 1(MCT4) [47], PDK 1 is involved in the inactivation of the enzyme pyruvate dehydrogenase which is responsible for the transformation of pyruvate to acetylCoA for the mitochondrial tricarboxylic acid(TCA)/Krebs Cycle. LDHA prevents pyruvate from gaining entry in to TCA by transforming pyruvate to lactate in addition to MCT4 facilitates extrusion of lactate from cells.

Sequentially, the major influence of HIF 1-α on glucose metabolism is switching energy metabolism from mitochondrial respiration to glycolysis. Nevertheless, mitochondrial oxidative metabolism possesses key part in the regulation of insulin liberation[48]. the main exposition for the inimical actions in reference to HIF 1-α on insulin liberation is amelioration of mitochondrial actions(Figure2C). Interestingly, therapy of diabetic mice by utility of HIF 1 hampering agent PX-478 results in improvement of insulin liberation along with glucose intolerance[45], indicating that hampering HIF 1-α might be a plausible treatment for type2 diabetics(Figure2D). Overall such outcomes point that a harmonious in addition to sufficient quantities of HIF 1-α actions is imperative for the normal insulin liberation by pancreatic ßcells.

Compared to that HIF 2-α a paralog(created by gene duplication) of HIF 1-α further undergoes dimerization with HIF 1ß for the activation of target genes in reaction to hypoxia. Nevertheless, HIF 1-α as well as HIF 2-α possess unique Part in ßcells .The manner described earlier, ßcells particular Hif 1-α KO mice illustrate dysfunctional insulin liberation along with glucose intolerance[39] Compared to that HIF 2-α insufficiency in ßcells does not lead to dysfunctional insulin liberation along with glucose intolerance in mice getting normal chow diet[48]. A chronic escalation in mitochondrial metabolism escalates electron flux in the electron transport chain(ETC) leading to escalated generation of reactive oxygen species(ROS) [49]. HIF 2-α possesses significant part in the controlling of the cellular redox status by activation of the antioxidant gene expression Sod2 (encoding superoxide dismutase), as well as Cat(encoding catalase) in addition to confers protection against mitochondrial injury by ROS[50]. Frequently there is reduced expression of the antioxidant genes in the islets of ßcells particular Hif 1-α KO mice along with such mice form dysfunctional insulin liberation along with glucose intolerance on getting HFD[49]. Such outcomes point that HIF 2-α is involved in preservation of ßcells working in situations of metabolic excess by stimulating generation of antioxidant genes expression.

4. Part of Transcriptional Suppressors in Hypoxic ßcells

Working of the HIFs is basically in the form of activators of transcription ; nevertheless, suppression of transcription further takes place for hampering events which possess considerable energy requirement in case of hypoxic situations[51]. Actually, 5% of genes inclusive of certain genes implicated in insulin liberation caused downregulation in hypoxic islets along with MIN6 ßcells [32,33,52], pointing that genes suppression portrays one more adaptive reaction to hypoxia in ßcells. Global gene expression evaluation displayed that basic- helix -loop-helix family member E40 (BHLHE40) in addition to activating transcription factor 3(ATF3) represent hypoxia stimulated transcriptional suppressors in Hypoxic ßcells (Figure3) [33].



Legend for Figure 3.
Courtesy ref no-35-The transcriptional repressor basic helix-loop-helix family member E40 (BHLHE40) is highly induced in hypoxic ß-cells. BHLHE40 inhibits insulin secretion by suppressing the expression of musculoaponeurotic fibrosarcoma oncogene family A (MAFA), a transcription factor that regulates insulin exocytosis, and peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α), which plays important roles in mitochondrial biogenesis and adenosine triphosphate (ATP) production.

BHLHE40(alias DEC1/SHARP2/STRA13) portrays a member of basic- helix -loop-helix family in addition to works by binding to DNA at the Class EB motifs[53]. The transcription factor musculoaponeurotic fibrosarcoma oncogene(MAFA) which possesses a key part in glucose stimulated insulin liberation,by controlling gene implicated in insulin exocytosis inclusive of Stxbp1(encoding MUNC 18-1) as well as Stx1a (encoding syntaxin A) [55]. Peroxisome Proliferator Activated Receptor γ Coactivator -1α(PGC-1α) whose encoding gets done by Ppargc1α controls mitochondrial biogeneration as well as ATP generation[55]. Remarkable induction of the transcriptional suppressor BHLHE40 expression in ßcells by hypoxia along with suppresses insulin liberation by suppressing expression of Mafa in addition to Ppargc1α.. Persistently ßcells particular Bhlhe40 insufficiency results in improvement of insulin liberation along with glucose intolerance in ob/ob mice.

ATF3 further represses the expression of genes implicated in glucose metabolism inclusive of Ins1(encoding insulin1) Ins2(encoding insulin2) in addition to Irs2(encoding insulin Receptor substrate-1(IRS-2)] [33,56]. Additionally, the hypoxia stimulated upregulation of the proinflammatory Il1b as well as proapoptotic Noxa genes along with activation of caspase-3 get suppressed by Atf3 insufficiency in MIN6 ßcells [33,56,57].Such observations further point that the transcriptional suppressor ATF3 is implicated in hypoxia stimulated ßcells impairment in addition to elimination.

5. Controlling of Various Stress Pathways in ßcells by Hypoxia

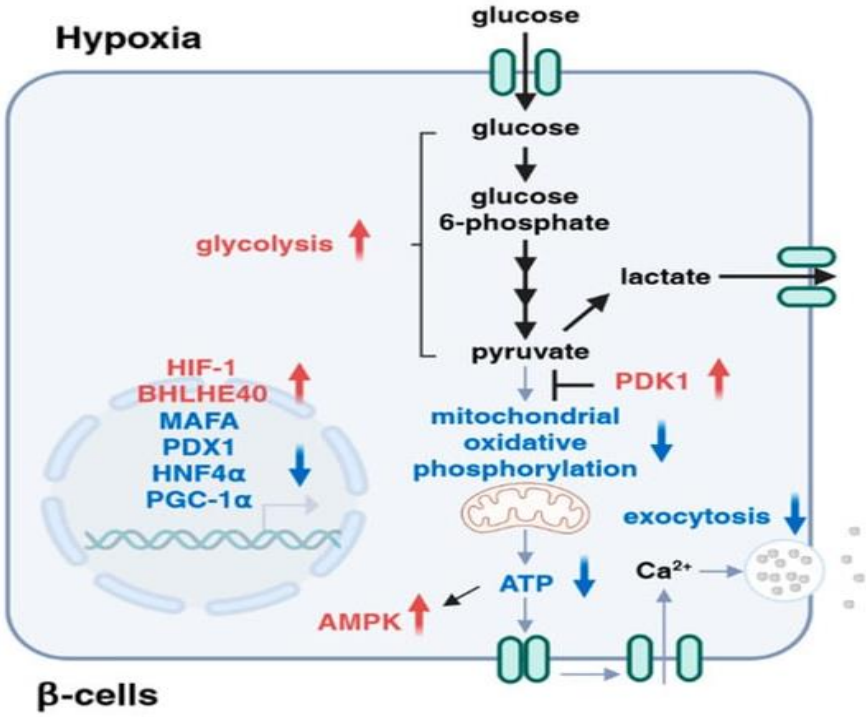
5’ adenosine mono phosphate (AMP)-activated protein kinase(AMPK) portrays an evolutionary preserved serine /threonine kinase. Activation of AMPK takes place in reaction to energy stresses for instance hypoxia by sensing escalated quantities of AMP as well as/or adenosine di phosphate: ATP ratio by hampering anabolic events which generate ATP[58]. Hepatocyte nuclear factor 4 alpha (HNF-4α) represents a transcription factor from the nuclear receptor super family which possesses significant key part in insulin liberation[59]. It was observed by the group of Yamagataet al.[60], that hypoxia stimulated AMPK activation diminished insulin liberation by diminishing the stability of HNF-4α [60]. Thereby downregulation of HNF-4α by activation of AMPK might be responsible for the dysfunctional insulin liberation in case of hypoxic situations.

Dysfunctional protein homeostasis(alias proteostasis) in the ER results in accrual of unfolded along with aberrantly folded protein alias ER stress, resulting in activation of the ER unfolded protein responses(UPRER) for the the amelioration of proteostasic stress[61]. Hypoxia escalates ßcells demise by hampering the expression of adaptive UPRER

genes inclusive of Hspa5(encoding heat shock protein family A member 5) Hsp90b1 (encoding heat shock protein90 beta family member1)Fkbp11 (encoding FKBP prolyl isomerase 11) in addition to spliced Xbp1(encoding X-box binding protein 1). Such hampering actions of hypoxia modulated by the activation of c-Jun-N-terminal kinase (JNK) as well as DNA damage inducible transcripts3 however are autonomous of HIF 1-α[62]. UPRER getting inactivated might be the cellular mechanistic mode behind escalated cell demise by hypoxic stress .

OS gets stimulated in tissue in case of escalated glucose situations. Noticeably, βcells possess considerable susceptibility specifically to ROS in view of their expression of minimal quantities of antioxidant enzymes inclusive of glutathione peroxidase(GPx), catalase(CAT) , as well as mitochondrial manganese SOD along with ROS formed in βcells decline insulin genes expression reducing the expression in addition to /or DNA binding actions of pancreatic as well as duodenal homeobox 1 (PDX1) transcription facto[63]. Interestingly, hypoxia further escalates ROS generation at the mitochondrial ETC[64]. Such outcomes robustly point that hypoxia stimulated ROS generation further is implicated in βcell impairment .

From these findings documented above it is clear that hypoxia impacts a plethora of events cascade of at the time of glucose stimulated insulin liberation . Particularly hypoxia ameliorated insulin liberation by switching glucose metabolism from mitochondrial respiration to glycolysis via the activation of HIF 1. Hypoxia further hampered insulin liberation by repressing the expression of MAFA(exocytosis) as well as Peroxisome Proliferator Activated Receptor γCoactivator -1α(PGC-1α)via the activation of transcriptional suppressor BHLHE40 . Additionally, the hypoxia stimulated activation of AMPK resulted in downregulation of the expression of HNF-4α resulting in aberrant insulin liberation. Moreover, hypoxia stimulated ROS generation hamper insulin gene expression via the decontrolling of PDX1(seeFigure4) .

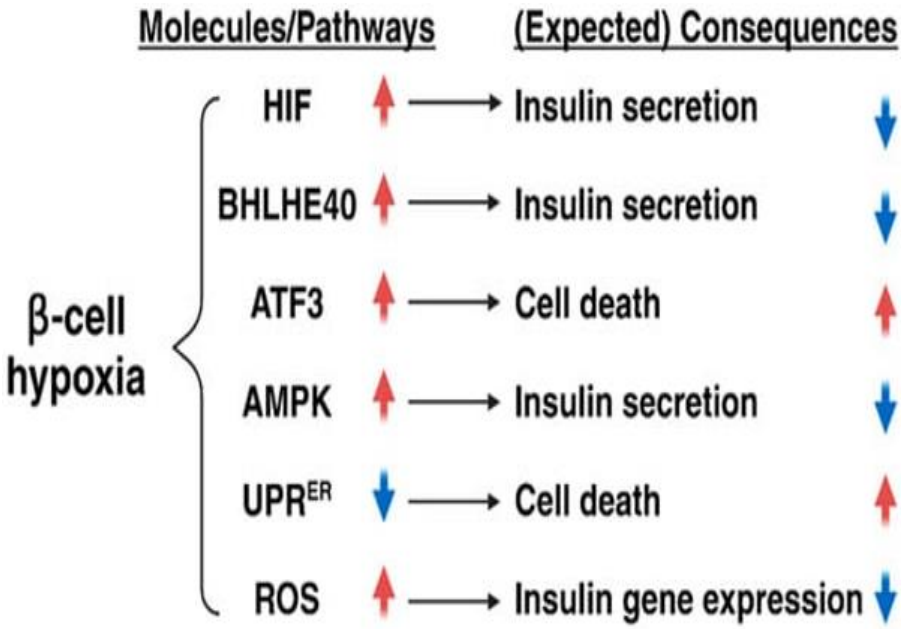


Legend for Figure 4

Courtesy ref no-35-Roles of hypoxia in insulin secretion. Hypoxia affects multiple steps during the processes of glucose-stimulated insulin secretion, including dysregulation of transcription factors (e.g., MAFA, PDX1, and HNF4α), attenuation of mitochondrial activities, activation of AMPK, and inhibition of exocytosis

6.Conclusions

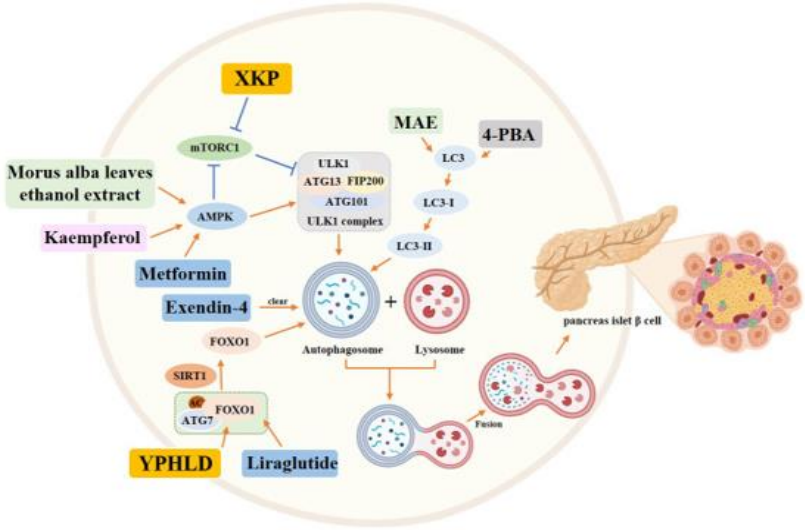
Diabetes implicates a clinical scenario where pancreatic βcells are engulfed in a vicious cycle which leads to a dysfunctional insulin reaction to glucose generated hyperglycemia that sees to it that βcells lose their efficacy in reference to insulin liberation that leads to a improvement of hyperglycemia that causes a minimum of part restoration of βcell working [3]. Hypoxia guarantees proneness of βcells to impairment along with failure in addition to hampering of HIF 1-α actions as well as repression of BHLHE40 leads to improvement of insulin liberation along with hyperglycemia in case of animal models of diabetes, pointing that hypoxia might work in the form of an innovative therapeutic target for type2diabetes in addition to improvement of hypoxia might work as advantageous for the propagation of βcells impairment in T2D. Nevertheless, hypoxia further stimulates ATF3 expression, activation of AMPK inactivation of UPRER along with ROS generation (seeFigure5) .



Legend for Figure 5.
Courtesy ref no-35-Roles of hypoxia in ß-cell function and number. Hypoxia causes impaired insulin secretion through the induction of hypoxia-inducible factor 1 (HIF-1) and basic helix-loop-helix family member E40 (BHLHE40). Hypoxia also suppresses insulin secretion through the activation of adenosine monophosphate-activated protein kinase (AMPK) and the induction of reactive oxygen species (ROS), whereas, it promotes ß-cell death via the induction of activating transcription factor 3 (ATF3) and the inhibition of the endoplasmic reticulum unfolded protein response (UPRER).

Moreover, HIF 1-α basically guides the reaction to acute hypoxia as well as its expression gets diminished at the time of continuous hypoxia[65]. Thereby the robustness along with time period of hypoxia may result in activation of adaptive reaction in ßcells in a differential manner. Further work would yield greater insight in the germane aiding of influence of every adaptive pathway in the event of manner ßcell hypoxia would be essential for buttressing our understanding regarding pathophysiological mechanistic modes of T2 diabetes mellitus . Greater work would aid in provision of influence regarding innovative information in reference to influence of hypoxic stress over ßcells impairment in addition to the efficacy of ßcells hypoxia in the form of antidiabetic therapeutic target.

Moreover the impairment of ß cells possess the capacity of generating via different mechanistic modes, inclusive of OS/ER or hypoxic stress, in addition to through inducing cytokines; such events result in apoptosis, unregulated autophagy as well as and do not proliferate. Transdifferentiation amongst ß cells along with α cells takes place in some pathological situations, in addition to and upcoming corroboration pointing that the ß-cell dedifferentiation or transdifferentiation might be responsible for the diminished ß-cell mass found in patients with robust T2DM. FOXO1,portrays a crucial transcription factor in insulin signalling(rev in detail by us in ref 20and23,63],. Liang et el. [66],further documented HIF 1-α/ FOXO1axis regulated autophagy conferred protection for ßcell survival in case of hypoxia in human islet by utility of CoCl2 escalating ß-cell apoptosis as well as choloroquine aggravated autophagy hampering in case of FOXO1KO accelerated apoptosis with immunofluorescent staining reported that significant reduction in LC3 in addition to p62/SQSTMW expression quantities which were negatively associated with glycated haemoglobin A1c (HbA1c) inpatients with robust T2DM. Thereby HIF 1-α/ FOXO1 axis controlled autophagy which is of advantage for ßcells survival under hypoxia in human islets. Furthermore,emerging reports have displayed advantage of restoration of autophagy in pancreatic ßcells as a therapeutic target for type2Diabetes as displayed by Zhao etal. [67], as well as we had detailed autophagy comprehensively previously [68]. Thereby targeting hypoxia as well as autophagy might be the next line of treatment for preventing robust T2DM the way illustrated in figure 6 by different plant extracts and tradional Chinese medicines[rev in det inref no67] .



Legend for Figure 6

Courtesy ref no-67-Role of autophagy in pancreatic islet ß cells in the diabetic state. Yellow rectangle: Traditional Chinese compounds; Blue rectangle: Chemical drugs; Pink rectangle: Monomers from Chinese Herbal; Gray rectangle: Experimental Chemicals. →: activate: ⊣: inhibit.

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