Pharmacology of Diabetes Mellitus (DM)

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Diabetes Mellitus

- classification (Expert Comittee; 2003)
  - Type 1 Diabetes Mellitus (IDDM)
    - severe and/or absolute insulin deficiency
    - <30 years (childhood, young adulthood)
    - viral infection, immunological dysfunction (autoAB)
    - insulin replacement!!!
    - life-threatening complications
  - Type 2 Diabetes Mellitus (NIDDM) (90-95%)
    - relative insulin deficiency
    - adulthood, elderly
    - multifactorial (genetic-, environmental factors)
    - insulin oversecretion! - tissue resistance! – impaired insulin action
    - „metabolic X" syndrome
  - Type 3 Diabetes Mellitus
    - elevated glucose levels
      - pancretectomia, pancreatitis, drug induced, etc.
  - Type 4 Diabetes Mellitus
    - gestational DM
    - 4-5% of all pregnancies
    - insulin therapy
    - oral antidiabetics – CI!!!

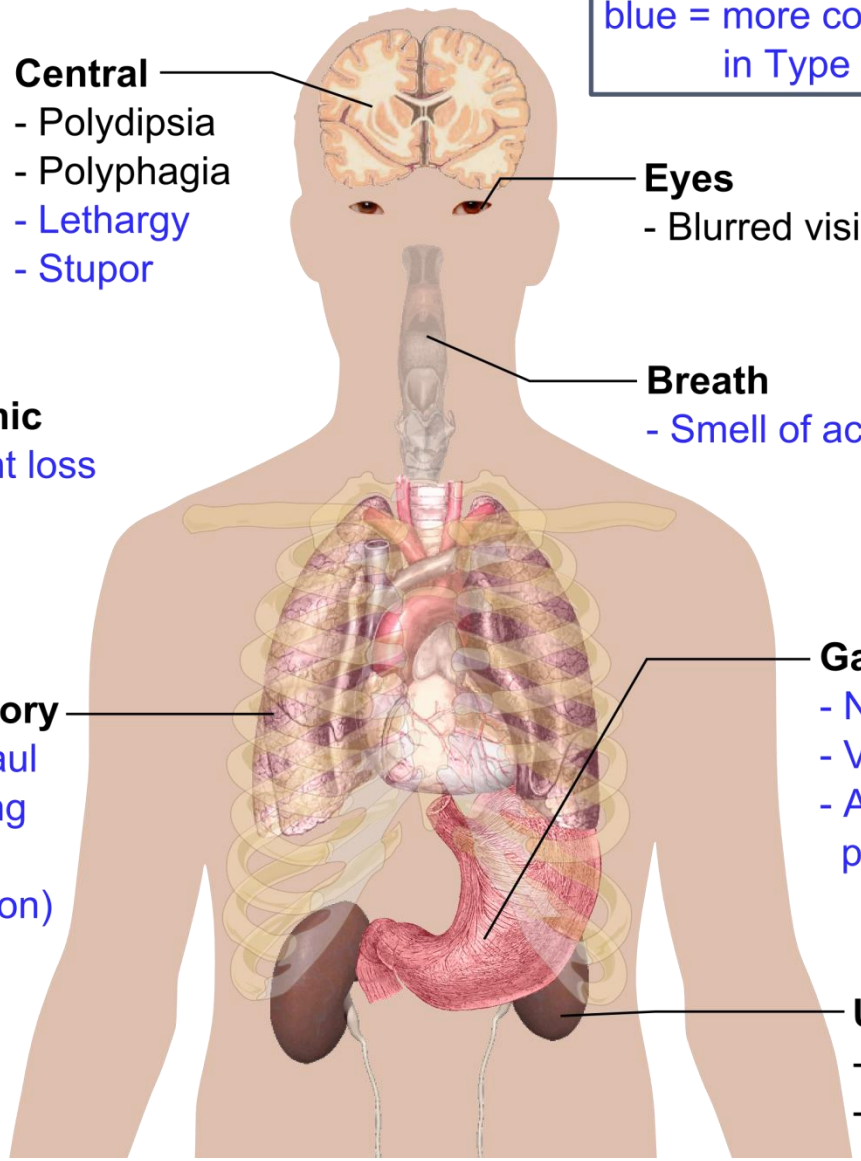
<u>Complications of DM (AGE/AGP)</u>

- macroangiopathy
  - stroke
  - ACS
- microangiopathy
  - diabetic nephropaty
  - diabetic retinopathy
  - diabetic neuropathy

Main symptoms of

Diabetes

blue = more common in Type 1



Central
- Polydipsia
- Polyphagia
- Lethargy
- Stupor

Eyes
- Blurred vision

Breath
- Smell of acetone

Systemic
- Weight loss

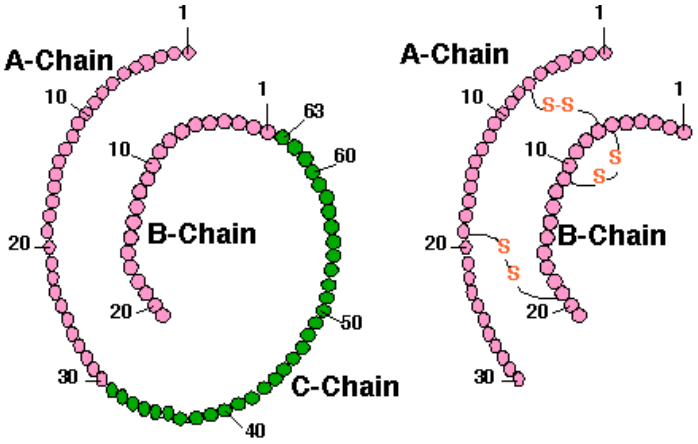
Respiratory
- Kussmaul breathing (hyper-ventilation)

Gastric
- Nausea
- Vomiting
- Abdominal pain

Urinary
- Polyuria
- Glycosuria

Insulin

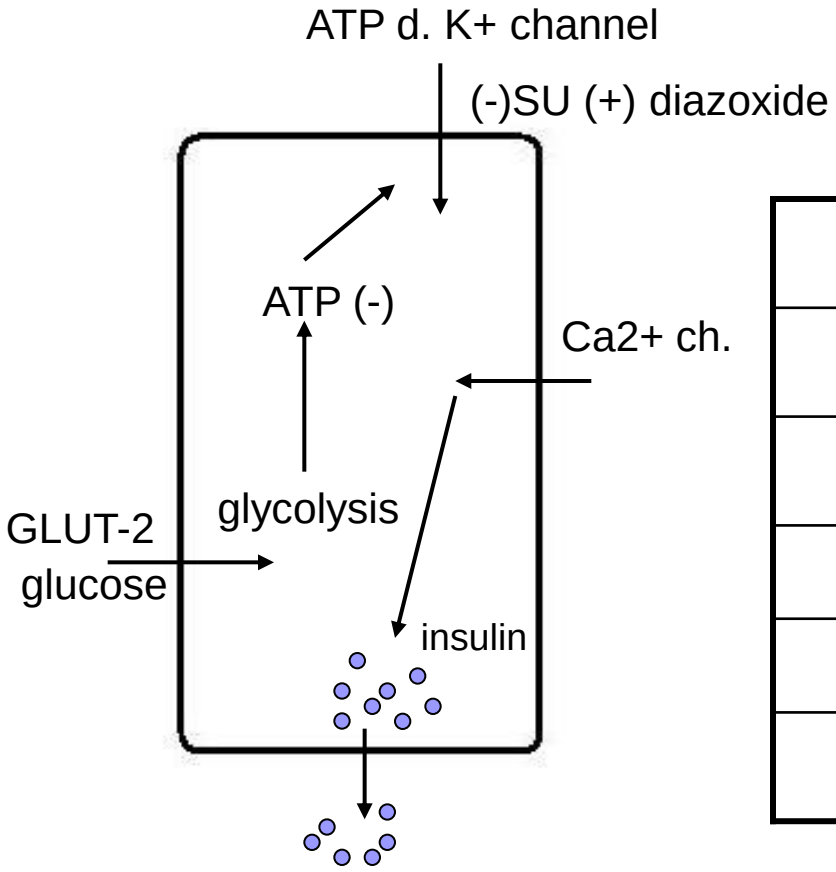
- anti-diabetic hormone
- chemistry
  - contains 51 amino acids –
  - 2 chains (A,B)– disulfide bridges
  - proinsulin (Golgi apparatus) –
    insulin + C-peptide (equimolar dose!)



- secretion
  - pancreatic β cells
    - stimulated by
      - glucose
      - hormones: incretines (GLP-1, GIP), CCK, vagal activity
    - inhibited by
      - somatostatin, leptin, FFA, triglycerides↑

- degradation
  - liver (60%), kidney (35-40%)

Pancreatic secretion



Cell types	Appr. percent of islet mass	Secretory product
A cell	20	Glucagon, proglucagon
B cell	75	Insulin, proinsulin, C-peptide, amylin
D cell	3-5	Somatostatin
G cell	1	Gastrin
F cell	1	Pancreatic polypeptide

- Insulin receptor
  - represented in „target cells”
    - liver, muscle, adipose tissue
  - heterodimer structure - 2α 2β subunits
  - autophosphorylation, Tyr-kinase activity
  - phosphorilation pathways (IRS, PI3 kinase, MAP kinase)

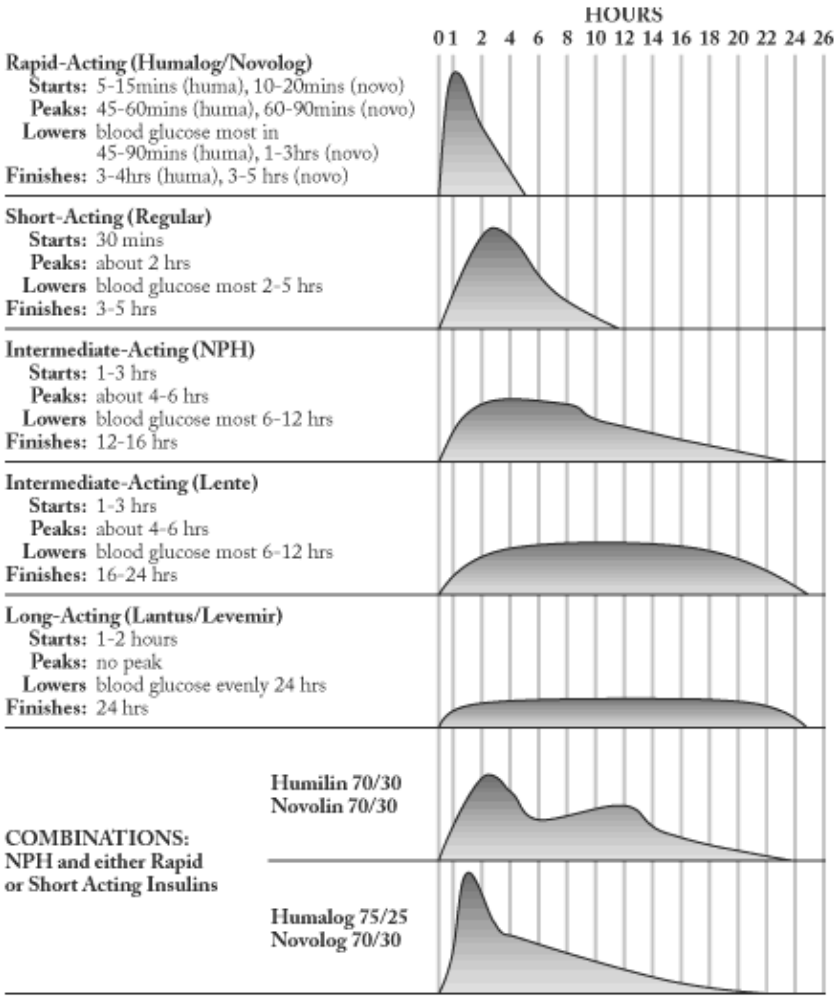
- Effects of insulin
    - anabolic hormone, antidiabetic!, lipogenetic! effects
  - liver
    - promotes glucose storage as glycogen (induces glucokinase, glycogen synthetase, inhibits glycogen phosphorylase)
    - increase glucose transport (GLUT-4)
    - stimulates TG synthesis
    - inhibits of glycogenolysis
    - inhibits conversion of fatty acids and amino acids to ketoacids
    - inhibits converion of aminoacids to glucose
  - muscle
    - increases protein synthesis
      - increases amino acid transport
    - increased glycogen synthesis
    - increased glucose transport (GLUT-4)
  - adipose tissue
    - increased triglycerid storage
    - induce LPL (lipoprotein lipase), hydrolyze triglycerides from lipoproteins
    - glycerol-3-phosphate↑ - TG synthesis↑
    - inhibits i.c. lipase (hormone-sensitive-lipase)

Insulin therapy

- daily insulin demand: 40 IU (1IU=28mg)
- circulating insulin:
  - basal insulin value: 5-15μU/mL
  - postprandial insulin value: 60-90 μU/mL
- application: subcutaneously!!!
- Aim: to reproduce the normal, physiologic insulin secretion, (to replace the background-, basal overnight-, fasting-, prandial (mealtime) insulin)
- Insulin production: recombinant DNA techniques
- Classification
  - rapid acting
    - insulin LisPro (Humalog)
    - insulin Aspart (Novolog)
    - insulin GluLisine (Apidra)
  - short acting
    - Regular Novolin R
    - Regular Humulin R
  - intermediate acting
    - NPH insulin (Humulin N)
  - long acting
    - insulin detemir (Levemir)
    - insulin glargine (Lantus)
  - premixed insulins

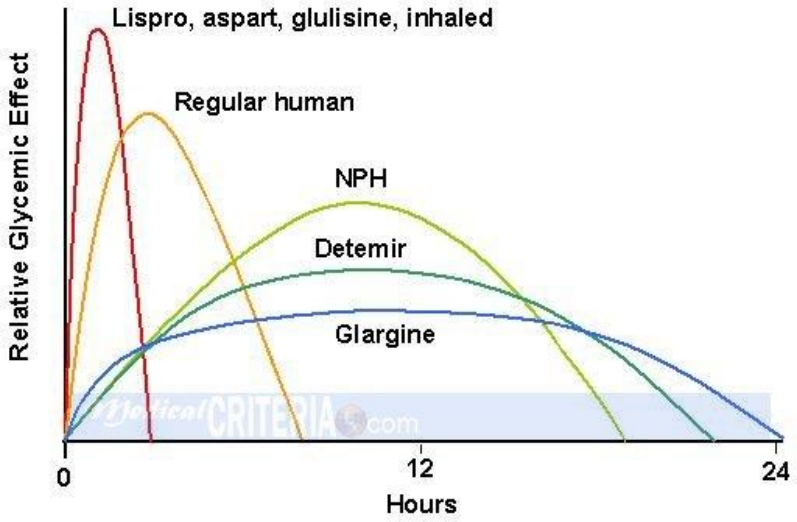
Insulin therapy

- Rapid acting insulin
  - rapid onset, early peak action
  - most similar to physiologic insulin effect
  - applied before meal (immediately)
  - lowest variability of absorption (≈5%)
  - prandial insulin replacement (two phases of insulin secretion)
    - insulin lispro
      - monomeric insulin analog
      - Prolin B28-B29
      - Lysine B29-B28
    - insulin aspart
      - Prolin B28 - Aspartic acid
      - inhibits insulin self aggregation
    - insulin glulisine
      - Asparagine B3 – Lys
      - Glutamic acid B29 – Lys
- Short acting insulin
  - regular insulin – complexed in cristalline zinc
  - hexameric structure – delayed absorption, prolonged effect
  - 30-45min before meal to avoid pp. hyperglycaemia – hypoglycaemia (mismatch)
  - variability of absorption (≈25%)
  - dose dependent duration of action (complex forming)
  - only one that allowed iv. application – dilution!



Insulin therapy

- Intermediate acting insulin
  - NPH insulin (neutral protamine Hagedorn, isophane)
  - combination of insulin and protamine
  - variability of absorption ≈50%
  - mixed forms
- Long acting insulin
  - insuline glargine
    - peakless action, broad plateau
    - background insulin replacement
    - low pH
      - slow dissolve at neutral pH – prolonged effect
      - not mixed with other prep.!
  - insuline detemir
    - myristic acid (C-14 fatty acid) attached
    - increased self aggregation – slow absorption



- Mixtures of insulin
  - rapid acting insulines are often mixed with NPH (no effect on absorption)
  - NPL (NPH+lispro) 50-50%, 75-25%
  - NPA (NPH+aspart) 70-30%

Insulin therapy

- Insulin regimens
  - Intensive Insulin Therapy
    - exact det.of daily insulin requirement
      - 50%- basal, background, insulin requir.
      - 50%- prandial, postprandial, high gl.level corrections
    - formulas – food types - CALCULATION
    - intensive glucose control
  - Conventional Insulin Therapy
    - insulin application – evidence based (fix doses)
  - IIT vs. CIT ???
  - Insulin delivery systems (insulin pumps)
    - sc. application
    - CSII (continuous subcutan insulin infusion)
      - open-loop system
      - closed loop system???

Insulin therapy

- Complications
  - hypoglycaemia
    - background:
      - inadaequte carbohydrate consumption
      - unusal physical exertion
      - large doses of insulin
    - symptoms:
      - sweating, tachycardia, palpitations, altered behaviour (agression), nausea, hunger
    - treatment
      - glucose administration – CAVE: unconsciousness! i.v.!!!
      - 1 mg glucagon s.c., i.m.
  - insulin allergy
    - rare condition
  - immune insulin resistance
  - lipodistrophy
    - injection sites

Regulation of insulin release in humans

- stimulants of insulin release
  - glucose, mannose
  - leucin
  - vagal stimulation
  - SUs
- amplifiers of glucose induced insulin release
  - hormones (incretin effect!!!)
    - GLP-1 (glucagon like peptide)
    - GIP (gastric inhibitory peptide)
    - secretin, gastrin, glucagon
  - neural amplifiers
    - β adrenoceptor stimulation
  - amino acids
    - Arg
- inhibitors of insulin release
  - neural
    - α adrenerg drugs
  - humoral
    - somatostatine, leptine
  - diazoxide,
  - phenytoin,
  - vinblastin, colchicin

Classification of oral antidiabetics

- Insulin secretagogues
  - SUs
  - meglitinide derivatives
  - D-phenylalanine derivatives
- biguanides
  - metformin
- thiazolidendiones
- α-glucosidase inhibitors
- incretin based therapy
- amylin analogues
- Na^+-glucose cotransport inhibitors

Oral antidiabetic agents
Insulin secretagogues

- Sulfonylureas
  - mechanism of action
    - ↑insulin release from pancreatic B cells
      - inhibits ATP sensitive K+ channels – B cell depolarization
    - long term action reduces serum glucagon levels

  - drug class
    - first generation SU
      - tolbutamide
        - UGDP (Univ. Group Diab. Progr.) – ↑cardiavascular risk
        - UKPDS – no such findings
        - safe for elderly patients
      - chlorpropamide
        - CI in patients with hepatic or renal failure
        - a.e.: prolonged hypoglycaemia (t1/2: 32 hours)
      - tolazamide
        - shorter half life, than chlorpropamide

    - second generation SU
      - glibenclamid (Gilemal)
        - safer, than 1st generation SU
        - lower CV risk/ hypoglycaemic effect
      - glimepirid (Amaryl)
        - potent and effective
        - 1mg p.o.
      - glipizide
        - short half life

Oral antidiabetic agents
Insulin secretagogues

- meglitinide derivatives
  - mechanism of action
    - ↑insulin release from pancreatic B cells
      - inhibits ATP sensitive K+ channels – B cell depolarization
    - two binding sites on channel (SU-one b.s.)
  - drug types
    - repaglinide
      - rapid onset of action
      - metabolized in liver: CYP3A4
      - dose: before each meal 0,25-4mg
      - coappl: biguanides
      - appl.: allergy to SUs

- D-phenylalanine derivative
  - mechanism of action
    - ↑insulin release from pancreatic B cells
      - inhibits i.r. ATP sensitive K+ channels – B cell depolarization
  - nateglinide
    - rapid onset of action

Oral antidiabetic agents
Biguanides

- mechanism of action
  - reduce hepatic glucose production
    - activating AMPK (AMP activated protein kinase)
  - facilitating glucose uptake (liver, muscle)
  - stimulating glycolysis
  - slow glucose absorption from GIT
  - reduction of plasma glucagon levels
  - ↓food intake (appetite lowering effect)
  - ↓insulin resistance
  - ↑HDL ↓LDL

- drug types
  - metformin
    - not metabolized
    - impair the metabolism of lactic acid! – lactate acidosis
    - first line th. of Type 2 DM
    - UKPDS
      - ↓risk of macroangiopathy/microangiopathy
    - dose 500mg-2000mg/day
    - a.e.: nausea, diarrhea, impaired Vit. B12 absorption, not recommended with contrast-material (X-ray)

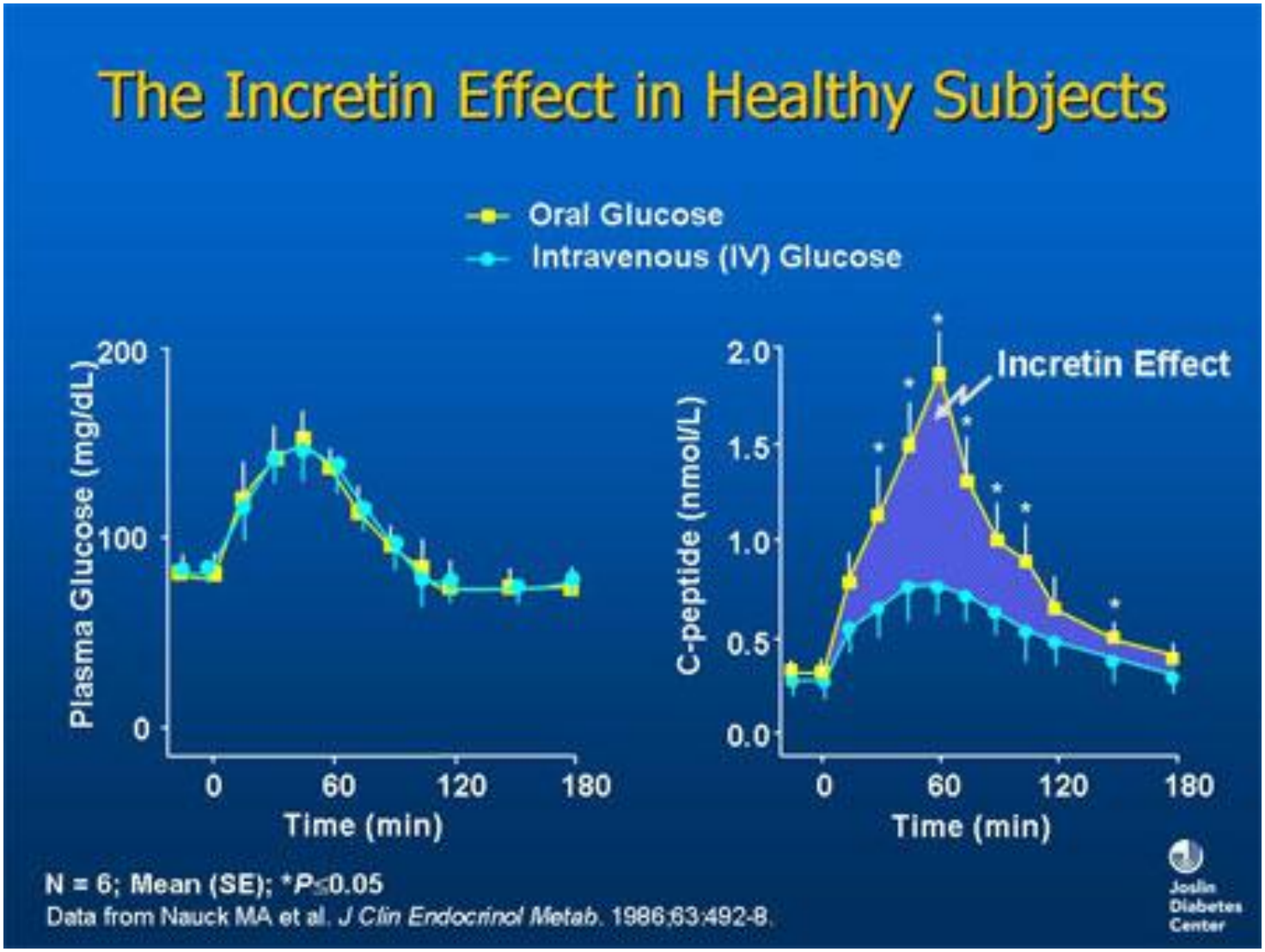
Oral antidiabetic agents
Thiazolidendiones

- mechanism of action
  - agonism of PPAR-γR (fat, muscle, liver – endothel, ovarium, imm.cells)
  - effects mainly on adipocytes
    - ↑ glucose uptake and utilization
    - ↓ synthesis of resistin
    - ↓ synthesis of cytokines and lipid hormones
    - slow onset – nuclear receptor
  - drug types
    - pioglitazone
      - metabolized by CYP2C8, CYP3A4 (CAVE: OAC!)
      - reduces CV mortality (macroangiopathia)
      - triglyceride lowering effect (anti-obesity drug)
      - 15-30mg/day
      - increased risk of heart failure
    - rosiglitazone
      - 4-8 mg/day
      - fluid retention
      - monotherapy in type 2 DM
      - coapplication.: biguanides, SU
    - troglitazone
      - withdrawn (hepatotoxicity)
      - beneficial effects in PCOS

Oral antidiabetic agents
α-glucosidase inhibitors

- mechanism of action
  - competitive inhibition of intestinal α-glucosidase enzymes (sucrase, maltase, dextranase, glucoamylase)
    - only monosacharids can be transported out of the intestinal lumen
    - ↓ monosacharid absorption, ↓ postprandial hyperglycaemia
  - acarbose, miglitol
  - 25-50 mg/day
  - a.e.: flatulence, diarrhea, abdominal pain (undigested carbohydr.)
  - STOP-NIDDM – great success

Incretin based therapy



Oral antidiabetic agents
Incretin based therapy

- exenatide, liraglutide
  - mechanism of action
    - synthetic analog of GLP-1
    - multiple actions
      - enhance glucose-mediated insulin secretion
      - supression of postprandial glucagon release
      - slow gastric emptying
      - central loss of appetite
    - appl.: sc. injection
    - injected 60 min before meal
    - a.e.: nausea, vomiting, weight loss
    - coapplication: biguanides, sulfonylureas (hypoglycaemia!!!)

- sitagliptin, saxagliptin
  - mechanism of action
    - inhibitor of DPP-4 (dypeptidil-peptydase-4)
    - inhibiting degradation og incretines (GLP-1, GIP↑)
      - increase glucose mediated insulin secretion
      - decrease glucagon levels
    - appl.: p.o. (OA=85%)
    - 100mg/day
    - a.e.: headache
    - coapplication: biguanides, thiazolidendiones

Oral antidiabetic agents
Amylin analogues

- Pramlintide
  - mechanism of action
    - synthetic analog of amylin (IAPP-Islets Amyloid Polypeptide)
      - suppress glucagon release
      - delay gasric emptying
      - anorectic effects in CNS
    - metabolized by kidneys
    - appl.: sc. (immediat. before eating)
      - Type 1 and Type 2 DM
    - a.e.:
      - hypoglycaemia
      - nausea

Oral antidiabetic agents
Na^+-glucose cotransport inhibitor

- dapagliflozine
  - mechanism of action
    - inhibits SGLT2 (proximal tubule-90% of glucose reabsorption)
    - decreased glucose reapsorption (excreted with urine)
  - insulin-independent action
  - appl.: p.o.
  - a.e.: safe and well-tolearated
  - coapplication: biguanides, sulfonylureas, insulin

Complex therapy of DM

- Type 1 DM
  - insulin therapy
- Type 2 DM
  - CHANGE IN LIFESTYLE (glycaemic index!!!)
  - oral antidiabetics
    - biguanides
    - SU
    - TZD’s
  - insulin
- Type 4 DM
  - insulin