Medical Hypotheses 73 (2009) 363–369

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Pulsatile intravenous insulin therapy: The best practice to reverse diabetes complications?

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articleinfo

Article history:
Received 14 February 2009
Accepted 17 February 2009

summary

In the basal state and after oral ingestion of carbohydrate, the normal pancreas secretes insulin into the portal vein in a pulsatile manner. The end organ of the portal vein is the liver, where ~80% of pancreatic insulin is extracted during first pass. In Type 1 diabetes, pancreatic insulin secretion is nearly or completely absent whilst in Type 2 diabetes the normal pattern is absent, abnormal, or blunted. Exogenous subcutaneous insulin treatment results in plasma insulin concentrations that are not pulsatile and a fraction of normal portal vein levels. Oral hypoglycemic agents also do not result in normal pulsatile response to a glucose load. Due to hypoglycemia risk, intensive treatment is not recommended after serious complications develop. Consequently, no conventional therapy has proved effective in treating advanced diabetes complications. Beta-cell replacement using whole pancreas or islet transplantation has been utilized to treat certain problems in Type 1 diabetic patients, but still unavailable for all diabetics. Pulsatile intravenous insulin therapy (PIVIT) is an insulin therapy, which mimics the periodicity and amplitude of normal pancreatic function. Numerous studies show PIVIT effective in preventing, reversing, and reducing the severity and progression of diabetes complications, however, the mechanisms involved with the improvement are not clearly understood. Here, we review the cellular basis of normal and abnormal insulin secretion, current treatments available to treat diabetes, the physiologic basis of PIVIT and possible mechanisms of action.

Background

Diabetes mellitus is a global problem with devastating human, social and economic impact and with a growing prevalence. It is currently estimated that 250 million people around the world suffer from diabetes mellitus, with over 380 million predicted to have the condition by the year 2025 [1]. It affects nearly 21 million people in the United States [2]. Type 1 diabetes (T1DM) juvenile or insulin-dependent diabetes is due primarily to insulin deficiency caused by autoimmune destruction of the pancreatic beta cells; the major pathogenic factor in Type 2 diabetes or adult-onset or non-insulin-dependent diabetes (T2DM) is insulin resistance, resulting in a functional or relative insulin deficiency [3]. Maintaining acceptable glycemic control in T2DM may require exogenous insulin administration if resistance results in insufficient effect from endogenous pancreatic secretion, or subsequent beta cell exhaustion develops. During the nearly 80 years since its discovery, insulin therapy in the treatment of diabetes has led to only partial success in the treatment of hyperglycemia and even less in preventing the chronic complications that often decrease life expectancy and adversely affect quality of life [4,5]. Disappointing insulin efficacy in the treatment of long standing diabetes may be less due to the quality of exogenous insulin than to the possibility of physiologic ''inadequacy'' or ''inappropriateness'' of its method of administration [6].

Although pulsatile insulin secretion has been reported in normal subjects [7], the current commonly used methods of therapeutic insulin administration are not pulsatile. A lesser known treatment, pulsatile intravenous insulin therapy (PIVIT), also referred to as chronic intermittent intravenous insulin infusion therapy (CIIIT) or hepatic activation (HAT), involves once-a-week sessions during which pulsatile intravenous insulin and concurrent oral glucose or quantified amounts of carbohydrate are administered according to a standard protocol and under medical supervision, typically on an outpatient basis [8]. Although PIVIT has shown advantages for patients with both T1DM and T2DM, the mechanisms involved with the improvement are not clearly understood.

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doi:10.1016/j.mehy.2009.02.042

This review highlights the pathophysiology of insulin secretion, discusses current therapies for managing diabetes and proposes possible mechanisms that may explain the observed prevention or amelioration of diabetes complications by pulsatile intravenous insulin therapy.

Hypothesis

We hypothesize that diabetes complications might be attenuated or improved by PIVIT, through enhanced expression of insulin receptors and consequently, improved hepatic metabolism and amelioration of insulin resistance in individuals with diabetes.

Evaluation and discussion of the hypothesis

Physiology of insulin secretion

In normal subjects, insulin in the basal state and after stimulation is secreted in a pulsatile manner [7]. Pulsatile release of insulin leads to oscillations of insulin concentrations, especially in the portal vein [9], that are much smaller but detectable in the systemic circulation. In the fasting state, these insulin secretory pulses occur at intervals of 5–15 min [10]. The discovery of plasma insulin oscillations dates back to 1977 from studies in the fasting monkey [11]. Two years later, the insulin pulses were also demonstrated in humans [7]. The appearance of regular plasma insulin oscillations in the portal vein requires not only coordination of the beta cells in the islet but also coordination between the islets of the pancreas. When the endogenous insulin production is suppressed by somatostatin, pulsatile delivery of insulin has a greater hypoglycemic effect than continuous delivery [12], although it does not happen always [13]. An important step towards resolving the nature of the oscillations was taken when it was shown that the isolated perfused pancreas produced pulsatile release of insulin [14]. The pulses were amplitude-regulated and had a periodicity of 6 min. Similar oscillations were also observed in blood from persons with a transplanted pancreas [15]. The pulsatile pattern was further traced to the individual isolated islet, which also showed amplitude-regulated oscillations of insulin release with similar periods as previously described in the perfused pancreas and in vivo [16].

In a pancreatic beta cell, glucose is phosphorylated to glucose-6-phosphate by glucokinase. After conversion of glucose-6-phosphate to fructose-6-phosphate there is further phosphorylation to fructose-1,6-bisphosphate by phosphofructokinase. The oscillatory behavior of phosphofructokinase induces corresponding variations in the glycolytic and mitochondrial ATP production, which in turn make the ratio of the cytoplasmic concentrations of ATP and ADP (ATP/ADP) vary rhythmically. Oscillations in the ATP/ADP ratio induce corresponding rhythmic changes in the permeability of the ATP-sensitive K^+-channels. The regular depolarization causes openings of the voltage-dependent calcium channels. The periodic influx of Ca^{2+} ions produces the oscillations in the cytoplasmic Ca^{2+} concentration [17]. Periodic and co-ordinated increases in the ATP/ADP ratio and cytoplasmic Ca^{2+} concentration produce episodic exocytosis of insulin granules [18] (Fig. 1). The intermittent high cytoplasmic Ca^{2+} concentrations are adequate for triggering exocytosis but decrease the risks for an intracellular overload of Ca^{2+} in the beta cell and inhibit the initiation of apoptotic signals in the cell [19].

Insulin secretion in diabetes

The potential clinical importance of pulsatile insulin release was understood when it was found that persons with Type 2 diabetes demonstrated an altered plasma insulin pattern. It may be a contributing factor to the development of insulin resistance and glucose intolerance. Furthermore, in persons with diabetes, pulsatile delivery of insulin was superior to continuous delivery [20]. Indeed, in one study, 40% less insulin was required when insulin was infused in a pulsatile manner [21]. Supporting such a view, the regularity of plasma insulin pulses from the perfused pancreas was decreased when the neurotoxin tetrodotoxin was included in the perfusate [22]. The poor secretory response of the islets and the gradual reduction of the amplitude of the insulin pulses observed in the Type 2 diabetic islet responding to the sulfonylurea administration support the idea that Type 2 diabetes is associated with an inadequate supply of energy in the beta cell to maintain secretion. However, in one of the very few studies with islets from glucose-intolerant individuals, glucose-induced oscillations in Ca^{2+} were recorded with similar frequency as in normal individuals [23]. The main finding of the study is that all 20 individual islets isolated from three subjects with Type 2 diabetes released insulin in a pulsatile manner [24]. Also, relatives of persons with T2DM as well as T1DM were found to have derangements in their plasma insulin oscillations [25]. Such findings have raised the idea to use analysis of the kinetics of plasma insulin release as a diagnostic tool since these changes in the rhythmicity of plasma insulin oscillations could be an early marker for the development of diabetes [26]. The frequency, when it can be resolved, of plasma insulin oscillations in persons with diabetes is very similar to that observed in normal persons [27]. However, the ability of entrainment to oscillations in the plasma glucose concentration with different frequencies seems to be lost in persons with diabetes. Recently, insulin oscillatory activity with a period of 10 min was described in persons with Type 2 diabetes [28]. Smaller amplitudes of the insulin pulses in persons with Type 2 diabetes [28] give a smaller signal-to-noise ratio and make it more difficult to discern the pulses. Supporting the significances of reductions in amplitude of insulin pulses in diabetes, as opposed to aberrations in rhythmicity, baboons exposed to streptzotocin demonstrated reduced amplitude of plasma insulin oscillation without affect on frequency [29]. An interpretation of the observations of 'brief irregular oscillations' in plasma insulin from persons with diabetes might be that there is a defective pulse generation in the beta cell. For this reason much attention has been placed on finding the pulse generating mechanism with the intention to restore it in these patients.

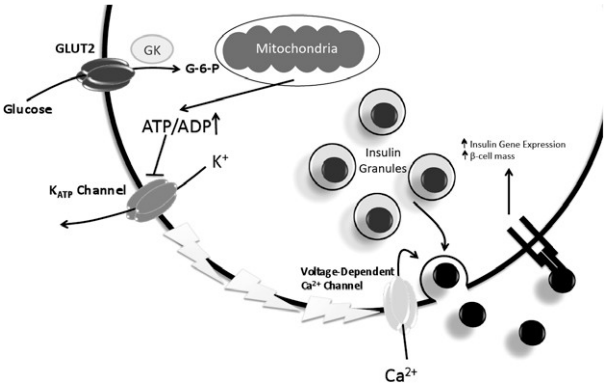

Fig. 1. Glucose sensing, insulin secretion, and insulin feedback in pancreatic b-cells.

Current therapies for diabetes

Current strategies to treat diabetes include reducing insulin resistance using glitazones, supplementing insulin supplies with exogenous insulin, increasing endogenous insulin production with

sulfonylurea's and meglitinides, reducing hepatic glucose production through biguanides, and limiting postprandial glucose absorption with alpha-glucosidase inhibitors. Biological targets are also emerging such as insulin sensitizers including protein tyrosine phosphatase-1B (PTP-1B) and glycogen synthase kinase 3 (GSK3), inhibitors of gluconeogenesis like pyruvate dehydrogenase kinase (PDH) inhibitors, lipolysis inhibitors, fat oxidation including carnitine palmitoyltransferase (CPT) I and II inhibitors, and energy expenditure by means of beta 3-adrenoceptor agonists [30]. Agents that stimulate insulin secretion (glucose [31], sulfonylurea's [32], and incretin hormones [33]) increase burst mass, whereas inhibitory factors (like somatostatin [34]) lead to a decrement.

Repaglinide augments first-phase insulin secretion as well as high-frequency insulin secretory burst mass and amplitude during glucose entrainment in patients with Type 2 diabetes, while regularity of the insulin release process was unaltered [35]. The sulfonylurea agent gliclazide augments insulin secretion by concurrently increasing pulse mass and basal insulin secretion without changing secretory burst frequency or regularity. However, the treatment of individuals with T2DM with sulfonylurea has its obvious limitations in not alleviating the problem with impaired metabolism. The reports suggest a possible relationship between the improvement in short-term glycemic control and the acute improvement of regularity of the in vivo insulin release process [36]. In healthy subjects receiving a continuous glucose infusion, GLP-1 specifically increased the secretory burst mass and amplitude of pulsatile insulin secretion, whereas burst frequency was not affected [34]. Some reports suggest a normalization of the pulsatile pattern of insulin secretion by GLP-1, which supports the future therapeutic use of GLP-1-derived agents [37]. However, inhibition of gastrointestinal motility observed with GLP-1 and its analogs should be considered [38].

Insulin therapy

Banting and Best first used insulin extracted from bovine pancreata to treat a boy with T1DM in Toronto in 1922 [39]. Until the 1990s, the most commonly prescribed insulin's were extracted from bovine or porcine pancreata. There was a concern then that beef or pork insulin would lead to the production of antibodies, increasing insulin resistance. Human insulin (Humulin line) was then manufactured in 1981 using recombinant DNA technology to synthesize the alpha and beta chains of insulin within Escherichia coli. The newest insulin's are insulin analogs [40] or designer insulin's. Most studies comparing human and analog insulin use found that postprandial glucoses were lower and hypoglycemic episodes were lower, particularly overnight, with the newer analogs [41]. Cefalu reported that after a 3-month study in 26 patients with T2DM, there was no significant change in pulmonary function, whereas blood sugar control improved when patient were switched from orals or insulin injections to inhaled insulin use at mealtimes and bedtime [42]. The inhaler delivered consistent doses of insulin, similar to injected insulin in bioavailability and potency. Intrapulmonary insulin delivery has been preferred to intranasal delivery, because the latter would require the use of surfactants to allow insulin to cross the nasal mucosa, and the bioavailability of the dose is low at no more than 10%. Insulin use is associated with weight gain. In the Diabetes Control and Complications Trial (DCCT) trial, the patients on intensive insulin regimens gained 5.1 kg versus those on conventional therapy who gained 2.4 kg [4]. In the UKPDS study, those on insulin or insulin secretagogues gained weight (10.4 kg for insulin users and 3.7 kg for those using sulfonylureas) [5]. Not all studies showed a benefit in lowering the HbA1c with insulin administration and none of them mimics the pulsatile fashion of normal insulin secretion.

Islet transplantation

Conventional subcutaneously administered insulin therapy, whether using intermittent injections or continuous pump delivery accomplishes imperfect glycemic control, has attendant risks of hypoglycemia, does not prevent micro-vascular complications in a significant number of patients, and involves considerable personal inconvenience. Beta-cell replacement is an attractive potential therapy for certain T1DM patients. Whole cadaver pancreas transplantation frequently performed simultaneously during kidney transplantation in patients with diabetic end-stage renal disease, allows longstanding insulin independence in most patients [43]. Whole pancreas transplantation carries significant surgical morbidities and finite mortality risks. Intra-hepatic islet transplantation via the portal vein is a relatively safe procedure. Potential advantages of the intra-hepatic route of islet transplantation include delivery of insulin directly to the liver. In health, insulin is secreted by the pancreas enters the portal venous circulation and immediately transits the liver, where more than 80% is extracted during the first passage. Treatments based upon replication of normal insulin signaling and insulin extraction by the liver require portal delivery of pulsatile insulin [44]. It has been reported that insulin secretion in islet transplant recipients is pulsatile and that glucose-induced insulin secretion is accomplished through amplification of pulse size. Furthermore, it has been also observed via a direct trans-hepatic catheterization approach that hepatic first-pass insulin extraction is similar in patients after intra-portal islet autotransplantation and healthy control subjects, implying that insulin secreted from islet grafts is delivered into hepatic sinusoids rather than into the hepatic central vein [45]. Current clinical islet transplantation can accomplish insulin independence just for 3–5 years [46]. Proposed hypotheses are that the intra-hepatic environment is toxic as a consequence of exposure of islets to high concentrations of immunosuppressive drugs (first pass) and/or relatively low oxygen concentrations [47]. Exposure of the liver sinusoids to high local concentrations of insulin secreted from intra-portal islet grafts may have other metabolic consequences. Hepatic steatosis occurs in a subgroup of patients after successful intra-portal islet transplantation [48]. Graft failure was associated with reversal of this lesion [49]. Such findings could indicate that insulin released by intra-portal islet grafts into the liver sinusoids induces lipid deposition, e.g., via promoting the esterification of free fatty acids within the hepatocytes.

PIVIT

Pulsatile intravenous insulin therapy is one of the treatments for diabetes involving the delivery of insulin intravenously and in a pulsatile fashion. Briefly, a PIVIT session is six hours long and consists of three one-hour treatments, each followed by a ''rest" hour. During a treatment hour a programmable infusion device administers pulses of bolus (formerly ''fast-acting") soluble insulin every six minutes into a hand or forearm vein. During treatment, a metabolic cart is used hourly to monitor the respiratory quotient (RQ), thus confirming improved carbohydrate utilization in real-time. RQ measures the ratio of carbon dioxide production to oxygen consumption in exhaled air and reflects the predominant fuel being metabolized. Metabolism of glucose yields a RQ of 1.0, protein a RQ of 0.8 to 0.9, and lipid a RQ of 0.7. A significant RQ increase during PIVIT indicates transition toward the carbohydrate predominant metabolism of health; diabetic persons typically utilize lipid oxidation as their main source of energy production. Blood glucose determination is performed at least every thirty minutes during treatment and more often if clinically indicated. Both RQ and blood glucose measurements are used to determine appropriate insulin and glucose dose changes during each activation hour of PIVIT.

There is evidence PIVIT treatment exposes hepatic sinusoids to concentrated pulses of insulin that approximate those seen in healthy subjects [8]. During radiologic studies of the liver, using intravenously administered contrast, the recommended time delay between examination of the hepatic artery and portal vein phases is 25–30 s [50]. Intravenous boluses of insulin during PIVIT can be expected to reach the hepatic parenchyma via the hepatic artery and portal vein with similar sequence and timing preserving the pulsatile nature of the intravenously administered PIVIT insulin signal as it reaches the liver. The hepatic artery contribution is via the arterial tree whereas the larger portal vein contribution is from blood that has first perfused the capillary beds of the abdominal organs drained by the portal vein. Sequential sampling from the contra-lateral arm during PIVIT [51] demonstrated insulin pulsations of generally the same magnitude and periodicity as reported by Song et al. from the portal vein of non-diabetics [52]. A reasonable inference is the portal vein delivers PIVIT insulin signals to the hepatic sinusoids of similar magnitude and periodicity as those measured from the contra-lateral arm. Both instances are similar insofar as the portal venous blood that carries the PIVIT insulin pulse to the liver and the blood sampled from the contra-lateral arm during PIVIT have each perfused a capillary bed.

Peripheral venous administration of PIVIT ultimately reaches the liver via both the systemic and portal circulations. Concentrated insulin pulses in the systemic circulation also perfuse other major vessel rich organs including the kidneys, central nervous system, lungs, and heart. In health, organs other than the liver are not exposed to insulin in this fashion due to hepatic transit and first pass extraction of pancreatic secreted pulsatile insulin. The ''supra-normal" insulin signals provided by PIVIT to organs other than the liver (eyes, brain, nerves, kidneys, cardiovascular system) may have beneficial effect through each organ's insulin receptors, possibly contributing to the clinical improvements observed in patients.

Brittle diabetes and hypoglycemic unawareness

Type 1 DM is an intrinsically unstable condition. However, the term ''brittle diabetes" is reserved for those cases in which the instability, whatever its cause, results in disruption of life and often recurrent and/or prolonged hospitalization. It affects 3/1000 insulin-dependent diabetic patients, mainly young women. Its prognosis is poor with lower quality of life scores, more micro-vascular and pregnancy complications and shortened life expectancy. Three forms have been described: recurrent diabetic ketoacidosis, predominant hypoglycemic forms and mixed instability. Main causes of brittleness include malabsorption, certain drugs (alcohol, antipsychotics), defective insulin absorption or degradation, defect of hyperglycemic hormones especially glucocorticoid and glucagon, and above all delayed gastric emptying as a result of autonomic neuropathy. Psychosocial factors are very important and factitious brittleness may lead to a self-perpetuating condition. Once psychogenic problems have been excluded, therapeutic strategies require firstly, the treatment of underlying organic causes of the brittleness whenever possible and secondly optimizing standard insulin therapy using analogs, multiple injections and consideration of Continuous Subcutaneous Insulin Infusion. Alternative approaches may still be needed for the most severely affected patients. Islet transplantation, which restores glucose sensing, should be considered in cases of hypoglycemic unawareness and/or lability especially if the body mass index is <25, but with current immunosuppressive protocols patients must have normal renal function and preferably no plans for pregnancy. Implantable pumps have advantages for patients who either weigh more than 80 kg or have abnormalities of kidney or liver function or are highly sensitized [53]. PIVIT has also shown advantages for the patients. There is a report on long-term treatment with PIVIT on twenty Type 1 diabetics with brittle diabetes. The patients received the treatment for an average of 41 months. HbA1c significantly decreased from the baseline of 8.5% to 7.0% at the end of study. Major hypoglycemic events significantly decreased from 3.0 to 0.1/month and minor hypoglycemic events from 13.0 to 2.4/month at the end of the study [54]. The exact mechanism by which PIVIT decreased HbA1c levels and the frequency of hypoglycemic events has to be determined.

Diabetic nephropathy

Diabetic nephropathy has become a worldwide epidemic, accounting for approximately one third of all cases of end-stage renal disease. With increasing prevalence of diabetes and a global prevalence of micro-albuminuria of 39%, the problem is expected to grow. Improved management of diabetes aimed at improved glycemic control, to avoid initiation of diabetic nephropathy, and antihypertensive treatment blocking the renin–angiotensin system, to avoid its progression, need to be implemented, particularly in high-risk patients [55]. End-stage renal disease develops in 50% of Type-1 diabetes patients with overt nephropathy within 10 years and in more than 75% by 20 years in the absence of treatment. In T1DM, a greater proportion of patients have micro-albuminuria and overt nephropathy at or shortly after diagnosis of diabetes. Treatment interventions in diabetic nephropathy include glycemic control, treatment of hypertension, hyperlipidemia, cessation of smoking, protein restriction, and renal replacement therapy. Multifactorial approach includes combined therapy targeting hyperglycemia, hypertension, micro-albuminuria, and dyslipidemia [56]. PIVIT has shown positive effects on BP control in T1DM with nephropathy, [57] possibly through improvement in endothelial function. The exact mechanism by which PIVIT slows the progression of overt diabetic nephropathy remains to be determined. This effect could also favorably influence the intra-glomerular hemodynamics and delay the progression of diabetic renal disease. However, PIVIT's antinephropathic effects may not arise directly from glycemic or BP control. One hypothesis is that the restoration of non-diabetic physiologic insulin concentrations in the portal system may directly trigger unknown mechanisms that protect renal function to a significant degree. Another possibility is that various mechanisms crucial to protecting the glomerulus may have a higher sensitivity to pulsatile, as opposed to continuous, administration of exogenous insulin. Experiments in animals have indicated that glomerular expression of transforming growth factor b, the key mediator between hyperglycemic and mesangial cell stimulation toward overproduction of extracellular matrix, is stimulated by hyperglycemia, hypoinsulinemia, or both [58], and PIVIT tends to reverse both hyperglycemia and hypoinsulinemia. The exact mechanism by which PIVIT slows the progression of overt diabetic nephropathy remains to be determined.

Diabetic neuropathy

Diabetic polyneuropathy (DPN) is the most common late diabetic complication, and is more frequent and severe in the Type 1 diabetic population. Currently, no effective therapy exists to prevent or treat this complication. Hyperglycemia remains a major therapeutic target when dealing with DPN in both Types 1 and 2 diabetes, and should be supplemented by aldose reductase inhibition and antioxidant treatment. However, in the past few years, preclinical and clinical data have indicated that factors other than hyperglycemia contribute to DPN, and these factors account for the disproportionality of prevalence of DPN between the two types of diabetes. Insulin and C-peptide deficiencies have emerged as important pathogenetic factors and underlie the acute metabolic

abnormalities, as well as serious chronic perturbations of gene regulatory mechanisms, impaired neurotrophism, protein–protein interactions and specific degenerative disorders that characterize Type 1 DPN. It has become apparent that in insulin-deficient conditions, such as T1DM and advanced T2DM, both insulin and C-peptide must be replaced in order to gain hyperglycemic control and to combat complications. As with any chronic ailment, emphasis should be on the prevention of DPN; as the disease progresses, metabolic interventions, be either directed against hyperglycemia and its consequences or against insulin/C-peptide deficiencies, are likely to be increasingly ineffective [59]. There is evidence showing that replacement of C-peptide in T1DM prevents and even improves DPN [60]. The sequential abnormalities in the molecular regulation of normal nerve fiber regeneration in the insulinopenic BB/Wor-rat, compared to the near normal situation in the hyperinsulinemic BB/Z-rat, are primarily due to impaired insulin action rather than hyperglycemia [61]. The normal nocturnal fall in blood pressure is associated with glucose metabolism and arterial wall distensibility [62].

Abnormal circadian blood pressure rhythm has been reported to be associated with the development of diabetic autonomic neuropathy [63]. The result of a randomized controlled clinical study has shown an improvement of abnormal circadian blood pressure rhythm in IDDM patients who received weekly PIVIT for 3 months besides their intensive insulin therapy [64]. Orthostatic hypotension is another manifestation of diabetic autonomic neuropathy. It is defined as a decrease in diastolic blood pressure >10 mm HG or decrease in systolic blood pressure >30 mmHg after 2 min of standing. Patients treated with weekly PIVIT reported complete relief from dizziness and fainting when they stood up and blood pressure no longer dropped precipitously with upright posture [65].

Potential mechanisms

The insulin receptors (IR) play a central role in insulin signaling by being autophosphorylated and then activated after binding to insulin. The activated IR phosphorylates several adaptor/scaffold molecules including Shc, APS, CAP and Cb1. Recruitment of the Grb2/SOS complex to tyrosyl phosphorylated Shc leads to activation of the MAPK cascade, which promotes RNA synthesis. Phosphorylation of IR also leads to recruitment of effectors such as the lipid kinase, phosphoinositide 3-kinase (PI3K). Activation of PI3K leads to generation of PIP3 in the inner leaflet of the plasma membrane, resulting in recruitment and activation of Ser/Thr kinases including phosphoinositide 3-dependent kinase 1/2 (PDK1/2), and Akt. Phosphorylation of downstream substrates, including the mammalian target of rapamycin (mTOR) and Glycogen Synthase Kinase-3b (GSK3b) promotes increased protein and glycogen synthesis. Phosphorylation of APS, CAP and Cb1 leads to recruitment of CrkII and C3G which promotes the activation of TC10. The activation of Akt, and TC10 are required for maximal insulin-stimulated translocation of GLUT4 transporter from an intracellular compartment to the plasma membrane (Fig. 2). There are four family members of insulin receptors; two of them have been studied extensively. The insulin receptor substrates IRS-1 and IRS-2 share a similar structure, however, IRS-1 functions primarily in skeletal muscle, pancreatic islets and adipose tissue whilst IRS-2 plays the dominant role in liver. Therefore, in addition to its endocrine effects leading to glucose uptake in muscle and adipose tissue and glycogen storage in liver, insulin has autocrine effects on b-cells, regulating gene transcription, proliferation, glucose metabolism and insulin biosynthesis [66]. IRS-1 are not linked to changes in insulin exocytosis and or feedback on GLUT2 receptors. They are in ensuring that b-cells have sufficient preproinsulin mRNA stores to allow insulin biosynthesis and to maintain b-cell mass [67]. A

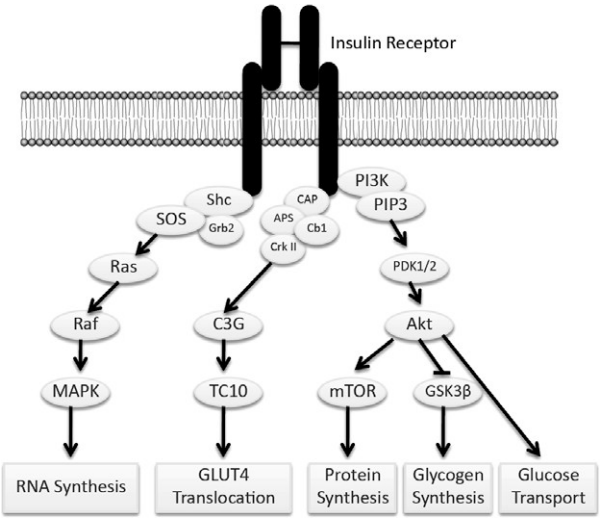

Fig. 2. Insulin signaling pathways.

mouse model recently demonstrated that selective inactivation of the gene encoding the insulin receptor of the beta cell was associated with loss of insulin secretion in response to glucose and a progressive impairment of glucose tolerance [68].

Since insulin is released to the portal vein, any change in insulin secretion will cause changes of portal vein insulin concentration. Hence, the first candidate cells facing the insulin changes are the hepatocytes in the liver. In Type 1 diabetics, hepatic glucose production has been reduced by 25–30% when the same amounts of insulin were delivered in a pulsatile manner rather than constant way [23]. Adipose tissue also shows improved insulin sensitivity when insulin is administered in a pulsatile fashion [69]. The greater hypoglycemic action of pulsatile delivery is likely related to enhanced expression of insulin receptors on target tissues. When hepatocytes were perfused with either a constant or an oscillatory insulin concentration, insulin receptor expression was significantly higher when exposed to oscillatory insulin [70]. Attenuated plasma oscillatory patterns might lead to down-regulation of insulin receptors, of particular potential importance with the finding that the beta cell is itself equipped with insulin receptors [71].

Conclusion

PIVIT has shown several benefits for both T1DM and T2DM patients when added to routine insulin regimens and appears to significantly reduce the progression of diabetic nephropathy and neuropathy. Plausible explanations include sustained improvement of hepatic carbohydrate metabolism from pulsatile insulin delivery to hepatic sinusoids via the hepatic artery and portal vein that mimics normal pancreatic function, or yet to be elucidated effects on local hemodynamic or metabolic conditions within target tissues subjected to pulsatile insulin exposure resulting in insulin receptor overexpression. The apparent enhancement of hepatic function with PIVIT treatments may also be the result of sustained improvement in enzymatic activity within hepatocytes themselves and help with detoxification of waste products from the liver. The exact mechanism by which PIVIT improves the aforementioned situations has yet to be determined in well-controlled animal research series. Another avenue that has yet to be extensively studied is examining the effects of the combination of islet transplantation and PIVIT therapy. Islet transplantation is appropriate for specific indications affecting a subset of Type 1 diabetic patients and may be improved by the administration of PIVIT therapy for several months before and after islet transplantation.

Acknowledgements

The authors would like to thank the University of California, Irvine and The North American Foundation for the Cure of Diabetes for their financial support of this research, and Kristin Wills, University of California, Irvine, for her assistance in the preparation of this manuscript for publication.

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