Oral Antidiabetic Agents

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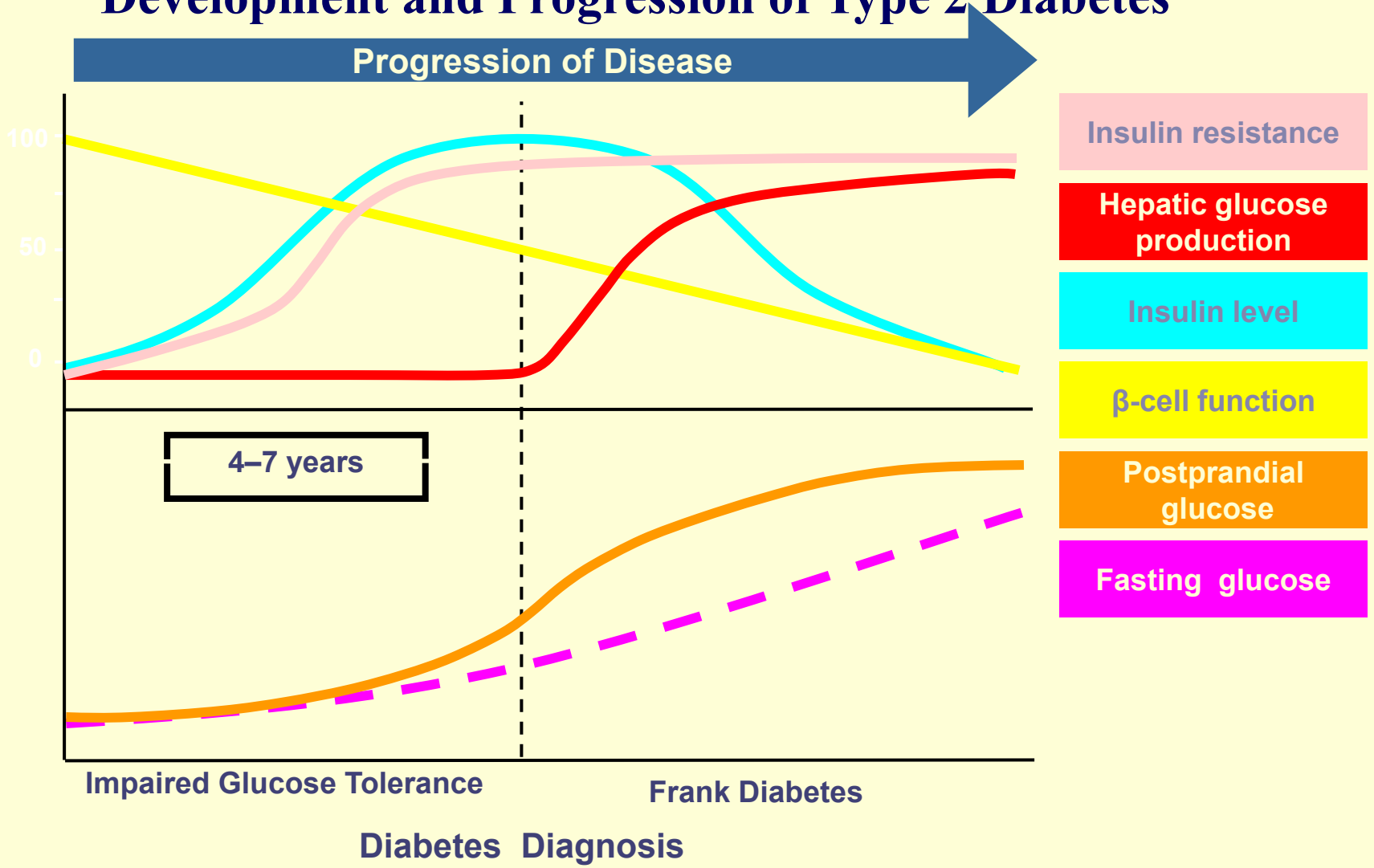
Development and Progression of Type 2 Diabetes*



ADA guidelines, 2008 recommend…

Table 8—*Summary of glycemic recommendations for adults with diabetes*

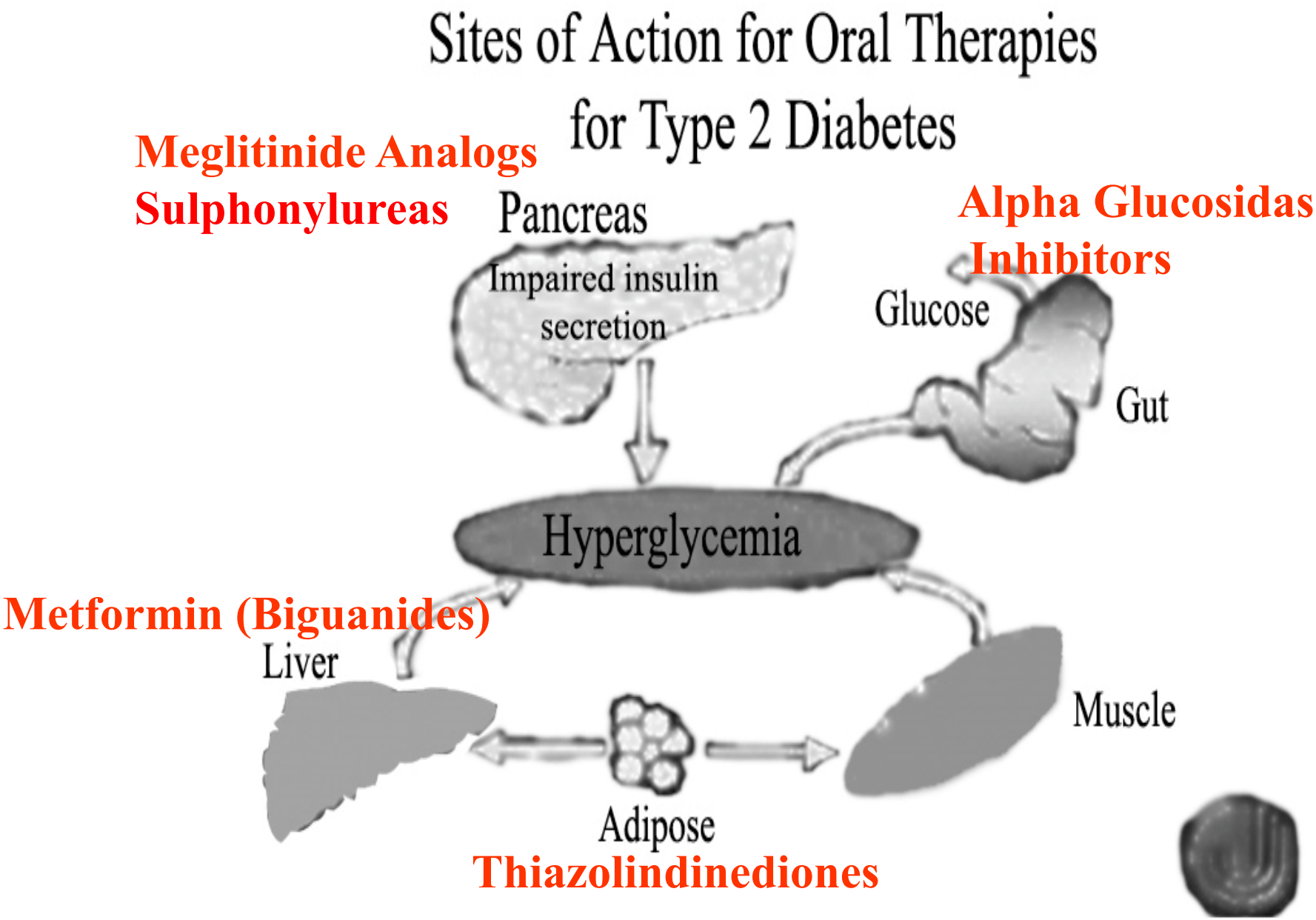
A1C	<7.0%*
Preprandial capillary plasma glucose	70–130 mg/dl (3.9–7.2 mmol/l)
Peak postprandial capillary plasma glucose†	<180 mg/dl (<10.0 mmol/l)

Key concepts in setting glycemic goals:

- A1C is the primary target for glycemic control
- Goals should be individualized based on:
  - duration of diabetes
  - pregnancy status
  - age
  - comorbid conditions
  - hypoglycemia unawareness
  - individual patient considerations
- More stringent glycemic goals (i.e., a normal A1C, <6%) may further reduce complications at the cost of increased risk of hypoglycemia
- Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals

*Referenced to a nondiabetic range of 4.0–6.0% using a DCCT-based assay. †Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.

Sites of Action for Oral Therapies for Type 2 Diabetes



Spectrum of Oral Hypoglycaemic Agents

•Biguanides	•Metformin (Biguanides)
•Sulphonylureas	•Glybenclemide, Glicliazide Glipizide, Glimepiride
•α-Glucosidase inhibitors	• Acarbose , Miglitol, Voglibose
•Meglitinide analogues	• Repaglinide, Nateglinide
•Thiazolidinediones	• Rosiglitazone , Pioglitazone
DPPV-4 Inhibitors	• Sitagliptin, Vildagliptin, Saxagliptin

What is the role of an ideal oral hypoglycaemic agent?

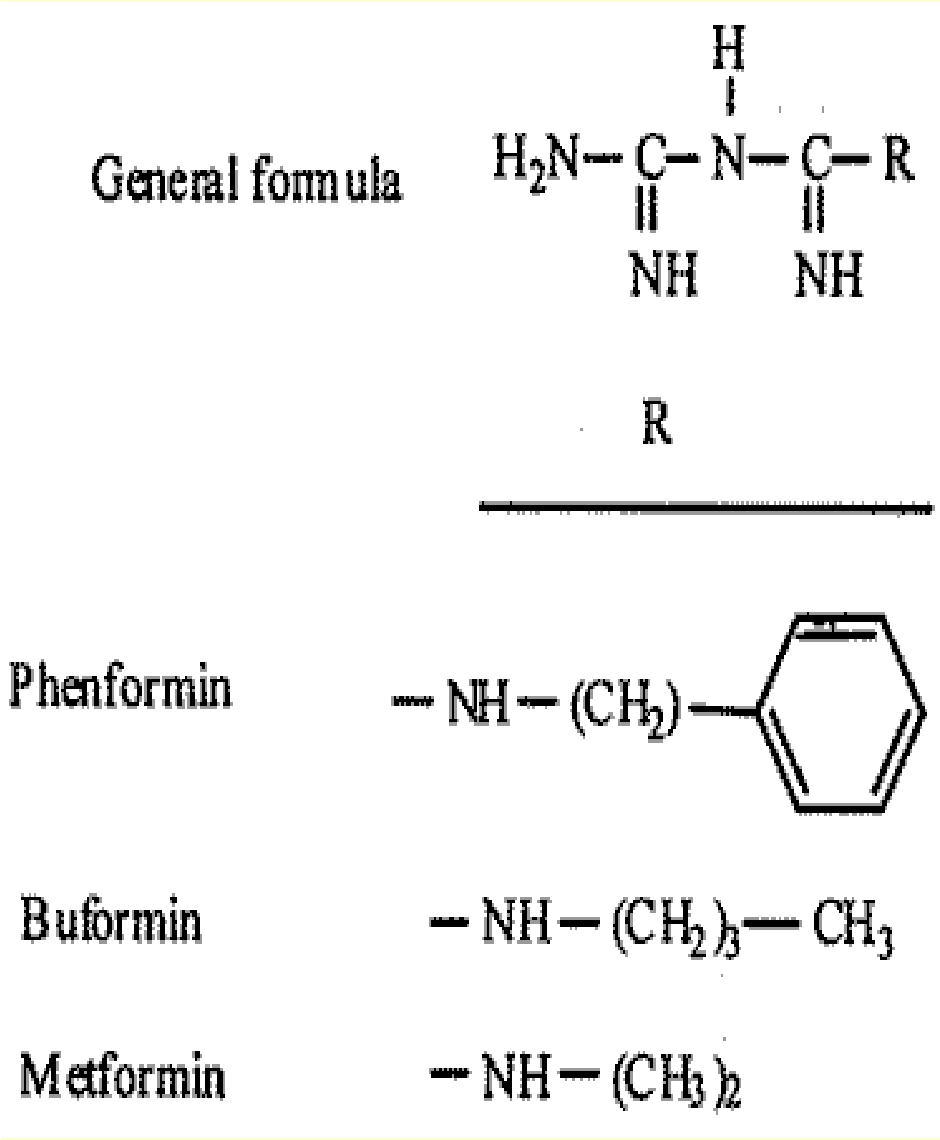
Conserve islet cell function

- delay the subsequent use of insulin.

Improve patient compliance- single daily dosing.

Reduce the incidence of hypoglycaemic events

Biguanides



Act by inhibiting liver gluconeogenesis & increasing insulin sensitivity in other tissues

Metformin is not metabolized, but excreted intact in 2-5 h

Metformin

By ADA and EASD guidelines

The primary drug of choice for diabetes

Metformin

Indicated in most Type 2 DM

Contraindicated in:

a) Malabsorption or GI disturbances

b) Low BMI---?less than 21kg/m2…….marked weight loss

c) Organ Failure: Creatinine: >1.4mg/dl

Liver failure: Acute/Chronic

Cardiac Failure

Hypotension/Sepsis

Active Vitamin B12 Deficiency

GI intolerance

Relative Contraindication: Age

Initiate:

- after meals
- 250 to 500mg twice or thrice a day
- Increase gradually if required in 1 or 2 weeks
- mild loose stools in 10% initially, which reduces gradually

-persistent loose stools in 5%

-Sustained released forms: more effective- vehicle excreted in stool

Metformin:

Dosing from 500mg twice daily to
1 gramme thrice a day

Advantages:

Perpetuates weight loss

Can be combined with insulin
to reduce insulin requirements

Disadvantages:

Nausea, Vomiting and diarhorrea(5%)

Vitamin B12 Deficiency (0.5%)

Repaglinide/ Nateglinide

Nonsulphonylurea insulin secretagogues

Mechanism:

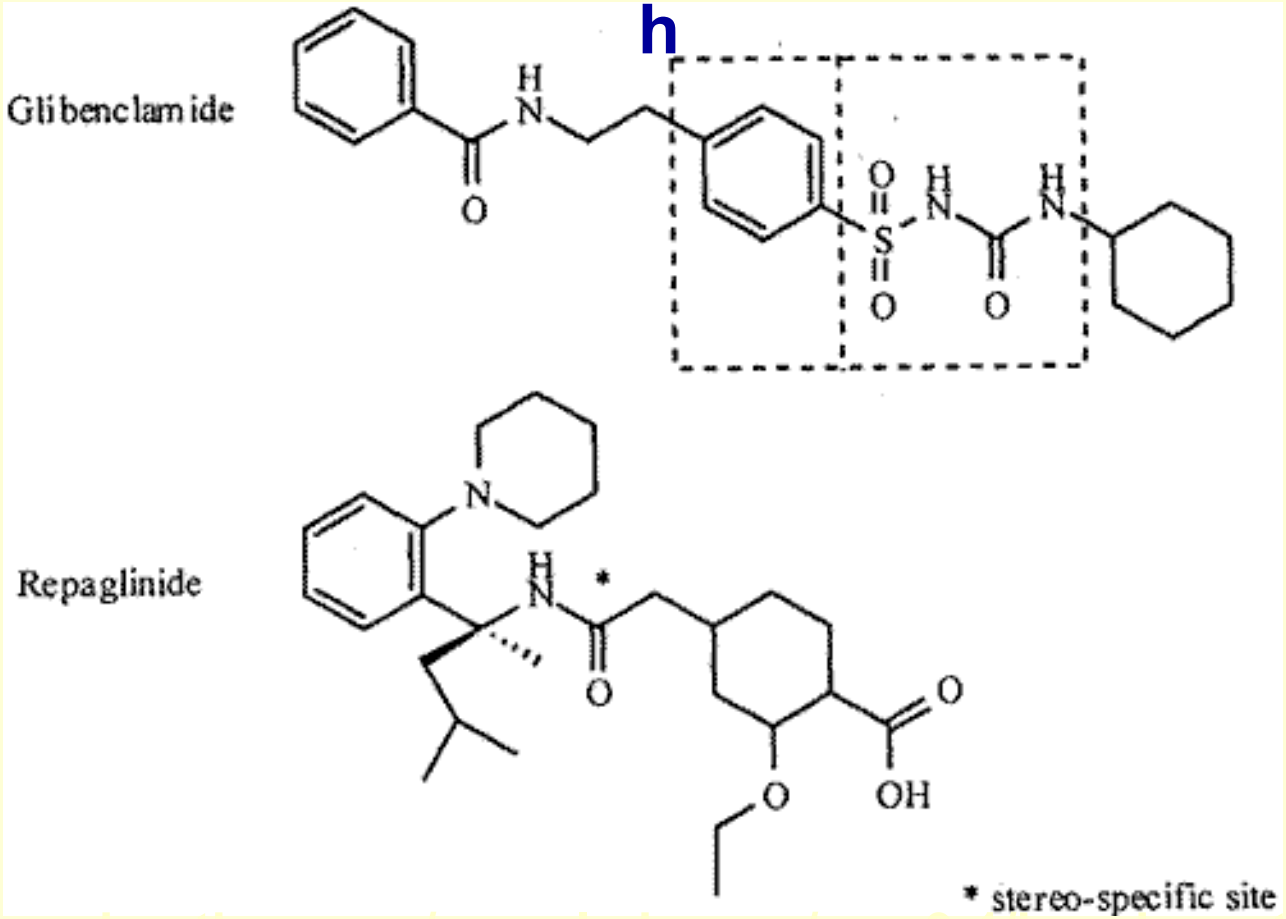
Closes ATP-sensitive potassium channels on ß-cells.

Binds to a site distinctly separate from the sulphonylureas.

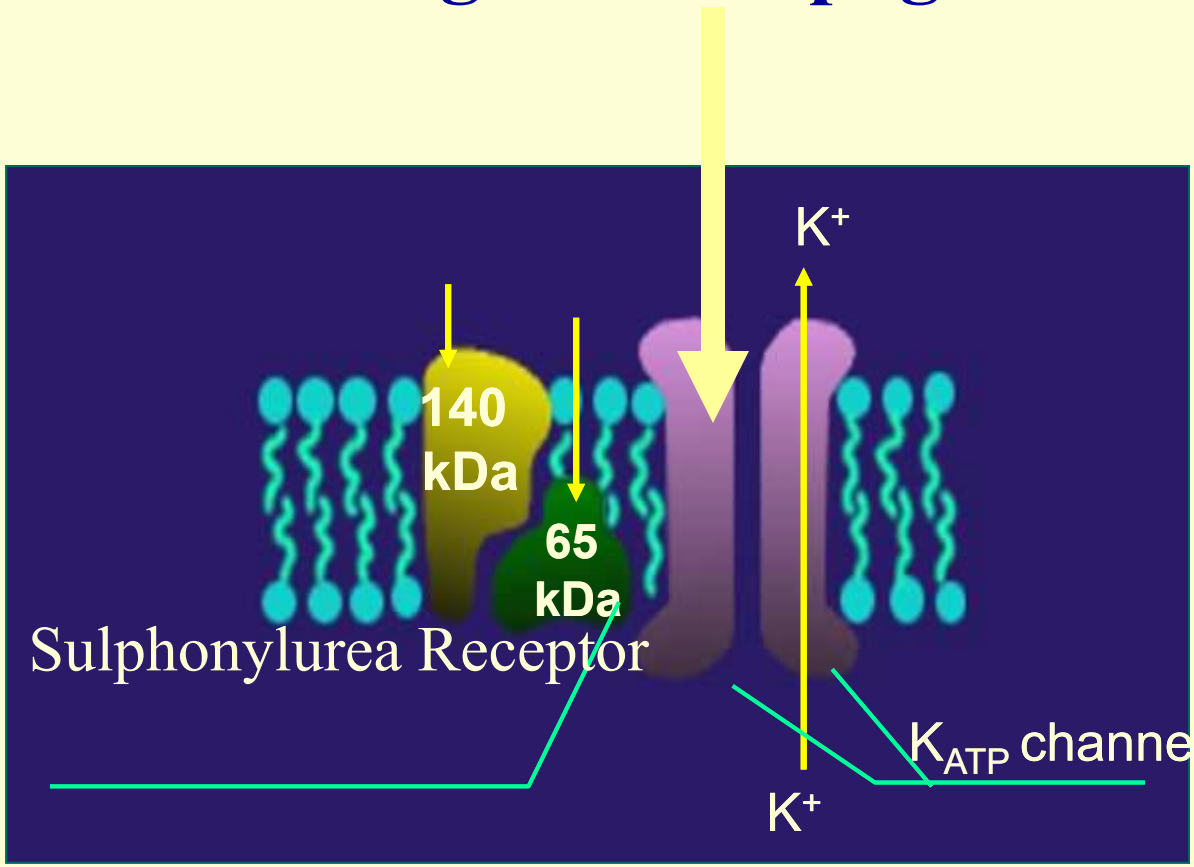
Meglitinide Analogs

Bind to ß cells via SU receptor

Rapid absorption, metabolism & clearance, $T_{1/2}$ < 1 h



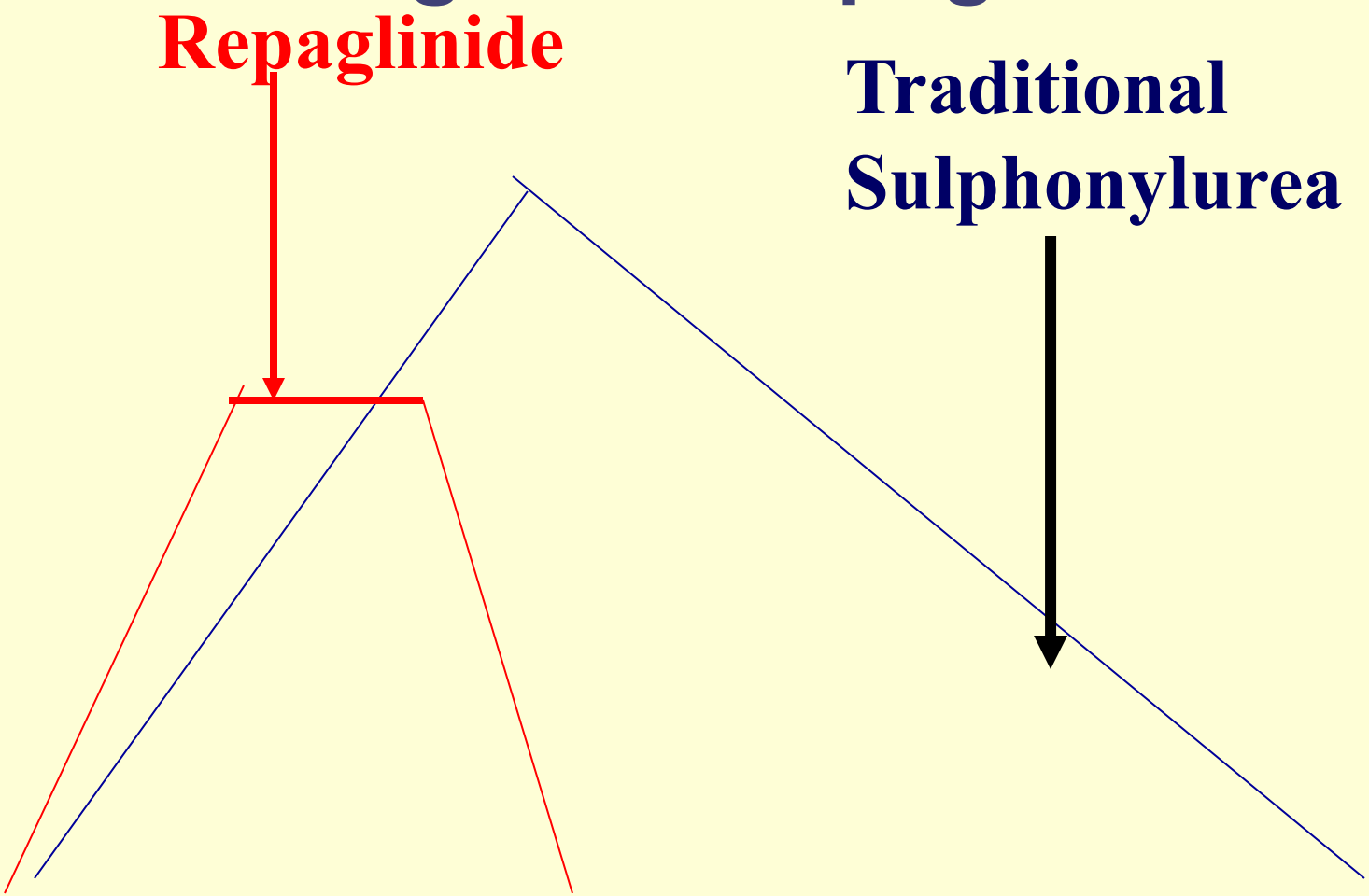
Nateglinide/Repaglinide



Quicker attachment

Earlier Detachment

Insulin Levels in Nateglinide/Repaglinide



Advantages of Nateglinide/Repaglinide

- Flexibility in mealtime dosing- 'Ramzan Drug'
- No significant increase in bodyweight
- Can be utillised in mild to moderate renal failure
- Nateglinide: approved in hepatic failure

Dosage: Repaglinide:

0.5mg/1mg/2mg/4mg per dose per meal

Nateglinide: 60mg/120mg per dose per meal

- Lower incidence of hypoglycemia

Useful Situations

- elderly patients in whom hypoglycaemia is a concern
- patients with kidney failure or mild hepatic impairment
- patients taking low-dose sulphonylureas who encounter problems with hypoglycaemia
- Patients with irregular meal patterns

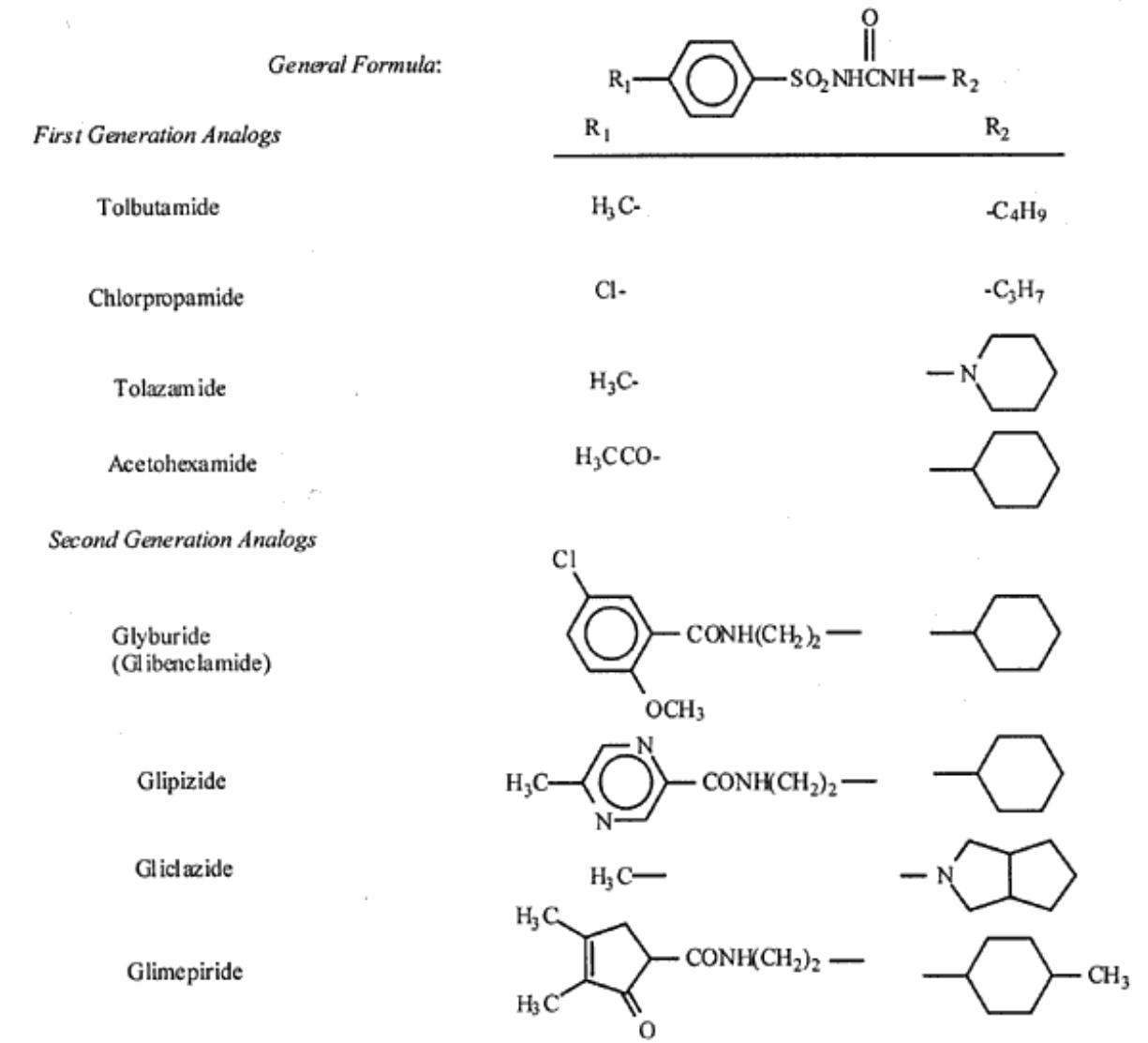
Int J Clin Pract. 2003 Jul-Aug;57(6):535-41.

Disadvantages of Metaglinide derivatives

Works predominantly in mild hyperglycaemia

Less convincing with fasting hyperglycaemia

First line drug with little adjuvant potential



Sulfonylureas

Stimulate insulin release from ß cells via binding to the SU receptor = K^+_{ATP} channel

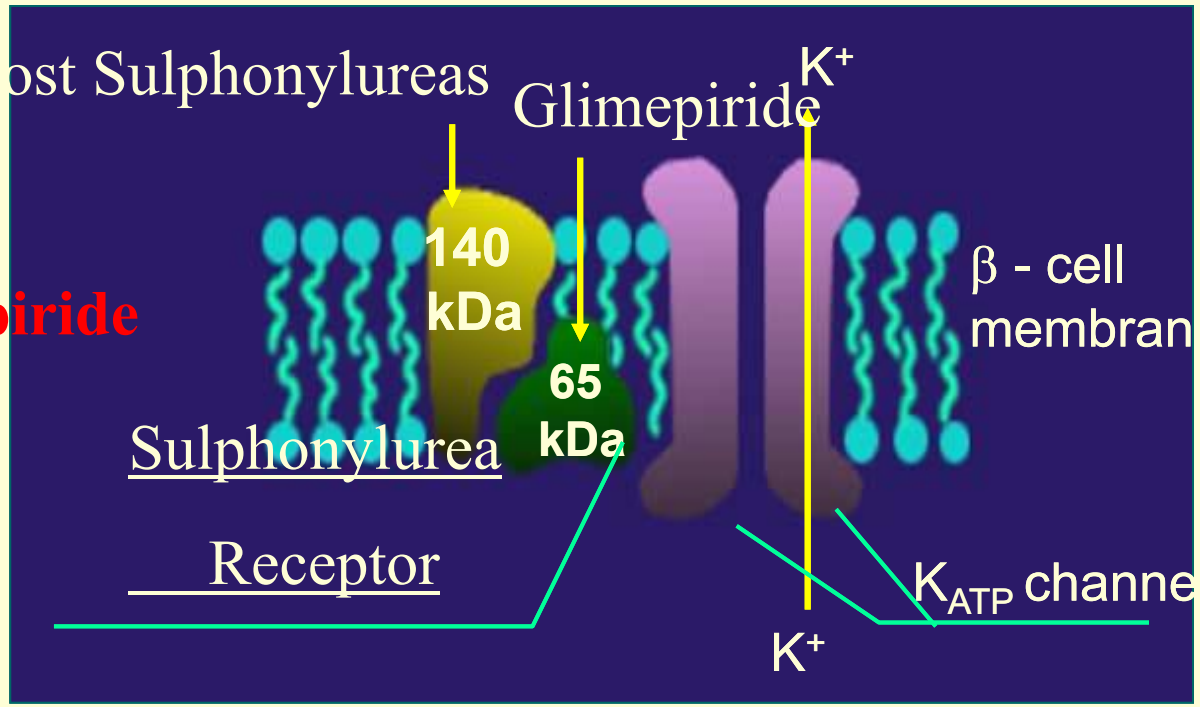
Mostly long metabolic $T_{1/2}$

Glimepiride

Modes of action: Glimepiride

Glimepiride

GLUT-4



So What ??

65kDa Component absent in Cardiovascular System

Safer to use in patients with a higher cardiovascular risk

Type II Diabetes and Exercise

Improvement in insulin Sensitivity:

Activates intracellular GLUT-4 glucose transporters

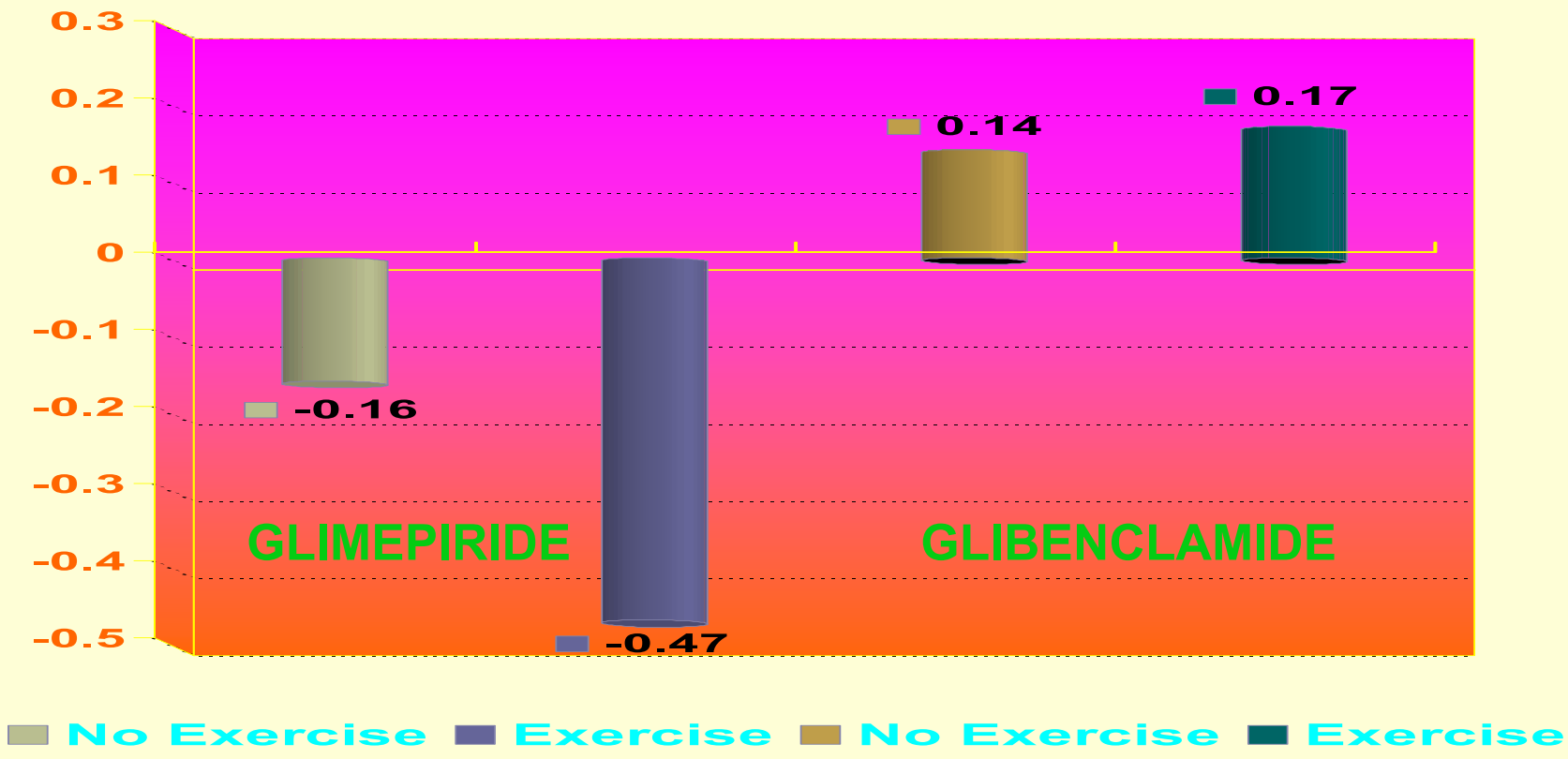
(Effect lost in 48 hours)

Conventional Sulphonylureas:

failure of insulin suppression

Hypoglycaemia / overeating in the morning/ weight gain.

Insulin Suppression During Exercise



Advantages of Glimepiride (Over other sulphonylureas)

- Single daily dosing
- Comparable hypoglycaemic side effect profile to glipizide
- Safer in the presence of cardiac disease (SU-receptor –ve)
- Peripheral action conserves endogenous insulin
- Safer to use in the physically active

Disadvantages of Glimeperide

- ***Impact on glycosylated haemoglobin variable.***

- ***Dosage:***

  1mg – 8mg per day

Glibenclemide 2.5mg twice a day
to 10mg twice a day

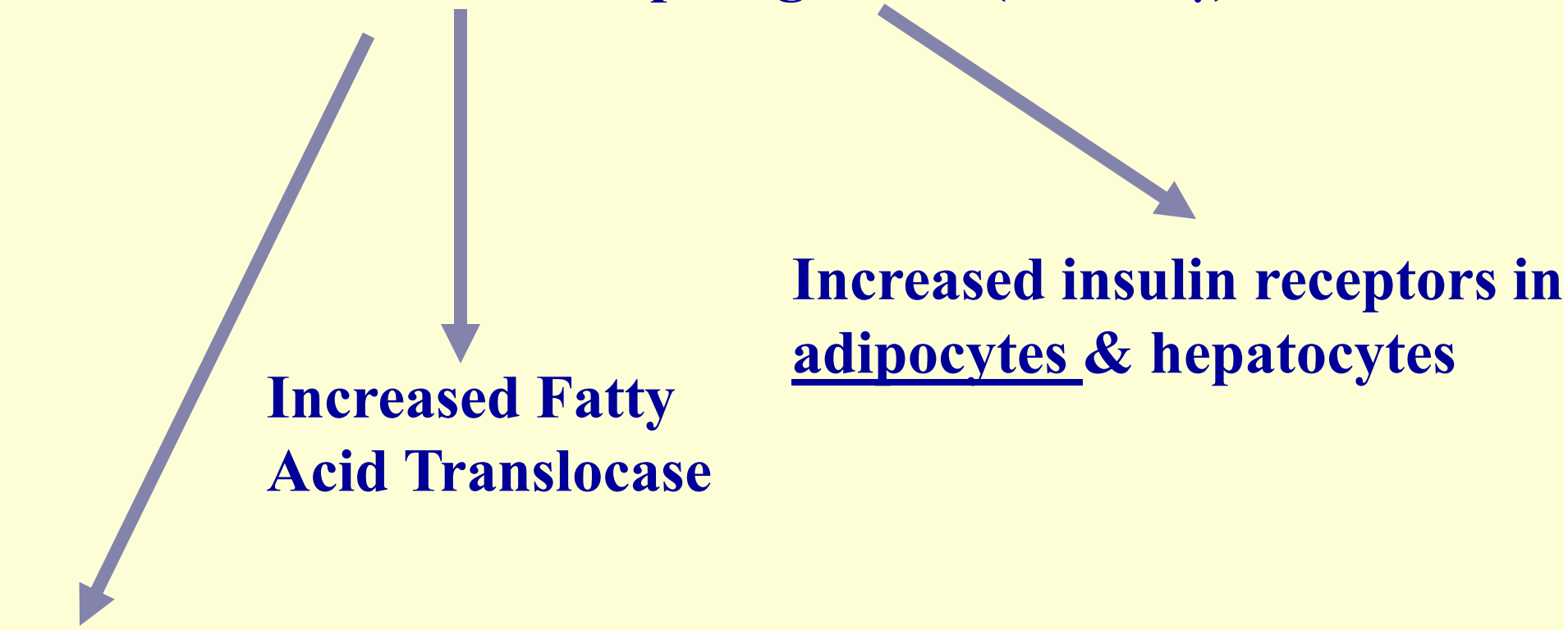
Glipizide 2.5mg twice a day
to 10mg twice a day

Gliciazide 40mg twice a day
to 160mg twice a day

15 minutes Before meals

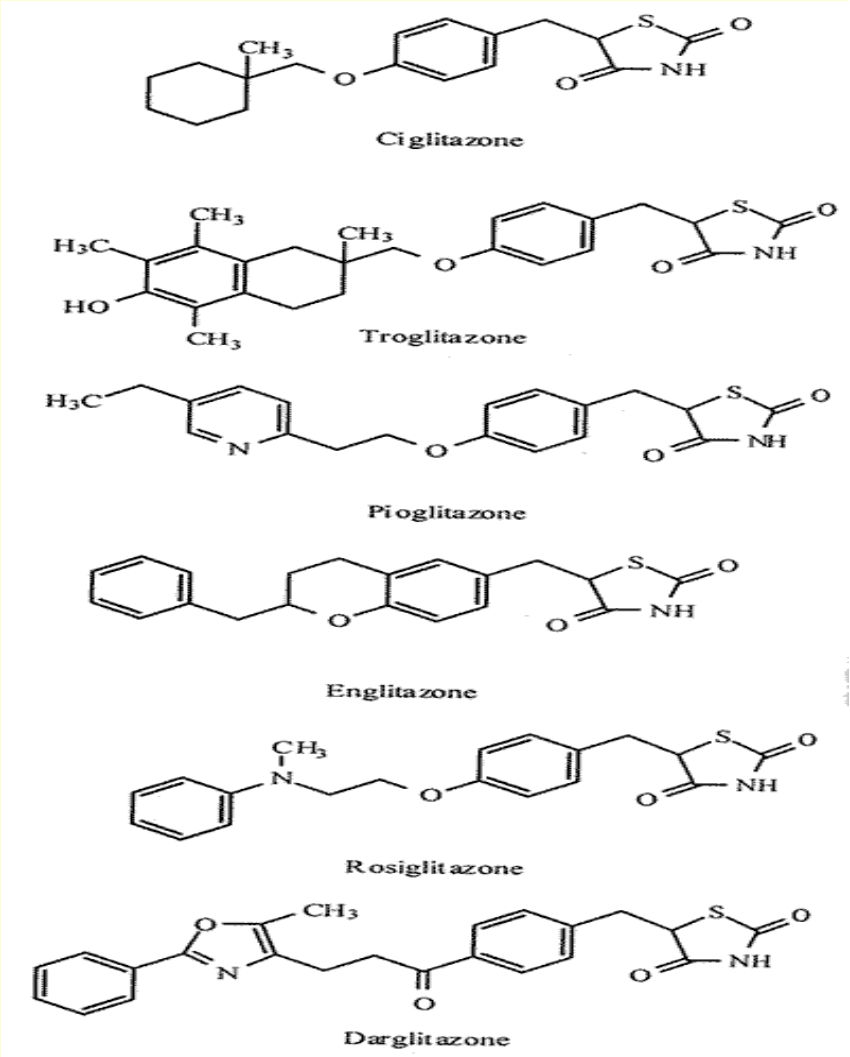
Rosiglitazone & Pioglitazone

Activate nuclear peroxisome proliferator activated receptor gamma (PPAR-γ)

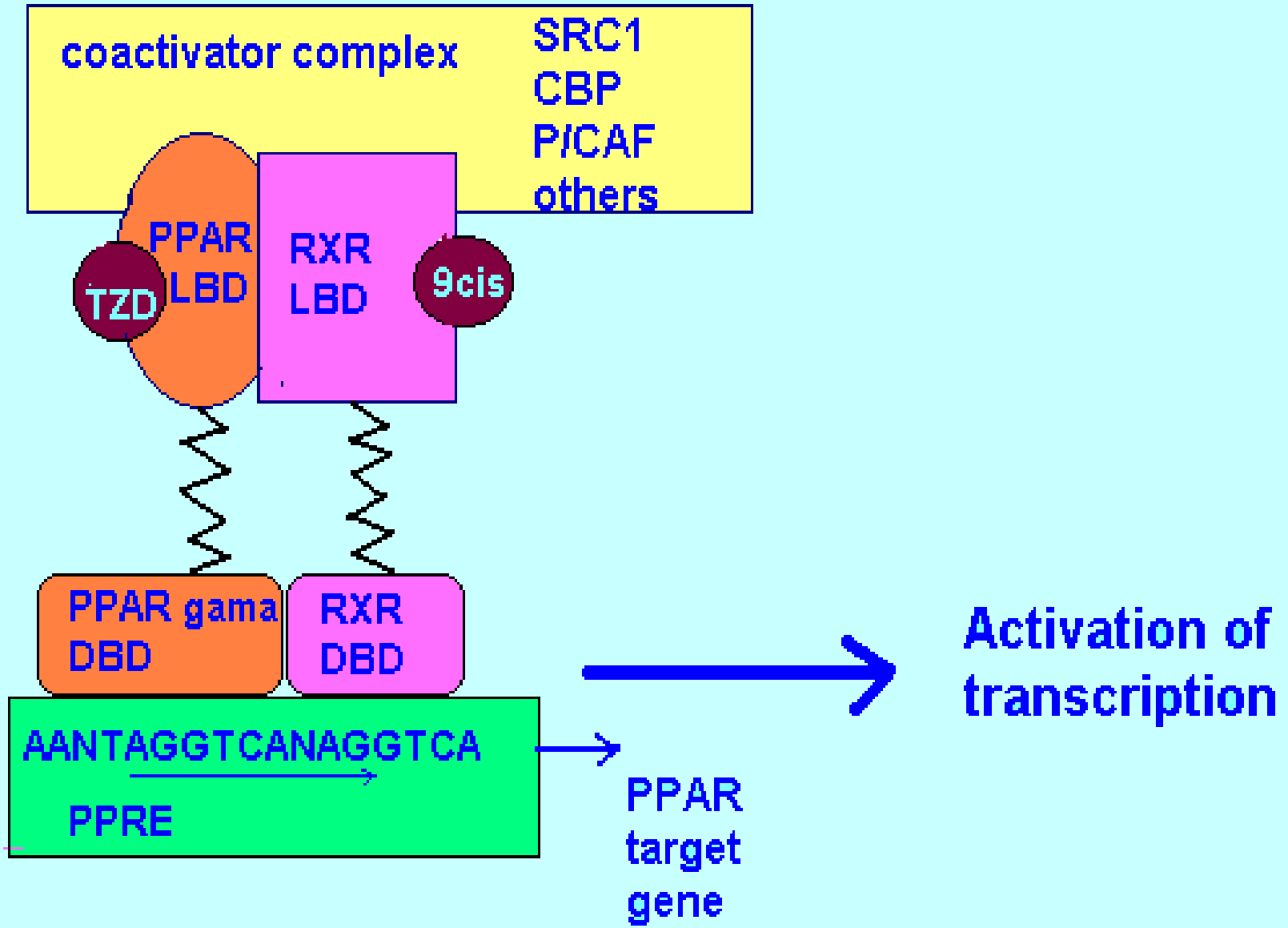


Thiazolindinediones

- Partial mimics of insulin actions, may bind insulin receptor or act through the peroxisomal proliferator activated receptor γ
- Metabolized with a long half life



Mechanism of TZD activation of transcription by PPAR gamma



Special Consideration

Hepatic Impairment

Therapy should not be initiated if the patient exhibits clinical evidence of active acute or chronic liver disease of increased serum transaminase levels

Fatty liver per se is not a contraindication

Thiazolidinediones- the impact

- Reduction in white adipose tissue
- Reduced Triglycerides
- Increase in brown adipose tissue- weight gain
- Increased LDL(10-15%) – buoyant fraction
- Oedema

Thiazolidinediones- The Advantages

Important second / third line drug

Monotherapy

Potential single daily dose with Pioglitazone

Lowered blood pressure

No Hypoglycaemia

Progressive rise in HDL levels

Thiazolidinediones-The Advantages(contd)

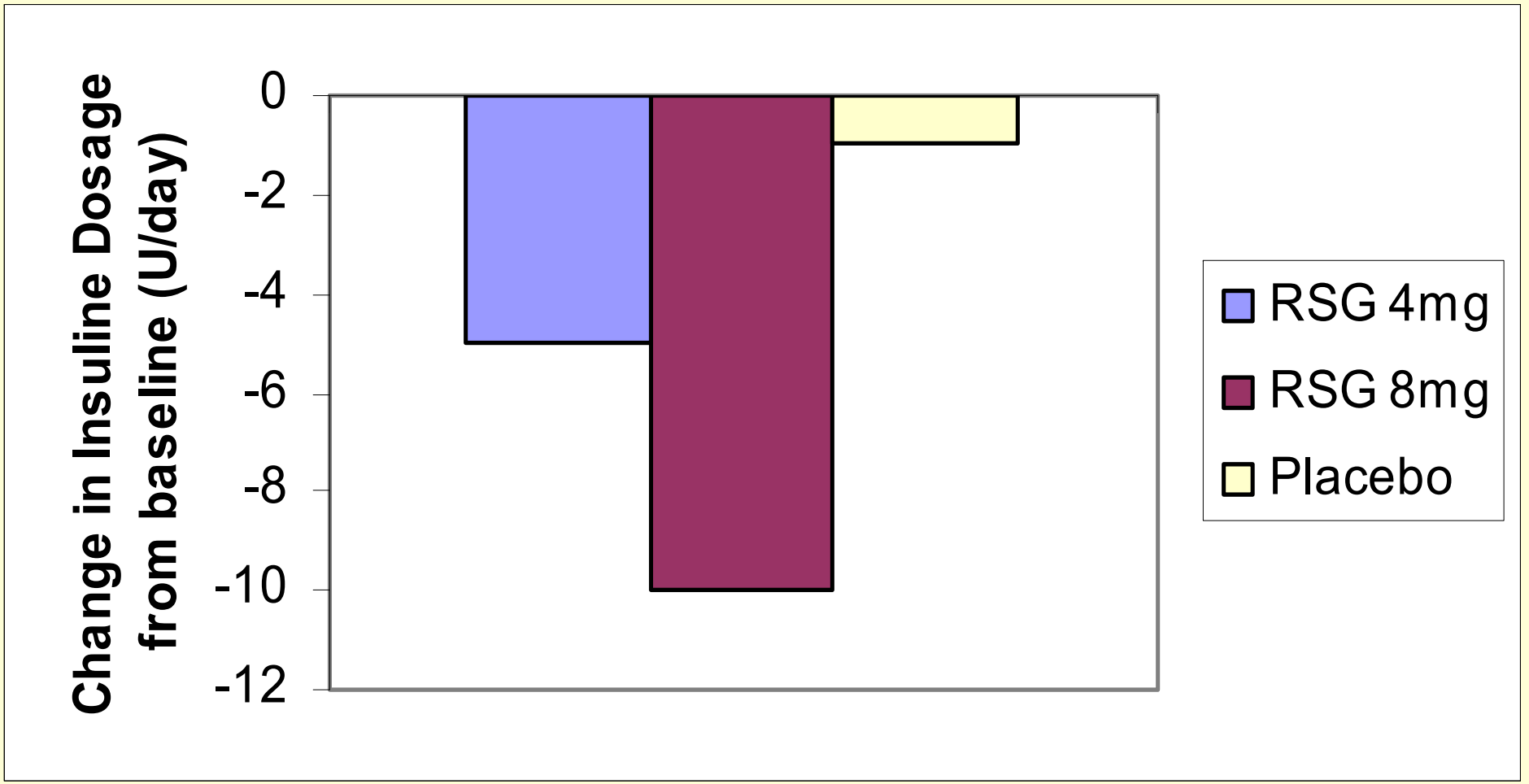
Potential reduced microalbuminuria

Reduced Vascular Intimal Thickening (impact on macrophage function)

Combined effectively with insulin

Safe in moderately severe renal failure

Rosiglitazone: Combination with Insulin



Thiazolidinediones- the disadvantages

- Potential weight gain (2-4 kg)
- LDL elevation (Mainly over 1st 2 months)
- Oedema
- Worsens Osteoporosis
- Containdicated in Grave's Ophthalmopathy, Macular Oedema
- Occasional fluid overload
  (therefore avoid in Ischemic heart Disease)

Rosiglitazone vs Pioglitazone adversity profile

A slightly higher prevalence of volume overload incidents with Rosiglitazone

More evidence of vascular endothelial improvement with Pioglitazone

Alpha Glucosidase inhbitors

Work on the brush border of the intestine
cause carbohydrate malabsorption

Advantages:
Selective for postprandial hyperglycaemia
No hypoglycaemic symptoms

Disadvantages:
Abdominal Distension and flatus
Only effective in mild hyperglycaemia

- Acarbose- 25 mg to 50mg thrice a day
- Miglitol- 25mg to 100mg thrice a day
- Voglibose- 0.2 to 0.3 mg thrice a day

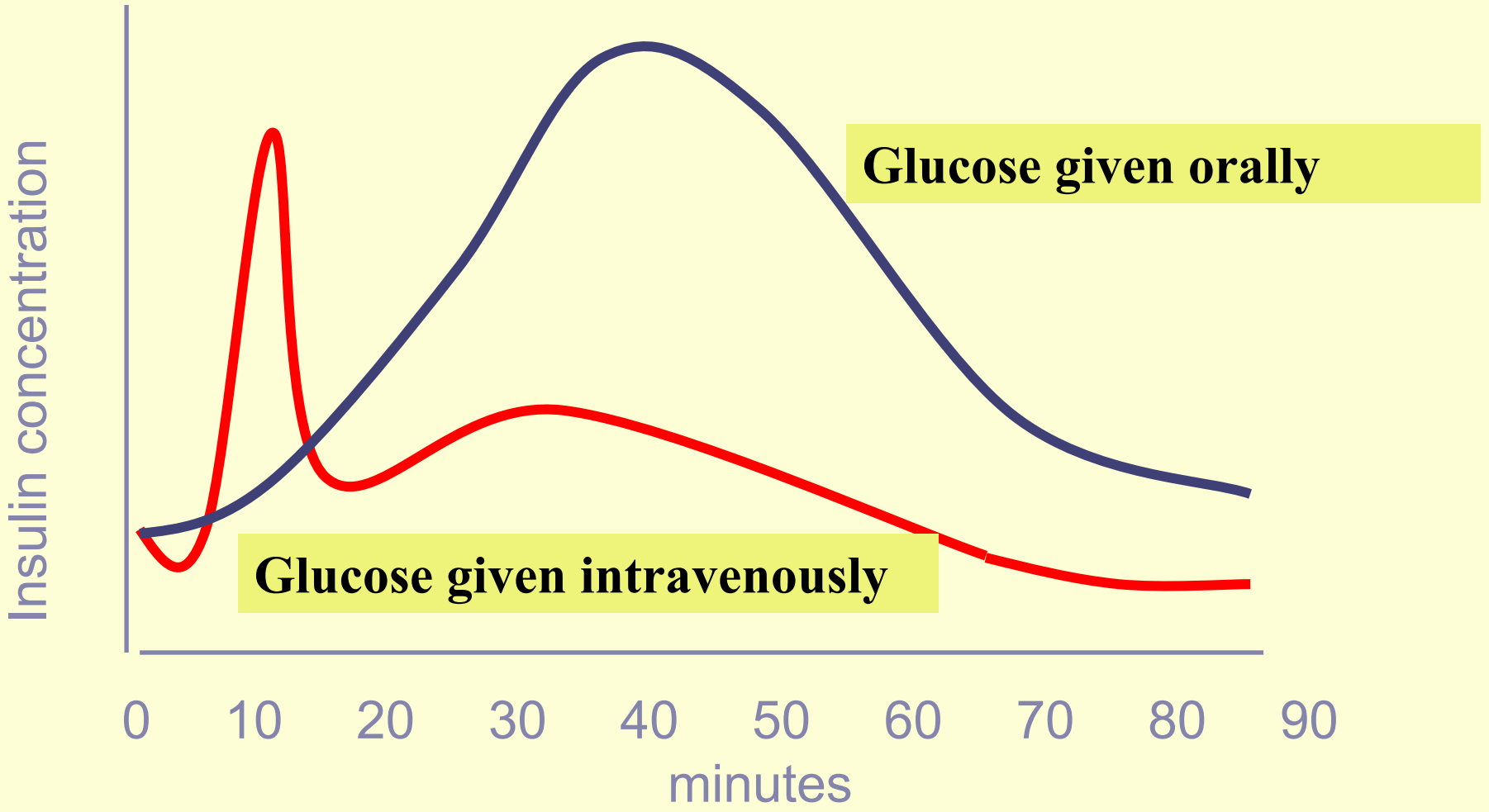
Contraindications

- an inflammatory bowel disease, such as ulcerative colitis or Crohn's disease; or any other disease of the stomach or intestines
- ulcers of the colon
- Intestinal Obstruction
- kidney disease.

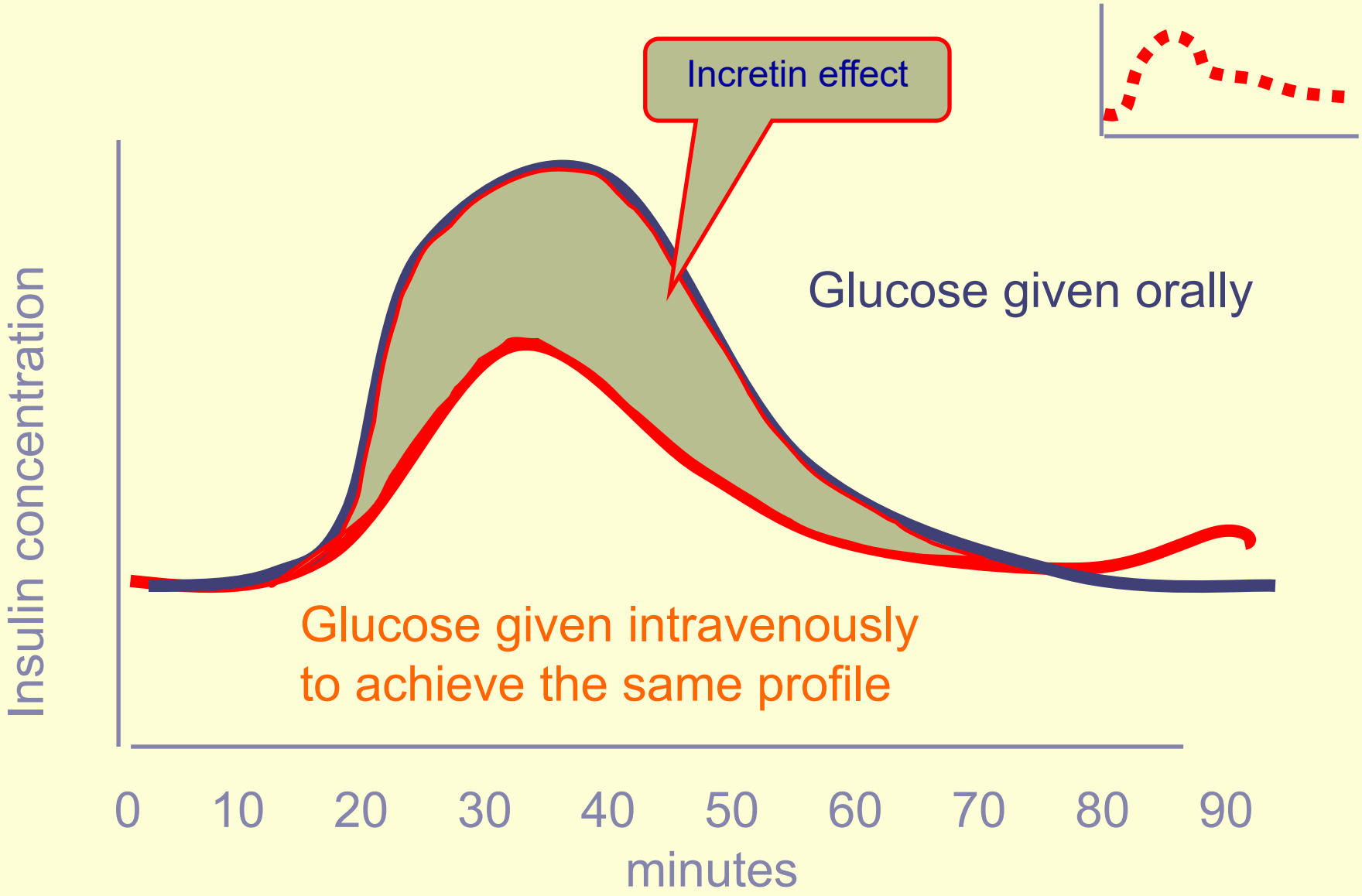
Incretin concept

- Insulin secretion dynamics is dependent on the method of administration of glucose
- Intravenous glucose gives a marked first and second phase response
- Oral glucose gives less marked first and second phase insulin response, but a prolonged and higher insulin

Insulin secretion profiles



Iso-glycaemic profiles



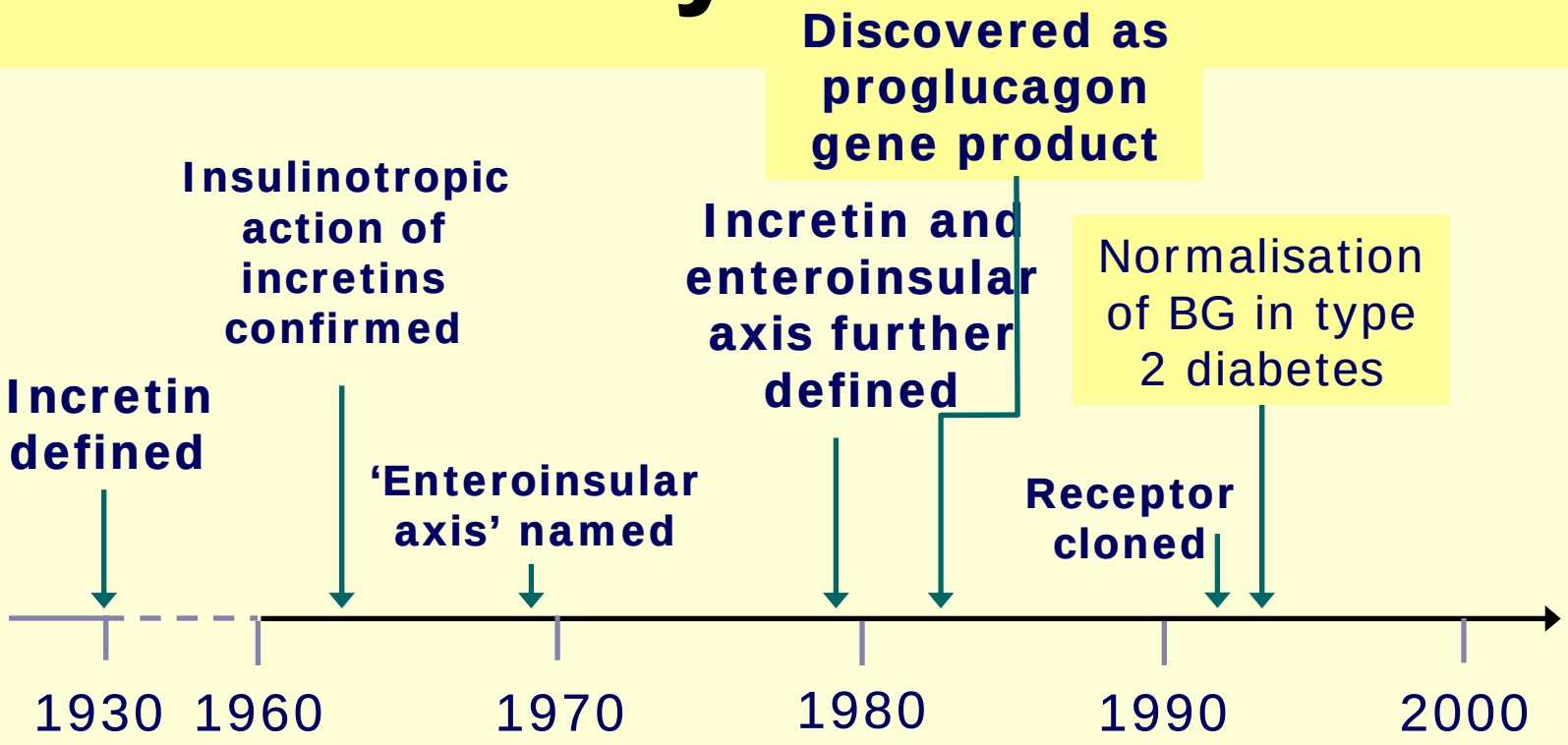
What are the incretins?

- **GIP: Glucose-dependent insulinotrophic polypeptide**
  Small effect in Type 2 diabetes.

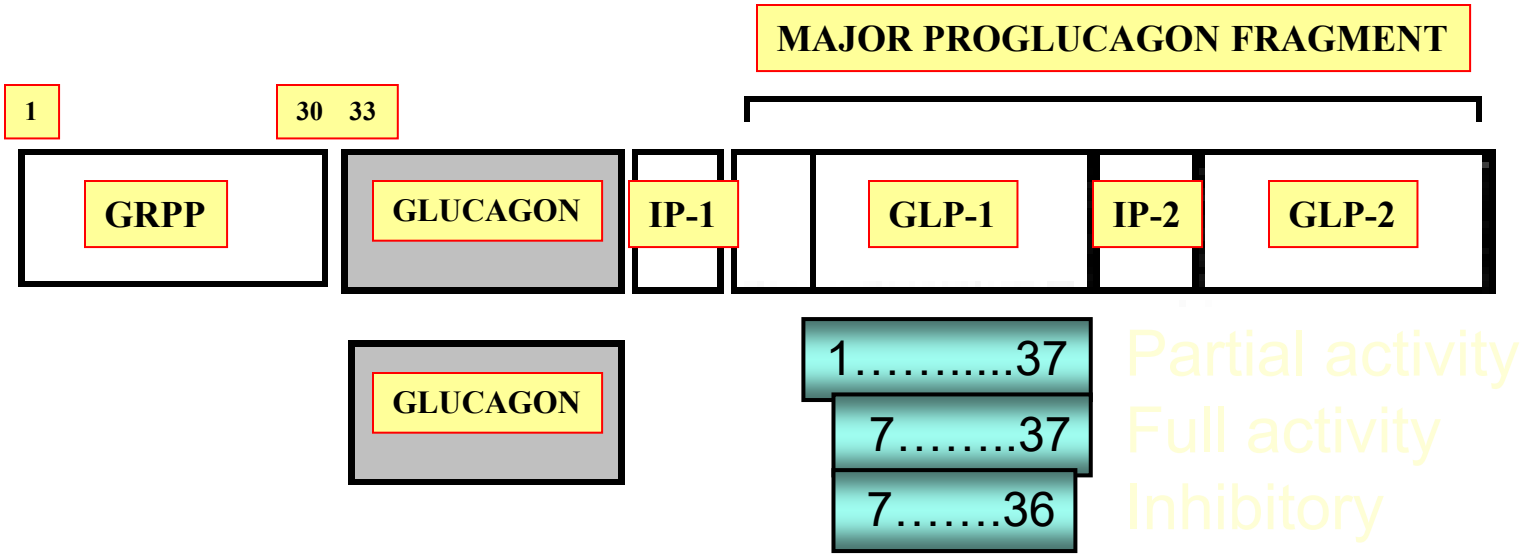
- **GLP-1(glucagon-like peptide 1)**
  augmented in the presence of hyperglycaemia.
  Action less at euglycaemia and in normal subjects.

- **Pituitary Adenylate Cyclase Activating Peptide (PACAP)**

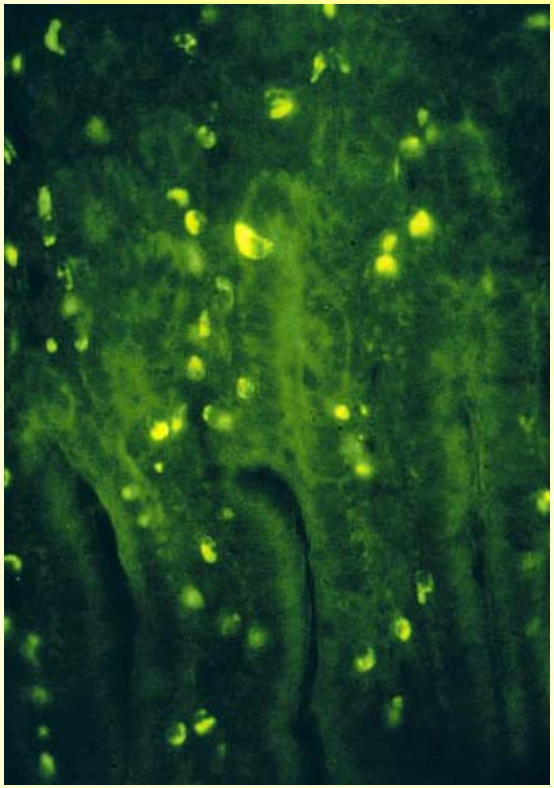
History of GLP-1



Proglucagon genome: pancreas and gut



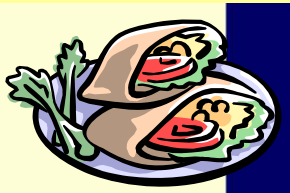
GLP-1 localisation



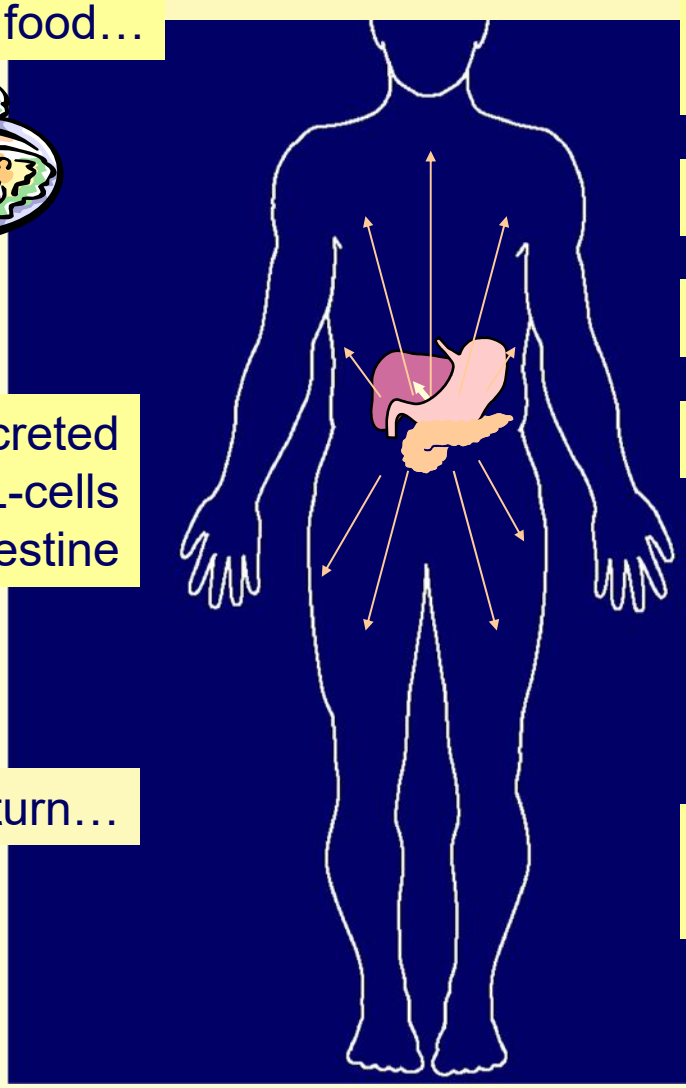
- Cleaved from proglucagon in intestinal L-cells (and neurons in hindbrain/hypothalamus)
- Secreted in response to meal ingestion
- Cleared via the kidneys

GLP-1 Modes of Action in Humans

Upon ingestion of food…



GLP-1 is secreted from the L-cells in the intestine



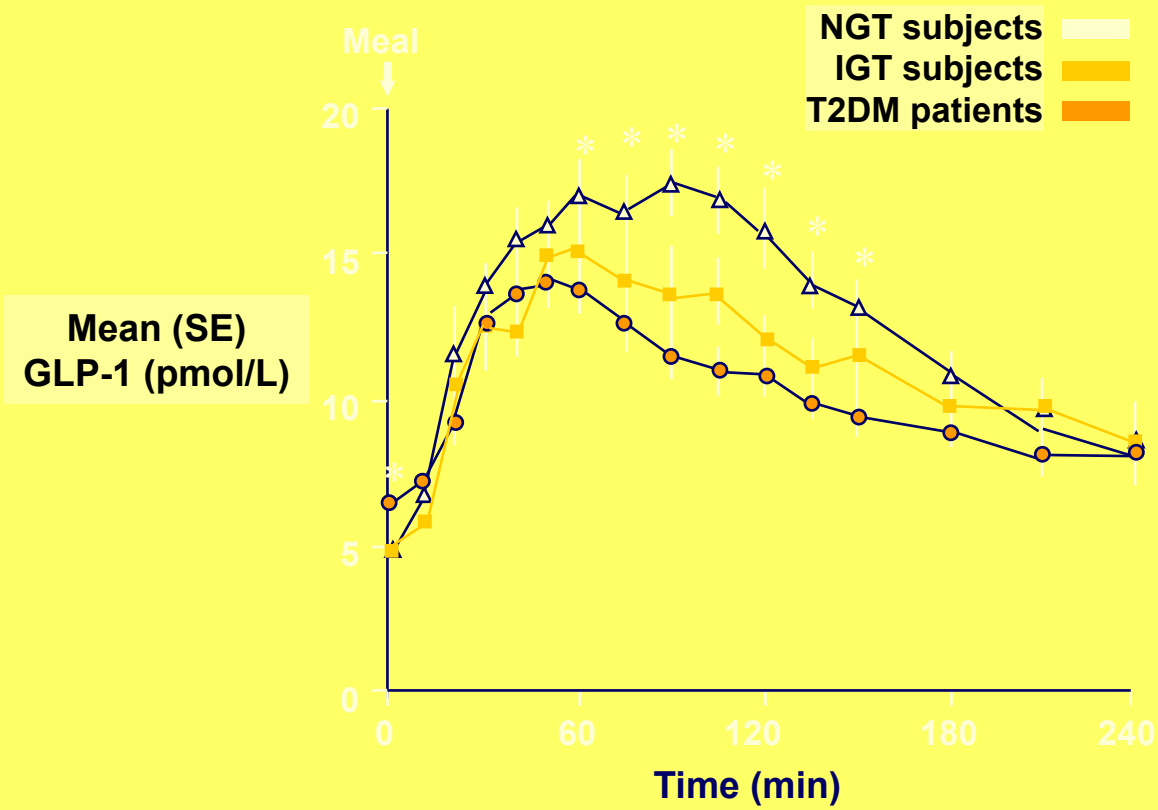
This in turn…

- Stimulates glucose-dependent insulin secretion
- Suppresses glucagon secretion
- Slows gastric emptying
- Reduces food intake

Long term effects demonstrated in animals…

- Increases beta-cell mass and maintains beta-cell efficiency

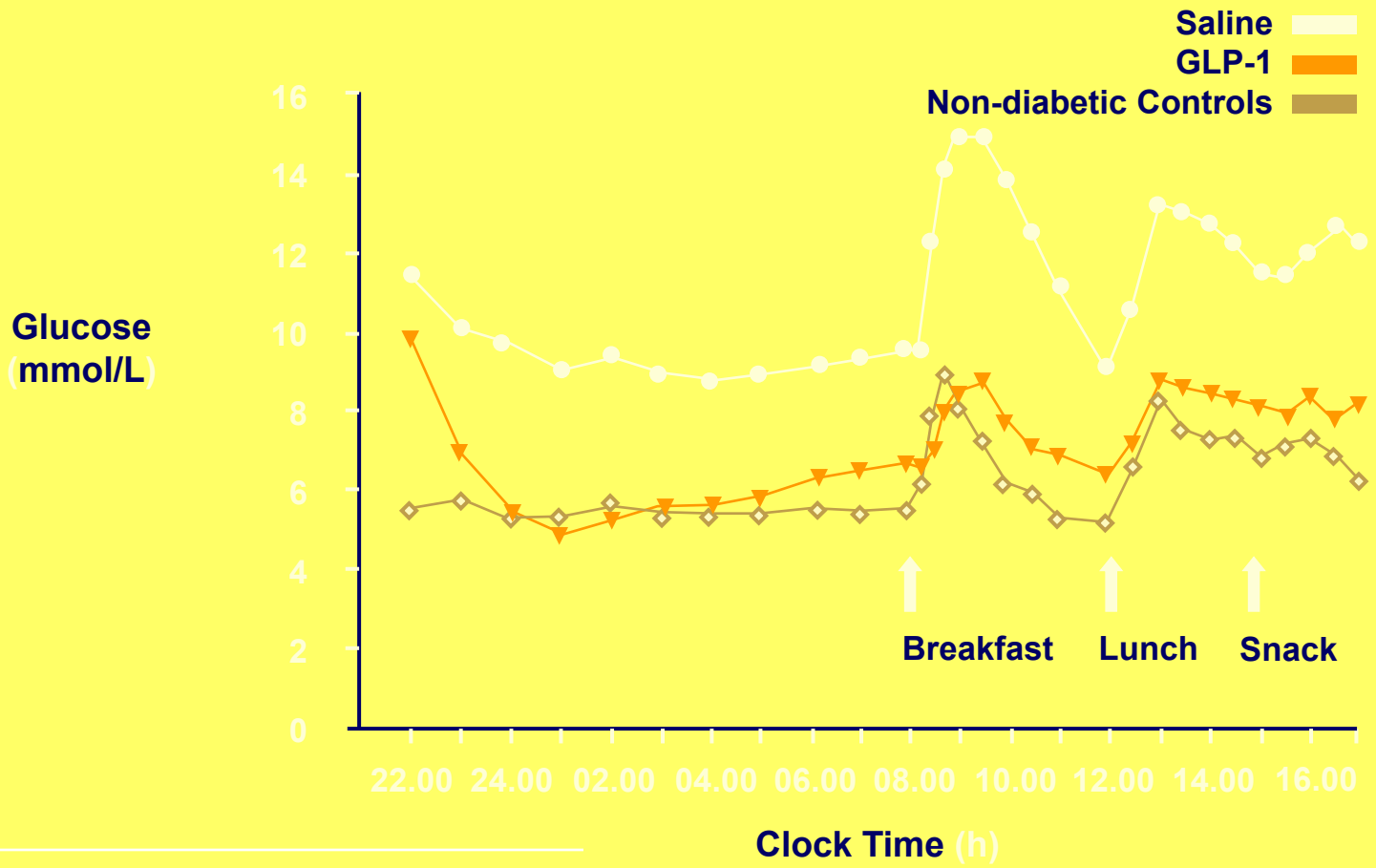
Postprandial GLP-1 Levels are Decreased in Subjects With IGT and Type 2 Diabetes



* P <0.05 between T2DM and NGT group.

Data from: Toft-Nielsen M, et al. *J Clin Endocrinol Metab* 2001; 86:3717-3723

Effect of GLP-1 Infusion on Glucose Concentration in Patients With Type 2 Diabetes (Previously on OHAs)



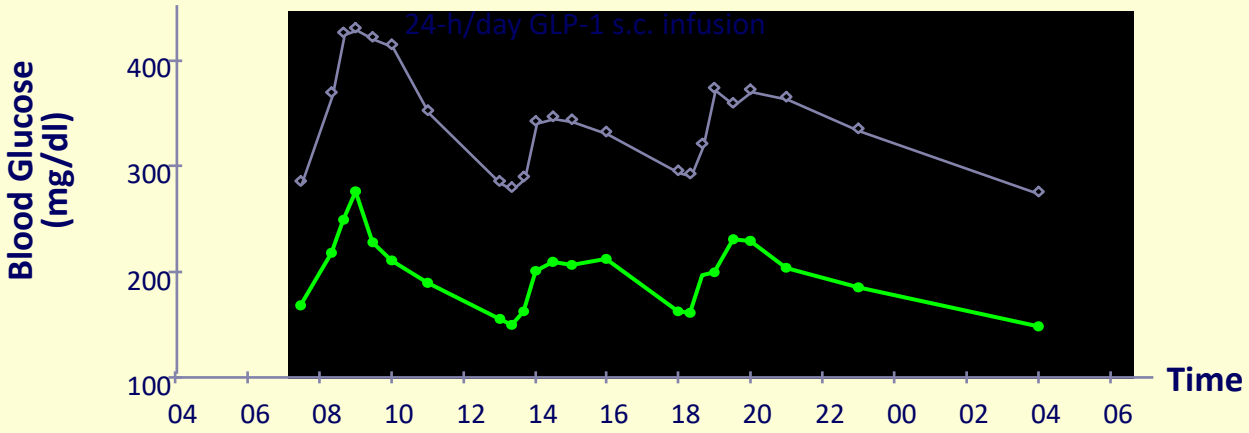
GLP-1 IV infusion (1.2 pmol/kg/min)

Data from: Rachman J, et al. *Diabetologia* 1997; 40: 205-211

Now for the bad News……..

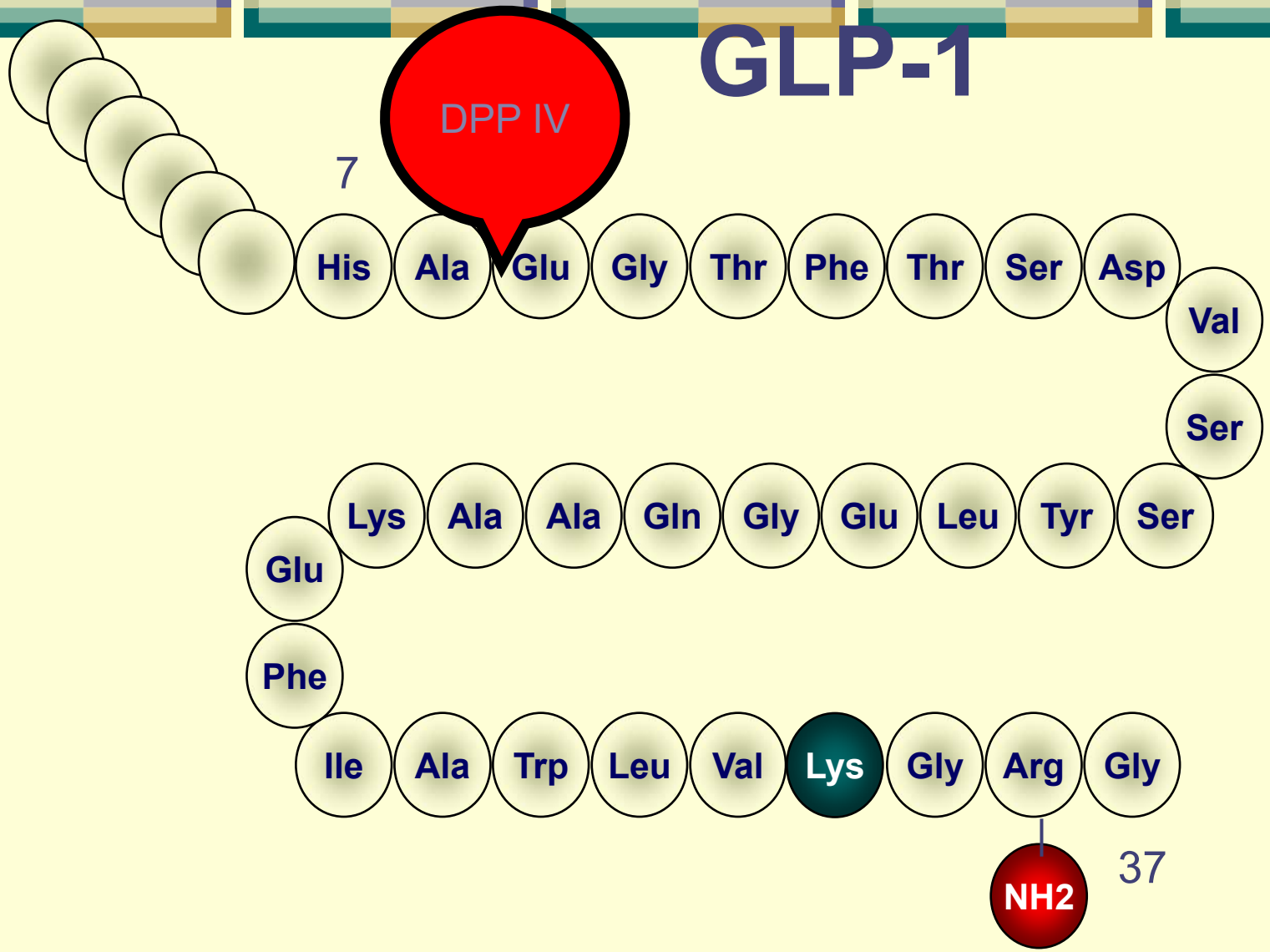
GLP-1 is short-acting

Blood glucose profiles



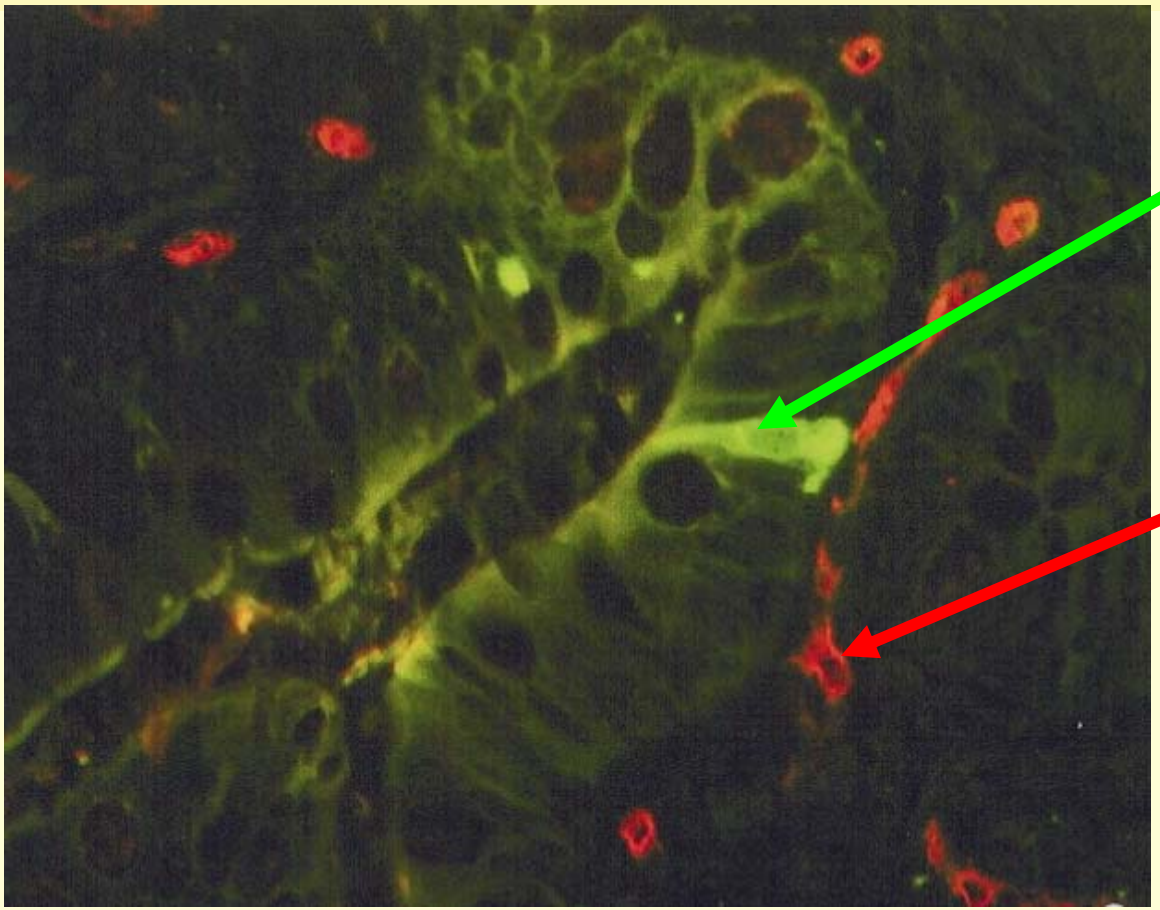
Modified from J Larsen et al: Diabetes Care 2001; 24:1416-1421

GLP-1



Native GLP-1 has short duration of action
($t_{1/2}$=2.6 minutes) when given intravenously

Native GLP-1 is rapidly degraded by DPP-IV



Human ileum, GLP-1 producing L-cells

Capillaries, DiPeptidyl Peptidase-IV (DPP-IV)

Adapted from: Hansen *et al*. *Endocrinology* 1999:140(11):5356-5363

DPP-IV action

GIP [1–42]

GLP-1 [7–36 amide]

(biologically active)

DPP-IV action

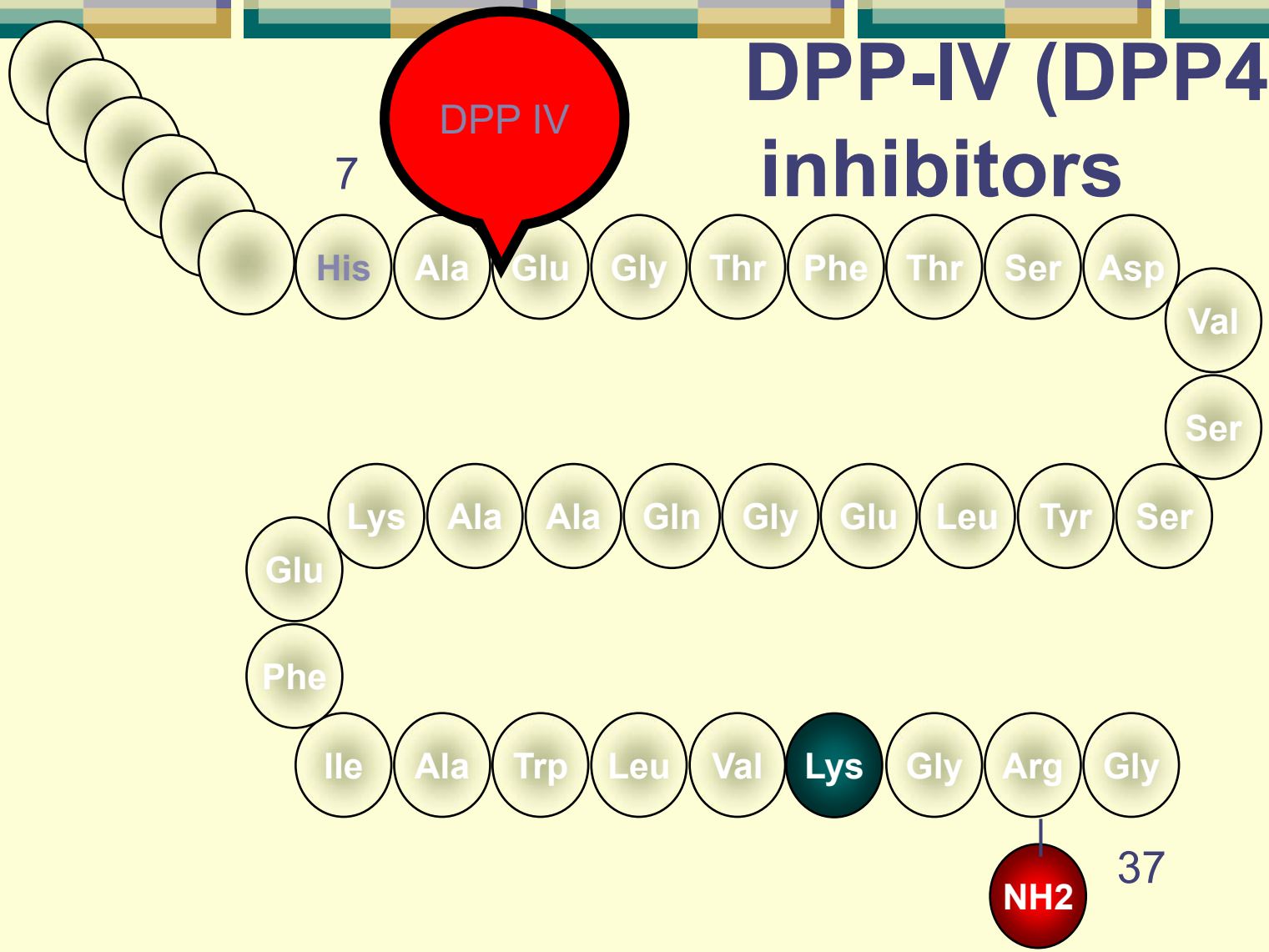
GIP [3–42]

GLP-1 [9–36 amide]

(biologically inactive)

So is that a dead-end for drug development in this area .....?

DPP-IV (DPP4) inhibitors



Dipeptyl- peptidase inhibitors

Sitagliptin

Vildagliptin

Saxagliptin

Septagliptin

Allogliptin

Sitagliptin - Overview

- **1st approved member of a new class of OAHA - DPP-4 inhibitor**
- **Potent, highly selective, reversible and competitive inhibitor of DPP-4 enzyme**
- **Approved by the FDA on October 17 2006. EU approval March 2007**

Mechanism of Action of Sitagliptin

Ingestion of food

GI tract

Release of active incretins GLP-1 and GIP

Pancreas

β cells

α cells

Glucose dependent

↑ Insulin (GLP-1 and GIP)

↑ Glucose uptake by peripheral tissues

↓ Blood glucose in fasting and postprandial states

Sitagliptin (DPP-4 inhibitor)

X

DPP-4 enzyme

Inactive GLP-1

Inactive GIP

Glucose-dependent

↓ Glucagon (GLP-1)

↓ Hepatic glucose production

- Incretin hormones GLP-1 and GIP are released by the intestine throughout the day, and their levels increase in response to a meal.

Concentrations of the active intact hormones are increased by sitagliptin, thereby increasing and prolonging the actions of these hormones.

Clinical Pharmacology of Sitagliptin: Pharmacokinetics and Drug Interactions

- **Pharmacokinetics**
  - **T_{max} (median): 1 to 4 hours postdose**
  - **Apparent $t_{1/2}$ (mean): 12.4 hours**
  - **Metabolism: approximately 79% excreted unchanged in urine**
  - **Based on in vitro data, sitagliptin does not inhibit CYP isozymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19, or 2B6 or induce CYP3A4**

Adverse Experiences Reported in ≥3% of Patients and Greater than Placebo[a]

	Sitagliptin 100 mg[c] **n = 1082**	Placebo[c] **n = 778**
Upper Respiratory Tract Infection	6.8	6.7
Nasopharyngitis	4.5	3.3
Diarrhea	3.0	2.3


Sita-gliptin

Summary – Safety + Tolerability

7 specific AEs

Chills

Naso-pharyngitis

Meniscus lesions

Nasal congestion

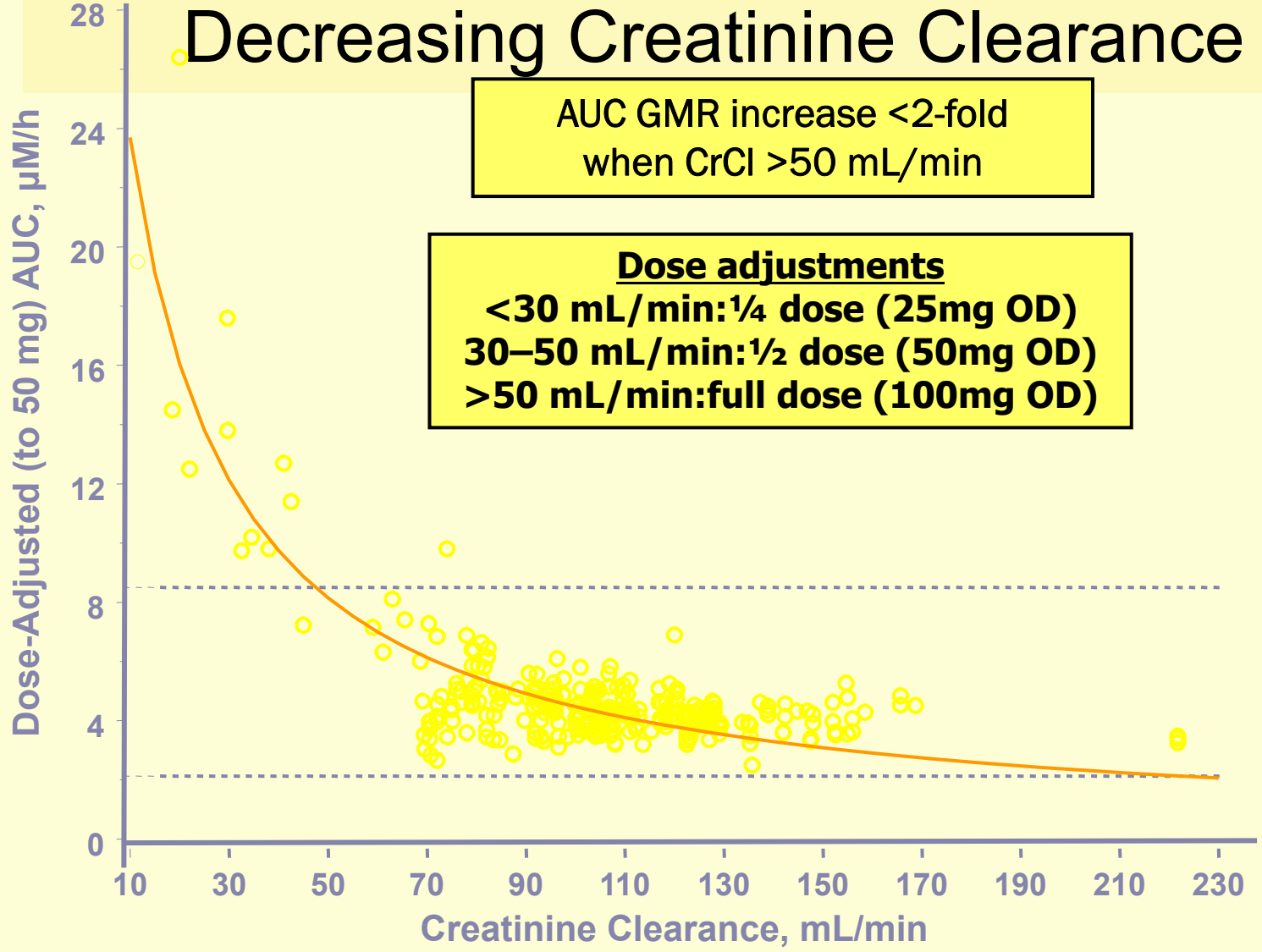
Contact dermatitis

Osteoarthritis

Tremor

Pooled safety. Stein et al. ADA 2007

Sitagliptin AUC_{0-inf} Increased With Decreasing Creatinine Clearance



Sections 2; 12.3

Patients With Renal Insufficiency

Renal Insufficiency	Mild	Moderate	Severe and ESRD*
Increase in Plasma AUC of Sitagliptin†	~1.1 to 1.6-fold increase‡	~2-fold increase	~4-fold increase
Recommended Dose	100 mg no dose adjustment required	50 mg	25 mg

Sitagliptin Has a Weight Neutral Profile

- **Monotherapy studies**
  - **No increase in body weight from baseline with sitagliptin compared with a small decrease in the placebo group**
- **Add-on to metformin**
  - **A similar decrease in body weight for both treatment groups**
- **Add-on to pioglitazone**
  - **No significant difference in body weight between treatment groups**
- **Noninferiority vs Sulfonylurea**

  A significant reduction in body weight with sitagliptin versus weight gain with glipizide

Saxagliptin

Review of Safety and Tolerability

Saxagliptin: Incidence of Adverse Events

Overall Incidence of Adverse Events Was Similar to Placebo

Pooled Analysis of Adverse Reactions Occurring in ≥5% of Patients and More Commonly Than Placebo

In Monotherapy and Add-On Therapy Studies*

Percent of Patients

	Saxagliptin 5 mg (N=882)	Placebo (N=799)
Upper respiratory tract infection	7.7%	7.6%
Urinary tract infection	6.8%	6.1%
Headache	6.5%	5.9%

- **Hypersensitivity-related events (such as urticaria and facial edema) were reported in 1.5% who received Saxagliptin 5 mg, Saxagliptin 2.5**

*Prespecified pooled analysis of 2 monotherapy studies, the add-on to MET study, the add-on to the SU glibenclamide study, and the add-on to a TZD study; 24-week data regardless of glycemic rescue.

Incidence of Adverse Events in Initial Combination With MET

Adverse Reaction Occurring in ≥5% Patients and More Commonly Than MET Plus Placebo

In Initial Combination With MET Study*

Percent of Patients

	Saxagliptin 5 mg + MET (N=320)	MET + Placebo (N=328)
Headache	7.5%	5.2%
Nasopharyngitis	6.9%	4.0%

*Metformin was initiated at a starting dose of 500 mg daily and titrated up to a maximum of 2000 mg daily.

Jadzinsky M et al. *Diabetes Obes Metab.* 2009;11:611-622.

Saxagliptin: Discontinuation of Therapy Due to Adverse Events

- Discontinuation of therapy due to adverse events occurred in **3.3%** and **1.8%** of patients receiving Saxagliptin and placebo, respectively

Most Common Adverse Events Associated With Discontinuation of Therapy*

	Percent of Patients		
	Saxagliptin 5 mg (N=882)	Saxagliptin 2.5 mg (N=882)	Comparator (N=799)
Lymphopenia	0.5%	0.1%	0.0%
Rash	0.3%	0.2%	0.3%
Blood creatinine increase	0.0%	0.3%	0.0%
Blood creatine phosphokinase increase	0.2%	0.1%	0.0%

- There was a dose-related mean decrease in absolute lymphocyte count observed with Saxagliptin

*Reported in at least 2 patients treated with Saxagliptin

Drug Interactions and Use in Specific Populations

Drug Interactions

Saxagliptin should be limited to 2.5 mg when coadministered with a strong CYP3A4/5 inhibitor (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin).

Use in Specific Populations

Pregnant and Nursing Women: There are no adequate and well-controlled studies in pregnant women

Pediatric Patients: Safety and effectiveness of Saxagliptin in pediatric patients have not been established.

Saxagliptin: Renal Impairment

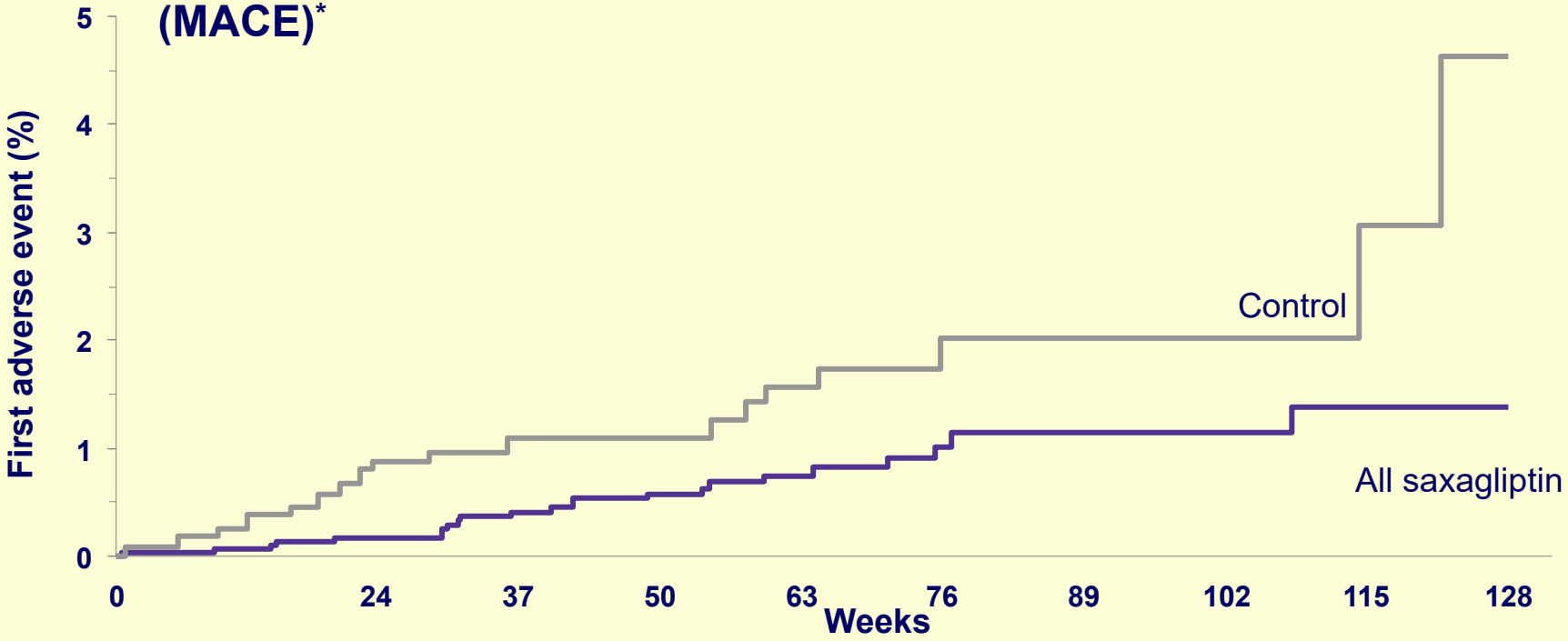
- Mild Impairment, creatinine clearance [CrCl] ≤50 mL/min: No dosage adjustment
- Moderate or severe renal impairment, or with end-stage renal disease (ESRD) requiring hemodialysis (creatinine clearance [CrCl] ≤50 mL/min). Saxagliptin 2.5 mg is recommended.
- Saxagliptin should be administered following hemodialysis when used in that scenario. Saxagliptin has not been studied in patients undergoing peritoneal dialysis.
- Assessment of renal function is recommended prior to initiation of Saxagliptin and periodically thereafter.

Saxagliptin: Hepatic Impairment

- In subjects with hepatic impairment (Child-Pugh classes A, B, and C)
  - Mean Cmax and AUC of saxagliptin were up to 8% and 77% higher, respectively, compared to healthy matched controls following administration of a single 10 mg dose of saxagliptin.
  -
  - The corresponding Cmax and AUC of the active metabolite were up to 59% and 33% lower, respectively, compared to healthy matched controls.
- These differences are not considered to be clinically meaningful.
- No dosage adjustment is recommended for patients with hepatic impairment

Cardiovascular events: Saxagliptin controlled Phase 2b/3 pooled population

Time to onset of first primary Major Adverse Cardiovascular Event (MACE)*



Patients at risk

Control	1,251	935	860	774	545	288	144	123	102	57
All saxagliptin	3,356	2,615	2,419	2,209	1,638	994	498	436	373	197

* Primary MACE was defined as was defined as stroke (cerebrovascular accidents), MI, and CV death

Comparing the Gliptins

	Sitagliptin	Vildagliptin	Saxagliptin
Dosing	OD	BD	OD
Renal Failure	Approved	Not Approved	Approved
Hepatic Failure	No info	No info	Safe
With Insulin	Not Approved	Approved	Studies Pending
On Bone	Improved BMD?	Unknown	Unknown
Infections	Slight increase UTI, URI	Neutral	Neutral
Cardiac Impact	Reduced post ischaemic stunning	Neutral	?reduced CV mortality

Which is the appropriate oral hypoglycaemic agent to use and when?

Determinants of OAD usage

1)Body Mass Index : Metformin, Gliptins
BMI> 22kg/m2

2)Presence of GI symptoms: Sulpha, Gliptins, Glitazones

3)Renal Dysfunction: Gliptins,Glitazones(+/-),Sulpha (variable)

4) Aging Meglitinides, Gliptins(?)

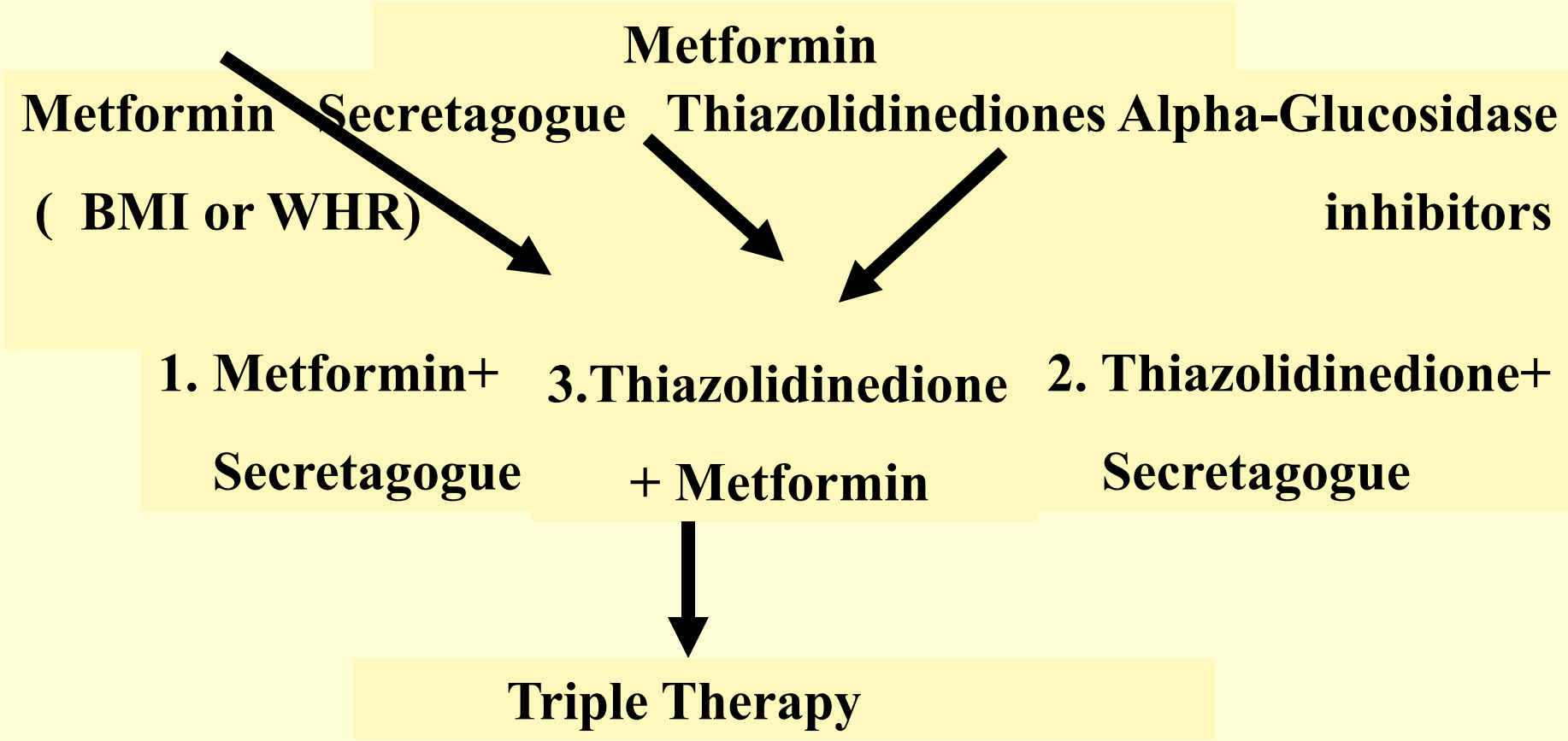
5) Hepatic Dysfunction Nateglinide, Saxagliptin(?)

6) Compliance Gliptins, Glitazones,

7) Cost Metformin, Sulphas, Glitazones

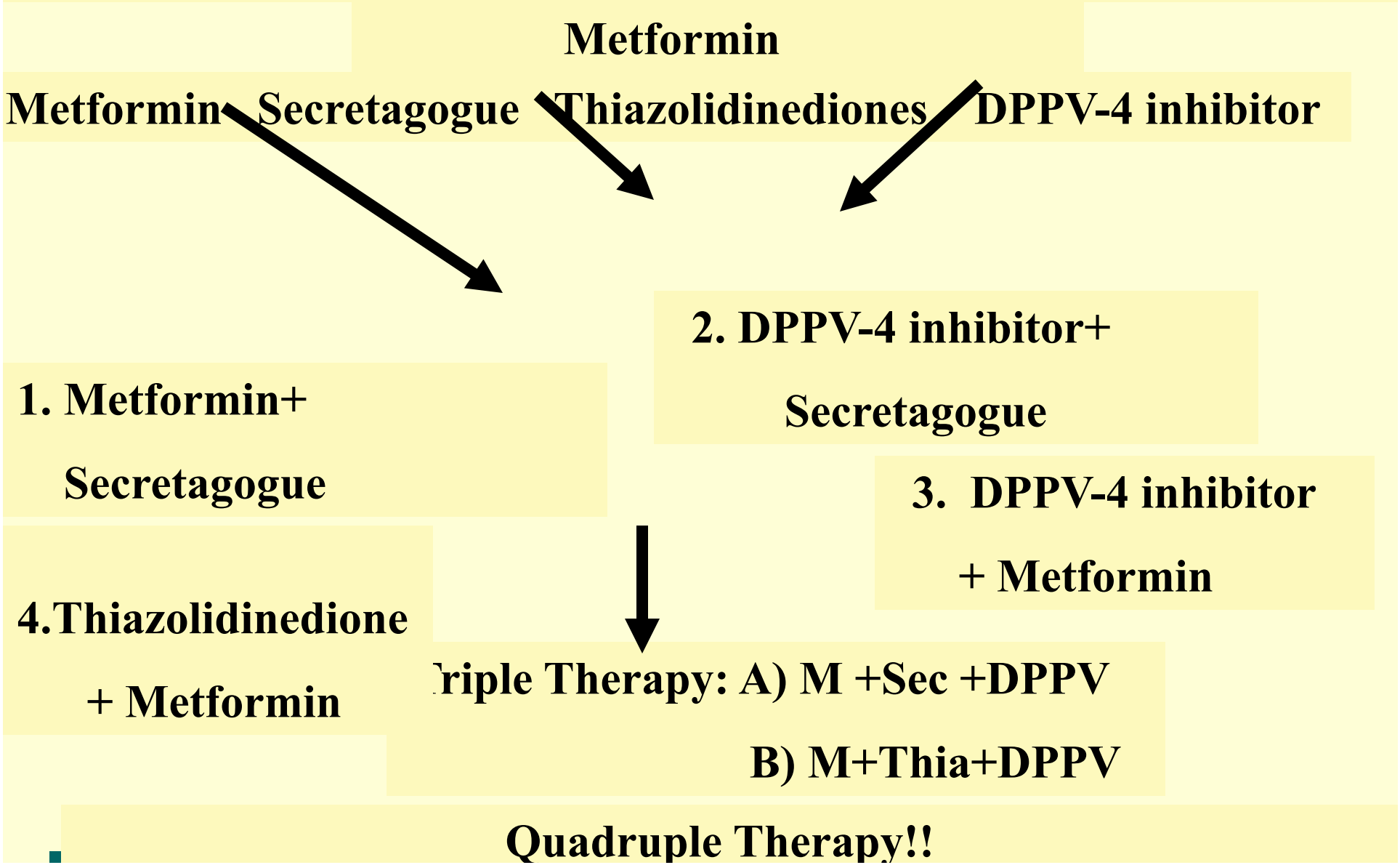
Therapeutic Algorithm

for Oral Hypoglycaemic Drugs…….Yesterday.

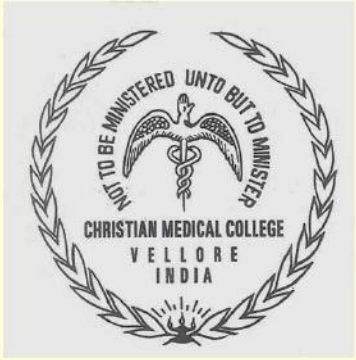


Therapeutic Algorithm

for Oral Hypoglycaemic Drugs…….Today.



Thank You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