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New description of vagal nerve commanted intrapancreatic taste buds and blood glucose level: An experimental analysis

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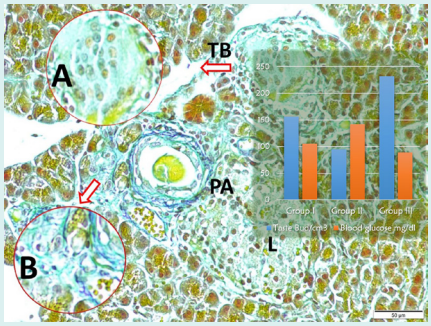
Abstract

Introduction: There have been thousands of neurochemical mechanism about blood glucose level regulation, but intrapancreatic taste buds and their roles in blood glucose level has not been described. We aimed to investigate if there are taste buds cored neural networks in the pancreas, and there is any relationship between blood glucose levels.



Methods: This examination was done on 32 chosen rats with their glucose levels. Animals are divided into owned blood glucose levels. If mean glucose levels were equal to 105 ± 10 mg/dL accepted as euglycemic (G-I; n = 14), 142 ± 18 mg/dL values accepted as hyperglycemic (G-II; n = 9) and 89 ± 9 mg/dL accepted as hypoglycemic (G-III; n = 9). After the experiment, animals were sacrificed under general anesthesia. Their pancreatic tissues were examined histological methods and numbers of newly described taste bud networks analyzed by Stereological methods. Results compared with Mann-Whitney U test $P < 0.005$ considered as significant.

Results: The mean normal blood glucose level (mg/dL) and taste bud network densities of per cm^3 were: 105 ± 10 mg/dL; 156±21 in G-I; 142 ± 18 mg/dL and 95 ± 14 in G-II and 89 ± 9 mg/dL and 232 ± 34 in G-III. *P* values as follows: $P < 0.001$ of G-II/G-I; $P < 0.005$ of G-III/G-I and $P < 0.0001$ of G-III/G-II. We detected periarterial located taste buds like cell clusters and peripherally located ganglia connected with Langerhans cells via thin nerve fibers. There was an inverse relationship between the number of taste buds networks and blood glucose level.

Conclusion: Newly described intrapancreatic taste buds may have an important role in the regulation of blood glucose level.

Introduction

Taste buds are well defined in the tongue, urethra, but not in the pancreas. Blood glucose level should be regulated via the intrapancreatic glucose-sensing neural web, which stimulated vagal fibers linked with that web. Because increased glucose level is a primary stimulator of glucose regulating vagopancreatic complex.[1] All taste information carry with facial, glossopharyngeal, vagal nerves are required for nutrition,[2] orgasmic taste sensations conveyed with pudendal nerves required for propagation,[3] mammarian taste buds are essential for lactation to baby nutrition[4] and all of them are necessary to avoid toxic materials. All taste information reaches the solitary nucleus, limbic forebrain,[5] reticular formations[6] insular cortex,[7] and endocrine organs to organize all metabolic cascades. Vagal nerve stimulation (VNS) via higher glucose levels increases pancreatic islet blood flow and insulin secretion.[8] An intrapancreatic ganglia-

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islet cell linked dense neural plexus forming vagal nerve[9] should include newly described glucose-sensing taste bud-like structures of the pancreas by ourselves. Probably intrapancreatic unmyelinated ganglion neurons around to blood vessels and islet cells[10,11] could innervate that glucose-sensing taste buds of the pancreas to secrete insulin. Although taste buds receptors[12] and glucose regulating neural mechanism has been described,[13] taste buds-like structures have not been defined in the pancreas. We examined if there is a link between blood glucose level and taste bud like structures in pancreas.

Materials and Methods

Animals

This examination was studied on 32 rats which were chosen according to blood glucose levels. Blood glucose levels were measured twice a day/consecutive two days. If blood glucose levels were 105 ± 10 mg/dL accepted as euglycemic (G-I; n = 14), 142 ± 18 mg/dL accepted as hyperglycemic (G-II; n = 9) and 89 ± 9 mg/dL hypoglycemic (G-III; n = 9). At the end of the experiment, all rats were sacrificed with general anesthesia following intracardiac formalin injection. Their pancreatic tissues were examined by Stereological methods. The numbers of pancreatic taste buds cored neural network and blood glucose levels were compared with the Mann-Whitney U test.

Tissue preparation

The pancreatic tissues with vagal and sympathetic nerves were gently removed and fixed in 10% formalin solution. The samples were embedded in the paraffin block and sectioned via Leica RM2125RT microtome (Leica Microsystems, Wetzlar, Germany). The pancreas tissues cut into 5-µm thick and consecutive 20 sections using a microtome. To determine histological architectures of the pancreatic taste buds, intrapancreatic ganglia, Langerhans cells, and connecting nerve fibers were examined. The sections were stained with H&E, aldehyde-fuchsin, S100, and gustducin and examined with a light microscope. To estimate the numbers of taste bud networks per cubic, millimeter, stereological, and Cavalieri's methods were used. Taste bud network numbers and glucose levels were analyzed statistically and $P < 0.005$ accepted as meaningful.

Results

Taste buds descriptions in pancreas

We detected taste buds-like structures arranged around pancreatic periarteriolar spaces similar to pine slices. Each taste bud of the pancreas opened in periarteriolar soft tissue compartments with their orifices within the microvilli of the adventitial surface. Taste bud cells have many apical microvilli, a dominant central nucleus in a dense cytoplasmic extension covered by epithelial cells connected with nerve fibers in the basal lamina. A pancreatic taste bud consisted of 5-7 spindle-shaped, modified epithelial cells. Each taste bud has a small orifice on the surface of the arteriolar regions. The base of the taste bud was surrounded by many thin myelinated nerve fibers. The basolateral membrane of taste cells formed a neural connection with many nerve fibers. The nerve fibers entered the base of the taste bud and probably transmit taste information to the brain. Some extensions of small nerve fibers arising from intrapancreatic ganglia ended in inside or bottom of the taste buds and the other extensions connected with Langerhans cells and named as taste buds cored network.

Microphotographic documentations as follows: histological view of the pancreas with pancreatic artery (PA), pancreas innervating vagal nerve branches, Langerhans cells, and thin brown colored nerve fibers (Fig. 1). Histological appearances of taste bud-like structures in the pancreas, and description of taste bud-like (TB) with a specific immunohistochemical method summarized in Fig. 2. Intrapancreatic ganglia, their neural extensions, and taste bud-like structures are seen in Fig. 3. Fig. 4 shows a histological view of the pancreas, pancreatic arteries, and appearances of taste bud-like structures around PA, Langerhans cells. Intrapancreatic taste bud/ganglia/Langerhans cells network, the discriminative

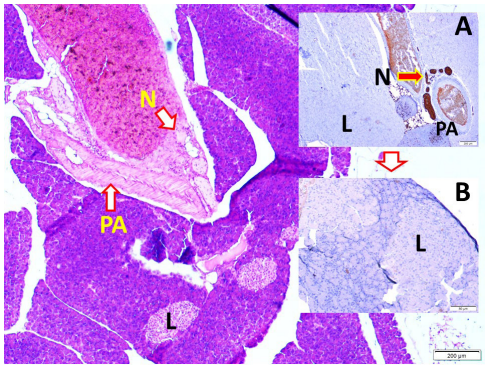

Fig. 1. Histological view of the pancreas with the pancreatic artery (PA), pancreas innervating vagal nerve branches (N), Langerhans cells (L), (LM, H&E, x4/Base; LM, S100, x4/A) and magnified form of Langerhans cells and thin brown colored nerve fibers (LM, S100, x20/B).

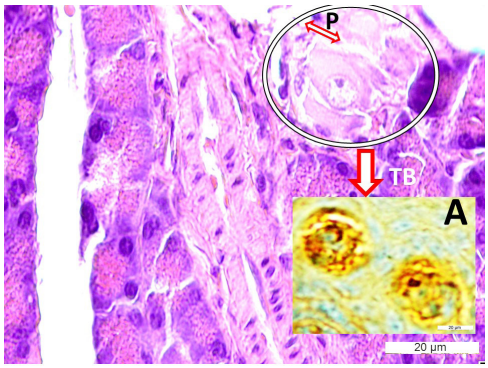

Fig. 2. Histological appearances of taste bud-like structures (TB in the circle) with consisting cells and apical pores (P) in the pancreas, (LM, H&E, x40/Base) and description of TB with specific immunohistochemical method (LM, Gustducine x40/A).

appearances of periarterial located taste bud just near of intrapancreatic ganglia in a magnified form, and, TB/PG/L centers connecting nerve fibers are seen in Fig. 5.

Numerical results of the experiment

The mean normal blood glucose level and taste bud densities per cm^3 of control animals were: 105 ± 10 mg/dL; 156 ± 21 in G-I; 142 ± 18 mg/dL and 95 ± 14 in G-II and 89 ± 9 mg/dL and 232 ± 34 in G-III. P values between that groups: $P < 0.001$ of G-II/G-I; $P < 0.005$ of G-III/G-I and $P < 0.0001$ of G-III/G-II. There was a linear relationship between the numbers of taste roseas and neuron density of geniculate ganglion neurons ($P < 0.005$). But, there was an inverse relationship between taste buds-neuron density of geniculate ganglia and blood glucose levels ($P < 0.0001$). The numbers of taste buds and glucose levels are summarized in Table 1.

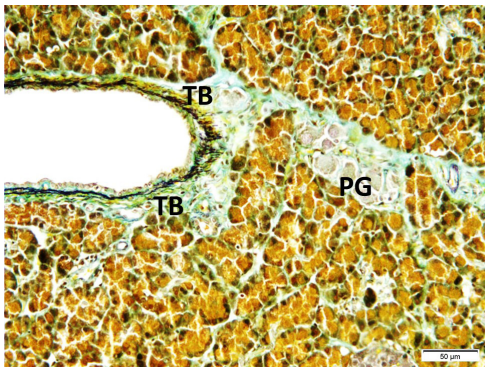

Fig. 3. Intrapancreatic ganglia (PG), their neural extensions, and taste bud-like structures (TB) are seen (LM, Aldehyde-fuchsin, x20).

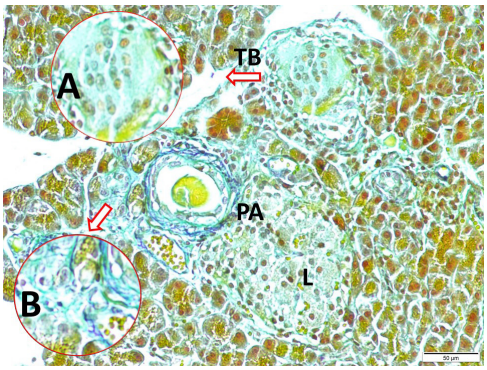

Fig. 4. Histological view of the pancreas, pancreatic arteries (PA), and appearances of taste bud-like structures (arrows-A/B) around PA, Langerhans (L) cells (LM, Aldehyde-fuchsin x20).

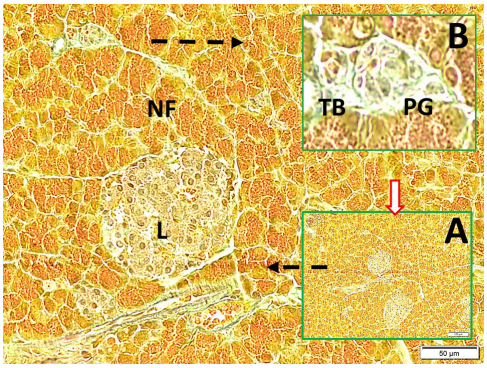

Fig. 5. Glucose level regulating intrapancreatic taste bud/ganglia/Langerhans cells network (LM, Aldehyde-fuchsin, x10/A), the discriminative appearances of a periarterial located taste bud (TB) just near of intrapancreatic ganglia (PG) in a magnified form (LM, Aldehyde-fuchsin, x40/B); and, TB/PG/L centers connecting nerve fibers are seen (LM, Aldehyde-fuchsin, x20/Base).

Discussion

Blood glucose level and regulation are essential for life because glucose is an important energy source for animals and a primary stimulator for insulin secretion in the pancreas. Tongue taste information conveys with facial, glossopharyngeal, vagal nerves[2]; genital-mammarial taste bud information carry with pudendal nerves in animals.[3,4] All of those networks may be responsible for body glucose regulation. Our previous studies have shown that blood glucose regulating mechanisms should include mammarial and genital taste buds in addition to oral taste buds and pancreas.

The pancreas has been accepted as an essential organ and the vagal nerve as a primary nerve for glucose regulation. A combination of pancreatic innervation by nodose ganglia, vagal dorsal motor nucleus, nucleus ambiguus, T6-L2 spinal ganglia, and coeliac ganglion[14] is essential for glucose regulation.[15,16] Glucose-recognizing pancreatic paraneurons are required for insulin release.[17] All taste information of tongue, mammary gland and genitalia reach to caudal regions of the solitary tract nucleus, limbic forebrain, reticular formation,[6] and insular cortex.[7] In the brain, primarily mediodorsal prefrontal cortex,[18] insular cortex,[19] lateral hypothalamus, amygdala and globus pallidus have also glucose-sensitive and glucose level monitoring neurons[20] to manage body glucose modulation. The sympathetic nervous system also mediates catabolic responses to glucose metabolism.[21] Our previous studies and publications proved that pleasure-creating hedonic sensations originating from taste bud including organs such as tongue, mammary gland and genitalia reach to the spinal cord and mentioned higher brain centers to regulate all body-organ glucose levels.[3,4]

How the pancreas feels blood sugar, which cell group firstly informs glucose regulation requirement, and how the first information is created in the pancreas has not yet been clearly defined. According to our hypotheses,

Table 1. Numerical values of study

	Group I (n=14)	Group II (n=9)	Group III (n=9)
Taste Bud/cm^3	156±21[a]	95±14[c]	232±34[b]
Blood glucose mg/dL	105±10[a]	142±18[c]	89±9[b]

All values given mean ± standard deviation, Group I: Normal, Group II: Hyperglicemic, Group III: Hypoglicemic.
[a] $P < 0.001$ between groups I/II; $P < 0.005$ between groups I/III; [c] $P < 0.0001$ between groups II/III.

there should be glucose-sensing cells, which co-working with the vagal nerve in the pancreas. Because vagal nerve determines to some extent sugar sense in tongue and probably informs pancreas to secrete insulin with facial nerves. Without a taste bud-vagal nerve complex as described in the pancreas, it will be difficult to understand the blood sugar-regulating mechanisms by the pancreas with the available information. Wherever the glucose-sensitive receptors of β-cells have been described for explaining insulin secretion[1] this theory doesn't explain the rationale mechanism of glucose regulation. Insulin-producing cell surfaces have sweet taste receptors[22] like in the stomach, pancreas, gut, liver, and brain.[12]

Intra and extrapancreatic ganglionar unmyelinated axons usually located adjacent to exocrine epithelial ducts, interlobular space, and blood vessels in the pancreas regulate glucose level.[10] That pancreatic ganglia receive visceral information from pancreatic exocrine and endocrine glands.[23] Endocrine pancreas innervated by intrapancreatic ganglia.[24] The intrapancreatic ganglia fibers and vagal fibers could innervate the taste receptors of the pancreas just as the tongue.[11]

Taste sensing receptor deficiency might result in glucose absorption and metabolism disorders.[25] Bilateral vagotomy abolished insulin response to glucose.[26] Bilateral gustatory cortex lesions rely on diabetes mellitus.[27] Hyperglycemia is common after ischemic lesions of the vagus nerve nuclei.[28] The second-generation antipsychotic drugs have the efficacy to treat schizophrenia but can cause diabetes mellitus.[29] If many drugs could cause autonomic ganglia/islet cells toxication induced diabetes mellitus, the deficiency of newly described intrapancreatic taste bud may rely on diabetes mellitus.

Clinical implications and importance of the study

The vagus nerve has a key function to regulate blood glucose level and neuromodulation techniques are more likely to succeed in type II diabetes treatment.[30] VNS has been used to reduce body blood glucose levels in diabetic rats by enhancing vagal efferent activity and the release of GLP-1.[31] Afferent VNS inhibits pancreatic insulin secretion. In contrast, efferent VNS stimulates pancreatic insulin secretion in treating type II diabetes.[32] The pathological insults of the vagus nerve cause diabetes in chronic alcoholism.[33] Altered insulin sensitivity/secretion causes diabetic cardiovascular autonomic neuropathy in recent-onset type 1 and type 2 diabetes.[34] Acute vagal stimulation alters glucose and insulin metabolism but chronic vagal stimulation improves insulin sensitivity substantially in diet-induced obesity by both peripheral and central mechanisms.[35] In that circumstances, we easily hypothesized that afferent fibers of vagal nerves may sense information of glucose sensing pancreatic taste buds, and efferent fibers of vagal nerves could be stimulated by glucose-sensing intrapancreatic taste buds/vagus circuitry to secrete insulin from the pancreas.

Research Highlights

What is the current knowledge?

√ Diabetes is a disease with a history as old as medical history. Although many in-depth studies have been conducted to enlighten its etiopathogenesis, there has not been enough focus on these taste buds located in the pancreas.

What is new here?

√ Stimulation of nerves or ganglia responsible for pancreatic innervation by means of mini neurostimulators may shed light on the future electrophysiological treatment of diabetes, which has until now been pharmacologically treated.

New ones in this study

The firstly described pancreatic taste buds are similar to the tongue mammarian gland or genitalia. That differentiation may reflect the innervating nerve differentiates described by previous studies.[36-38] According to our observations, glucose molecules stimulate taste buds in the pancreas and created information carry with afferent fibers of vagal nerves to brain centers and integrated pancreatic signals probably stimulate efferent fibers of vagal nerves to secrete insulin from the pancreas.

Limitation of the study

Insulin, HbA1c, glucagon, and required biochemical or radiological studies should be done.

Conclusion

The newly described taste buds cored network of the pancreas may have functioned as a pre-determinative role on the blood glucose level regulation, and starts new hardware and software examinations to understand secret mechanisms of diabetes mellitus

Future insights

We hope that this study will open new horizons in the diagnosis and treatment of type-2 diabetes mellitus. Tissue implantation or future neural networks can help insulin-dependent patients.

Funding sources

There was no funding for this study.

Ethical statement

The study protocol and permissions were reviewed and approved by the Ethics Committee for Animal Experiments, Faculty of Medicine, Ataturk University. The animals were managed, and the experiments were conducted according to the guidelines prescribed by the Committee.

Competing interests

None.

Authors' contribution

MDA and AA conceptualized and refined research ideas. MDA, OC, and MEA performed the literature search. EK, KAN, and RD conducted the experiments. MEA, OC, and EK performed collection and preparation

of datas. MDA, OC, MEA performed the writing and editing manuscript. All authors read and approved the final manuscript.

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