Extra pancreatic synthesis of insulin in different tissues and organs of human, animals and plant kingdom

Plant kingdom

It should also be mentioned that not a single form of life in the animal kingdom is known that does not need the hypoglycemic hormone [16,17], even yeast is also known to possess insulin receptor: we have found that the garlic (Allium sativum) bulbs has insulin like molecule (unpublished). As garlic plant is 500 million years old in the evolutionary tree it may indicate that insulin was a present even in the earliest period of life in earth.

Human and animal kingdom

In humans, a survey in the literature demonstrated the synthesis of the hormone in different cells including 1. Pancreas [18-20], 2. Liver [21-23], 3. Thymus [24], 4. Lymphocytes [23], 5. Brain and neurons [25-27], 6. Pituitary [25], 7. Hypothalamus [25], 8. Jejunum [28], 9. Ileum [28], 10. Cecum [28], 11. Adipocyte [24], 12. Spleen [24], 13. Bone marrow [24]. This list is not however complete, it is possible that there are many other cells capable of synthesizing insulin remain to be identified. The synthetic ability of some of above organs and their cells are briefly described below.

Pancreas: The pancreas was probably earliest organ identified

Extra pancreatic synthesis of insulin from carbohydrate derived energy for all living organisms.

It was concluded that the synthesis of insulin in different cells was essential to maintain the cellular integrity from carbohydrate derived energy for all living organisms.

Abstract

It is currently believed that insulin, an essential hormone for carbohydrate metabolism, is produced only in the pancreas. Many investigators on the other hand had reported that various cells in different organs of the body beside pancreas are also capable of synthesizing insulin. This hormone not only has a critical role in the carbohydrate metabolism, but the protein is also reported to prevent the atherosclerosis and hypertension. The multifunctional synthesis of the protein in different cells in various organs is presented in the review. Insulin was reported to be synthesized in the liver, brain, thymus, adipocytes, gastrointestinal tract, bone marrow and in the leucocytes. Insulin synthesis was confirmed by cDNA analysis, amino acid sequence and by bioassay of the hormone. Liver was found to synthesize insulin, and glucose was found to stimulate NO synthesis in the liver and NO thus produced stimulated insulin and Glut-4 synthesis in the liver. Insulin synthesis occurs not only in human but also all animals. The lymphocytes and the leucocytes in the circulation were found to synthesize insulin. It is possible that synthesis of insulin in leucocytes could be involved for the ready supply of insulin in the prevention of thrombosis in platelets which did not produce any insulin. The synthesis of insulin in different organs in many different animals has also been reported. It was concluded that the synthesis of insulin in different cells was essential to maintain the cellular integrity from carbohydrate derived energy for all living organisms.

Introduction

Ever since the discovery of insulin in 1921 by Best and Benting [1,2], an essential hormone for the systemic carbohydrate homeostasis, a protein, which was first to be determined for its chemical structure and molecular weight [3-5], remains in the public mind, in general, as a pancreatic protein. However there is no binding reason that the protein hormone could not be synthesized in other organ than pancreas only. It should be noted here that the gene-make up of all cells in any particular organism is identical, suggesting that a particular gene responsible for the expression of a particular protein in any cells would have the same gene in all other cells as well. The expression of all protein in cells is not possible due to the fact the gene expression of any protein is not only a multistep process, but a particular stimulus is needed to initiate the synthesis of a particular protein. For example, it should be mentioned here that the amylase produced in the parotid gland is identical to the amylase produced by pancreas [6,7]. Although insulin production was first identified in the pancreatic β cells [8,9] the synthesis of this protein identical to that in the pancreas has been reported to occur in many other organs and isolated cells beside pancreas in more recent time. This review summarizes some of these new findings related to the synthesis of the hormone in different organs.

It should be mentioned that the role of insulin in different metabolic and pathologic processes is so diverse that the effects of any other known hormone can be comparable to those of the hypoglycemic protein. The effect of insulin is not only essential to the carbohydrate metabolism but the hormone has critically important role ranging from the control of hypertension to the prevention of atherosclerosis leading to prothrombotic disorder to neuropathy [10-15]. Almost all life threatening diseases are further aggravated by the systemic reduction of insulin level.

Correspondence to: Asru K Sinha, Sinha Institute of Medical Science and Technology, 288, Kendua main road, Garia, 700 084, India, Tel: +91-9903792100, Fax: +91-33-24127905; E-mail: asruksinha@yahoo.com

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to synthesize insulin in its β cells. There are extensive literature are available are available in this area [8,9].

**Liver:** Indirect evidences are available for many years that liver disease including liver fibrosis (i.e. the replacement of hepatocytes by fibroblast [29]) infection with hepatic viruses were able to cause diabetic mellitus indicating that normal liver does synthesize insulin [29]. The hepatocytes from the adult normal liver have also been reported to synthesis insulin due to the expression of pro insulin genes in the presence of glucose [21-23]. The presence of stress induced protein identified to be dermcidin isoform-2 (Mr. 11Kda) in the liver has been reported to inhibit insulin synthesis in the presence of glucose to maintain the systemic glucose homeostasis [30,31].

The liver is unique in its ability to synthesize insulin, in that most of the pancreatic insulin received by the liver is destroyed, and for the synthesis of glycoligen (an insulin dependent process), the liver is capable of synthesizing its own insulin [21-23,32-34]. The influx of glucose into the hepatic cells is facilitated by the synthesis of Glut-4 by glucose itself through the synthesis of NO [35], similar to the case of adipocytes, independent of pancreatic insulin [36,37]. Indeed the adult hepatic stem cells can trans differentiate into pancreatic insulin producing cells [22]. The rat liver insulin has been reported to be indistinguishable from the pancreatic insulin as determined by different analytical methods [23]. However the insulin receptors in adipocytes, and in the liver membrane has been reported to be different [38,39], the role of glucose as the initiator of insulin synthesis and release in the pancreatic β cells are well known [8,9]. In the case of liver cells glucose has an even more unique role in the synthesis of secretion of insulin in that for the synthesis of insulin in the liver cells the presence of both NO and glucose are needed. The glucose was found to activate a constitutive form of nitric oxide synthase [GANOS, (glucose activated nitric oxide synthase)] that is essential for the synthesis of insulin through the synthesis of NO [35].

That NO has an essential role in the glucose induced insulin synthesis was further supported by the effect of estrogen or progesterone that was found to stimulate NO level at nM ranges [40]. As such, the treatment of alloxan treated type I diabetic mice model, by the injection of 3.5 µM estriol or even 3.5 nM progesterone was found to stimulate insulin synthesis even in these mice when the pancreas itself failed to synthesize any insulin [40]. These results demonstrated that in the presence of glucose and NO, the insulin synthesis can be “switched” over from the pancreas to liver in type I diabetes at least in the mice model. The reason for the failure of liver to synthesize insulin in the presence of glucose alone was determined to the presence of high amount of dermcidin isoform-2, a potent inhibitor of all forms of NOS. The inhibition of dermcidin by its antibody was found to be capable of inducing insulin synthesis in liver in the presence of glucose (unpublished). The involvement of dermcidin isoform-2, NO, glucose and Glut-4 (glucose transporter-4) is described diagrammatically in the (Figure 1).

**Brain:** Experiments using complementary DNA (cDNA) had demonstrated that adult human brain transcribes insulin mRNA encoding insulin as determined by PCR [25]. The pathogenesis of Alzheimer disease has been reported to be related to type II diabetes mellitus like condition in human brain [41,42]. In animals the expression of insulin gene was also found. The impaired insulin synthesis in brain has been related to the development of Alzheimer disease in brain in human [43]. The treatment of adult mice brain with glucose was similarly found to synthesize insulin as determined by in vitro translation of insulin mRNA (unpublished). Insulin gene is reported to be expressed in pituitary cells in the brain of tilapia fish in greater quantity than that in hypothalamus [25]. Insulin has also been reported to be released from neuronal cells in culture by the depolarization induced by K⁺ [27] and in the cloned rabbit neuronal cells through the synthesis of insulin mRNA in post natal rabbit brain [26].

**Insulin synthesis in the cells in lymphocytes and leucocytes in the circulation of human**

The deficiency of insulin either is type I diabetes mellitus or in type II diabetes mellitus is a well-known to be major risk factor for the development of atherosclerosis leading to acute coronary syndrome, a major killer disease of the human race [44-47]. The type II diabetes mellitus has been equated to atherosclerosis and the risk factor like dyslipidemia (hypercholesterolemia) has been directly related to the type II diabetes mellitus [48,49]. Insulin has been reported to be a global antithrombotic humoral factor due to the ability of the hormone to inhibit platelet aggregation [50]. As human platelets are anucleated cells and are incapable of synthesizing any protein, it is conceivable that the other cells in the circulation might provide the much needed locally available of insulin to prevent the acute coronary syndrome particularly when pancreatic production of insulin became impaired. Indeed, the systemic hypoglycemia has been reported to be a risk factor for acute coronary syndrome [51,52]. It has been reported that IM-9 lymphocytes in culture was capable of synthesizing insulin efficiently [23]. We have found that leucocytes in the human circulation were capable of synthesizing insulin in the presence of glucose as evidenced by in vitro translation of insulin mRNA (unpublished). This review indicates that the infusion of glucose in the circulation may avert the impending ACS (acute coronary syndrome) through the increase synthesis of insulin in the leucocytes that would inhibit the platelet aggregation to inhibit the condition.

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**Figure 1.** Diagrammatical representation of the role of glucose, nitric oxide (NO), dermcidin isoform-2 and Glut-4 in the synthesis of insulin in hepatocytes.
Discussion

In this article we have tried to present a general overview of the information regarding the extra pancreatic synthesis of insulin in human as well as in other forms of life. Insulin is a well-known hormone appreciated for carbohydrate metabolism in diabetes mellitus only but that the hormone is also involved in the prevention of thrombosis [50,53], stroke (both ischemic and hemorrhagic) [54], hypertension [55], Alzheimer’s disease remains largely unappreciated [56]. Also, semantically (the meaning of the word) “insulin” became largely inappropriate in that the word insulin originated from the “insula” in the islets of langerhans. Hundreds of researchers from different parts of the world had reported that insulin is also produced by different organs and cells of the body. And, as such, the word insulin is perhaps somewhat inappropriate, and perhaps has only “historical value”. In this context, it should be mentioned here that no other hormone in the animal kingdom has so many different functions both in the health and in diseases. The hormone is so essential for the maintenance for the life that even when insulin is injected in the system. The antibody against the hormone which is rapidly synthesized in the system does not interfere with the effect of insulin when the hormone was re-injected in the system. It should also be mentioned that the synthesis of other hormone and protein are sometimes occurred in the different site than the classically assigned issue. For example, synthesis of estrogens not only occurs in ovary but also in the fat cells and, similarly amyylase not only produced in the parotid gland but the same amyylase is also produced in the pancreatic cells. In that sense it would be unusual to think that a multifunctional insulin should be produced only in the pancreas.

Obviously, the list of organs that can synthesize insulin is not complete at present, as many more new discoveries will come to help our understanding of the fascinating hypoglycemic protein, a major transducer of energy from the carbohydrates releasing solar energy trapped in the molecules produced by photosynthesis. However, the time has come to go beyond the belief that pancreas is the only source of the protein hormone as the pancreas was found to be only one of the many organs and tissues werecapable of producing insulin for the maintenance of life process as a whole. It should be mentioned here that for the synthesis of the proteins, the information molecules of the genes, the required energy is derived from the hydrolysis of 4 phosphate bonds, particularly that from ATP and GTP for the synthesis of a single peptide bond. The above issue on the essential role of insulin in living systems however immediately brings forth the question why the hormone is so important for the survival of all forms of lives? The issue could be answered, at least partly, that all cells and its components are spontaneously degrading due to constant wear and tear of the proteins and the “ordered” cell structure is continuously becoming “disordered” (i.e the change of “entropy”) and the availability of the energy supply is essential to change the “disordered” condition to its “ordered” form obeying the 2nd law of thermodynamics which cannot be violated. Insulin is perhaps the most important transducer for the production of energy from the carbohydrates. It could be suggested that for the maximum efficiency of the energy transduction from the carbohydrate, insulin synthesis was made available in different tissues and cells in the evolutionary process for the ready supply of the energy transducer at demand.

It can be hypothesized that the protein (insulin) has so many diverse activities that should be produced only in the pancreas only to meet the multitude of physiologic/metabolic demands as presented in the text would be very unlikely. This is the only hormone known currently to be present in the numerous cells to carry out functions in cells to meet the immediate need without depending on the pancreatic supply of insulin for the energy transduction and for maintaining cellular integrity.

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