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Research Article

Glucose Homeostasis: The Ubiquitous Requirement for Insulin and Insulin-Like Function Throughout the Plant and Animal Kingdoms from Single Celled Organisms to Whales

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Abstract

This review examines the ability to maintain glucose homeostasis from throughout the animal kingdom from human to single celled organisms, then insects focused on the balance of hormone and hormone-like functions to maintain reasonable glucose control in the face of eating and fasting and other activities.

Islets in Mammals: 20 mammals, including humans, are examined in terms of islet structure, content, function, beta cell replication, spontaneous and induced diabetes.

Islets in Birds: 3 types of birds are examined by the same islet testing and spontaneous and induced diabetes.

Islets in Reptiles: 4 divergent reptiles are examined by the same islet testing and spontaneous and induced diabetes.

Islets in Fish: 5 types of fish are examined by the same islet testing and spontaneous and induced diabetes.

Insulin-like Substance in Mollusks: Only 1 type of mollusk is examined since it uses a shortened insulin B chain as a "venom" to attack small fish by hypoglycemia.

Insulin-Like Substance in One-Celled Organisms: 4 one-celled organisms are tested for their control of their glucose environment.

Insulin-Like Substance in Insects: 7 types of insects are examined for the role of insulin-like substances in their glucose environment.

Insulin-Like Substance in Plants: 65 plants are examined for selected plant tissues having any insulin-like activities and islet cell expansion in diabetic rodent models.

In terms of mammals, birds, reptiles, and fish, these evaluations show anatomic variance in islet cell type morphology but of little functional consequence. Islet cell types and their specific hormonal function remain in expected order between these species. Diabetes is predominantly a mammalian disorder with variances in the types with several species not commonly afflicted. One-celled organisms have insulin binding with similar structure and function with signals going to the nucleus and cell membrane. Insects have entirely different structures involved with fasting and feeding but have 40% homology with mammalian hormones with their energy substance trehalose, a double glucose molecule the target of altered insulin and glucagon. The search for insulin-like substances from multiple plants gave consistent glycemic responses tested in the rodents in most all tested with 8 suggesting stimulation of beta cell replication.

Keywords: *Glucose Homeostasis; Insulin; Glucagon; Somatostatin; Pancreatic Polypeptide; Ghrelin; Insulin Receptor; Type 1 Diabetes; Type 2 Diabetes; Metabolic Syndrome; Gestational Diabetes; Alloxan; Streptozotocin; Beta Cell Replication*

Abbreviations

BVDV: Bovine Diarrhea Virus; BW: Body Weight; Con-Ins-GI: Cone Snail Short Insulin B Chain; db: Diabetes; GI: Gastrointestinal; GK: Gray Kangaroo; GLP: Glucagon-Like Peptide; gm: gram; $HgbA_1c$: Hemoglobin A_1c; ICA: Islet Cell Antibody; IGF: Insulin Growth Factor; ILP: Insulin-Like Peptide; Ins 1: Mouse Insulin 1; Ins 2: Mouse Insulin 2; Ins A: Human Insulin A Chain; Ins B: Human Insulin B Chain; kg: Kilogram; mRNA: Messenger RNA; μ: Micron; mmol: Millimolar; NPY: Neuropeptide Y; NOD: Non-Obese Diabetic; PP: Pancreatic Polypeptide; %: Percent; RK: Red Kangaroo; RNA: Ribonucleic Acid

Introduction

Coming from an academic and clinical background in pancreas and islet research, development, and transplantation, I have frequently thought of how important glucose homeostasis must be throughout the animal kingdom and perhaps the plant kingdom, but had never explored it. This publication shares an exploration into multiple species broad efforts to maintain universal glucose homeostasis by examining pancreatic islet anatomy and function in mammals, birds, reptiles, mollusks, and fish as well as insulin-like substances in one-celled organisms, insects, and plants. These analyses will demonstrate the importance and the variety of solutions that have been developed to effectively manage the ability for these organisms to maintain their critical control of glucose homeostasis throughout their lifespans. It will also demonstrate that this effort has been developing for millions of years. But now, with recent findings in insects and plants, it appears insulin-like substances are over two billion years old. Their original presence in insects appears to have been in neuro-like structures. Yet, these older insulin-like structures have up to 40% insulin and glucagon chemical homology with human insulin and glucagon. Another critical structure to understand is the insulin and other islet hormone receptors. These complex hormone binding units define the specific functional responses these hormonal chemicals will initiate when functionally triggered by the proper hormone receptor. It is the chemical makeup of these hormone receptors that leads to these specifically unique binding responses for each of these hormones. This structure-function relationship is far more complex than defining the hormones themselves and will take longer to unravel all the mechanisms involved. It is also informative to note how different versions of the intended hormone structure can still trigger the appropriate response receptor designed for that receptor, even when in different species.

When insulin was discovered by Banting and Best [1,2] and published in 1922, it initiated the stage for the development of improved insulins for diabetes treatment. Initially, the clinical results of treating diabetes by starvation versus new insulin injections were truly dramatic (Figure 1). Over the years, the ongoing pharmaceutical industry's improvements of insulin drug therapy, glucose monitoring, and clinical advances in diabetic patient care have also been remarkable. Yet, along with these critical therapy advancements, come increased therapy costs. Thus, the last section of this publication adds 65 examples of insulin-like substances in plants that are being tested in rodent models. Perhaps the next 100 years following the discovery of insulin will bring entirely new approaches that can be developed to improve the treatment of diabetes and its secondary life-threatening complications.

Figure 1: *First Person to Receive Insulin Injections by Banting and Best - Replacing Starvation as a Treatment with Insulin Injections for Diabetics (From National Institutions of Health United States National Library of Medicine).*

Methods

This article is a review article written utilizing previously published articles as referenced in this text. The only additions made to these publications in this review were to create several new charts, graphs, and tables as well as discussion that were accomplished in order to combine these original publications into this current review. All previously published work has been referenced to their original publications.

Human pancreas development

Figure 2 graphically shows that the fetal development timeline of human islets begins with the formation of the dorsal bud and ventral bud of the gastrointestinal tract and their fusion by 6 weeks of gestation into what will eventually define the pancreas. Individual islet cells form at 8 weeks with acinar cells forming at 12 weeks. Fully formed and potentially functional islets appear at 20 weeks of gestation. The gastrointestinal tissues and the pancreas continue to develop into functional tissues with birth programmed at 9 months of gestation. This entire fetal process has recently been well described by Pan and Wright summarizing in their publication, "Pancreas Organogenesis: From Bud to Plexus to Gland" [3].

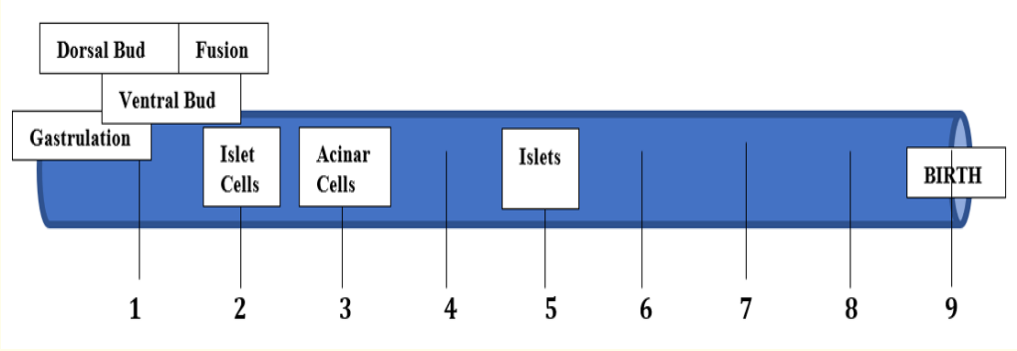


Figure 2: *Human fetal development of pancreas and islets.*

Human pancreatic islets

Human pancreatic islets consist of 5 specifically defined endocrine cells as shown below in table 1. In addition, there is a specialized fenestrated vascular endothelium networked throughout each islet that permits each islet cell type to interface directly next to these endothelial cells to effectively deliver their hormone products into circulation. Additional supporting cells complete the mixture including nerve endings, usually along vascular routes. There is also a terminal vascular sphincter on each outgoing islet vessel that is designed to clamp down in times of flight or stress and remain open when the body is not in an alarmed state, permitting excellent, direct blood flow through each islet. The recent publication by Susan Bonner-Weir [4] (Figure 3) demonstrates this human islet architecture associated with its vascularization and discusses historic and current understandings of islet cell content.

Human Islets are stained for β cells with insulin (red) and non-beta cells (green): α cells (glucagon), and δ cells (somatostatin). Unstained black spaces with white asterix are the larger vascular spaces within each islet. Small capillaries are not visualized [4].

Table 1 presents the 5 specific islet cell types in the human islet. The Alpha cell (α cell) representing 35-40% of islet cells produces glucagon that is released during fasting and increases the release of glucose and fatty acids from tissue stores as a response. It is scattered throughout the pancreas but is increased in the distal end or tail of the pancreas. The Beta cell (β cell) representing 55-75% of islet cells

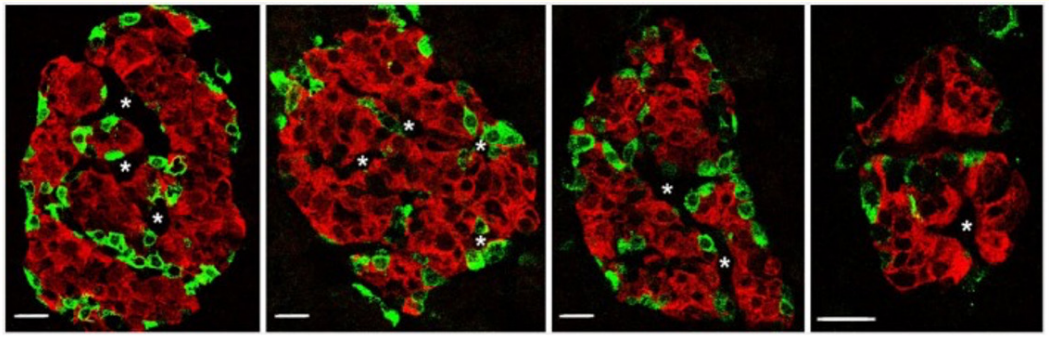


Figure 3: *Histology of human islets.*

produces insulin that is released with food intake that reduces glucose circulating in the blood after eating. It is scattered throughout the pancreas but also more concentrated in the tail. In Type 1 diabetes these β cells are attacked and destroyed by the immune system with that destruction seen throughout the pancreas. In Type 2 diabetes, the β cells seemed to be more destroyed in the head of the pancreas but are also damaged throughout the pancreas. The Somatostatin producing cell, or delta cell (δ cell) represents 5 - 10% of islet cells scattered throughout the pancreas but also located in the stomach and the brain. It functions to decrease insulin and glucagon as well as pancreatic polypeptide, gastro-intestinal and growth hormones. The Pancreatic Polypeptide, PP or gamma cell (γ cell) increases gastric juice and is stimulated by exercise and eating and is located predominantly in the head of the pancreas. The most recently discovered islet cell is the Grehlin producing or pi cell (π cell) that is located in the stomach and the head of the pancreas that increases during fasting that increases gastric and gastro-intestinal motility [5]. Figure 4 shows its typical location with the islets that is on their periphery. The earlier suggested C-, D-, and G-cells in table 1 turned out to be incorrect (Note: The author has designated PP cells as γ cells and ghrelin cells as π cells for convenience in this report).

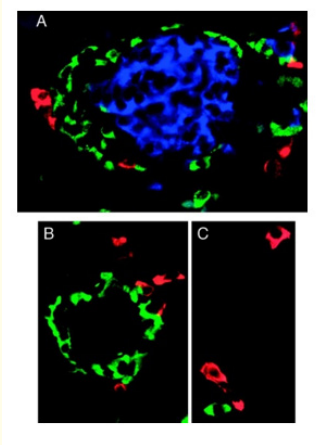


Figure 4: *Ghrelin Cells Associated with Human Islets. Ghrelin cells are the most recently discovered islet cell type [5]. They have a unique position on the periphery of human islets. Double- or triple-immunostained fetal human islets (22 weeks of gestation). Ghrelin red in all images. (A) Insulin (blue) and somatostatin (green). (B) Glucagon (green). (C) PP (green). Note that ghrelin is not co-localized with any of the four major islets hormones but remains on the islet periphery.*

Islet Cell Type	Primary Hormone	% of Islet Cells	Pancreas Location	Function	Discovery Dates	Type 1 Diabetes on Islets	Type 2 Diabetes on Islets
Alpha Cell α	Glucagon	35-40	Throughout, > Double in pancreas tail	Increase Glucose and Fatty Acids	1923, 1955, 1962	Not Noted	Not Noted
Beta Cell β	Insulin	55-75	Throughout, > Double in pancreas tail, less in large islets	Decrease Glucose	1907, 1922, 1957	Similar Loss Through-out	Greater Loss in Head
Delta Cell δ	Somatostatin	5-10	Throughout+ Gastric Antrum, Duodenum,and Brain	DecreaseInsulin, Glucagon, and PP, GI Growth hormones	1960-1962	Not Noted	Not Noted
PP Cell γ	Pancreatic Polypeptide	5-10	Pancreas Head	Increase gastric juiceElevated by eating and exercise	1974-1976	Not Noted	Not Noted
Ghrelin Cell π	Ghrelin	2-5	Stomach, Pancreas at periphery of islets, Fetal and Neonatal increased	Increases hunger with empty stomach, increases gastric acid, GI motility	1996, 1999, 2000, 2004	Not Noted	Not Noted
"C Cell"	Non-endo-crine	-	Non-granular Cells of various kinds	-	1931	-	-
"D Cell"	Now PP	-	-	-	1931	-	-
"G Cell"	Now Somato-statin	-	-	-	1931	-	-

Table 1: *Human pancreatic islet cell types.*

Islets from many different mammalian species

Table 2 expands the previous literature [6] and documents information on islets from 21 different mammalian species, including human describing their relative sizes, different islet cell types, structure of the islets, beta cell replication, and what type of diabetes can affect these islets. These results were originally published by the lead author, DJ Steiner [7] with the findings now being converted to this table. The animals include rodents to humans and on to the Baluga Whale.

The use of Alloxan and Streptozotocin has been routinely used to induce diabetes in rodents by selective beta cell destruction. This has found to be predominantly a rodent sensitivity [11,12]. It has been demonstrated that human islets were not affected by Alloxan or Streptozotocin. Yet, there are a few anecdotal reports in the literature using these agents outside of rodents in non-human primate studies.

The ability to undergo islet replication is uniformly present in all 21 species as far as embryonic islet cell replication and pediatric islet cell replication is concerned. However, the majority of islet cell replication is turned off around puberty in most all of the mammalian species. Only the rodents have ability to continue islet cell replication into adulthood. The rabbit and the dog have some limited islet replication into adulthood. But, specific studies in all of these species are quite limited, so this analysis of islet replication may not hold to be accurate with future studies.

Species	Relative Size	Islet Cell Types	Structure	Beta Cell Replication	Diabetes	Induced Diabetes
Human	50 to 400 microns, Increase in obesity	α 30-40%, β 55-75%, δ 5-10%, γ 5-10%,π 2-5%	Random distribution of cell types	In embryo and up to puberty	Type 1 Type 2 Gestation	Not applicable
Non-Human Primate	50 to 300 microns	α 10-20%,β 60-90%, δ 5%,γ rare%,π ?% cells	Reversed from rodent with α cell core and β cell mantle	In embryo and through puberty	Type 2 with islet amyloid deposits prominent	Streptozotocin induced
Rodent	Large range of size from 10 to 1000's cells/ islet	α 15-20%,β 80%,δ <10%, γ ?%,π ?% cells	β cell core with α cell mantle, Mice and Rats have unique two-gene insulins	In embryo, through puberty, and throughout life	No spontaneous diabetes, genetic db/ db strain	Readily produced with Alloxan and Streptozotocin
Rabbit	Large range of size and composition	α 25%,β 70%,δ <10% in clusters,γ ?%,π ?% cells	β cell core with α cell mantle, but heterogeneous in cell type locations	In embryo, through puberty, and limited throughout life	Rare spontaneous diabetes, but possible in obesity	Difficult to produce diabetes with Alloxan
Domestic Cat	Large range of size and location	Similar to Human distribution But quite varied	Heterogeneous mostly β cell in pancreas, but scattered outside in abdomen	In embryo, through puberty, but not later in life	Type 1 (less common) and Type 2 diabetes	Inducible diabetes possible but not reliably
Domestic Dog	Size depends on place in pancreas, but relatively small	α 30%,β 50%, δ 15% in clusters,γ ?%,π 4% cells	75% of β cells in islets with rest in acinar tissue, most of tail loaded with islets	In embryo, through puberty, but can expand in chronic pancreatic insufficiency syndrome	Type 1 and Type 2 (less common) diabetes	Partial pancreatectomy model, and difficult to produce with Alloxan
Fur Seal	Considerable differences in size and shape	Not specifically designated, but similar to cats and dogs	All β cells found within core of islets with α, δ, and others on periphery. γ cells are at one pole.	In embryo, through puberty, but not well known beyond	Not true diabetes, but can present with metabolic syndrome	Not known
Horse	Specific sizes not provided	α 30%, β 50%, δ 10% in clusters, γ ?%, π <1% cells, Except near duodenum with 12%π cells	β cells found only on periphery of islets over central mass of α cells, δ cells found between α and β cells. γ cells on periphery.	In embryo, through puberty, but not well known beyond	Type 1 diabetes, not Type 2, but can have metabolic syndrome	Not known

Cattle	Two different sized islets are found at 25-200 μ's and much larger islets, but the larger islet decrease with age	Specifics not provided	β cells found in central core with α cells on outer rim along with δ cells. γ cells localized in a dense group on periphery of islet	In embryo, through puberty, but not well known beyond	Type 1 diabetes, can be associated with bovine diarrhea virus (BVDV) and can have ICA's	Not known
Domest-Goat	No information provided on islet size	No specific breakdown of percentage of islet types	β cells are centrally located with α cells peripherally, δ cells arranged in ribbons from outer to inner regions, γ cells densely packed within the islet	In embryo, through puberty, but not well known beyond	Spontaneous Diabetes Occurs	Not known
Domestic-Sheep	No information provided on islet size	No specific breakdown of percentage of islet types	Only 60-80 days of fetal information available with β cells both in central clusters and outer areas with α cells peripheral. Both δ and γ cells focused peripherally	In embryo, through puberty, but not well known beyond	Spontaneous Diabetes Occurs	Alloxan induced diabetes
Domestic Pig	No information provided on adult islet size	No specific breakdown of percentage of islet types	β cells form the core of pig islets with most α cells located peripherally with δ cells and γ cells. There are differences of islet cell type in different pancreas lobes	In embryo, through puberty, but not well known beyond	Spontaneous Diabetes Occurs	Difficult to produce with Alloxan
Dromedary Camel	No information provided on adult islet size	No specific breakdown of percentage of islet types	β cells are the primary islet type and located in the center with α cells and δ cells. γ cells are also in the middle of islets and scattered in the exocrine tissues	In embryo, through puberty, but not well known beyond	Not known	Not known
Striped Hyena	No information provided on adult islet size	No specific breakdown of percentage of islet types	β cells are found both in the center and the periphery of islets as well as scattered in the acinar cells. α cells are only located peripherally. δ cells are dispersed in the islet with γ cells only in the peripheral.	In embryo, through puberty, but not well known beyond	Not known	Not known

African Elephant	No information provided on adult islet size	No specific breakdown of percentage of islet types	β cells are found in the islet center with α cells and δ cells located peripherally. Higher percentage of islets in body and tail than the head. A few π cells and some slender NPY cells are also in islets.	In embryo, through puberty, but not well known beyond	Metabolic factors related to diet and exercise, but no definitive demonstration of diabetes to date	Not known
Water Buffalo	No information provided on adult islet size	3 Sizes of Islets: 500 u, 150 u, and 10 u in diameter with different content	Large, 500 u islets mostly β cells with scattered α, δ and γ cells. 150u islets with core of β cells with α cells in ribbons outside with outer layer of δ and γ cells. The 10 u islets are mostly π cells with the other 3 types scattered within these	In embryo, through puberty, but not well known beyond	Not known	Not known
Three-Toed Sloth	No information provided on adult islet size	No specific breakdown of percentage of islet types	β cells located in the islet core with α cells located on perimeter, with α cells more prevalent than β cells	In embryo, through puberty, but not well known beyond	Not known	Not known
Marsupial RK = Red Kangaroo, GK = Grey Kangaroo, Opos = Opossum	Adult islet size: # cells/islet: RK = 43, GK = 33, Opos = 48	RK =α 70%, β 8%, GK =α 75%, β 15% Opos =α 50%, β 40%	RK + GK = β cells – peripheral, α cells –central, δ cells scattered, Opos = same for α and β cells γ cells in separate clusters	In embryo, through puberty, but not well known beyond	Spontaneous diabetes known to occur in red and grey kangaroos	Not known
Echidna	No information provided on adult islet size	β cells most common in mixed islet cell islets	Two Types: α, β, δ and γ cells; Or pure γ cells	In embryo, through puberty, but not well known beyond	Not known	Not known
Beluga Whale	No information provided on adult islet size	Mixed types with α and β cells with α cells = 40%, but from β cells 70% scattered	More common with α cells in periphery and β cells in the core	In embryo, through puberty, but not well known beyond	Not known	Not known

Table 2: *Islets from different mammalian species.*

Specific references for each of these studies are in the original publication.

Discussion of the key points of table 2

Changes in the type of a specific islet cell type in the core versus those in the periphery does not seem to adversely change islet function [9]. This published report documents in mammals that 15 of 21 species have the β *cells predominantly in the central core with the others having the* β *cells on the periphery or mantle of the islets [9]. Three species, Non-Human Primates, Horses, and Marsupials, have their* β *cells on the peripheral location or mantle. Three species, Human, Cat, and Echida, have their islet* β *cells in a mixed pattern. One species, Hyena, has its* β *cells fairly evenly mixed between the core and the periphery. There does not seem to be a correlation between specific islet cell type and its location within the islet regarding islet function. There also is no relationship to a susceptibility to develop diabetes by this islet structure analysis. It is important to note that the exploration of human pancreas development has led to exploration of the human embryonic stem cells [10] that have become a field of investigation itself.*

Mice and rats have genetically, two genes for insulin [13]. The mouse, Insulin 1 is on Chromosome 7 and Insulin 2 is on chromosome 11. In the rat, Insulin 1 and Insulin 2 are on the same chromosome but are separated. It is suggested that the Insulin 1 gene in the mouse was added during the evolutionary time that the mouse and rat split from a common ancestor. But both Insulin 1 gene and Insulin 2 gene in the mouse became jointly expressive during the development of the *Mus musculas domesticas* split from former mouse species that is the current type of house mouse that exists.

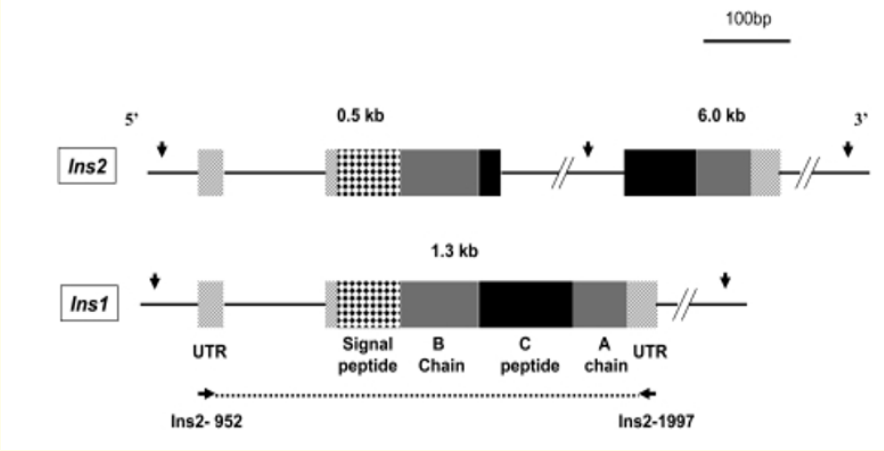


Figure 5: *Normal mouse has 2 insulin genes.*

Of significant interest in mammals is to identify which species can develop diabetes in their life span [14,15]. The species that readily develop both Type 1 and Type 2 diabetes are humans, cats, and dogs. In cats, Type 2 diabetes predominates over Type 1 diabetes while in dogs, Type 1 diabetes predominates over Type 2 diabetes. Rabbits demonstrate glucose intolerance with obesity, but not specific spontaneous diabetes. Non-Human Primates spontaneously develop Type 2 diabetes. Horses can develop Type 1 diabetes and the metabolic syndrome. Cattle can also develop Type 1 diabetes with a diarrhea syndrome. The goat may develop a form of Type 2 diabetes. Elephants do not develop diabetes but can demonstrate hyperglycemia based on diet and amount of exercise. In terms of marsupials, the grey and red kangaroos can also develop Type 2 diabetes. The fur seal can develop Metabolic Syndrome, but not diabetes. The fruit bat can have high glucose levels but does not have diabetes, as discussed below. The other mammals listed in table 2 that are not known to develop diabetes include the Camel, Hyena, African Elephant, Water Buffalo, 3 Toed Sloth, Echida, and the Baluga Whale.

Specific example of physical activity assisting in maintaining glucose homeostasis

As shown in table 3, the Fruit Bat feeds predominantly on liquid nectar found in specific flowers. Their islets represent 10% of the pancreas and are large and irregularly shaped. The α cells are 30% of an islet and are located on the periphery while the β cells are 50% of the islet and located within the center of the islets. The other islet cell types are either in clumps or scattered within the islets. Beta cell replication clearly takes place in the embryo and in young animals through puberty, but no information is available for islet expansion in adults. These animals experience very elevated glucose levels after eating without any evidence of elevated HgbA1c levels with their average of 3.9 +/- 0.3% nor any signs or symptoms of adverse effects from having such high glucose levels.

Special study of fruit bat, *Glossophaga soricina*

A special study was conducted to provide clarity as to how these animals eating these very high concentrations of glucose can maintain low HgbA1c levels with key results shown in figure 6 [16]. To better understand this study, one must realize that the only way these bats

Species	Relative Size	Islet Cell Types	Structure	Beta Cell Replication	Diabetes	Induced Diabetes
Fruit Bat	Islet cells represent 10% of pancreas and are large with irregular shape	α 30%,β 50%,δ 10% in clusters, γ ?%, π 15% cells	α cells found on periphery but not tight, β cells within, δ cells in clumps within, π cells scattered in islets	In embryo, through puberty, but not well known beyond	Not true diabetes, but have elevated glucose and insulin levels	Not known

Table 3: *Islets in nectar feeding bats.*
Specific references for each of these studies are in the original publication.

can eat is while they are continuously flying up to each flower where they stick their tongues down into the high glucose, liquid nectar similar to humming birds. As shown below in Figure 6 on the left, during a glucose tolerance test while resting where each animal received a single dose of glucose followed by blood testing for glucose levels out to 90 minutes. The baseline control of 0 glucose shows no elevation. However, the blood glucose levels increase significantly with each single, increasing glucose dose from 1.8, to 5.4, to 9 grams glucose/Kg body weight with resulting blood glucose peak levels of 12, to 20, to 27 mmol glucose/L, respectively. These high levels of blood glucose are of concern in inducing diabetic complications over the long term.

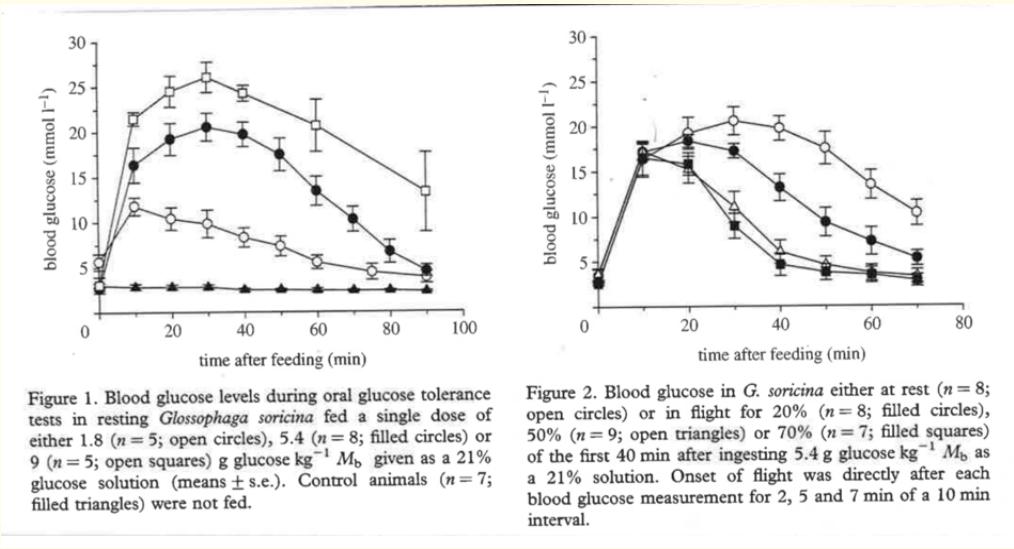


Figure 1. Blood glucose levels during oral glucose tolerance tests in resting *Glossophaga soricina* fed a single dose of either 1.8 ($n = 5$; open circles), 5.4 ($n = 8$; filled circles) or 9 ($n = 5$; open squares) g glucose kg^{-1} M_b given as a 21% glucose solution (means ± s.e.). Control animals ($n = 7$; filled triangles) were not fed.

Figure 2. Blood glucose in *G. soricina* either at rest ($n = 8$; open circles) or in flight for 20% ($n = 8$; filled circles), 50% ($n = 9$; open triangles) or 70% ($n = 7$; filled squares) of the first 40 min after ingesting 5.4 g glucose kg^{-1} M_b as a 21% solution. Onset of flight was directly after each blood glucose measurement for 2, 5 and 7 min of a 10 min interval.

Figure 6: *Control of blood glucose by exercise in nectar-feeding bats.*

However, the study on the right above combines a high glucose dose given but now adds the following important variable of exercise by flight. Giving the same glucose dose of 5.4 gm/kg BW, blood glucose levels were drawn over the same times. The open circles were samples taken at rest without flight. Then, increasing times of flight were forced with closed circles of 20% of time, open triangles of 50% flight, and closed squares at 70% flight. The 70% flight times represent the usual time spent in flight by these bats while eating the nectar in the flowers. Now this added flight exercise required in order to eat takes the concern for longer high glucose levels away and readily explains the normal HgbA1c levels that were observed at random in these fruit bats. Thus, these animals have avoided glucose induced toxicity at levels they consume due to their requirement to fly while eating. Their normal insulin responsiveness without flight exercise would not

have kept them out of diabetic complications and would have probably shortened their life spans by their recurrent high glucose levels causing diabetic complications.

Mammalian islet transplantation studies

There is a major literature on islet transplantation into mammalian diabetic recipients ranging from isografts to allografts to xenografts with marked success in eliminating diabetes [17-21]. Rodent transplant studies far outnumber other mammalian results. There is an interesting finding in mouse allograft and xenograft results to consider. It has been universally demonstrated that if one performs a mouse islet isograft of mouse islets injected into diabetic mouse recipients, it only takes 30 purified mouse islets to cure a diabetic mouse of their induced diabetes. However, if one performs a human islet xenograft into diabetic mice, it takes 4,000 human islets to routinely eliminate mouse diabetes in a single diabetic mouse with human islets. This result shows it takes 133 times the number of human islets than mouse islets to cure diabetes in a mouse. If one examines the insulin molecules, one finds a few simple differences. So, these implanted human islets are poorly functioning in diabetic mice most likely due to the fact that the mouse insulin receptor has a low sensitivity to the released human insulin.

Differences in rodent insulin

Insulin differences between mammalian species are relatively minor. Compared to human insulin with 51 amino acids and a molecular weight of 5808 Da, beef insulin has 3 amino acid differences and was used for many years to treat human diabetics. Similarly, porcine insulin is only 1 amino acid different and was also used for years to successfully treat human diabetics. All of these species insulins are stored as pancreatic hexamers inside the producing β cell granules, as shown in figure 5A. When the beta cell is stimulated to release some of its insulin granules, these hexamers are all converted back to the single molecule prior to the release of insulin into the body's vascular.

Figure 5A: *Human, beef, and pork insulin hexamers.*

Mouse insulin actually has more amino acids than human, porcine, or bovine insulin since these rodents have two types of insulin, Ins 1 and Ins 2 as shown in figure 5B [13]. The Ins 1 gene was retroposed from partially processed mRNA from the Ins 2 gene somewhere around the time the current mouse species split off from the rat around 20 million years ago. The Ins 2 gene seems to be complete, but both are expressed for normal glycemic control. The NOD mouse only has the Ins 1 gene that apparently causes it to become diabetic.

Ins2		*Ins1*	
	4445666677777778		11
	24791362047811223880		566916
	32643457817212043495		938434
MC81	CCTATATTAATGTATTTATG	MC55	GTTAGA
MC74	..C..........GA.T..	MC46	.C....
MC55	...G.G..G.....GA.T..	MC25	....T.
MC46	...........C.GA.T..	MC18	.....
MC25	T.....C....A.GAA.TCT	MC17	.....
MC18	.............GA.T..	MC13	.....
MC17	.............GA.T..	MC2	.....
MC13	.T...G....C...GA.T..	D57	.....G
MC2	.....G........GA.T..	D48	...G..
D57	.............GA.T..	D44	..C...
D48	.............GA.T..	D42	.....
D44	.........G....GACT..	D40	..C...
D42	....CG........GA.T..	D34	.....
D40	.....G.G......GA.T..	D6	A.....
D34	.............GA.T..		

Figure 5B : *Two types of insulin in mice.*

Specific insulin receptors required for regulated insulin function

The primary limiting factor in using different species insulins to treat diabetes lies in the insulin receptor (Figure 6A and 6B) since very precise configurations are required to obtain an efficient and appropriate response of binding different insulins within the recipient's specific insulin receptor [22,23]. The function of the insulin receptor also explains the increased dosage of unrelated donor islets for islet xenograft implants for human to mouse implants.

It is the binding of insulin to its receptor that initiates the signals that eventually result in lowering blood glucose concentrations. Ins A is the human insulin A chain and Ins B in the human insulin B chain.

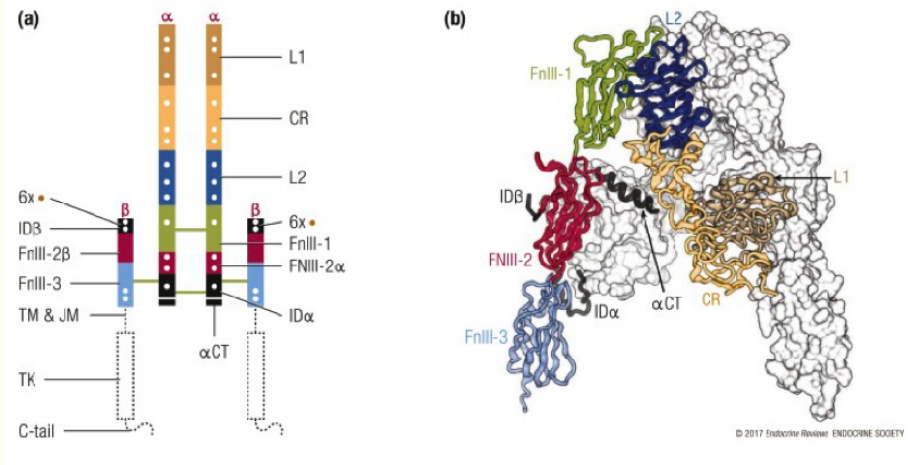


Figure 6A : *Human insulin receptor.*

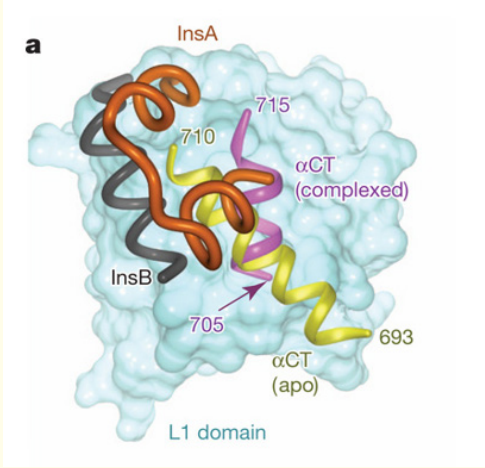


Figure 6B : *Human insulin receptor binding a single molecule of human insulin.*

Islets in birds

Species	Relative Size	Islet Cell Types	Structure	Beta Cell Replication	Diabetes	Induced Diabetes
Sparrow Mallard Chicken	No information provided on adult islet size	Dark Staining: α and δ cells with few β cells; Light Staining: Peripheral β cells and δ cells staining: α, β and δ cells	Depends upon species with examples of central β cells with others having peripheralβ cells. Chickens: islets concentrated in pancreas tail with γ cells in the head of pancreas	In egg through puberty, but not well known beyond	Spontaneous Diabetes not documented	By pancreas removal by surgery, but not very effective in certain bird species
Birds Ref [26]	No information provided on adult islet size	α, β, δ, γ cells within islet structures	Different areas of the pancreas contain differing concentrations of islet hormones	In egg through puberty, but not well known beyond	Spontaneous Diabetes not documented	By pancreas removal by surgery, but not very effective in certain bird Species Birds are very resistant to Alloxan and Streptozotocin

Table 4: *Islets in birds.*

Specific references for each of these studies are in the original publication.

Islets in Birds have a specific staining with dark islets and light islets described [24-27]. All islet cell types are represented. Interestingly, chickens have the majority of islets scattered throughout the pancreas. Different bird species have β cells located in the core while others have them concentrated in the mantle, similar to mammalian islets. Spontaneous diabetes has not been recorded in birds. Islet expansion has not been documented post-puberty. Interestingly, some bird species have had pancreatectomies without the development

of diabetes. This means that there are other locations of islets in some birds that have not been identified. It is also known that a group of genes in a segment of DNA are missing in birds that is thought to have occurred as far back as during the separation of birds from dinosaurs. But these lost genes do not involve insulin function.

A more definitive description of glucose homeostasis is found in reference [26]. Figure 1 from that reference is shown here as figure 7. This figure shows Plotting Plasma Glucose levels from 5 - 25 mM/L versus Log Body Mass from -5 to +10 for 97 bird species and 162 mammals. Interestingly, statistical analyses of these results show that the slope of these data for birds and mammals is the same at -0.44 so that these two species follow the same patterns of smaller animals having higher plasma glucose values than larger animals within the same species. However, there is a very significant difference between mammals and birds in terms of the plasma glucose levels. Extrapolating back to the y intercepts for these two species (Figure 7) shows that birds have 15.3 mM/L plasma glucose values while mammals have 7.6 mM/L plasma glucose values. These two values are significantly different at the $p < 0.001$ level. So essentially all birds carry a higher plasma glucose level than all mammals at similar body sizes. So, the question is what are the mechanisms and risks of these higher plasma glucose levels in birds. Along with the higher plasma glucose levels, birds have a higher metabolic rate, maintain a higher body temperature, and have longer life spans than mammals given equivalent body mass. So, the birds physiology has had to have developed different and more protective mechanisms than mammals to reduce the incidence of oxidative stress that would be expected with these metabolic levels in mammals.

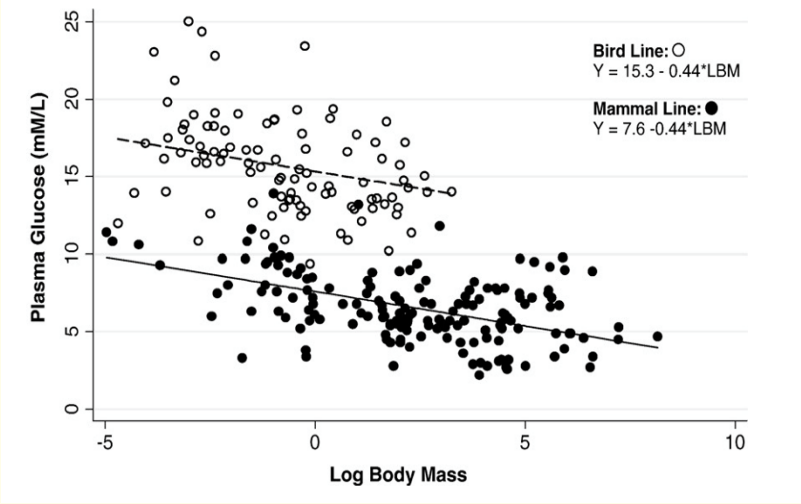


Figure 7: *Comparison of plasma glucose concentrations and log body mass in mammals and birds.*

Traditionally, oxidative stress is expressed by documenting levels of reactive oxygen species and significant glycation end products resulting from hyperglycemia. The first major difference is that bird mitochondria produce far less concentrations of superoxide and hydrogen peroxide than do rat mitochondria. Avian tissues also have much higher levels of endogenous anti-oxidants such as superoxide dismutase as well as oxygen radical scavengers: catalase, and glutathione peroxidase. In addition, birds produce much higher levels of uric acid that is another potent antioxidant. Another difference is in the intestinal absorption of glucose that is the birds' primary carbohydrate that immediately converts > 30% of the absorbed glucose to lactate before releasing it to the body. In poultry, their primary glucose source comes from starch that is eaten and converted back to glucose within the intestine by pancreatic amylase released from the pancreas by feeding.

In terms of the avian endocrine system, the pancreatic islets contain insulin producing β cells, glucagon producing α cells, somatostatin producing δ cells, and pancreatic polypeptide producing γ cells. Some birds, such as chickens, have insulin-producing β cells but a much lower percentage than mammals. In addition, glucose stimulated insulin release from bird islets requires much higher glucose levels than mammals. However, glucagon concentration stored in islet tissues are 8 - 10 times the levels observed in mammals. Birds are also hypersensitive to low blood glucose levels and very sensitive to glucagon release and will respond not only by glucose release but also release triglyceride, glycerol, and free fatty acids. Somatostatin release is similar to mammals but is believed to also be released by very high glucose levels. Pancreatic polypeptide functions in birds by suppressing insulin release and is involved in fat metabolism.

Islets in reptiles

Species	Relative Size	Islet Cell Types	Structure	Beta Cell Replication	Diabetes	Induced Diabetes
Lizards	Very large Islets	α cells more prominent than β cells But δ cells and γ cells included, Reptile islet hormones all react to mammalian islet antibodies	No separation of different types of islet cells, but δ cells and γ cells more likely in exocrine pancreas	In egg and through puberty, but not well known beyond	Spontaneous Diabetes not documented, unusual for hyperglycemia except for stress related, Single case report of glucagonoma that killed its host	Alloxan only kills β cells
Snakes	Size and shape varies but large in comparison to others, except lizards	α cells: 35% to 55% β cells: 25% to 40% most common in snakes and δ cells and γ cells also present	Islets in separate structure β cells: central location; α cells: peripheral location; but can be reversed in some species; π cells: separate from islets; some have no islet structure	In egg and through puberty, but not well known beyond	Spontaneous Diabetes not documented, unusual for hyperglycemia except for stress related	Not Known
Chelonians (Turtles)	Smaller islets than lizards and snakes	α cells more prominent than β cells But δ cells and γ cells included,	Some turtles have islet cells types in gastric and gut mucosa	In egg and through puberty, but not well known beyond	Spontaneous Diabetes not documented, unusual for hyperglycemia except for stress related Hyperglycemia post-hibernation	Not Known
Crocodilians	Smaller islets than lizards and snakes	β cells located centrally, α cells located peripherally δ cells and γ cells also present	Islets associated with larger pancreatic ducts	In egg and through puberty, but not well known beyond	Spontaneous Diabetes not documented unusual for hyperglycemia except for stress related	Not Known

Table 5: *Islets in Reptiles: Lizards, Snakes, Turtles, and Crocodilians.*
Specific references for each of these studies are in the original publication.

Reptile islets are generally noted to be much larger than many other species [27]. In general, α cells are more prominent in islets than β cells. There also are variations in islet type locations, even with some associated with pancreatic ductal cells and gastric and gut mucosal

cells. Islet cell replication is not observed outside the egg and growth through puberty. It is not unusual to observe hyperglycemia when reptiles are under stress, but specific diabetes has not been recognized.

Islets in fish

Species	Relative Size	Islet Cell Types	Structure	Beta Cell Replication	Diabetes	Induced Diabetes
Teleost	Unlike mammals, are located in separate structures	β cells - insulin, α cells - glucagon, Glucagon-Like, GLP, not like mammals, δ cell A Somatostatin 14 like mammals. δ cell B Somatostatin 25 not like mammals, Pancreatic Polypeptide not like mammals	A. Large compact, primary islet tissue by gallbladder B. β cells in Brockmann Body of islet tissue central with rim of α cells C. Also smaller islets seen scattered in pancreas depending upon species	Not observed	Not spontaneous	Alloxan and Streptozotocin variable model of diabetes by species
Lamprey	Unlike mammals, are located in separate structures	Similar to Teleost Islet Cell Types, but may lack α cells	Large compact islet tissue by gallbladder	Not observed	Not Spontaneous	Not Known
Eel	Typical mammalian sizes and locations	Not identified	Scattered Islets within pancreas similar to mammalian islets	Not observed	Not spontaneous	Not known
Catfish	Unlike mammals, are located in separate structures	32% β cells Insulin 23% α cells Glucagon 38% δ cells Somatostin	A. Large compact, primary islet tissue B. Smaller islets seen scattered in pancreas	Not observed	Not spontaneous	Not known
Carp	Unlike mammals, are located in separate structures	β cells centrally located in core α cells in periphery δ cells found in core	A. Large compact, primary islet tissue B. Smaller islets seen scattered in pancreas	Not observed	Develops Type 2 Diabetes Spontaneously	Not known

Table 6: *Islets in fish.*

Specific references for each of these studies are in the original publication.

Most fish islets are unique in that they are located within large structures, generally separated from the pancreas [29-36]. An exception is the eel, that has more mammalian islet structures. There are two types of these large islet cell containing structures: one is a large compact, primary islet cell containing structure, the second is called the Brockman Body that has large central area of islet cells surrounded by a mantle of acinar cells. In addition to these large islet structures in fish, there are also scattered islets within the exocrine tissue. Only the carp has been reported to develop Type 2 diabetes. While spontaneous diabetes has not been observed in other species, both alloxan and streptozotocin can induce diabetes in fish.

Unique insulin utilization by a mollusk

Species	Fish Hunting	Venom Insulin	Venom Target	Details of Venom Insulin	Induced Diabetes	Con-Ins G1 Action
Conus geographus Marine Cone nail. Also *c. tulpia* and *C. kinoshitai*	Release "poison" into sea water that is a venom insulin that binds rapidly	Con-Ins G1 Binds and activates vertebrate insulin receptor	Teleost fish that swim by ingest the venom insulin and get Hypo-glycemic	Insulin that does not form hexamers cluster so rapid acting. Model for new insulin for humans	Streptozotocin zebrafish and mice diabetes with high glucose	Reduces hyperglycemia in these diabetic fish and mice

Table 7: *Cone snail use of insulin as a venom to catch fish.*
Specific references for each of these studies are in the original publication.

Vertebrate insulin readily forms hexamers when in a pure form, as noted above. These Mollusk Cone Snails produce a short form of insulin only of the B arm that has had reductions and substitutions that permit rapid binding to the insulin receptor. It also does not form hexamers [37]. This model is being used by pharmaceutical companies to produce new, short armed insulins that can rapidly bind the vertebrate insulin receptor that then causes reduction of blood glucose levels. While all three species of Conus each make a different venom insulin, all three types function readily as a venom insulin.

Insulin-like substances in one-celled organisms

Species	Organisms	Insulin Binding	Simliar Structure	Nuclear Binding	Membrane Binding	Phylogenetic Ancient Origin
Protozoan	*Tetrahymena pyriformis*	Yes	Yes	Yes	Yes	Insulin-Like
Bacteria	*Escherichia coli*	Yes	Yes	Yes	Yes	Insulin-Like
Cynobacteria	*Synechocystis maxima*	Yes	Yes	Yes	Yes	Insulin-Like
Fungi	*Nurospora crassi*	Yes	Yes	Yes	Yes	Insulin-Like
	Aspergillus fumigatus	Yes	Yes	Yes	Yes	Insulin-Like

Table 8: *Insulin-like substance in one-celled organisms.*
Specific references for each of these studies are in the original publication.

Insulin-like substances do occur and are functional in these one-cell organisms that have been studied [38,39]. These studies confirm the phylogenetically ancient origin of the insulin molecular structure in demonstrating insulin-like functions raising the question if mammalian insulin arose from similar one-celled organisms and their insulin-like substances.

Insulin-like substances in insects

Insulin related peptides have been documented in all of these insect species tested [40-49]. However, their influences vary in the different species. Direct injection of mammalian insulin and glucagon have no effect. These insulin related substances originate from different locations and have varying effects on the specific species. They seem to relate to growth and development, foraging versus hive activities. There is evidence that some of these substances relate to reducing trehalose concentrations.

Species	Scientific Name	Insect Glucose Molecule	Anatomic Structures	Islet Similar Hormones	Effect on Trehalose	Explanations
Tobacco Horn Worm	*Maduca sexta*	Trehalose = double glucose, used as glucose in insects	Corpus Cardiacum = Neurohemal organ Corpus Allatum = Produces juvenile hormone	Insulin like 500pg insulin equiv and Glucagon like hormones extracted from these two structures	Insulin and Glucagon injections = no effect, Injections from 2 Corpus, decreased or increased Trehalose concentrations	Carbohydrate metabolism in insects is controlled by insulin-similar and glucagon-similar compounds
Indian Meal Worm	*Pladio puretella*	Trehalose = double glucose, used as glucose in insects	Corpus Cardiacum = Neurohemal organ Corpus Allatum = Produces juvenile hormone	Insulin like and Glucagon like hormones extracted from these two structures	Insulin and Glucagon injection = no effect, Injections from 2 Corpus, decreased or increased Trehalose concentrations	Carbohydrate metabolism in insects is controlled by insulin-similar and glucagon-similar compounds
Cockroach	*Periplaneta interpunctella*	Trehalose = double glucose, used as glucose in insects	Corpus Cardiacum = Neurohemal organ Corpus Allatum = Produces juvenile hormone	Insulin like and Glucagon like hormones extracted from these two structures	Insulin and Glucagon injection = no effect, Injections from 2 Corpus, decreased or increased Trehalose concentrations	Carbohydrate metabolism in insects is controlled by insulin-similar and glucagon-similar compounds
Silkmoth	*Bombyx mori*	Trehalose = double glucose, used as glucose in insects	Head of B. mori used to purify active agent	1st insect sourced N-terminal sequence homologous to vertebrate insulin and IGF (Insulin Growth Factor) - named "Bombyx"	A- and B - chains found 40% same as human insulin regulate nutrient-dependent growth and metabolism with similar equity in human IGF regulating growth of tissues	Documented similarities between human insulin and Insulin Growth Factor. Starving decreased *Bombyx,* Feeding stimulated its release with decrease in brain levels, regulating Trehalose
Honeybee	*Apis mellifera*	Trehalose = double glucose, used as glucose in insects	Corpus Cardiacum sourced insulin-like	Insulin like peptides ILP produced in neurons	Activity from fat body (liver/fat) of ILP's affect social foraging	ILP-1 and ILP-2 show differing activities from those taken from other areas
Blowfly	*Calliphora vomitoria*	Trehalose = double glucose, used as glucose in insects	Brain aspiration and alcohol extraction	Cross reaction with bovine insulin A and B chains, displaced bound insulin from rat liver plasma	Biological activity on rat fat cell, Reduced Trehalose and glucose in *Calliophora* post-neurosecretory cell removal	Source of this substance is from median neurosecretory cells
Locust Desert locus	*Locusta migratoria*	Trehalose = double glucose, used as glucose in insects	*Corpus cardiaca* sourced insulin related peptide	Insulin Related Peptides confirmed	Affected the reproductive cycles in males and females	From *corpus cardiac*a organ Related to Insulin Growth factors

Table 9: *Insulin-like substance in insects.*

Specific references for each of these studies are in the original publication.

Stimulating Insulin Release Substances in Plants

Species	Source	Extract Type	Animal Model	Beta Cell Replication	Stimulate Insulin	Effects
Acacia arabica (Leguminosae)	Seeds	Ingestion	Diabetic Rat Rabbit	No	Insulin Release	Hypoglycemia
Aegle marmelos (Rutaceae)	Leaf	Aqueous	Strep Diabetic Rats	No	Increased insulin secretion and uptake	Reduced Hyperglycemia
Agrimony Euptoria (Rosacae)	Leaf	Aqueous	Beta Cell Line BRIN-BD11	No	*In Vitro* Insulin Increase	*in vitro*
Alangium sativum (Alangiaceae)	Leaf	Methanol	Rat treated with dexamethasone	No	Presumed insulin release	Reduced Hyperglycemia Hyperlipidemia
Allium sativum (Alliaceae)	Leaf, Juice, Oil	Ethyl Ether None none	Alloxan diabetic rats and rabbits	No	Increased insulin secretion	Reduced Hyperglycemia
Aloe vera (Lillaceae)	Leaf	"Bitter Principle"	Diabetic rats	No	Increased insulin secretion	Reduced Hyperglycemia
Anno muricata (Annonaceae)	Not disclosed	Not disclosed	Strep Diabetic rats	No	Increased insulin release	Increased glucose uptake Reduced hyperglycemia
Asparagus racemosus (Liliaceae)	Root	Ethanol, hexane, Chloroform, Ethylacetate	Perfused rat pancreas, rat islets, cloned beta cells	No	Increased insulin release	Insulin tropism
Buhinia variegate (Caesalpiniaceae)	Leaf	Ethanol	Insulin-secreting cell line INS-1	No	Dose dependent insulin release	*In vitro*
Berberine	Direct	None	Rat Islets Fat cells	No	Increased insulin secretion	*In vitro* Fat cell insulin sensitized
Biophytum sensitivum (Oxalidaceae)	Leaf	Extract Reagent not disclosed	Rabbits	No	Increased insulin synthesis and release	Hypoglycemia
Boerhaavia diffusa (Nyctaginaceae)	Leaf Leaf	Chloroform Aqueous	Strep and Alloxan Diabetic Rats	No	Decreased blood glucose and Increased insulin	Reduced Hyperglycemia
Bougainvillea spectabilis (Nyctaginaceae)	Leaf	Ethanol	Strep Diabetic Rats	No	Increased hepatic glycogenesis	Reduced Hypoglycemia
Brassica nigra (Cruciferae)	Leaf	Aqueous	Not Disclosed	No	Increased pancreatic insulin	Reduced blood glucose levels

Cinnamon zeylaniucm (Lauraceae)	Plant	Not Disclosed	Isolated Islets	No	Increased Insulin Release	*In vitro*
Caesalpinia bonducella (Cesalpinaceae)	Plant	Aqueous Ethanol	Isolated Islets in Chronic Type II Diabetes Model	No	Increased Insulin Released	Reduced Blood Glucose Levels
Caffeine (0.01%)	Direct	None	90% PancX Diabetic Rat	Beta Cell Hyperplasia	Increased 1st and 2nd Phase Insulin	Reduced Blood Glucose Levels
Camellia sinensis (Theaceae)	Plant	Epigallocatechin gallate	Strep Diabetic Rats	No	Insulino-tropic Effect	Reduced Blood Glucose Levels
Capsicum frutescens (Solanaceae)	Plant	Not Disclosed	Strep Induced Type 2 Diabetic Rats	No	Increase insulin levels	Reduced Blood Glucose Levels
Catharanthus roseus (Apocyaceae)	Leaves and Twigs	Dichloro-Methane and Alcohol	Not Disclosed	No	Increase of insulin secretion	Reduction of oxygen radical damage
Citrullus colocynthis (Cucurbitaceae)	Pulp-Seeds	Ethanol Extract Multiple extracts	Alloxan Diabetic Rats, Isolated Islets, Rat Pancreas	No	Increase of insulin secretion Similar results	Reduced Blood Glucose Levels *In vitro*
Coccinia indica (Cucurbitaceae)	Plant	Dried	Human Study 500mg/kg PO for 6 weeks	No	Significant increase in insulin	Reduced Blood Glucose Levels
Cornus officinalis (Cornacese)	Plant	Alcohol Extract Methanol Extract	NIDDM Rats NIDDM Rats	Islet Proliferation	Increase in Glut 4 Increase insulin secretion	Increased insulin secreted Prevent islet toxicity
Elephantopus scaber (Asteraceae)	Plant	Acetone	Strep Diabetic Rats	Islet Proliferation	Increase in Insulin Secretion	Reduced Blood Glucose Levels
Enicostemma littoratle (Genbtianaceae)	Plant	Aqueous	Alloxan Diabetic Rats	No	Increased glucose-induced insulin secretion	Reduced Blood Glucose Levels
Ephedra distachya (Ephedraceae)	Plant	Alkaloids	Induced Diabetes in Mice	Islet Regeneration	Increased insulin levels	Reduced Blood Glucose Levels
Eriobotyra japonica (Rosaceae)	Plant	Not Disclosed	INS-1 cells	No	Increased insulin levels	*In vitro*
Euccalyptus globus (Myrtaceae)	Plant	Aqueous	Pancreatric Cell Line Abdominal Muscle Cells	No	Increased insulin secretion	*In vitro* Increased glucose utilization

Eugenia jambolana (Myrtaceae)	Seeds	Extract	Isolated islets normal and diabetic rodents	No	Increased insulin secretion	Inhibited insulinase activity from liver and kidney
Ficus bengalensis (Moraceae)	Plant Bark	Extract Extract	Normal and Diabetic Rats Rats and Alloxan Diabetic Dogs	No No	Increased insulin secretion Increased insulin secretion	Inhibited insulinase Hypoglycemia
Fermented Unsalted Soybeans	Not Done	Not Done	90% pancX Rats	Beta Cell Hyperplasia	Increased islet growth and differentiation factors	Increased insulin secretion
Geinstein or Prunetol	Not Done	Not Done	INS-1 cells, MIN6 cells, Mouse islets	No	Increased insulin secretion	cAMP/PKA pathway
Ginko biloba (Ginkgoaceae)	Plant	Extract	Normal Rats Humans	No	Increased insulin secretion	Lowered blood glucose
Radix glycyrrhizae (Fabaceae)	Plant	Extract + glycyrrhetinic acid	Isolated islets	No	Increased insulin secretion	Increased islet viability
Gymnema sylvestre (Ascipiadaceae)	Plant Leaves	Alcohol Water	Rat islets beta cell lines 27 T2Diabetic humans	Regeneration of beta cells *in vitro* and *in vivo*	Increased insulin secretion	Increased beta cells
Helicteres isora (Sterculiaceae)	Root	Butanol	Rats	No	Increased insulin sensitivity	Reduced Hyperglycemia
Hibiscus rosa sinensis (Malvaceae)	Plant	Ethanol	Rodent Oral dosing	No	Increased insulin release	Reduced Hyperglycemia
Hordeum vulgare (Gramineae)	Fruit	Not Done	NIDDM people Oral dosing	No	Increased insulin release	Reduced Hyperglycemia
Lepechinia caulescens (Lamiaceae)	Not Defined	Not Defined	Not Defined	No	Stimulated insulin release	Reduced Hyperglycemia
Medicago sativa (Fabaceae)	Plant	Aqueous	BRIN-BD11 islet cell line	No	Stimulated Insulin Secretion	*In viro*
Momordica charantia (Cucurbitaceae)	Fruit Juice Fruit green	Not Done Aqueous	Diabetic Rats Obese hyperglycemic mice	Increase in number of beta cells	Increased insulin secretion Recovery of damaged islets	Reduced Hyperglycemia
Mucuna pruriens (Leguminosae)	Seeds	Powdered	Rabbits |Alloxan treated rabbits	No	Increased insulin released	Lower Blood Glucose Levels
Nigella sativa (Ranunculaceae)	Oil	Not Done	Not Declared	No	Increased insulin released	Lower Blood Glucose Levels

Panax ginseng (Araliaceae)	Root	Not Done	Diabetic Mice	No	Increased insulin released	Lower Blood Glucose Levels
Pandanus odorus (Pandanaceae)	Plant	Extracted 4-Hydroxy benzoic acid	Rats	No	Increased insulin released	Lower Blood Glucose Levels
Prunella vulgaris (Labiatae)	Plant	Extracted Jiangtangsu	Diabetic Mice	No	Increased insulin released	Lower Blood Glucose Levels
Psidium guajava (Myrtaceae)	Plant	Extracted strictinin, isostrictinin, pedunculagin	Diabetic Humans	No	Improved sensitivity of cells to insulin	Lower Blood Glucose Levels
Pterocarpus marsupium (Fabaceae)	Plant Bark	Extracted Flavonoid, Epicatechin	Not Defined	No	Regranulate β cells Protective to β cells	Increased Insulin Release
Radix rehmanniae (Scrophulariaceae)	Rhizome	Extracted Pectin	Diabetic Mice	No	Increased insulin release	Lower Blood Glucose Level
Rehmania glutinosa (Scrophulariaceae)	Rhizome	Ethanol precipitate fraction hot water extract	Mice	No	Increased insulin release	Lower Blood Glucose Level
Ricinus communis (Euphorbiaceae)	Plant	Ethanol Extract	Diabetic Rats	No	Increased insulin release	Lower Blood Glucose Level Improved Lipids
Syzygium cumini (Rutaseae)	Fruit Pulp	Extract	Normal and Strep Diabetic Mice	No	Increased insulin release	Lower Blood Glucose Level
Salvia lavandifoilia (Lamiacea)	Plant	Not Defined	Not Defined	Increased number and Size of β cells	Increased insulin content	Lower Blood Glucose Level
Sarcopoterium spirosum (Rosaceae)	Plant	Aqueous	Hepatocytes	No	Glucose uptake increased	Increased insulin secretion
Selaginella tamariscina (Selaginellaceae)	Plant	Not Defined	Animal recipient not defined	No	Increased insulin release	Lower Blood Glucose Level
Semen coicus (Gramineae)	Seeds	Dried	Normal Rats Alloxan Diabetic Rats	No	Increased Insulin Rekease	Lower Blood Glucose Level
Smallanthus sonchifolius (Asteraceae)	Plant	Not Defined	Diabetic Rats	No	Increased Insulin Released	Lower blood Glucose Level

Stevia rebaudiana (Asteraceae)	Plant	Extract Glycoside steviosude	Mouse Islets INS-1 b cells	No	Increased insulin released	Lower Blood Glucose Level
Swetia chirayita (Gerntianaceae)	Plant	Extract Hexane "Swerchirin"	Rats Isolated Islets		Increased Insulin Release	Lower Blood Glucose Level
Swetia punicea (Gentianaceae)	Plant	Extract Ethanol and Ethyl acetate	STZ diabetic Mice	No	Increased Insulin Release	Lower Blood Glucose Level
Tabernanthe iboga (apocynaceae)	Plant	Aqueous	Not Defined	No	Increased Insulin Release	Lower Blood Glucose Level
Teucrium polium (Lamiaceae)	Plant	Aqueous Methanol = apigenin	Rats Diabetic rats	No Yes	Increased insulin Release Regenerate b cells	Lower Blood Glucose Level Lower Blood Glucose Level
Tinospora crispa (Menispermaceae)	Plant	Not Defined	Not Defined	No	Increased Insulin Release	Lower Blood Glucose Level
Tribuluks terrestris (Zygophyllaceae)	Plant	Not Defined	Normal Mice Alloxan Mice	No	Increased Insulin Released	Lower Blood Glucose Level
Trigonella foenum-graecum (Leguminosae)	Seeds	Not Defined Hydroxyiso-leucine amino acid	Not Defined	No	Increased Insulin Release	Lower Blood Glucose Level
Zizphus spina-christi (Rhamnaceae)	Leaves	Butanol xtract Christinin-A	Normal and Diabetic Rats	No	Increased Insulin Release	Lower Blood Glucose Level

Table 10: *Stimulating insulin release substance in plants.*
Specific references for each of these studies are in the original publication.

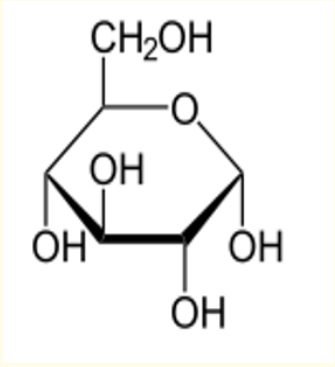
This major effort testing plant substances was done at the Pharmacognosy Research Laboratory at the Institute of Technology of Banaras Hindu University in India [50]. It should be noted that the majority of these 65 tests with plant components were tested in rats and mice. There were 9 studies observed in which beta cell expansion was documented following exposure to specific substances from plants. While the previous information regarding beta cell expansion were only successful in rodents, rats and mice, they were positive responses in all 65 agents tested in terms of increasing insulin release and lowering blood glucose levels. It remains to be tested if these 8 components from plants can stimulate higher mammalian and human islets to be able to be expanded. In addition, all of these specific studies demonstrated consistent increases in insulin release and lowering glucose levels.

With these 65 approaches all showing increased insulin release from their exposure from these plants to rodent islets, one has to wonder if there may be more than one of these that can increase insulin release from human islets. If this can be confirmed, then insulin-like plant substances may have a future in treating Type 2 diabetes patients. However, they may not play a role in Type 1 diabetes in humans, unless anti-inflammatory and anti-immune agents can be found in plants that could possible reduce the presence and regression of Type

1 diabetes beta cell destruction. If found, these agents could be combined with these insulin increasing effects of increased insulin release that could be important as a potential treatment for patients with either Type 1 or Type 2 diabetes.

Conclusion

Glucose homeostasis is a required mainstay for the metabolic well-being and survival of a multitude of animal species that include mammals, birds, reptiles, fish, and even single-celled animals. Glucose ($C_6H_{12}O_6$) a monosaccharide, is a simple sugar that is the most important energy source in living animals and is an important component in many carbohydrates. It has a readily stored form, glycogen, that is a large accumulation of glucose molecules $(C_6H_{12}O_6)_n$ as a polysaccharide that can be stored in animals predominantly in skeletal muscle and liver. It can also be rapidly broken down to glucose again as required by the organisms to meet their varying energy requirements.



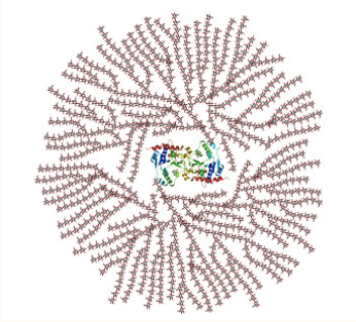


Figure 8: *Structure of glucose and glycogen.*

Glucose - $C_6H_{12}O_6$

Glucose is the most abundant simple sugar or monosaccharide in the plant and animal kingdoms. The largest producers of glucose are plants and algae using water (H_2O), carbon dioxide (CO_2) and energy from sunlight under photosynthesis. The storage form of glucose in plants is starch that is formed from glucose into a polysaccharide that is made up of amylose and amylopectin that also form branched structures, but smaller than glycogen. Glucose is the most important source of energy in all organisms in the world. Understanding its homeostasis is key to understanding how it is produced, stored, and utilized in both plants and animals.

Glycogen - $(C_6H_{12}O_6)30,000$

A core enzyme, glycogenin, in the liver and muscle polymerizes the first glucose molecules to initiate the glycogenic process that continues under glycogen synthase to add more glucose molecules. These additions continue to form multiple branches of glucose units

with the entire molecule containing up to 30,000 glucose units. This glycogen figure is a cross section representation of glycogen, with glycogenin in the middle [53].

The discovery of insulin for the treatment of Type 1 diabetes became a medical miracle overnight to replace starvation for insulin therapy to enable getting blood glucose levels under control. The current definition of human pancreatic islet cell makeup includes 5 specific, cellular types that each produce either insulin, glucagon, somatostatin, pancreatic polypeptide, or ghrelin. Insulin release in response to high glucose levels decreases elevated glucose concentrations. Glucagon release from low glucose levels increases glucose and fatty acid levels. Somatostatin release in response to low pH becomes an inhibitory hormone decreasing insulin, glucagon, pancreatic polypeptide and GI growth hormones. Pancreatic Polypeptide release from eating and exercise increases gastric juice. Ghrelin release from hunger and an empty stomach increase gastric acid and gastro-intestinal motility. There were 20 mammals, including human, evaluated regarding relative islet size, specific islet types and their locations within the islets, adult islet replication, the type of diabetes recorded and the type of induced diabetes recorded. It was found that 75% of these islets had beta cells centrally located with 25% peripherally located or mixed. In mammals, beta cells (insulin) form 55 - 75% of the islet cells except in marsupials, alpha cells (glucagon) form 35 - 40% of the islet cells, somatostatin producing and pancreatic polypeptide producing cells each form 5 - 10% of the islet cells, and ghrelin represent 2 - 5% of the islet cells. In terms of beta cell replication after birth and puberty, only rodents maintain the ability to continue islet cell replication into adults. Spontaneous diabetes, Type 1 and/or 2, develops in humans, non-human primates, cats, dogs, horses, cattle, goats, sheep, pigs, and red and gray kangaroos. Induction of diabetes experimentally with Alloxan or Streptozotocin, is predominantly successful in rodents with a little success in sheep and pigs. Some of the other species may develop the metabolic syndrome or exhibit hyperglycemia, but not true diabetes. Mice and rats also have two insulin molecules. Metabolic responses to the release of insulin and other islet hormones is mediated through specific hormone receptors that actually induce the appropriate and selective response.

In bird species, there in general are two types of staining islets with dark ones having very few β cells and the light staining ones with peripheral β cells in higher concentrations. Some bird species have β cells in the core while others have then in the periphery. Spontaneous diabetes is not found in birds. Inducing diabetes by pancreas removal is not uniformly successful in birds.

Reptiles have very large islets compared to mammals and have higher percentages of α cells than β cells. It is not uncommon in reptiles for islet cells to also be scattered throughout the pancreas. Reptiles seem to have all islet cells represented, except for ghrelin that has not been studied well as yet. Spontaneous diabetes is not documented in reptiles, but hyperglycemia can be induced under stress. Alloxan has been noticed to specifically kill beta cells in lizards. Replication of reptilian islets has not been noted.

Fish species have a common anatomically islet difference than mammals in that the majority of islet cells are located in large, separated structures with some additional islets scattered throughout the exocrine pancreas. These large islet cell containing structures are either in compact primary islets near the gall bladder only with islet cells or are located in Brockman bodies that contain islet cell cores with surrounding exocrine cells on the periphery. Islet cell types are in general similar to mammals except that there is a second somatostatin hormone containing cells and pancreatic polypeptide is not like the mammalian hormone. Only the carp species has been noted to spontaneously develop Type 2 diabetes. Yet, Alloxan and Streptozotocin induced diabetes has been successful in Teleost fish.

Only one Mollusk was identified for interest in this report which is the cone snail. These sea creatures are able to produce a small portion of the B chain of the mammalian insulin molecule that is able to activate hypoglycemic responses to the vertebrate insulin receptor. The cone snails release this venom insulin into the sea waters in their immediate area. When a teleost fish swims by it becomes hypoglycemic, making it easy prey for the cone snail.

In terms of one-celled organisms, Protozoan, Bacteria, Cynobacteria and Fungi have been identified to perform binding to insulin with similar structure to mammalian insulin that results in both nuclear binding and membrane binding to result in glucose changes. These insulin-like molecules are similar to mammalian insulin.

Evaluation of insulin-like substances were evaluated in insects. There are significant differences from the mammalian carbohydrate metabolism in insects, but remarkable similarities in cause and functions. A major difference in insects is that the primary sugar molecule is called trehalose, but it is actually two glucose molecules that can be separated. The major differences are in the types of organs that handle glucose and insulin in the insects. The origin of insulin-like substances that work on permitting trehalose to be used by the insects are more from neural head and chest of these insects. Two organs, corpus cardiaca and corpus allatum, are able to produce and release insulin-like and glucagon-like compounds whose functions are similar to the mammalian hormones. The insect's carbohydrate metabolism is controlled by their own specific hormones. The insect insulin-like substance has a 40% homology with the A and B chains of mammalian insulin and glucagon. It has also been shown that mammalian insulin and glucagon do not function in insects, most likely due to major differences in their hormone receptors as well as the substances themselves.

The final study discussed here involved the evaluation of 65 plant substances that may affect mammalian islet hormone stimulation and responding glucose responses. The predominant study animals were rats and mice, but some rabbits were used as well as some isolated islets and insulin-producing cell lines. The basic design tested parts of plants such as seeds and leaves that had different extraction chemicals used on predominantly diabetic rodents. The outcomes were to determine if glucose stimulated insulin could be observed as well as decrease in the animals' diabetic hyperglycemia. It is not clearly defined as to how these 65 plant substances came to be selected. However, all 65 plant sourced candidates resulted in an increase in insulin and a resultant decrease in hyperglycemia. In a few cases, that positive response depended upon how the same plant substance was produced for testing, for example by aqueous or alcohol extractions.

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Volume 2 Issue 7 September 2019