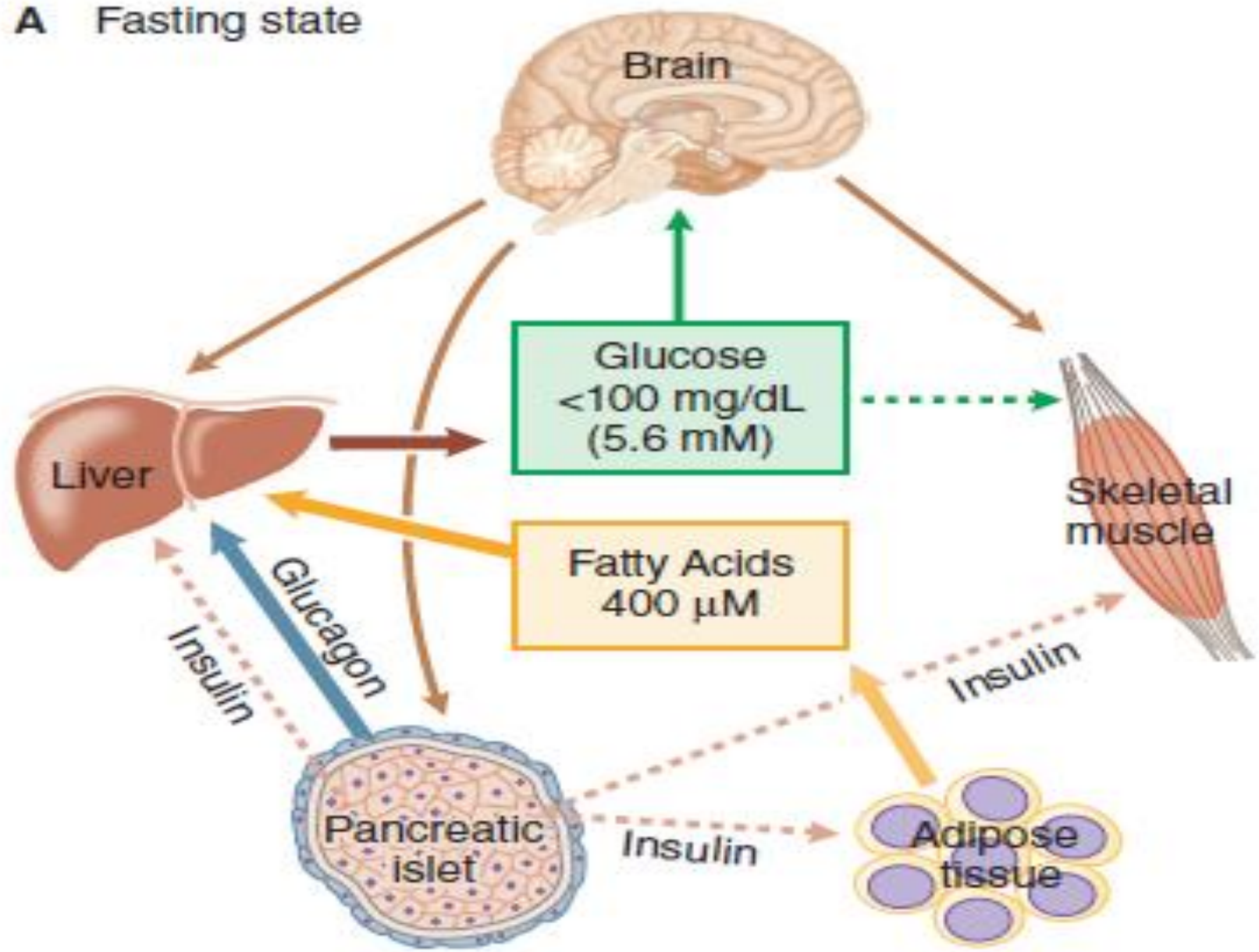
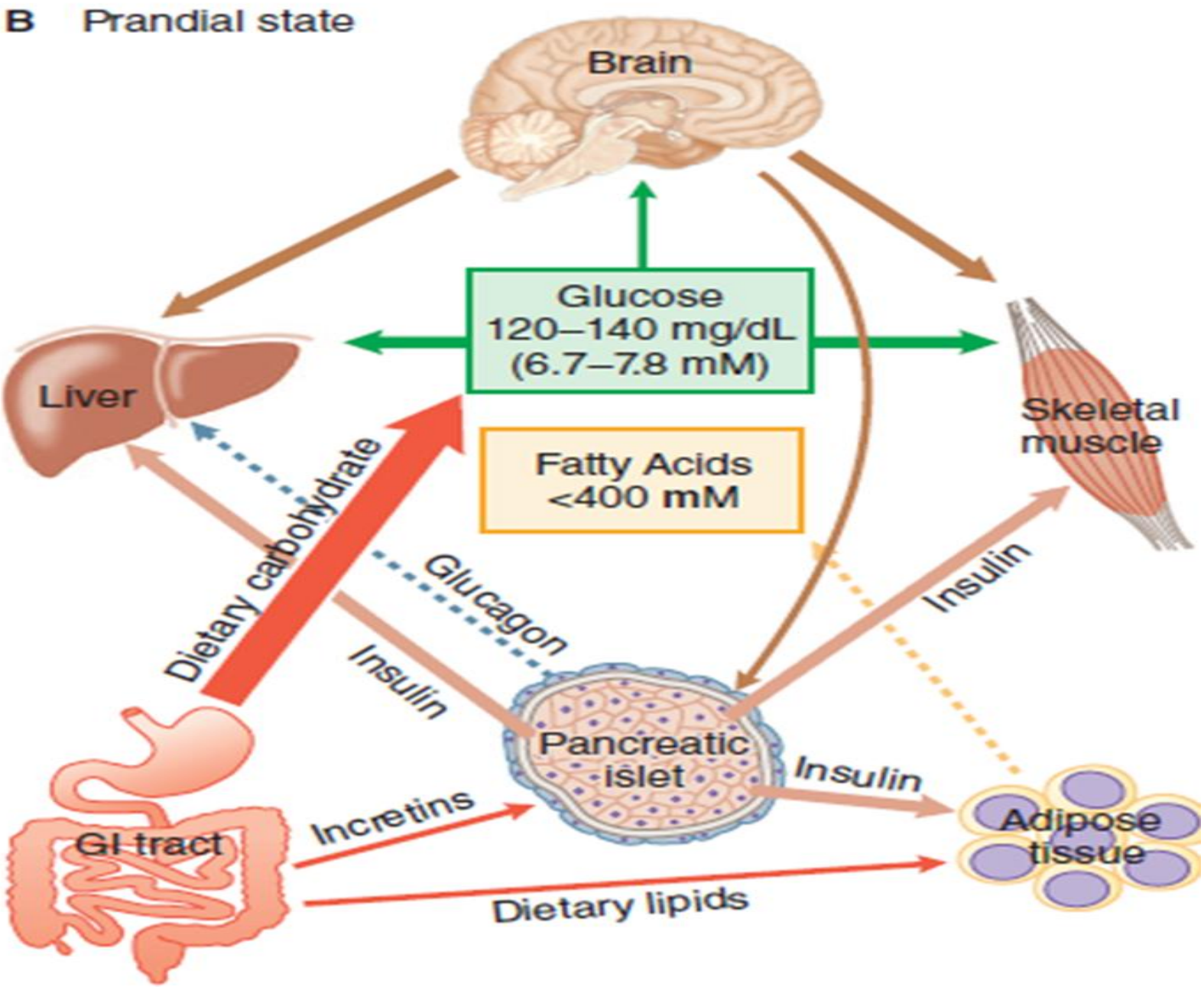
PHARMACOLOGY OF ENDOCRINE PANCREAS

PHARMACOTHERAPY OF DIABETES MELLITUS

Insulin, glucagon, and glucose homeostasis



Insulin, glucagon, and glucose homeostasis



Endocrine Pancreas

Islets of Langerhans --- main cell types

Beta (or β) cells --- **insulin**

Alfa cells --- **glucagon**

Delta cells --- **somatostatin**

PP cells --- **pancreatic polypeptide**

Epsilon (ε) cells --- **ghrelin**

B cells also secrete a peptide **amylin**:
influences Gut motility and speed of glucose absorption.

INSULIN --- first protein for which amino acid sequence determined (Sanger's group, 1955).

Two peptide chains A and B of 21 and 30 amino acid residues, respectively. 20% of immuno-reactive insulin in plasma --- proinsulin and intermediates.

Main factor controlling synthesis and secretion

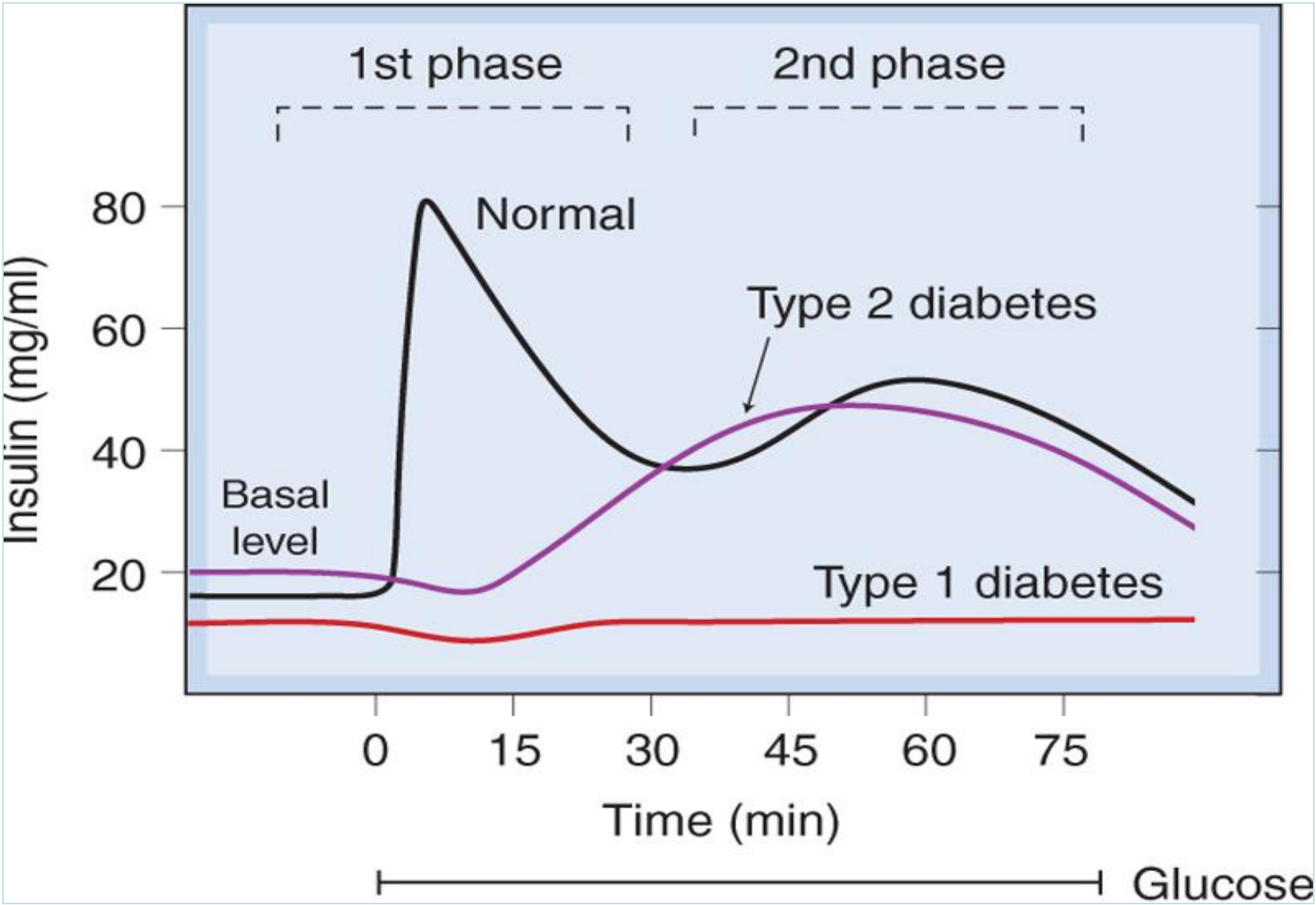
--- Blood glucose concentration

--- the absolute glucose concentration

--- rate of change of blood glucose.

Stimuli for insulin release	Inhibitory stimuli
Aminoacids (arginine & leucine)	Galanin (an endogenous K^+ ATP activator)
High conc of fatty acids	Somatostatin, insulin itself, Leptin
Parasympathetic stimulation, β2 stimulation	Sympathetic stimulation (α2)
Peptide hormones of gut: gastrin, Secretin, Cholecystokinin, Glucose insulinotropic peptide, Glucagon like peptide, Enteroglucagon.	Adrenaline, hypoxia, hypoglycemia, exercise, hypothermia, surgery or severe burns, chronically elevated blood glucose. Low conc of fatty acids.
Sulfonylurea receptors +	Diazoxide, phenytoin etc

INSULIN RELEASE



Pharmacokinetics

- One-fifth of insulin stored is secreted daily.
- Basal insulin values of 5–15 μU/mL with a peak rise to 60–90 μU/mL during meals

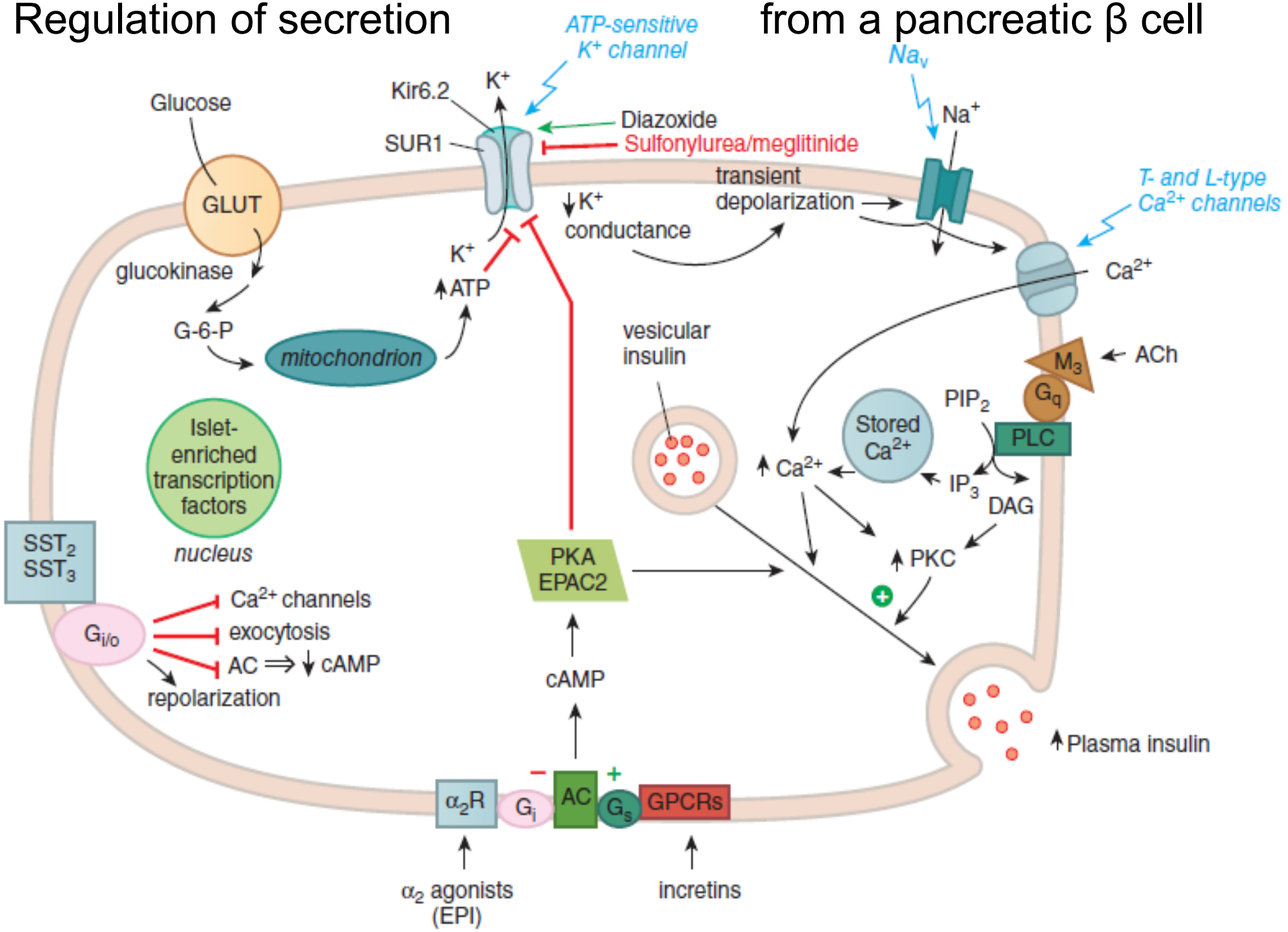
Insulin Degradation

- Liver clears 60%
- Kidney removes 35-40%.

Insulin-treated diabetics receiving s.c. insulin injections, ratio is reversed.

Half-life of insulin in plasma is 3 - 5 minutes.

Regulation of secretion from a pancreatic β cell



Insulin Actions

--- Anabolic

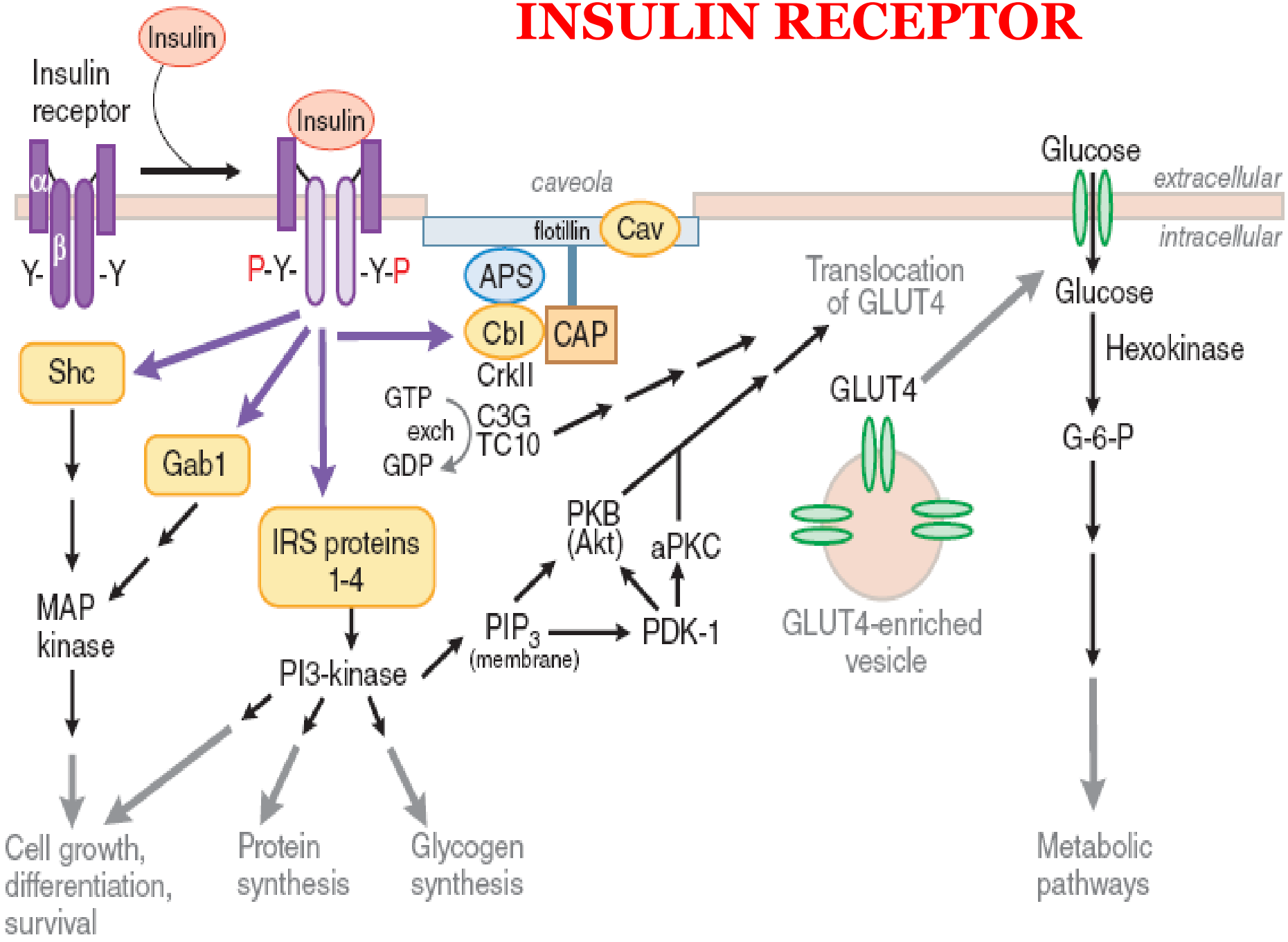
--- Insulin signaling critical for uptake, use, and storage of glucose, lipids, and amino acids.

--- Stimulates glycogenesis, lipogenesis, and protein synthesis; inhibits catabolism of these compounds.

--- Stimulates transport of substrates and ions into cells, promotes translocation of proteins between cellular compartments.

--- Regulates action of specific enzymes, and controls gene transcription and mRNA translation.

INSULIN RECEPTOR



DIABETES MELLITUS Types

Type 1 --- Absolute insulin deficiency

Predisposition to recurrent **ketoacidosis** in the absence of insulin therapy.

Autoimmune destruction of pancreatic β-cells or **idiopathic** in some cases.

Type 2 --- Tissue resistance to action of Insulin combined with deficiency of insulin secretion.

Dehydration --- a life-threatening condition called **Nonketotic hyperosmolar coma**

Type 3 --- multiple other specific causes of an elevated blood glucose: pancreatectomy, pancreatitis, nonpancreatic diseases, drug therapy, etc

Type 4 --- Gestational diabetes (GDM)

Impaired glucose tolerance --- pregnant woman without a previous history of diabetes.

Approximately 4% of all pregnancies.

Increased risk of fetal abnormalities and adverse birth outcomes.

Increased lifelong maternal risk of chronic diabetes.

TABLE 47–3 SOME DRUGS THAT MAY PROMOTE HYPERGLYCEMIA OR HYPOGLYCEMIA

HYPERGLYCEMIA	HYPOGLYCEMIA
Glucocorticoids; thyroid hormone	β Adrenergic antagonists
Antipsychotics (atypical, others)	Theophylline
Protease inhibitors	ACE inhibitors
β Adrenergic agonists; epinephrine	Salicylates, NSAIDs
Thiazide diuretics	LiCl
Hydantoins (phenytoin, others)	Ethanol
Opioids (fentanyl, morphine, others)	Pentamidine
Diazoxide; nicotinic acid	Bromocriptine
Interferons; amphotericin B	
Acamprosate; basiliximab; asparaginase	

Criteria for diagnosis of Diabetes

Random plasma glucose concentration ≥200 mg/dL, accompanied by symptoms (fatigue, polydipsia, polyuria, weight loss).

FPG (Fasting plasma glucose) >126 mg/dL

Post prandial Plasma glucose >200 mg/dL at 2 h after 75 g glucose administration.

FPG of 100 – 126 mg/dL (6 – 7 mmol/L) reflect impaired fasting glucose regulation.

HbA_{1c} = or >6.5%

Risk Factors for Type 2 Diabetes Mellitus

- Age >45 years
- Obesity (BMI >25 kg/m2), physical inactivity
- First degree relative of type 2 diabetics
- African-American, Hispanic, or Native American ethnic background
- Personal history of gestational diabetes mellitus or delivery of a baby weighing >9 lb
- Hypertension
- HDL cholesterol ≤ 35 mg/dL and/or fasting triglyceride concentration ≥250 mg/dL
- Personal history of impaired fasting glucose or impaired glucose tolerance

Goals for glycemic control

- preprandial blood glucose of 80 – 120 mg/dL
- postprandial blood glucose < 180 mg/dL
- bedtime blood glucose of 100 – 140 mg/dL.
- hemoglobin A1C values 6.5 --- 7%

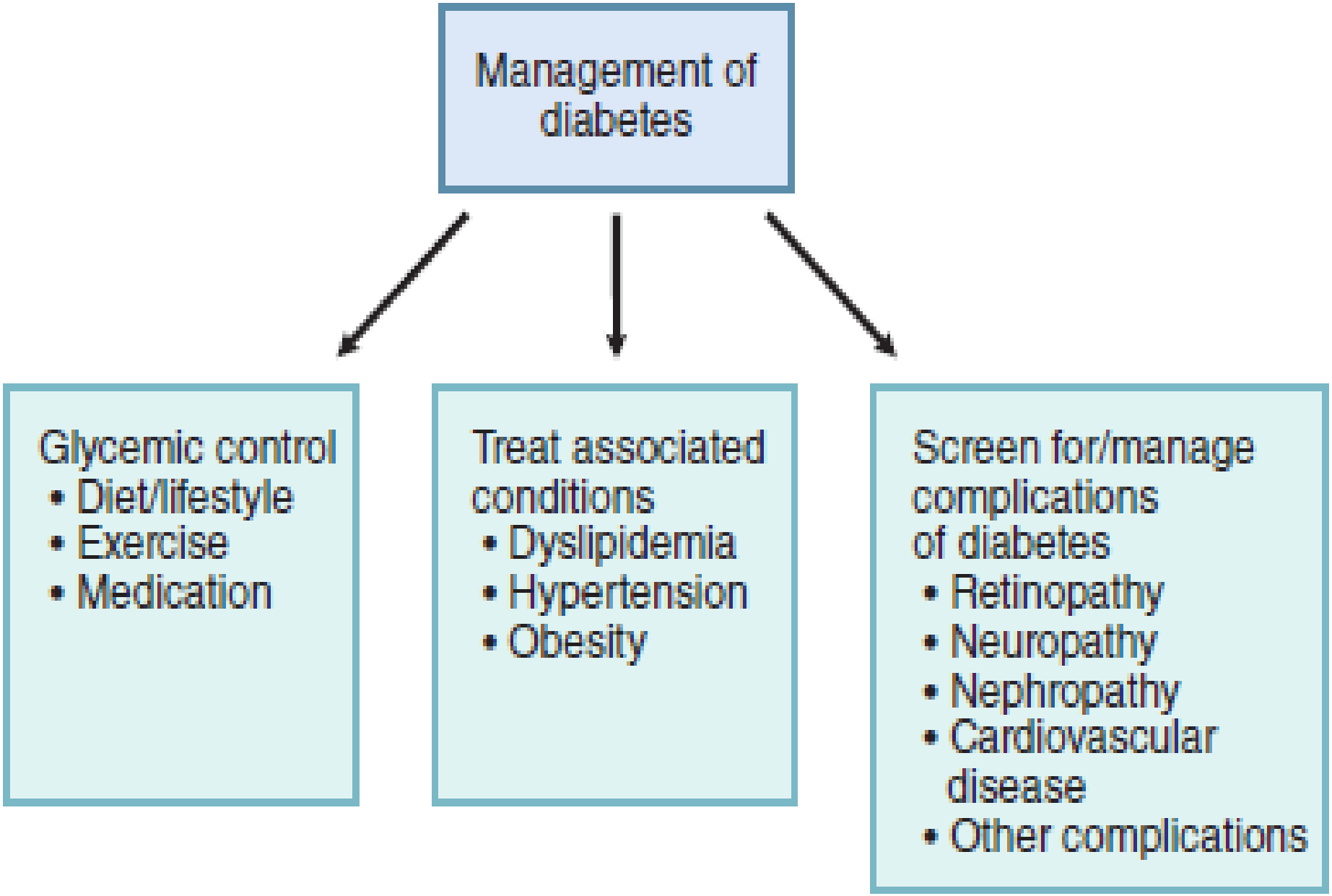
Management of diabetic complications

Aggressive treatment of modifiable risk factors (smoking, hypertension, dyslipidemia)

HMG-CoA reductase therapy

Achieve blood pressure <130/85 mm Hg.

COMPREHENSIVE DIABETES CARE



Therapeutic Guidelines

Type 1 --- treated with insulin

Type 2 --- asymptomatic & glucose values <300 mg/dL; 3 – 6 months trial of diet modification and exercise --- before drug therapy.

Reduction in intake of saturated fat and increase in complex carbohydrates in diet.

Symptomatic patients or patients with glucose values >300 mg/dL

Initiate drug therapy + dietary intervention.

GLUCAGON --- single-chain polypeptide

Structural homology with Secretin, VIP and GIP

Actions

Increases blood glucose, breakdown of fat and protein. Stimulates glycogen breakdown and gluconeogenesis, inhibits glycogen synthesis.

Clinical uses of glucagon

- Route : i.m. or s.c. as well as i.v.
- Hypoglycaemia in unconscious patients.
- Acute cardiac failure precipitated by β-adrenoceptor antagonists.

CONTROL OF BLOOD GLUCOSE

Hypoglycemia to a critical degree --- multiple neurohormonal responses --- restore concentration to normal range

Responses --- pancreatic glucagon release, sympathetic nervous system activation, hypothalamic–pituitary–adrenal release of growth hormone, cortisol and epinephrine.

Symptoms of hypoglycemia --- symptoms of adrenergic stimulation.

INSULIN HISTORY

Banting, Best and Collip --- beef insulin to a diabetic for the first time in 1922

Purity of animal insulins slowly improved.

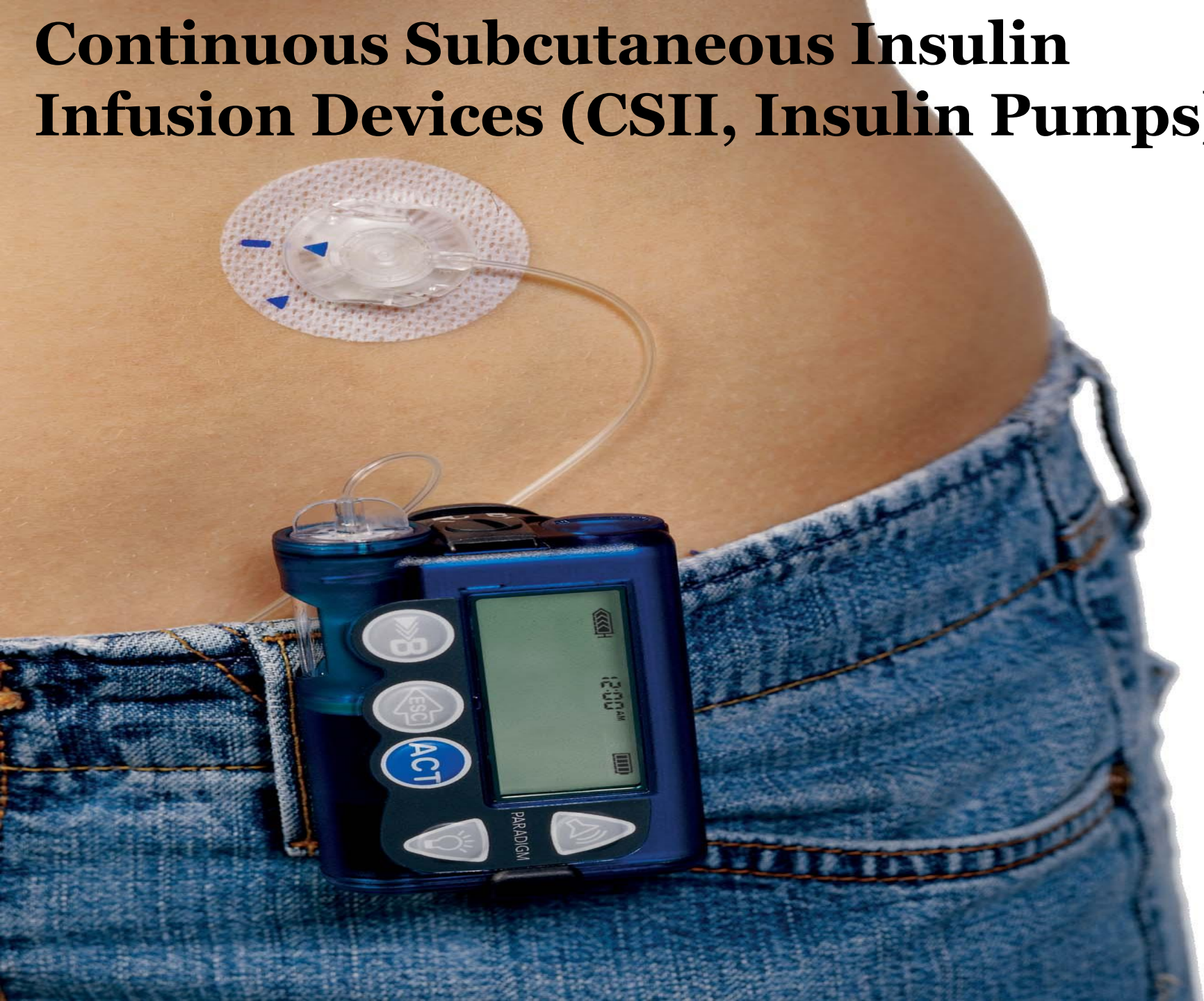
1930s and 1940s --- crystallization of insulin with zinc and combination with protamine --- prolongation of insulin action --- intermediate acting insulins.

Human insulin --- recombinant DNA technology --- 1980

1990s ---- insulin analogs --- lispro and aspart.


300
270
240
210
180
150
120
90
60
30

Continuous Subcutaneous Insulin Infusion Devices (CSII, Insulin Pumps)



Short Acting Insulins

Preparation	Species source	Concentration
Insulin Lispro	Human analog	U-100, U-200
Insulin Aspart	Human analog	U-100
Insulin Glulisine	Human analog	U-100
Regular Insulin	Human	U-100, U-500
Regular Insulin Inhaled	Human	---

Long Acting Insulins

Preparation	Species source	Concentration
NPH Insulin	Human	U-100
Insulin Glargine	Human analog	U-100, U-300
Insulin Detemir	Human analog	U-100
Insulin Degludec	Human analog	U-100, U-200

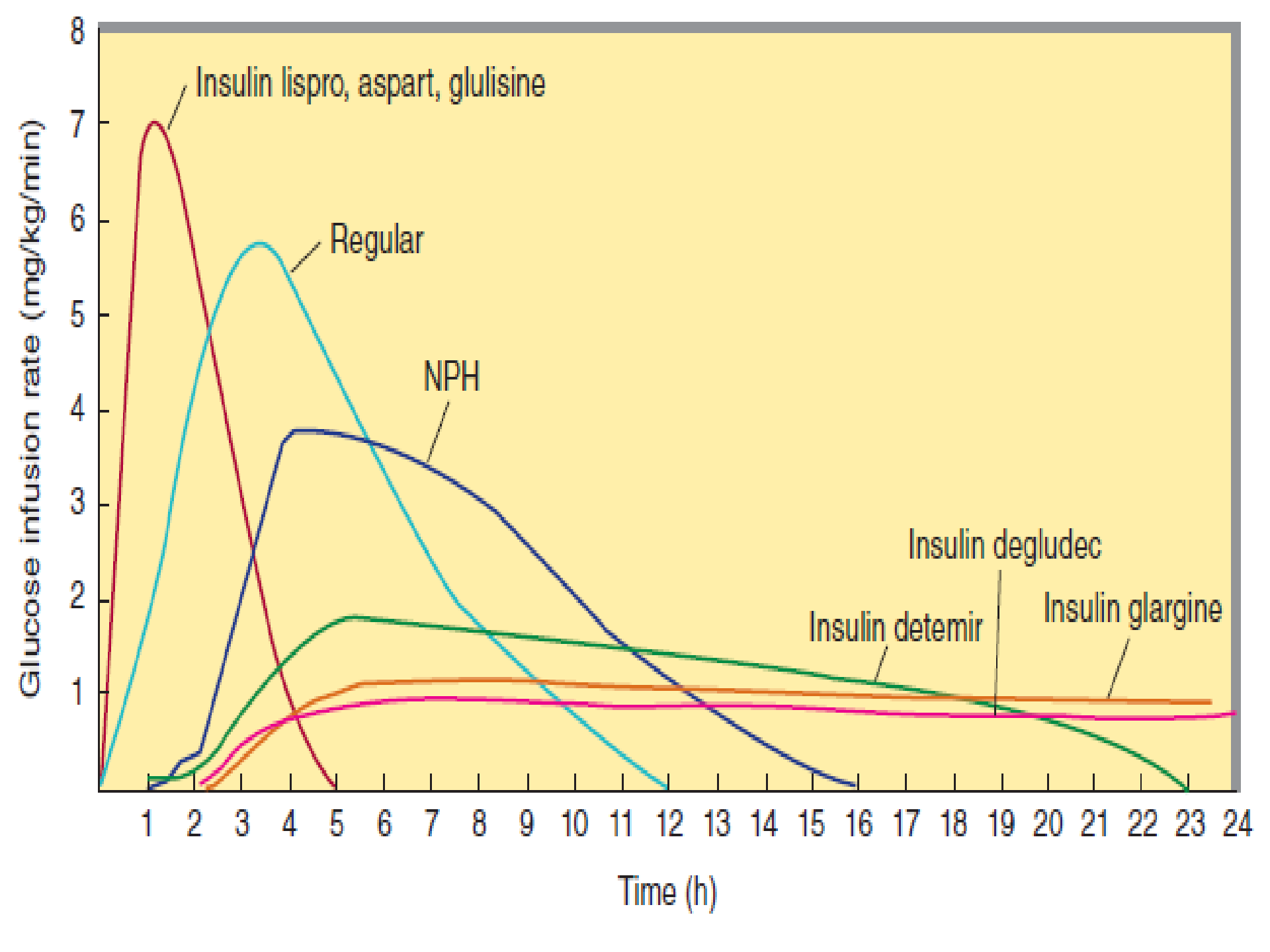
Premixed Insulins

Preparation	Species source	Concentration
70 NPH/ 30 Regular	Human	U-100
75/25 NPL, Lispro	Human analog	U-100
50/50 NPL, Lispro	Human analog	U-100
70/30 NPA, Aspart	Human analog	U-100
70/30 Degludec, Aspart	Human analog	U-100

Human Insulin Preparations

Insulin Preparation	Onset*	Peak*	Duration*
Rapid (ultrashort) Acting:			
• Lispro insulin*	0.25	0.5-1.5	2-4
• Aspart insulin*	0.25	0.5-1.5	2-4
• Glulisine insulin*	0.25	0.5-1.5	2-4
Short-acting			
• Regular insulin	0.5-1	1-2	4-6
• Inhaled insulin	0.5-1	1-2	4-6
Longer-acting			
• NPH insulin	2-4	4-6	12-18
• Insulin detemir*	1-2	Flat response	12-20
• Glargine insulin*	1-2	Flat response	18-24
• Degludec*	1-2	Flat response	24-42

*Time in hours. * Newer Insulin analogs


Glucose infusion rate (mg/kg/min)
8
7
6
5
4
3
2
1
Insulin lispro, aspart, glulisine
Regular
NPH
Insulin degludec
Insulin detemir
Insulin glargine
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
Time (h)

INSULIN THERAPY

s.c. delivery differs from physiological secretion

--- does not reproduce the normal rapid rise and decline as endogenous insulin.

--- insulin diffuses 1st to peripheral circulation instead of portal circulation. Thus portal / peripheral insulin concentration is not physiological, this may alter the influence of insulin on hepatic metabolism.

--- However it leads to near normal glycemia.

Factors That Affect Insulin Absorption (s.c.)

--- Site of injection, type of insulin, s.c. blood flow, smoking, regional muscular activity at the site of the injection, volume and concentration of injected insulin, and depth of injection.

--- Abdomen is the preferred site of injection.

--- Others sites are buttock, anterior thigh, or dorsal arm.

--- Rotation of injection sites advocated to avoid lipohypertrophy or lipoatrophy.

--- Refrigeration recommended, formulations of soluble insulin are stable at 25°C.

Regular insulin

Also given i.v. or i.m.

Only insulin formulated at concentrations of 500 units/mL (Insulin U-500). This is for s.c. route only not for i.m. or i.v. administration.

Intravenous infusions of insulin

--- patients with ketoacidosis

--- during the perioperative period

--- during labor and delivery,

--- in intensive care situations

In these situations requirements change rapidly

Rapid acting insulin analogs --- retain monomeric or dimeric configuration : **lispro**, **aspart** and **glulisine.** (monomeric insulins)

Dissociate into monomers rapidly --- rapid absorption, short duration of action --- earlier hypoglycemic response.

Injection just or 15 minutes before a meal --- glycemic control same as regular insulin given 30 min before a meal.

Approved by FDA for continuous subcutaneous insulin infusion (CSII) pump use.

Insulin lispro

Identical to human regular insulin except at positions B28 and B29, where sequence of two residues has been reversed

Insulin aspart

Replacement of proline at B28 with aspartic acid.

Insulin glulisine

Glutamic acid replaces lysine at B29 and lysine replaces asparagine at B23.

Intermediate-acting insulins

Dissolve more gradually when administered subcutaneously --- durations of action longer.

Neutral protamine Hagedorn (NPH) **insulin** (isophane insulin suspension) --- suspension of insulin in a complex with zinc and protamine in a phosphate buffer.

Dose regulates the action profile.

The action of NPH is highly unpredictable, and its variability of absorption is upto 50%.

Insulin Glargine (peakless insulin)

2 arginine molecules added to B chain carboxyl terminal and glycine replaces asparagine at A 21 position. Microprecipitates form after s.c. injection.

Clear solution with pH=4. Cannot be mixed with short acting insulins formulated at neutral pH.

Given once daily anytime during the day. In combination with rapid-acting insulin (at mealtimes) --- suitable for both type 1 and type 2 diabetics.

Insulin detemir

Recombinant human insulin --- deletion of threonine at B-30 and addition of 14-carbon fatty acid chain to the amino acid at B-29

Reversibly binds albumin by its fatty acid chain --- slowly released from albumin.

Consistent action --- 24 hours --- improved glycemic control with little or no weight gain

Reduced risk of hypoglycemia compared to NPH insulin.

Administered once or twice daily.

Insulin degludec

Threonine at position B30 is deleted; is conjugated to hexadecanedioic acid at position B29. Forms multihexameric complexes that slow absorption; also binds well to albumin.

Inhaled Insulin

Liquid form of human insulin delivered with an electronic device --- delivers insulin when inhalation velocity is optimal.

Set to administer desired dose in 1U increments --- rapid onset of action --- duration of action of 5 to 10 hours.

Clinical uses of insulin

Type 1 diabetics require long term insulin.

Diabetic ketoacidosis --- i.v. insulin

Many Type 2 diabetics ultimately need insulin.

Short-term i.v. treatment of type 2 diabetics for
--- Surgeries
--- Infections
--- Myocardial infarction
--- Uncontrolled gestational diabetes
--- Emergency treatment of hyperkalaemia

Daily Requirements

Insulin production --- normal, thin, healthy person --- 18 to 40 units/day

Type 1 DM --- average dose is 0.6 to 0.7 units /kg body weight per day --- range 0.2 to 1 units/kg per day

- Total daily insulin requirement in units --- weight in pounds divided by four or 0.55 times person's weight in kilograms

Obese patients require more (about 2 units/ kg per day) --- resistance of peripheral tissues to insulin.

Insulin regimens: include multiple injections of long-acting or short-acting insulins to achieve euglycemia.

Basal/bolus regimen: basal administration of long-acting insulin before breakfast or at bedtime and preprandial injections of short-acting insulin. (multiple injections)

Split-mixed regimen --- pre-breakfast and pre-supper injection of a mixture of short- and long-acting insulins. (2 injections)

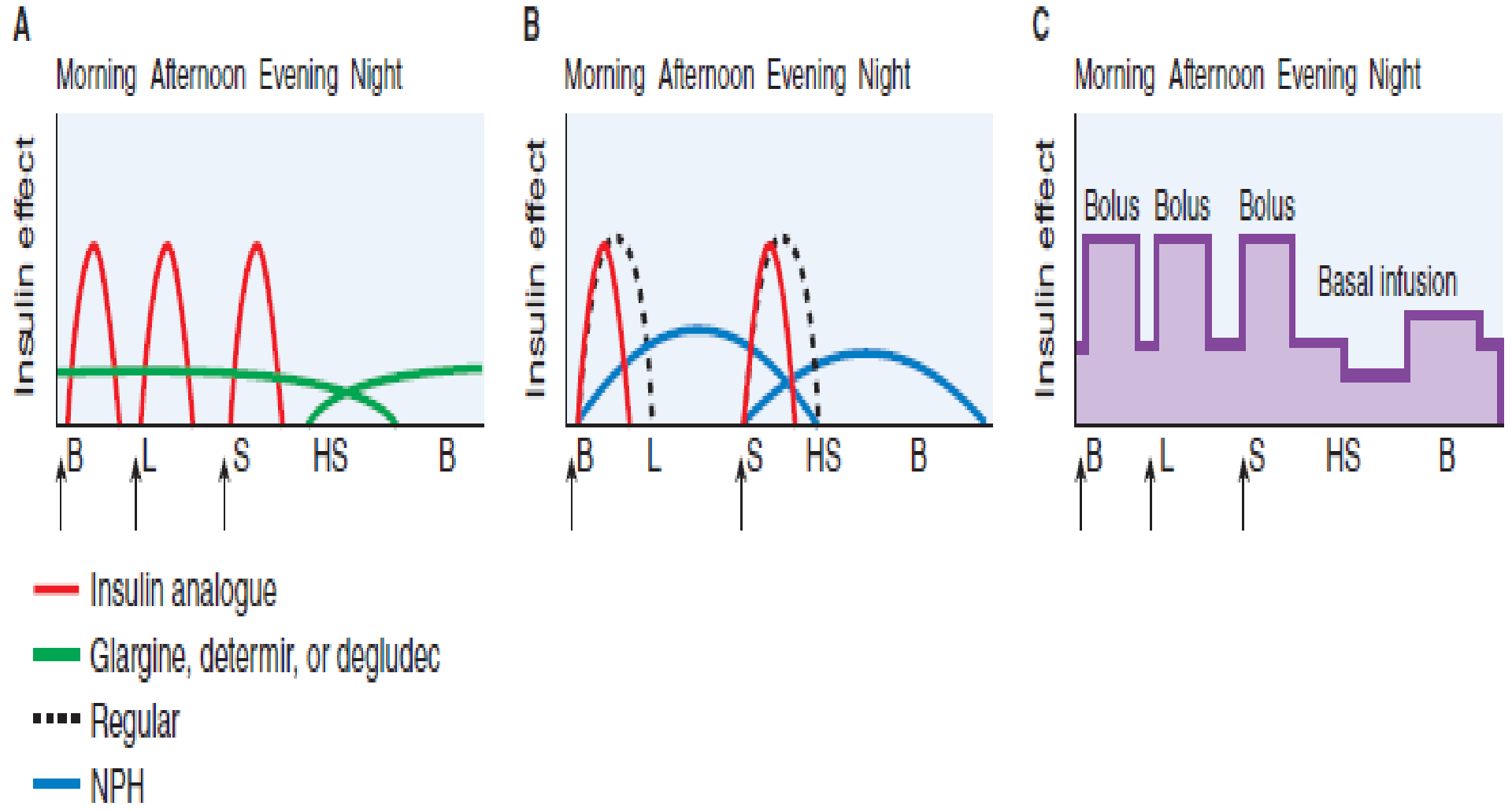
Split - mixed regimen

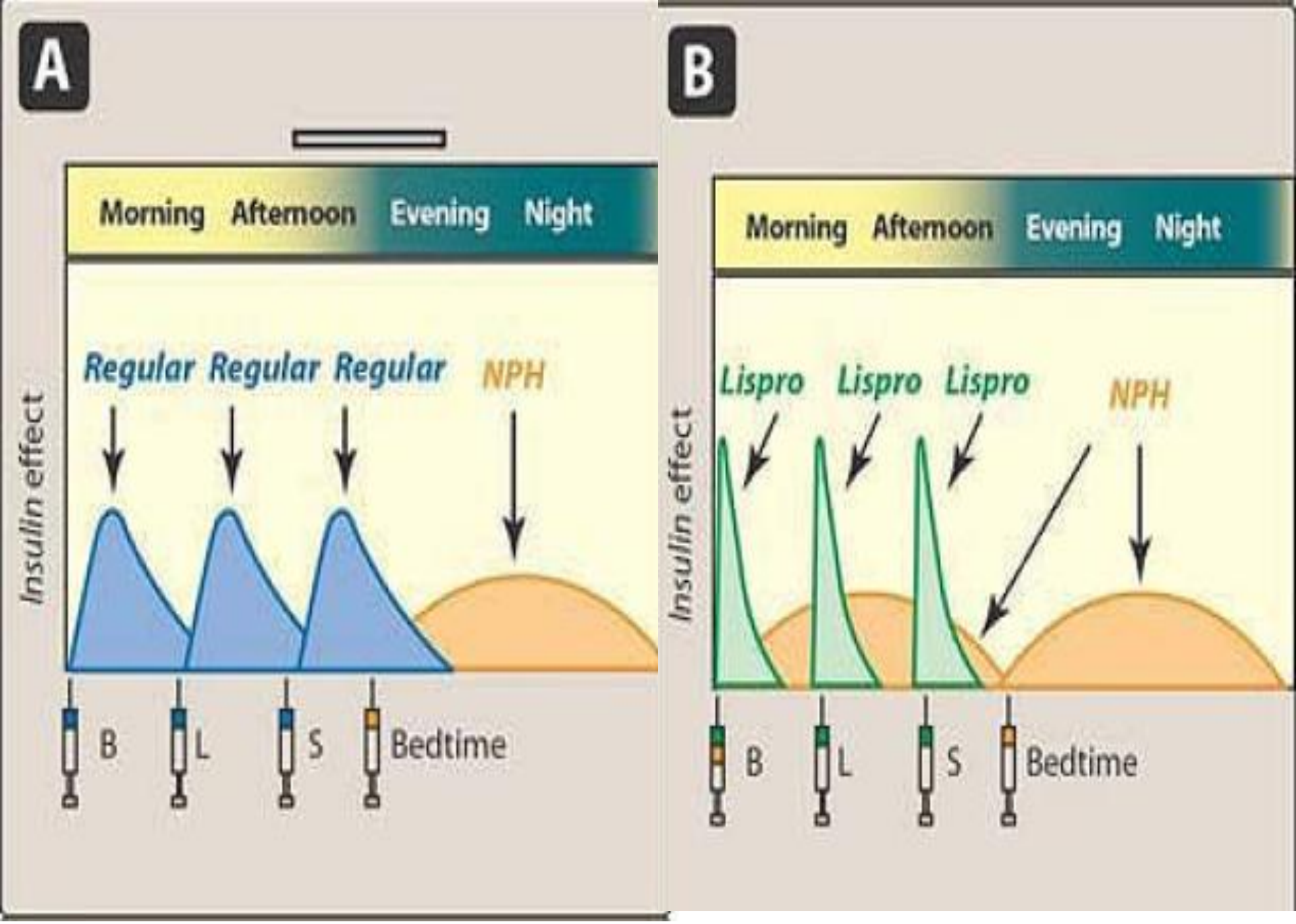
Total dose given as

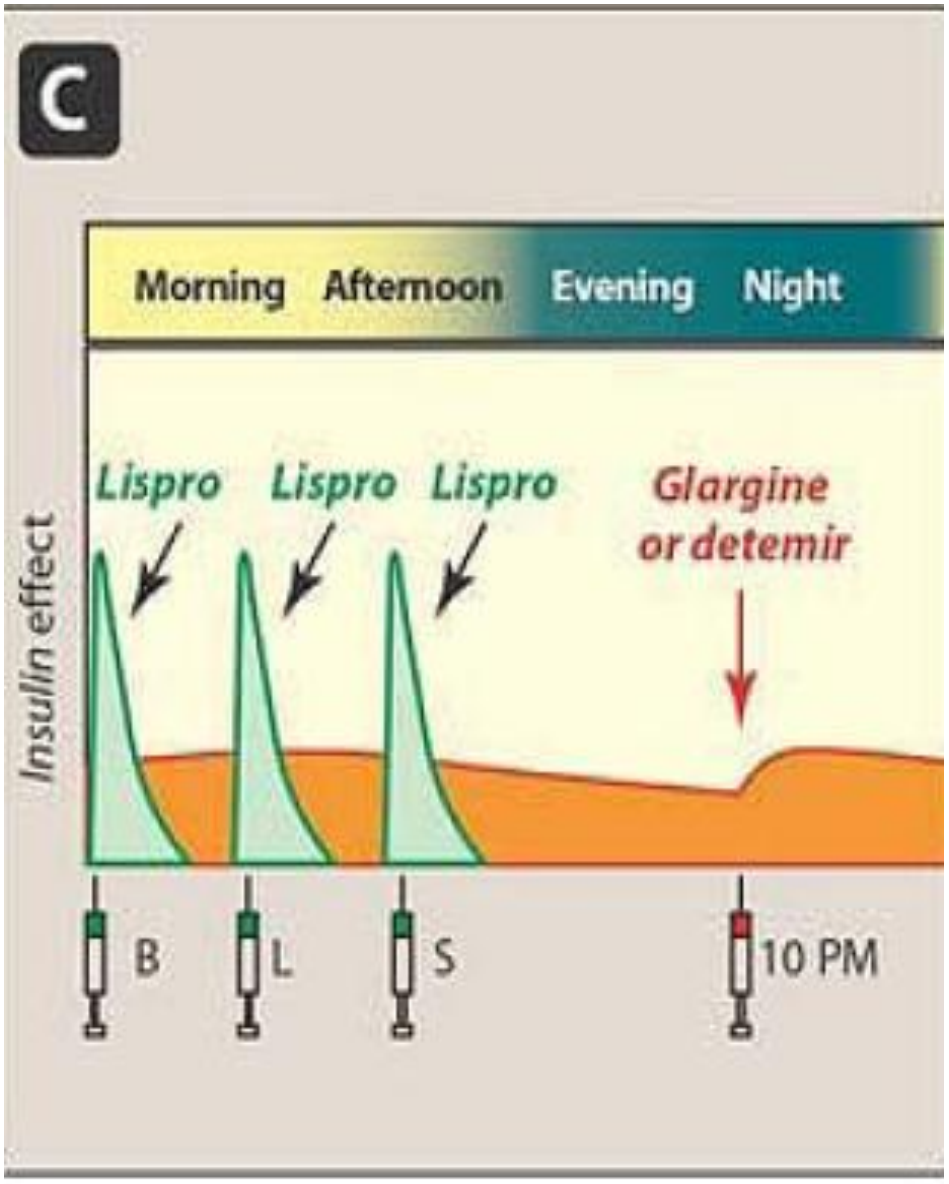
2/3 – before breakfast (2/3 NPH + 1/3 regular)

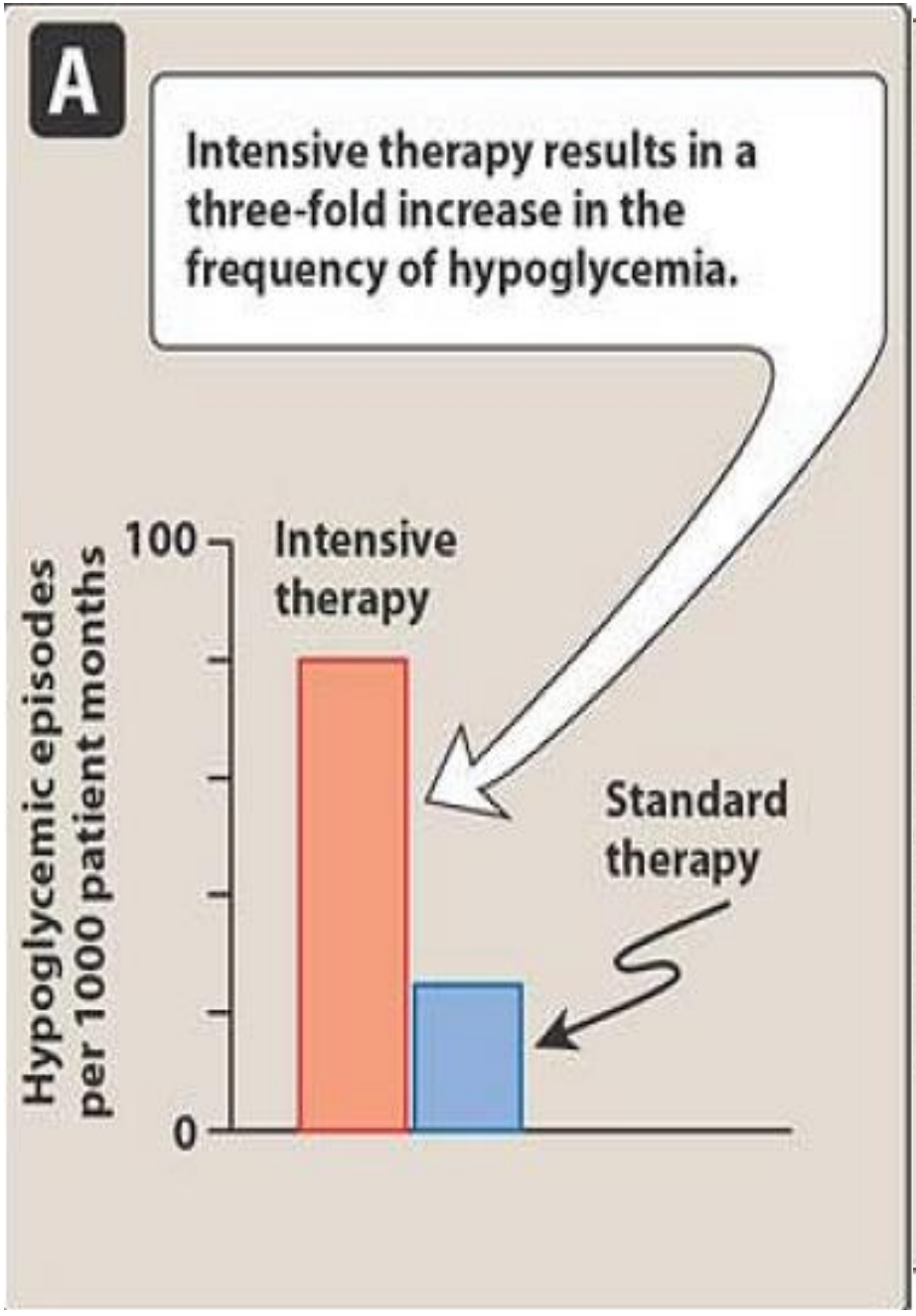
1/3 – before dinner (½ - NPH + ½ regular)

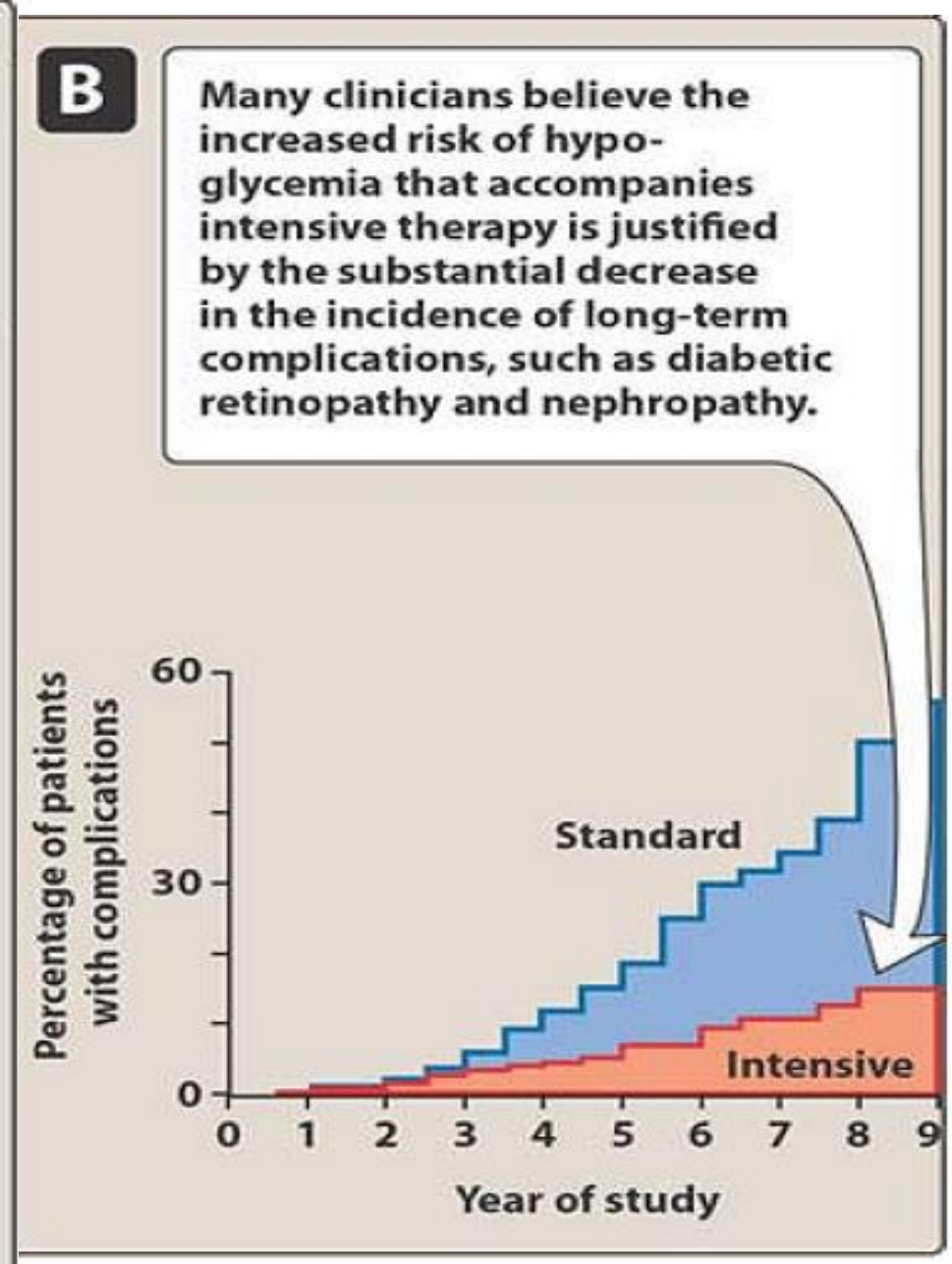
If predinner dose not sufficient to control hyperglycemia through the night --- evening dose divided into predinner dose of regular insulin followed by NPH insulin at bedtime


A
Morning Afternoon Evening Night
Insulin effect
B L S HS B
B
Morning Afternoon Evening Night
Insulin effect
B L S HS B
C
Morning Afternoon Evening Night
Insulin effect
Bolus Bolus Bolus
Basal infusion
B L S HS B
Insulin analogue
Glargine, determir, or degludec
Regular
NPH


A
Morning
Afternoon
Evening
Night
Regular
Regular
Regular
NPH
Insulin effect
B
L
S
Bedtime
B
Morning
Afternoon
Evening
Night
Lispro
Lispro
Lispro
NPH
Insulin effect
B
L
S
Bedtime


C
Morning
Afternoon
Evening
Night
Lispro
Lispro
Lispro
Glargine
or detemir
Insulin effect
B
L
S
10 PM


A
Intensive therapy results in a three-fold increase in the frequency of hypoglycemia.
Hypoglycemic episodes per 1000 patient months
100
0
Intensive therapy
Standard therapy


B
Many clinicians believe the increased risk of hypo-glycemia that accompanies intensive therapy is justified by the substantial decrease in the incidence of long-term complications, such as diabetic retinopathy and nephropathy.
Percentage of patients with complications
60
30
0
Standard
Intensive
0 1 2 3 4 5 6 7 8 9
Year of study

Complications of Insulin Therapy

Hypoglycemia --- inadequate food intake, physical exertion, large dose of insulin.

An identification and some form of rapidly absorbed glucose, should be carried.

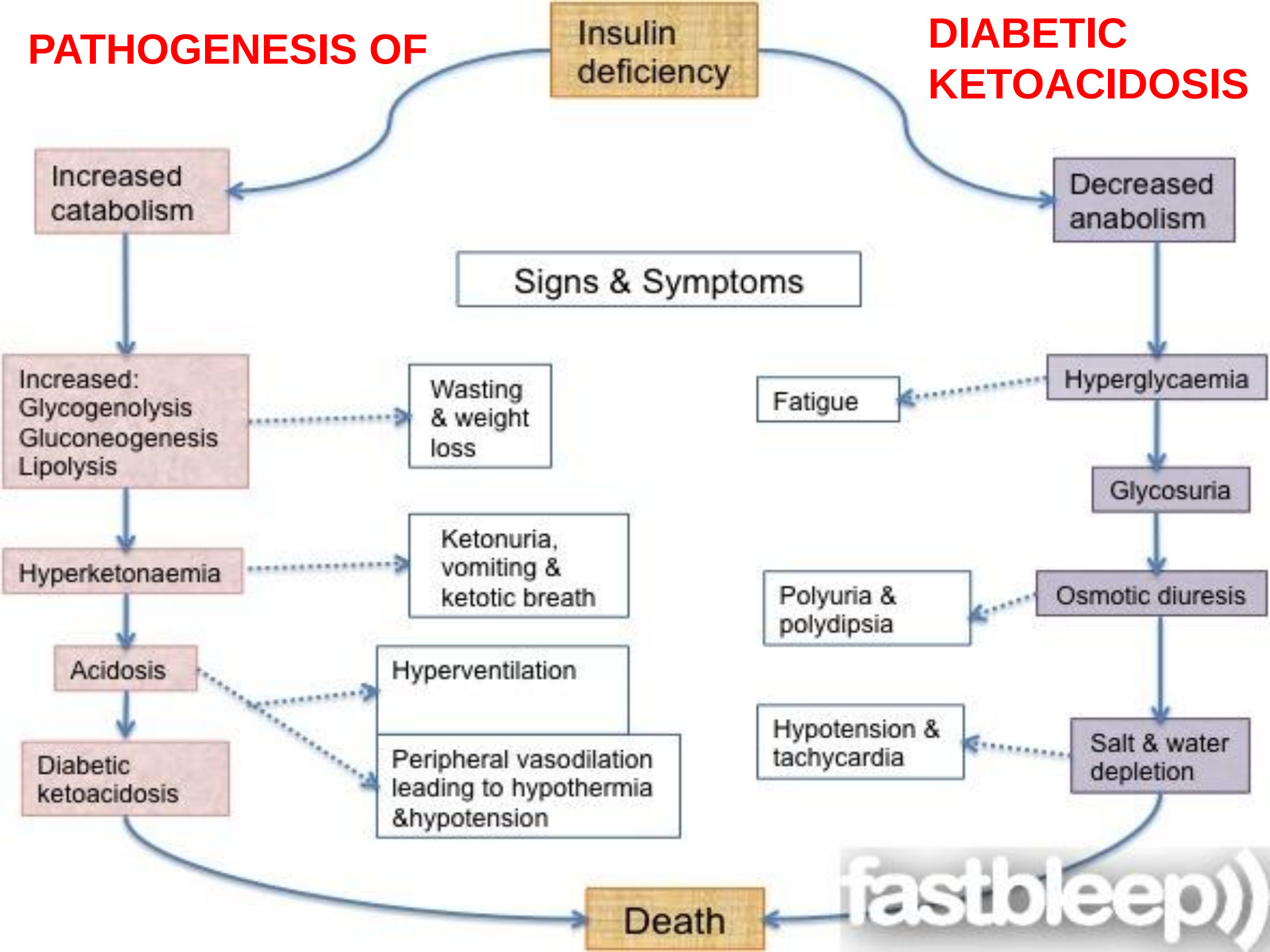
Glucose administration: simple sugar / glucose, preferably liquid. Dextrose tablets, glucose gel, sugar-containing beverage or food.

Severe hypoglycemia: 20–50 mL of 50% glucose soln by i.v. infusion over 2–3 minutes.

Allergic reactions to recombinant human insulin are due to the small amounts of aggregated/ denatured insulin, minor contaminants, or because of sensitivity to protamine, Zn^{2+}, etc.).

Immune Insulin Resistance --- low titer of circulating IgG anti-insulin antibodies neutralize action of insulin rarely.

Modest weight gain
Lipohypertrophy of subcutaneous fatty tissue.
Increased Cancer Risk ???


PATHOGENESIS OF
DIABETIC KETOACIDOSIS
Insulin deficiency
Increased catabolism
Decreased anabolism
Signs & Symptoms
Increased: Glycogenolysis Gluconeogenesis Lipolysis
Wasting & weight loss
Fatigue
Hyperglycaemia
Glycosuria
Hyperketonaemia
Ketonuria, vomiting & ketotic breath
Polyuria & polydipsia
Osmotic diuresis
Acidosis
Hyperventilation
Hypotension & tachycardia
Salt & water depletion
Diabetic ketoacidosis
Peripheral vasodilation leading to hypothermia &hypotension
Death

Diabetic ketoacidosis

- Acute emergency
- Accelerated breakdown of fat to acetyl-CoA --- in the absence of aerobic carbohydrate metabolism --- converted to acetoacetate and β-hydroxybutyrate and acetone --- acidosis.

- Patients always severely dehydrated --- **fluid replacement** --- first priority.
- **Insulin** urgently stops ketogenesis.

- Objective --- supply continuously moderate amount of insulin.

Soluble regular insulin

I.V. infusion: Bolus dose of 0.1-0.2 U/kg i.v. followed by 0.1U/kg/hr isotonic saline infusion.

Within 4-6 hours blood glucose ≈ 300 mg/dl.
Then rate of infusion reduced to 2-3 U /hr.
When patient fully conscious s.c. insulin restarted

Using pump --- allows independent control of insulin and electrolyte administration.

Stringent precautions against septicaemia.
Reasonable rate of fall: 75-100 mg/100 ml/hr

Glucose

Given only when plasma concentration in blood falls below renal threshold --- roughly ≤300mg/dl.

If given above renal threshold concentration --- increased osmotic diuresis --- further dehydration and potassium and magnesium loss occurs.

When blood glucose level falls to 300mg/dl, fluid replacement changed from isotonic saline to 5% glucose, at the same rate.

Intravenous fluid and electrolytes

More deficiency of water than saline.

If hypernatraemia --- indication for half isotonic (0.45%) solution.

If patient has a fluid deficit of above 5 litres

- 1 litre in the 1st hour,
- 2 litres in next 4 hours,
- 4 litres in next 24 hours, watch for signs of fluid overload.

Fluid replacement also causes fall in blood glucose by dilution.

Potassium

Even if normal or high --- plasma conc falls briskly with i.v. saline (by dilution) and insulin draws potassium into cells within minutes.

KCl added to 2nd and subsequent litres of fluid according to plasma potassium (patient should be passing adequate urine)

If S. K^+< 3.5 mmol/l add 40 mmol/l of fluid, if 3.5 - 5.0 mmol/l add 20 mmol/l of fluid, if > 5.0 mmol/l no need for potassium supplementation.

Bicarbonate (isotonic)

Only if plasma pH is < 7.0 and peripheral circulation is good. Insulin corrects acidosis.

Successful treatment of diabetic ketoacidosis and complications (aspiration of stomach contents, infection, shock, thromboembolism, cerebral oedema) required.

Mild diabetic ketosis

If conscious and no nausea or vomiting for at least 12 h --- iv therapy unnecessary
Small doses insulin given s.c. 4-6-hourly, and fluids orally.

Hyperosmolar nonketotic diabetic coma

Type 2 diabetics --- severe dehydration, blood sugar (> 600 mg/100ml) **and lack of ketosis and acidosis.**

Treatment

Isotonic (0.9%) saline --- at half the rate as for ketoacidotic coma and with less potassium than in severe ketoacidosis

Insulin requirements less than in ketoacidosis

Patients more liable to thrombosis --- prophylactic heparin used.

Oral Agents

--- Type 2 diabetes that cannot be managed by diet and exercise alone.

--- Diabetes onset after 40years

--- less than 5 years when starting treatment

--- obesity at presentation

--- Fasting blood sugar < 200 mg/ dl

--- insulin requirement < 40 U/day

--- no ketoacidosis or a history of it, or any other complication.

Not useful for patients of Type 1 diabetes

Oral hypoglycaemic drugs

- Biguanides (metformin)
- Sulfonylureas (tolbutamide, glibenclamide)
- Meglitinides(nateglinide & repaglinide)
- Thiazolidinediones (rosiglitazone, pioglitazone)
- α-Glucosidase inhibitors: acarbose
- Dipeptidyl Peptidase – IV Inhibitors - Sitagliptin
- Incretin Analogs - Exenatide
- Pramlintide

Sulphonylureas	Daily dosage mg	Duration of action hrs
1st generation		
Chlorpropamide	100-500	>48
Tolazamide	100-1000	12-24
Tolbutamide	1000-3000	6-12
2nd generation		
Glimepiride	1-8	24
Glipizide	5-40	12-18
Glipizide (extended release)	5-20	24
Glyburide	1.25-20	12-24
Glyburide (micronized)	0.75-12	12-24

Mechanisms of action of sulfonylureas

1) Stimulation of insulin release from B cells of pancreas due to block of ATP sensitive K+ channels --- (Major)

2) Reduce hepatic glucose production (minor)

3) Increase peripheral insulin sensitivity (minor)

4) Reduce serum glucagon concentration (minor)

5) Reduce hepatic clearance of insulin (minor)

ADME

- Food and hyperglycemia reduce absorption.
- Sulfonylureas with short half-lives --- more effective when given 30 min before eating.
- Bound to albumin (90% to 99%) --- least for chlorpropamide and greatest for glyburide.

Adverse effects :

Weight gain, hypoglycemia.

Hepatic / renal insufficiency : delayed excretion --- drug accumulation --- hypoglycemia.

Other ADRs --- nausea and vomiting, cholestatic jaundice, agranulocytosis, aplastic and hemolytic anemias, hypersensitivity reactions, and dermatological reactions.

Disulfiram like reaction.

--- Increased cardiovascular mortality ???

--- **Glyburide** is a safe alternative to insulin for diabetes in pregnancy

--- Sulfonamides, clofibrate, and salicylates displace sulfonylureas from plasma proteins

Biguanides --- Metformin.

Mechanism of Action

- Antihyperglycemic not hypoglycemic.
- Activation of AMP activated protein kinase leading to stimulation of hepatic fatty acid oxidation, glucose uptake, nonoxidative glucose metabolism and reduction of lipogenesis and gluconeogenesis
- No effect on insulin release, no hypoglycemia even in large doses.
- No effects on secretion of glucagon, cortisol, growth hormone or somatostatin.

Fixed-dose combinations with glipizide, glyburide, pioglitazone, repaglinide and sitagliptin available.

In some cases --- **weight reduction**

Treat **infertility in women** with polycystic ovarian syndrome --- improves ovulation, menstrual cyclicity; reduces androgen levels and hirsutism.

Precautions

Renal disease, past history of lactic acidosis, chronic hypoxic lung disease

Acute side effects (20% patients)

- Diarrhea, abdominal discomfort, nausea, metallic taste, anorexia.

Minimized --- increase dose slowly and take it with meals.

- Intestinal absorption of vitamin B12 and folate decreased during chronic therapy

- Cationic drugs eliminated by proximal renal tubular secretory system --- cimetidine, furosemide, nifedipine compete with it.

Meglitinide analogs

Repaglinide , Nateglinide

Mechanism of action

Same as sulphonylureas so not combined with them. Rapid onset, short duration of action.

Effective in early release of insulin after a meal --- postprandial glucose regulators.

Combined therapy --- with metformin or thioglitazones **better than monotherapy**.

Pharmacokinetics and fate:

- Orally ingested just before meals.
- Metabolized --- inactive products by CYP3A4 in the liver and excreted via bile.

Adverse effects

Hypoglycemia --- less than sulfonylureas.
Secondary failure after prolonged use.
Inhibitors of CYP3A4 --- enhance the glucose lowering effect of repaglinide
Inducers of CYP3A4 Drugs --- opposite effect.

Weight gain is less than sulfonylureas

Thiazolidinediones

Rosiglitazone and **pioglitazone**.

Mechanism of Action --- Agonists for nuclear **P**eroxisome **P**roliferation **A**ctivating **R**eceptor **γ** --- regulate carbohydrate and lipid metabolism

Increase insulin sensitivity in peripheral tissue.

Lower glucose production by liver. Increase glucose transport into muscle and adipose tissue.

Monotherapy / additive to metformin, sulfonyl-ureas, or insulin. Pioglitazone has FDC with alogliptin.

Absorption, Excretion and Dosing

- Once a day. Bioavailability unaffected by food.
- Maximum clinical effect observed at 6 to 12 weeks.
- Metabolized by liver
- Safe in renal insufficiency

Precautions and Adverse Effects.

- Anemia, **weight gain**, edema and plasma volume expansion --- edema more likely when combined with insulin.
- Monitor liver function, visual function.

α-glucosidase Inhibitors

Acarbose, Miglitol, Voglibose

- Inhibit the action of α-glucosidase in the intestinal brush border.
- Reduce intestinal absorption of starch, dextrin and disaccharides.
- Postprandial rise in plasma glucose blunted in both normal and diabetic subjects.
- Also Increase release of GLP-1 into the circulation.
- No effect on insulin release, no hypoglycaemia.

Other pharmacological actions

- No weight gain. Reduce progression from impaired glucose tolerance to type 2 DM.
- Improve hemoglobin A1c levels.

P/k --- Administered just before meals. Most effective with starchy, high fiber diet.

Combined with other agents and/or insulin.

Adverse effects

- Malabsorbtion, flatulence, diarrhea and abdominal bloating.
- Contraindicated in patients with stage 4 renal failure

INCRETIN MIMETICS

GLP1 Agonists	Daily dosage (mg)	Dosing frequency
Albiglutide	30-50	Weekly
Dulaglutide	0.75-1.5	Weekly
Exenatide	2	Weekly
Liraglutide	0.6-1.8	Daily
Lixisenatide	0.010-0.020	Daily
GLP2 Agonist: Teduglutide	for treatment of short-bowel syndrome	

Incretin Mimetics (s.c.)

- Improve glucose-dependent insulin secretion.
- Inhibits post prandial glucagon release.
- Delays gastric emptying, reduces appetite.
- Normalizes fasting and postprandial insulin secretion. Promote B-cell proliferation.
- Used as monotherapy / adjunctive therapy with oral drugs or basal insulin for type 2 diabetics not achieving glycemic targets.
- **Weight loss.**
- Postprandial hyperglycemia reduced.
- HbA1c levels decline.

ADME

given as a subcutaneous injection with the help of pen injectors.

- **Adverse Effects**
- i.v. or s.c. causes nausea and vomiting (CNS). GI side effects of these drugs wane over time.
- Typical delay of gastric emptying. In absence of other hypoglycemics, hypoglycemia is rare.
- Possible association of exenatide treatment with pancreatitis.
- Contraindicated in medullary carcinoma of thyroid

Dipeptidyl Peptidase IV Inhibitors: Sitagliptin

Inhibit the enzyme responsible for inactivation of incretin hormones --- GIP and glucagon-like peptide-1 (GLP-1).

--- Increase insulin release in response to meals.

--- Reduce inappropriate secretion of glucagon.

--- Slow gastric emptying.

--- Decrease appetite.

--- Improvement in both fasting and postprandial hyperglycemia.

--- No affect on body weight.

As monotherapy or in combination with a sulfonylurea, metformin or a glitazone.

Pharmacokinetics and fate

- Food does not affect absorption.
- Excreted unchanged in the urine.
- Dosage adjustments in renal dysfunction.

Adverse effects

Well tolerated (not known in detail) --- most common adverse effects being nasopharyngitis and headache.

Synthetic Amylin Analog --- Pramlintide

- Indicated as adjunct to mealtime insulin therapy in patients with Type 1 or Type 2 diabetes.
- Delays gastric emptying, decreases postprandial glucagon secretion and improves satiety.
- Administered s.c. immediately prior to meals.
- Dose of rapid / short-acting insulin decreased by 50% prior to meals to avoid hypoglycemia.
- Not mixed with any insulin in same syringe

Adverse effects --- nausea, anorexia and

Sodium-glucose co-transport-2 (SGLT-2) inhibitor --- Dapagliflozin

- Lower blood glucose in type 2 DM, and cause weight loss. Single daily dose produces round-the-clock glucosuria and lowers blood glucose levels.

- Predispose to urinary and genital infections, electrolyte imbalance and increased urinary frequency.

- Tolerability and safety to be established.

Bile acid sequestrant : Colesevelam

- Interruption of the enterohepatic circulation and a decrease in farnesoid X receptor (FXR) activation. FXR has multiple effects on cholesterol, glucose, and bile acid metabolism.
- GI complaints, hypertriglyceridemia increase.

Bromocriptine

- Nausea, fatigue, dizziness, vomiting, and headache.

They have very modest efficacy in lowering glucose levels, and their use for this purpose is questionable.

Type 2 diabetes- Assess A1c

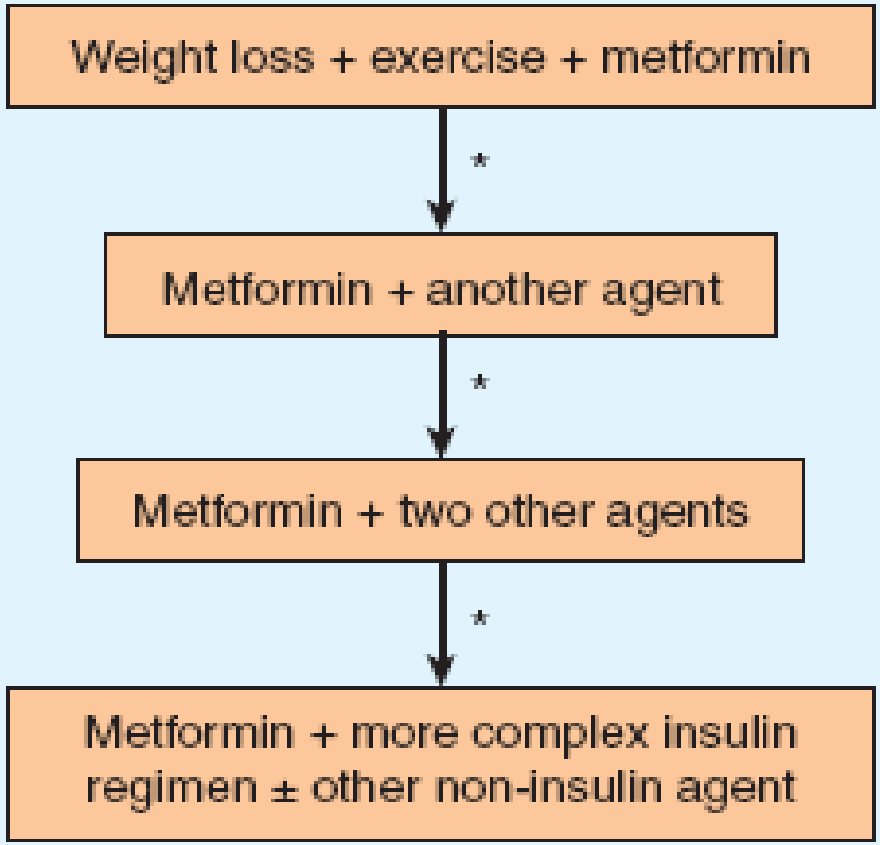
- Diabetes Education, nutrition, exercise
- Metformin, screen for complications

Reassess A1c

- Metformin plus
- Second Oral hypoglycaemic

Reassess A1c

- Metformin + 2 Agents
- Metformin + Insulin



* Step taken if needed to reach individualized HbA_{1c} target after ~ 3 months.