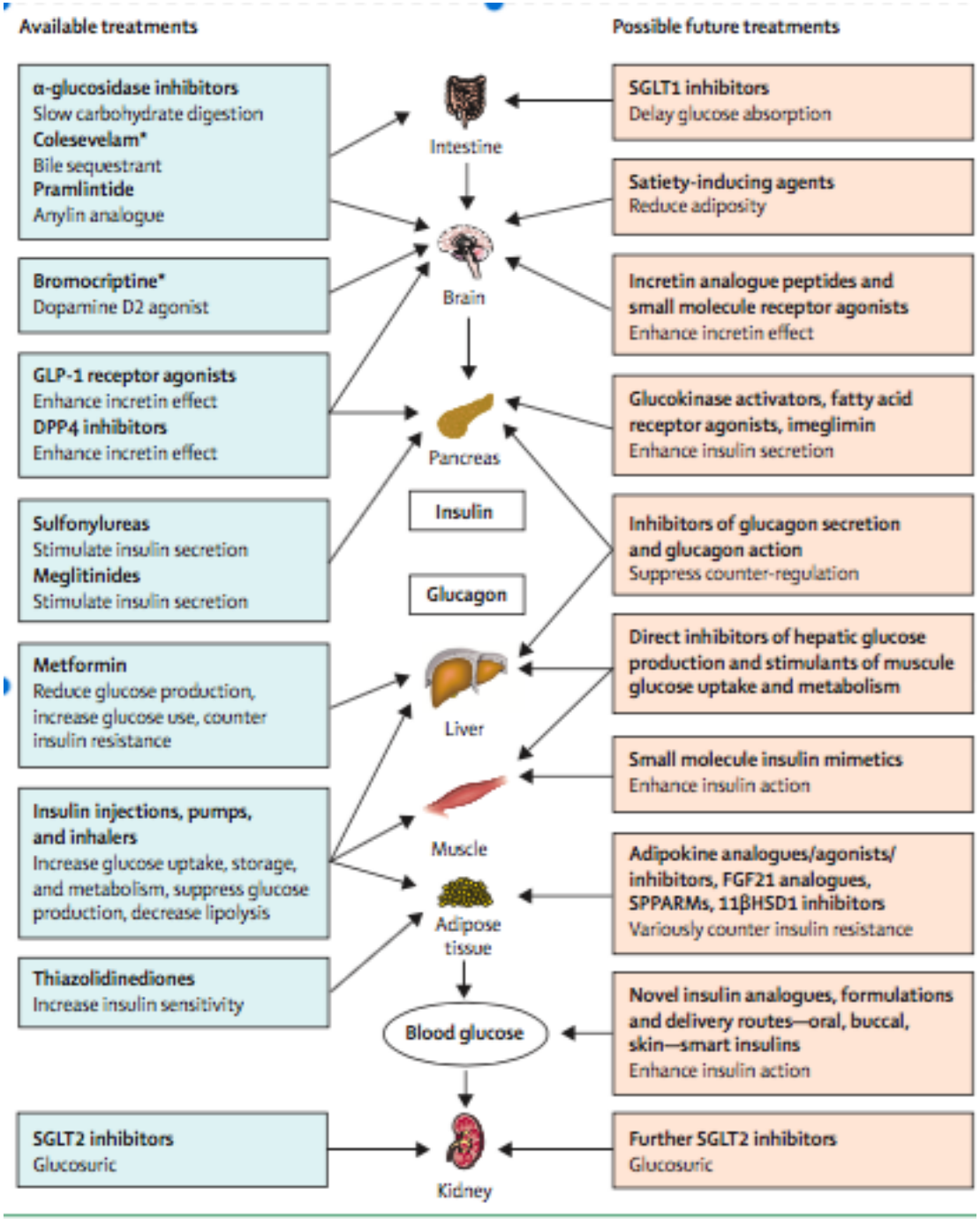
Diyabet Tedavisinde Güncel Yaklaşımlar

Dr.Nalan METİN AKSU
HÜTF Acil Tıp AD
17.03.2017


Available treatments
Possible future treatments
α-glucosidase inhibitors
Slow carbohydrate digestion
Colesevelam*
Bile sequestrant
Pramlintide
Amylin analogue
Bromocriptine*
Dopamine D2 agonist
GLP-1 receptor agonists
Enhance incretin effect
DPP4 inhibitors
Enhance incretin effect
Sulfonylureas
Stimulate insulin secretion
Meglitinides
Stimulate insulin secretion
Metformin
Reduce glucose production, increase glucose use, counter insulin resistance
Insulin injections, pumps, and inhalers
Increase glucose uptake, storage, and metabolism, suppress glucose production, decrease lipolysis
Thiazolidinediones
Increase insulin sensitivity
SGLT2 inhibitors
Glucosuric
Intestine
Brain
Pancreas
Insulin
Glucagon
Liver
Muscle
Adipose tissue
Blood glucose
Kidney
SGLT1 inhibitors
Delay glucose absorption
Satiety-inducing agents
Reduce adiposity
Incretin analogue peptides and small molecule receptor agonists
Enhance incretin effect
Glucokinase activators, fatty acid receptor agonists, imeglimin
Enhance insulin secretion
Inhibitors of glucagon secretion and glucagon action
Suppress counter-regulation
Direct inhibitors of hepatic glucose production and stimulants of muscle glucose uptake and metabolism
Small molecule insulin mimetics
Enhance insulin action
Adipokine analogues/agonists/ inhibitors, FGF21 analogues, SPPARMs, 11βHSD1 inhibitors
Variously counter insulin resistance
Novel insulin analogues, formulations and delivery routes—oral, buccal, skin—smart insulins
Enhance insulin action
Further SGLT2 inhibitors
Glucosuric

	Mechanism of action	Glucose-lowering effect	Development status	Comments
Glucokinase activators	Increase glucokinase activity in pancreatic islets and liver	Increase insulin secretion and hepatic glucose uptake	Phase 3	Challenges of hypoglycaemia and durability
GPR40 (also known as FFAR1) and GPR119 agonists	Activates fatty acid receptors in pancreatic islets and gut	Increase insulin secretion and enteroendocrine L-cell incretin secretion	Phase 1–3	TAK-875 (GPR40 agonist) discontinued in phase 3
Imeglimin	Close mitochondrial transition pores	Increases insulin secretion and decreases gluconeogenesis	Phase 3	
Exenatide implantable osmotic pump	GLP1 receptor agonist	Mimics effects of GLP1	Phase 3	Active for 6–12 months
Oral and subcutaneous semaglutide	GLP1 receptor agonist	Mimic effects of GLP1	Phase 2–3	Oral drug has similar efficacy to subcutaneous injection
Non-peptide GLP1 receptor agonists	GLP1 receptor agonist	Mimic effects of GLP1	Preclinical	Proof of concept
Omarigliptin (once-weekly)	DPP4 inhibitor	Increase endogenous incretin action	Phase 3	Efficacy similar to sitagliptin
TGR5 (also known as GPBAR1) agonists	Stimulate bile acid receptors in ileum	Increase L-cell incretin secretion	Preclinical	Preliminary observations
Fixed-ratio combinations: GLP1 receptor agonists with insulin	GLP1 receptor agonist and basal insulin	Mimic effects of GLP1 and insulin at same time	Phase 3	Insulin degludec and liraglutide combination was recently approved and insulin glargine and lixisenatide combination is in development
Hybrid and chimeric designer peptides	Agonism or partial antagonism of selected peptides	Mimic effects of selected incretins and other peptides	Preclinical	Proof of concept
Glucagon receptor antagonists	Decrease glucagon action	Decrease hepatic glucose output	Preclinical to phase 2	Several drugs identified in preclinical studies, restricted clinical progression
Insulin receptor signalling potentiators	Prolong Tyr phosphorylation of insulin receptor B-subunit	Increase insulin action	Preclinical	Proof of concept—eg, PTP1B (also known as PTPN1) inhibitors and vanadium salts
SGLT1 and 2 inhibitors	Selectively decrease SGLT1 (also known as SLC5A1) and SGLT2 (also known as SLC5A2) activity in gut and kidney	Increase renal glucose elimination; delays gut glucose absorption; changes incretin secretion	Phase 2–3	Efficacy shown in initial clinical studies
Non-peptide adiponectin receptor agonists	Adiponectin R1/R2 agonists	Increase insulin action	Preclinical	Proof of concept
FGF21 analogues	FGF21 receptor agonists	Increase insulin sensitivity and improves lipid profile	Phase 1	Might act partly through adiponectin
GPR120 (also known as FFAR4)	Activates fatty acid receptors in adipose and other tissues	Increases insulin sensitivity and adipogenesis	Preclinical	Proof of concept
Selective peroxisome proliferator-activated receptor modulators	Selective peroxisome proliferator-activated receptor alpha, gamma, and delta agonists	Increase insulin sensitivity, adipogenesis or lipid profile, and islet β-cell viability	Phase 1–2	Opportunity to selectively enhance efficacy and reduce unwanted effects
11β hydroxysteroid dehydrogenase-1 inhibitors	Inhibit 11β hydroxysteroid dehydrogenase-1 conversion of cortisone to cortisol in liver and adipose tissue	Increase insulin sensitivity and improves lipid profile	Phase 1–2	Challenge to prevent compensatory rise in concentration of adrenocorticotropic hormone
Fructose-1,6 bisphosphatase inhibitors	Increase fructose-1,6 bisphosphatase activity	Decrease hepatic glucose output	Phase 2	Initial clinical studies show efficacy
Adenosine monophosphate kinase activators	Increase adenosine monophosphate kinase cellular effects on nutrient metabolism	Increase glucose uptake and metabolism	Preclinical	Proof of concept

This list is not comprehensive but shows the various mechanisms and stages of development represented in this Review

Table 1: List of some potential new glucose-lowering medications for type 2 diabetes

Diabetologia (2016) 59:1795–1805
DOI 10.1007/s00125-016-4022-4

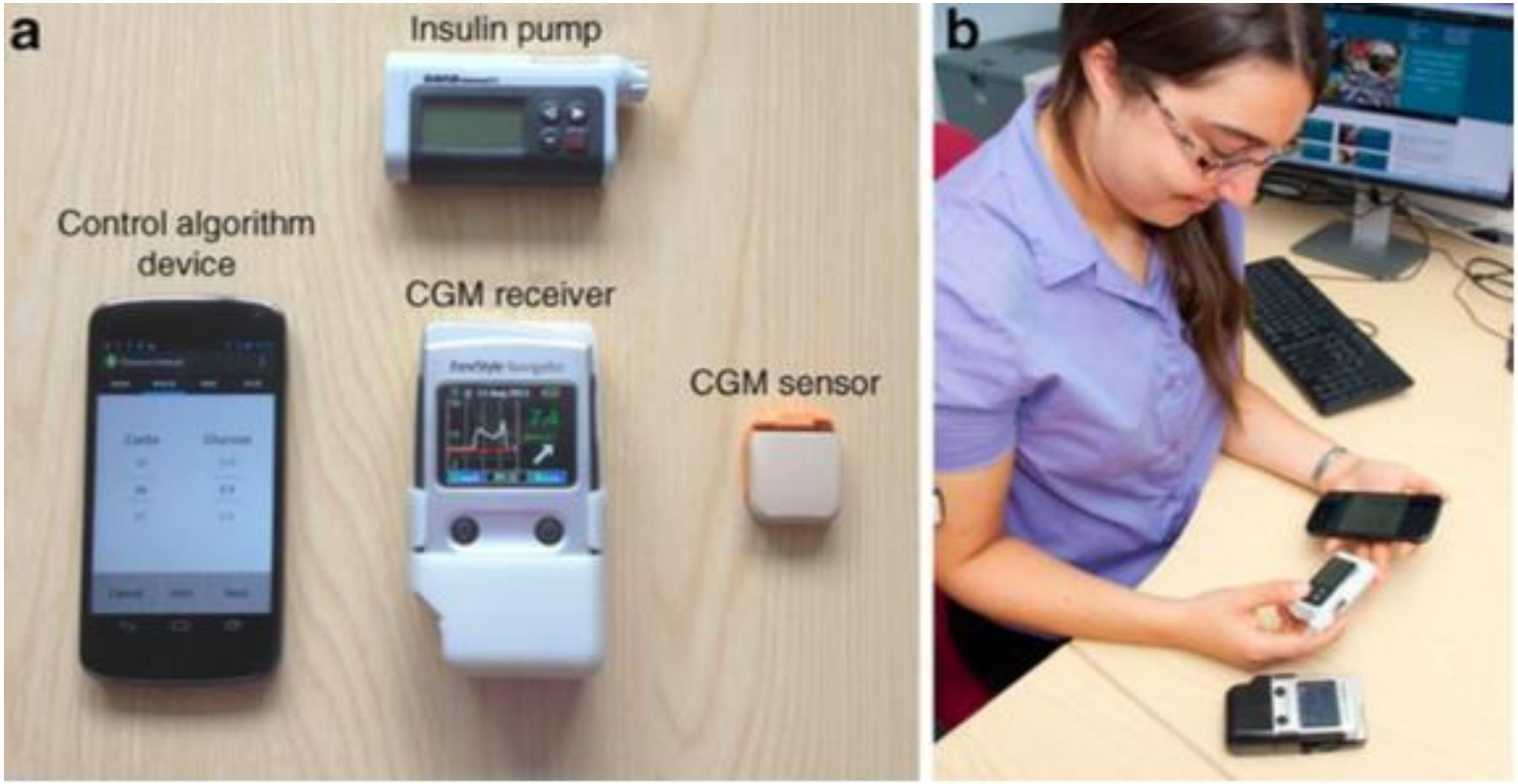
REVIEW

Coming of age: the artificial pancreas for type 1 diabetes

Hood Thabit[1,2] · **Roman Hovorka**[1,3]

- 1960: kapiller glukozmetreler
- 1970: insülin pompa tedavisi
- Kapalı loop sistem:
- devamlı glukoz monitorizasyon sistemi ve sensörü
- Insülin pompa sistemi
- mobil kontrol algoritm cihazı

- Glukoz <70 mg/dl =>pompa otomatik stop.
- Biyohormonal pompa: insülin
- glukagon
- Amaç: Tip1 DM'de gece hipoglisemilerini önlemek


a
Insulin pump
Control algorithm device
CGM receiver
CGM sensor
b

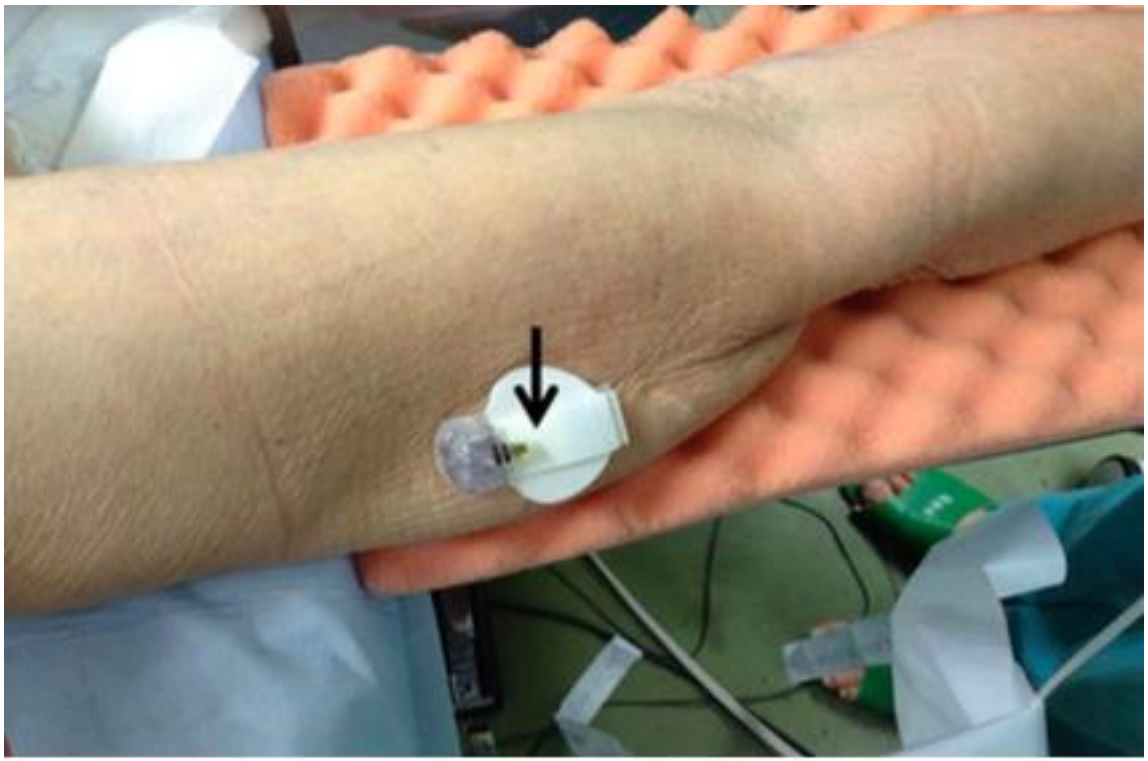
J Artif Organs (2016) 19:209–218
DOI 10.1007/s10047-016-0904-y

REVIEW

Artificial Liver, Pancreas

Current topics in glycemic control by wearable artificial pancreas or bedside artificial pancreas with closed-loop system

Kazuhiro Hanazaki[1] · Masaya Munekage[1] · Hiroyuki Kitagawa[1] · Tomoaki Yatabe[2] · Eri Munekage[1] · Mai Shiga[1] · Hiromichi Maeda[1] · Tsutomu Namikawa[1]



ig. 1 Representative real-time CGMS, the iPro®2 (Medtronic Co
td., USA) (*arrow*)

- Subkutanöz interstisiyel sıvıdaki glukoz miktarını ölçüyor.
- Bu değerler sistemik sirkulasyondaki glukoz değeri ile korele bulunmuş.
- Ölçümler her 10 sn'de bir yapılıyor
- Wireless aktarıcı ile glukoz sensöre her 5 dak'da bir aktarılıyor.
- 1 glukoz sensör 6 gün kullanılabiliniyor.
- ↑ ve ↓ değerlerde alarm verir.

Fig. 2 Bionic pancreas with a bi-hormone pump system that comprises insulin and glucagon pumps (edited quotation from website of http://www.artificialpancreas.org/)

- Daha iyi glisemik kontrol sağlıyor.
- Daha az hipoglisemik ataklar oluyor.
- Fizyolojik duruma daha yakın
- Daha fazla çalışmalara ihtiyaç var.

DIABETES/METABOLISM RESEARCH AND REVIEWS
Diabetes Metab Res Rev 2017; **33**: e2822.
Published online 21 June 2016 in Wiley Online Library (wileyonlinelibrary.com). **DOI**: 10.1002/dmrr.2822

REVIEW ARTICLE

The role of insulin pump therapy for type 2 diabetes mellitus

- Glisemik kontrolde amaç HbA1c < %7
- Ted: Kilo kaybı, diyet ve oral ilaç
- Zamanla insülin rezervi azalır,insülin ihtiyacı ↑
- Tedaviye insülin eklenmesi glisemik kontrolü ↑
- Tip 2 DM lerde insülin pompa tedavisiyle ilgili ilk RKÇ
- 2014'de "OpT2mise"
- Tip 2 DM'lerde günlük multiple doz insülin ve subkutanöz devamlı insülin tedavisini karşılaştıran çalışmalar yetersiz.

J Artif Organs (2016) 19:209–218
DOI 10.1007/s10047-016-0904-y

REVIEW

Artificial Liver, Pancreas

Current topics in glycemic control by wearable artificial pancreas or bedside artificial pancreas with closed-loop system

Kazuhiro Hanazaki[1] · Masaya Munekage[1] · Hiroyuki Kitagawa[1] · Tomoaki Yatabe[2] · Eri Munekage[1] · Mai Shiga[1] · Hiromichi Maeda[1] · Tsutomu Namikawa[1]

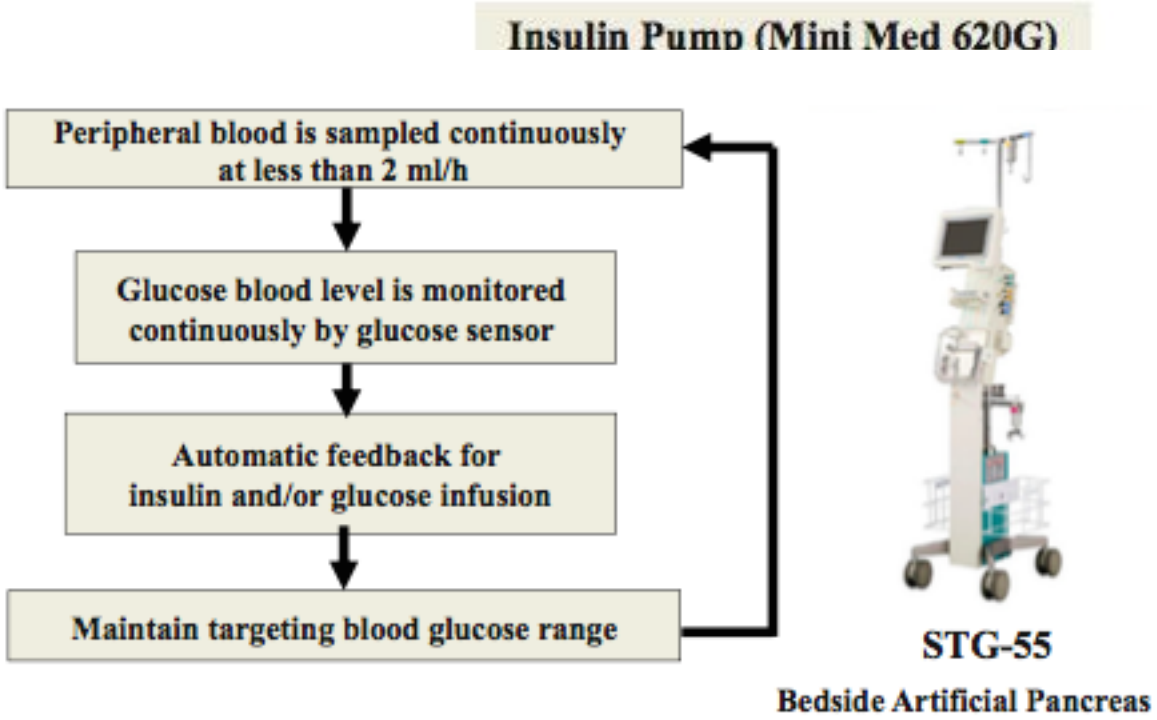


Fig. 4 Bedside artificial pancreas with closed-loop system: STG-55 (Nikisso Co. Ltd., Japan)

omprising a real-time CGMS (iPro®2) and mono-insulin pump ystem (MiniMed® 620G; Medtronic Co. Ltd., USA)

Available online at
ScienceDirect
www.sciencedirect.com
Elsevier Masson France
EM|consulte
www.em-consulte.com/en

Review

The role of natriuretic peptides in diabetes and its complications

Ying Feng, Da Wang, Huili Bi, Huijuan Zhang*

Department of Endocrinology, First Affiliated Hospital of Harbin Medical University, 23 Youzheng Street, Nangang District, Harbin 150001, China

ARTICLE INFO

Article history:
Received 3 July 2016
Received in revised form 6 October 2016
Accepted 30 October 2016

Keywords:
Diabetes
Diabetes complication
Natriuretic peptides

ABSTRACT

This review aimed to summarize recent findings on the role of natriuretic peptides (NPs) in diabetes and its important complications. Although the treatment of diabetes mellitus has benefited from recent advances, aggressive glycemic control can increase the risk of hypoglycemia and weight gain. Therefore, innovative therapies are required to address this issue. Natriuretic peptides (NPs) may have such novel therapeutic potential. NPs comprise a family of structurally related peptides, including atrial, brain, C-type, and dendroaspis. Each of these NPs has a wide range of specific functions to regulate and maintain cardiovascular, renal, and endocrine homeostasis. NPs exert their effects by interacting with three receptor subtypes including NPR-A, NPR-B, and NPR-C. The coronary NP system has been suggested to be involved in regulating water and salt balance, as well as vascular remodeling. In this review, we provide evidence that NPs play an important role in diabetes mellitus and its related complications including macrovascular and microvascular disorders. NPs hold promise as markers for early diagnosis, risk

Growth hormone-releasing hormone (GHRH) is produced by the hypothalamus and

frontiers in Endocrinology

MINI REVIEW
published: 10 October 2016
doi: 10.3389/fendo.2016.00129

Check for updates

Growth Hormone-Releasing Hormone in Diabetes

Leonid E. Fridlyand[1], Natalia A. Tamarina[1], Andrew V. Schally[2,3] and Louis H. Philipson[1,4]*

ways as to how the GHRHR pathway can interact with glucose and other secretagogues

Growth hormone-releasing hormone (GHRH) is produced by the hypothalamus and stimulates growth hormone synthesis and release in the anterior pituitary gland. In addition, GHRH is an important regulator of cellular functions in many cells and organs. Expression of GHRH G-Protein Coupled Receptor (GHRHR) has been demonstrated in different peripheral tissues and cell types, including pancreatic islets. Among the peripheral activities, recent studies demonstrate a novel ability of GHRH analogs to increase and preserve insulin secretion by beta-cells in isolated pancreatic islets, which makes them potentially useful for diabetes treatment. This review considers the role of GHRHR in the beta-cell and addresses the unique engineered GHRH agonists and antagonists for treatment of type 2 diabetes mellitus. We discuss the similarity of signaling pathways activated by GHRHR in pituitary somatotrophs and in pancreatic beta-cells and possible ways as to how the GHRHR pathway can interact with glucose and other secretagogues

Diabetologia
DOI 10.1007/s00125-016-4175-1

REVIEW

Chronomedicine and type 2 diabetes: shining some light on melatonin

Andrew C. Forrestel[1] · Susanne U. Miedlich[1] · Michael Yurcheshen[2] · Steven D. Wittlin[1] · Michael T. Sellix[1]

Herein we review our understanding of molecular clock control of glucose homeostasis, detail the influence of circadian disruption on glucose metabolism in critical peripheral tissues, explore the contribution of melatonin signalling to the aetiology of type 2 diabetes, and discuss the pros and cons of melatonin chronopharmacotherapy in disease management.

nalan.metinaksu@hacettepe.edu.tr