Diabetes – Oral Agents Pharmacology

University of Hawai‘i Hilo Pre-Nursing Program

NURS 203 – General Pharmacology

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Learning Objectives

- Understand the role of the utilization of free fatty acids in diabetic ketoacidosis
- Understand the role and actions of insulin
- Understand the role and actions of glucagon
- Understand each drug class mechanism of actions
- Understand adverse effects of medications that limit their use
- Understand important kinetic parameters of the medications/medications classes

What is Diabetes?

- A metabolic disease in which the body's inability to produce any or enough insulin causes elevated levels of glucose in the blood.

- Not enough insulin
- Increase insulin resistance

Diagnosis of Diabetes

- Hemoglobin A1c
- Blood glucose levels
- Test those who are at increased risk for DM…….

Table 2.1—Criteria for the diagnosis of diabetes

A1C ≥6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*

OR

FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*

OR

2-h PG ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

OR

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

*In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

Increased Risk for DM

Table 2.2—Criteria for testing for diabetes or prediabetes in asymptomatic adults

1. Testing should be considered in all adults who are overweight (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) and have additional risk factors:
   - physical inactivity
   - first-degree relative with diabetes
   - high-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - women who delivered a baby weighing >9 lb or were diagnosed with GDM
   - hypertension (≥140/90 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
   - women with polycystic ovary syndrome
   - A1C ≥5.7%, IGT, or IFG on previous testing
   - other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
   - history of CVD
2. For all patients, particularly those who are overweight or obese, testing should begin at age 45 years.
3. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results (e.g., those with prediabetes should be tested yearly) and risk status.

The Pancreas

Glucagon

- Released by alpha cells of the pancreas
- Is catabolic
  - Responsible for the break down of:
    - fats, sugars, & amino acids

Insulin

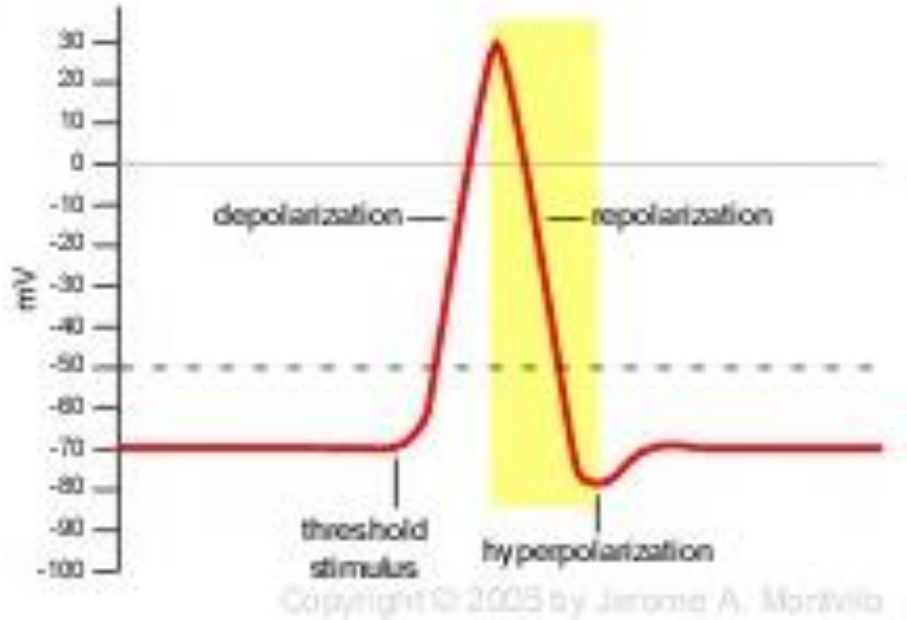
- Released by the beta cells of the pancreas
- Is anabolic
  - Responsible for storage of:
    - Fats, sugars, & amino acids

- Other cell types and hormones
- δ – Somatostatin

Diabetes & Potassium

Hypokalemia

- Inhibit the release of insulin
- Leads to elevated blood sugars
- Hyperpolarizes cells



Hyperkalemia

- Insulin deficiency leads to chronic increase in serum potassium
- Glucose & insulin given
  - Push potassium into cells

Fatty Acids for Energy

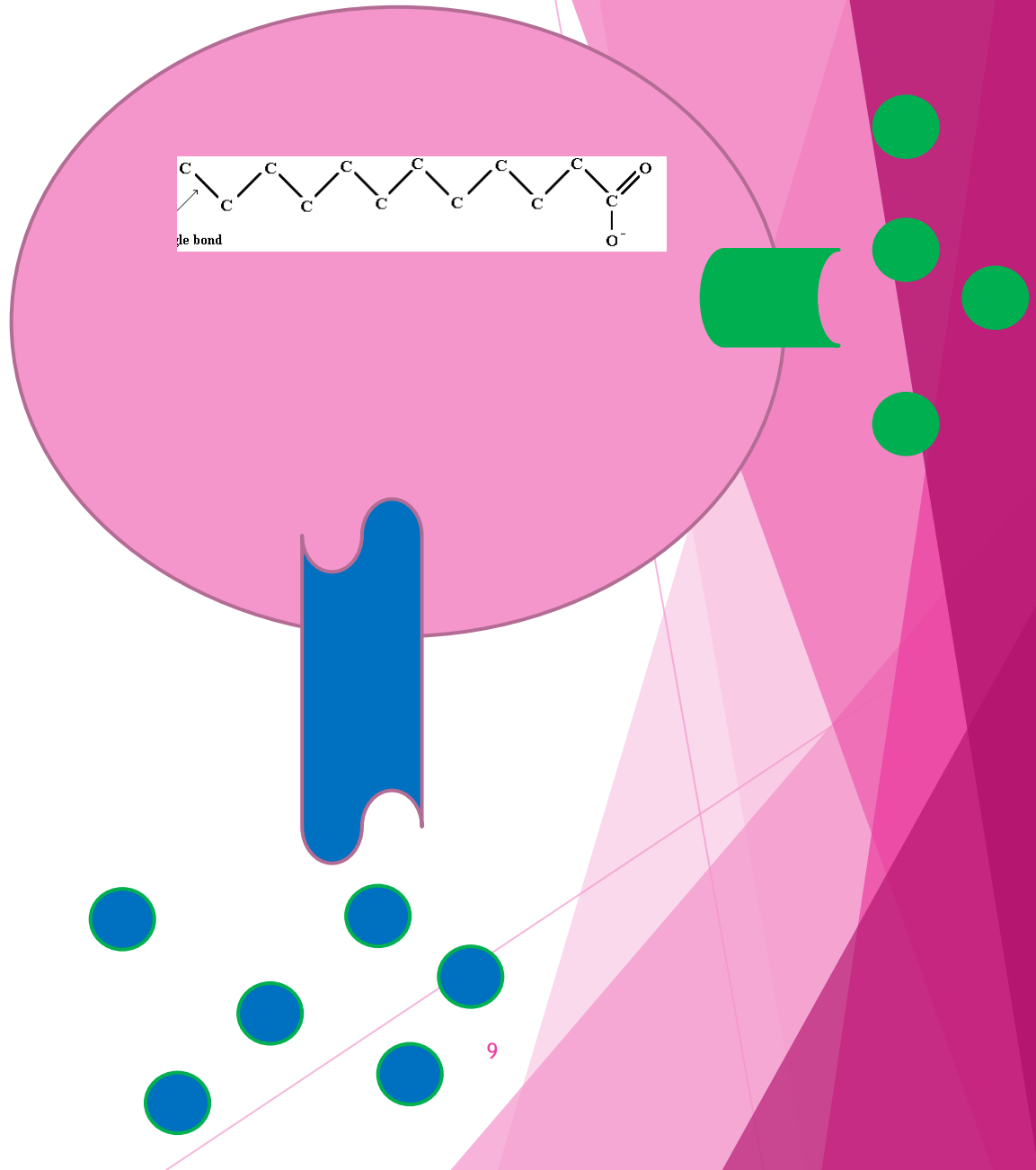
In the absence of insulin this process takes place!!

- Inhibited by insulin
- Use of fatty acids for energy
- Survival “starvation” mode
  - Save proteins
  - Utilize free fatty acids
- Breakdown of FFAs
  - Ketones – may be used as an energy source
    - Feeds the brain
    - Inhibits the break down of proteins (AA – amino acids)
    - EVENTUALLY LEADS TO KETOACIDOSIS - DKA

Fatty Acids for Storage

Insulin

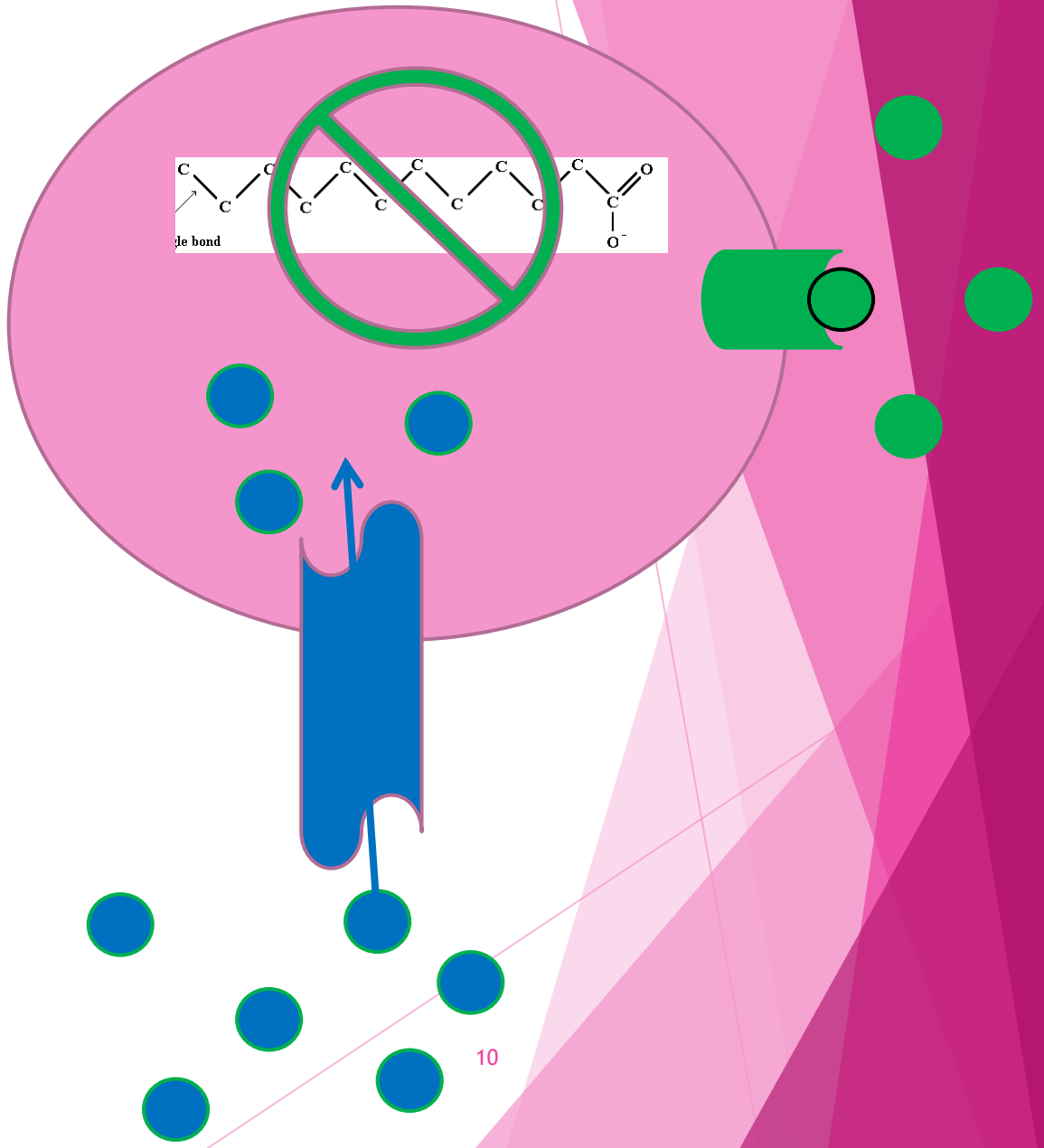
- Binds to its receptor
- Allows the utilization of glucose for the Krebs Cycle = energy
- Inhibits the break down of FFAs
- Promotes the storage of FFAs



Fatty Acids for Storage

Insulin

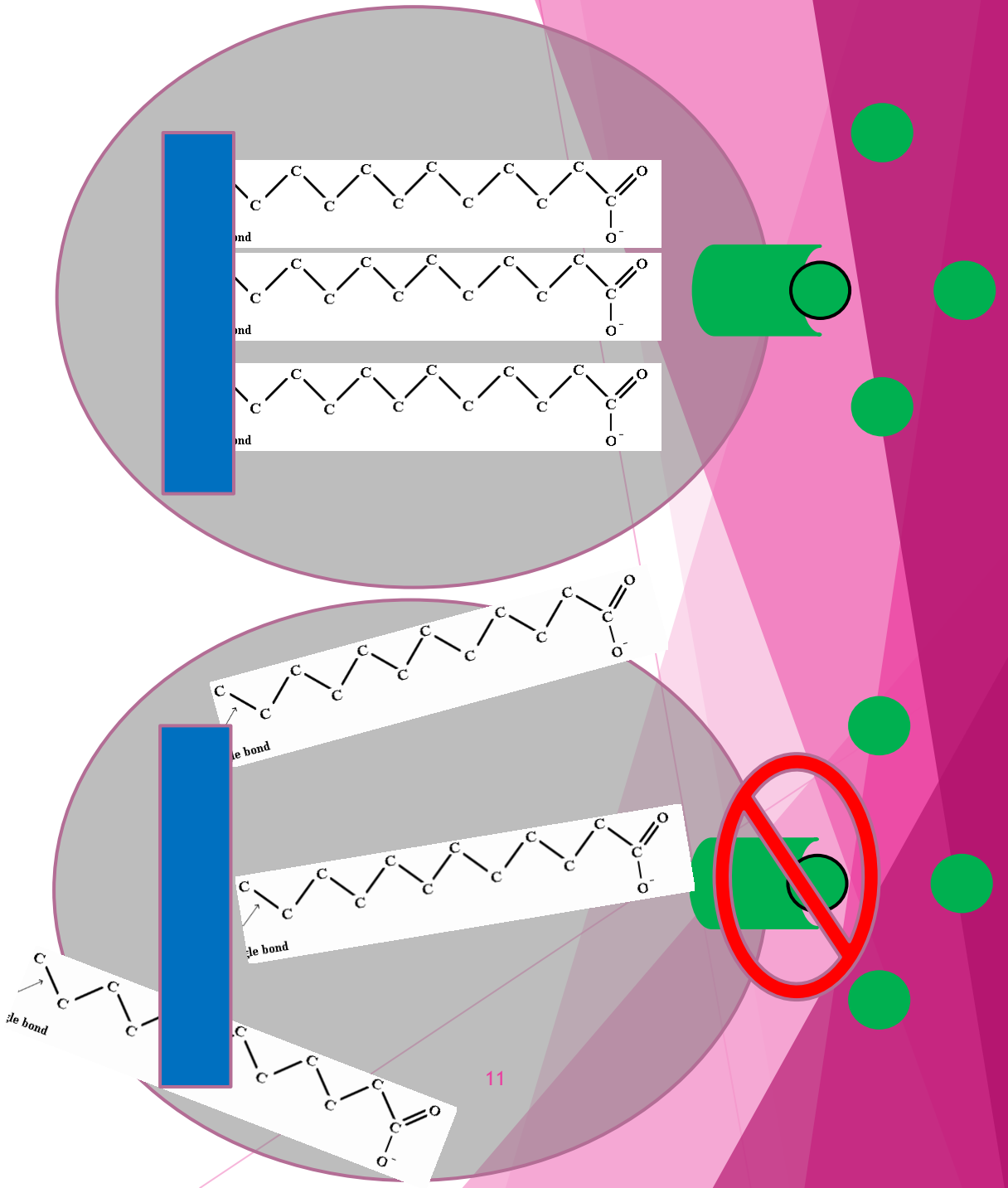
- FFAs
  - Are stored as triglyceride instead
  - Triglycerides are stored in our adipose cells
  - Insulin suppresses the release of TG from the adipose cell



Fatty Acids for Storage

Adipose cell

- Under normal circumstances
  - Stored as TGs
  - Break down inhibited by insulin
- Decreased insulin or increased insulin resistance
  - Insulin does not bind its receptor
  - TG get broken down into FFAs



Insulin – Clear blood of glucose

Increases

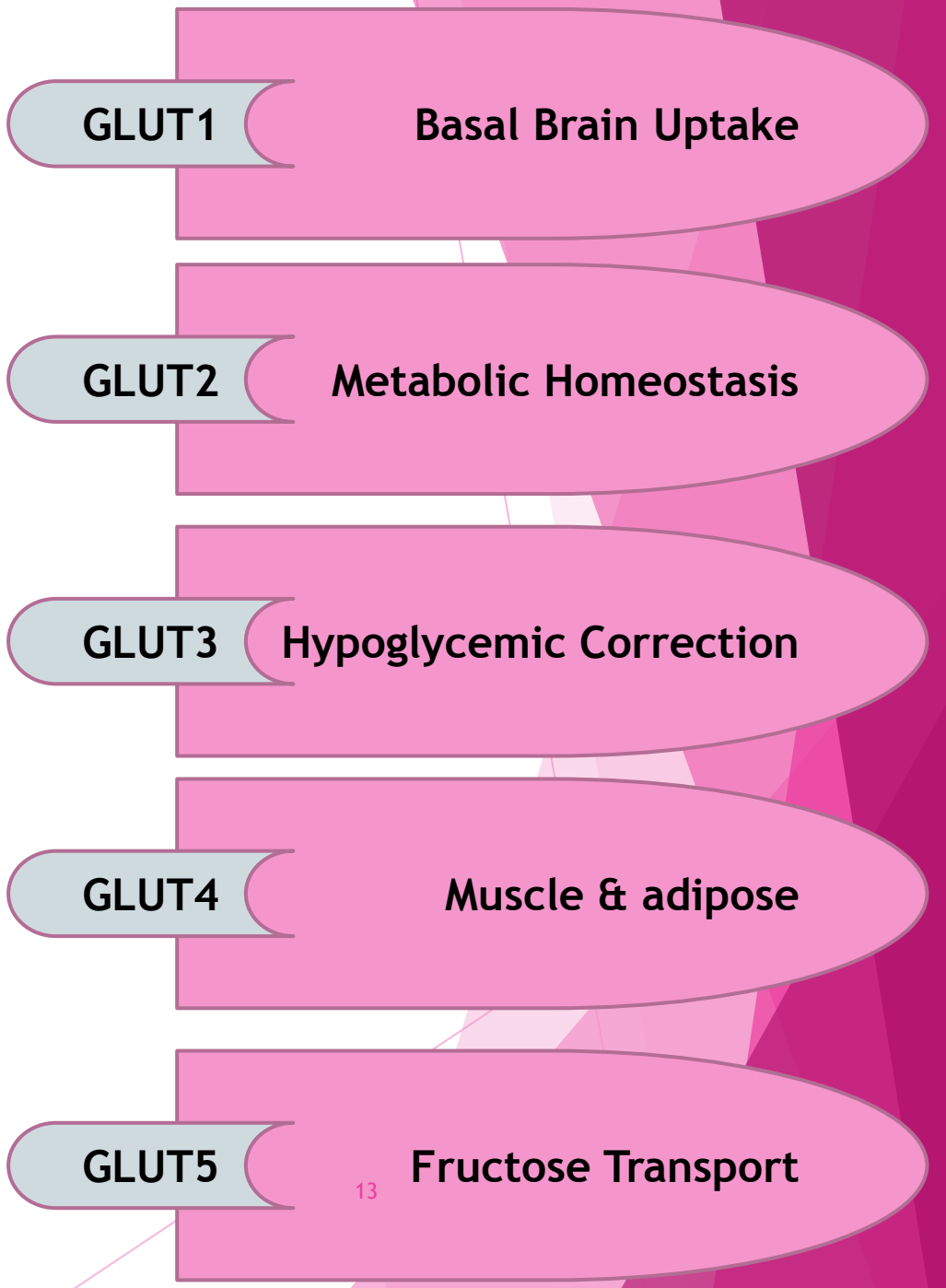
- Glucose storage
- Glucose as an energy source
- Fat storage

Decreases

- Glucose production
- Fat breakdown
- Fat as an energy source
- Ketone bodies

Glucose

- GLUT1
  - Red blood cells, BBB, basal glucose supply
  - Medium affinity
- GLUT2
  - Liver, pancreas, small intestines
  - Low affinity
- GLUT 3
  - Neurons, kidney, brain
  - High affinity
- GLUT 4
  - Skeletal/cardiac muscle & fat cells
  - Medium low affinity
- GLUT 5
  - Small intestines
  - Medium affinity



What Does a Diabetic Patient Look Like?

Type 1

- Does not make insulin
- Thin
- Depends on hemoglobin A1c

Type 2

- Insulin resistant
- Obese
- Increase in serum TGs

Oral Medications to Treat Hyperglycemia

- Sulfonylureas
- Biguinides
- Alpha glucosidase inhibitors
- Meglitinides
- Thiazolidinediones
- Dipeptidyl peptidase IV (DPP IV) inhibitors
- Bile acid sequestrant (BAR)
- Sodium-glucose co-transporter 2 (SGLT 2) inhibitors (New)

Sulfonylureas – long acting secretagogues(squeezers)

First Generations

- Fallen out of favor
  - Equally effective
  - Increase incidence of adverse effects

2nd Generations

- MOA (main)
  - Increase release of insulin
- Kinetics
  - Well absorbed – slowed by food
  - Highly protein bound
  - Low distribution (protein binding)
  - Metabolized by CYP2C9 (warfarin)
  - Half lives vary (daily dosing – BID)

Sulfonylureas – long acting secretagogues(squeezers)

- ADRs
  - Hypoglycemia
  - Weight gain
  - Sulfa drug
- Drug interactions
  - CYP enzyme inhibitors/inducers
  - Alcohol
    - Disulfiram-like reaction (nausea/vomiting)

Biguanides - Metformin

- MOA
  - Increased sensitivity to insulin
  - Decrease hepatic glucose production
  - Reduce carbohydrate absorption
  - DOES NOT CAUSE HYPOGLYCEMIA – NO INSULIN SECRETION
- Kinetics
  - Bioavailability – 50%
  - Distribution – High (Vd - ~1000 L) accumulated in RBCs
  - Protein binding – none
  - Metabolism – none
  - Half life – 1.5-3 hours (extended release formulations available)
  - Excretion – Urine (unchanged)

Biguanides - Metformin

- ADRs
  - Diarrhea
  - Nausea
  - Fatigue
  - Avoid in:
    - Alcoholics – Lactic acidosis
    - Uncontrolled heart failure
- Drug interactions
  - Contrast dyes – must be held

Alpha-Glucosidase Inhibitors

- MOA
  - Inhibits the absorption of carbohydrates in the small intestines
- Kinetics

- Acarbose
  - Absorption
    - Active drug not absorbed
  - Metabolism
    - Gut bacteria in GI tract & digestive enzymes
  - Elimination
    - 2 hours
  - Excretion
    - 35% urine
    - 65% feces

- Miglitol
  - Absorption
    - Complete
  - Metabolism
    - None
  - Elimination
    - 2 hours
  - Excretion
    - Urine - unchanged

Alpha-Glucosidase Inhibitors

- ADRs
  - Flatulence, abdominal cramping, bloating, diarrhea
    - Should decrease with use
- Contraindications
  - IBD

Meglitinides – Short-acting Secretagogues

Nateglinide (Starlix)

- Kinetics
  - Absorption – Rapid
  - Bioavailability – 73%
  - Protein binding – 98%
  - Duration – 4 hours
  - Metabolism – CYP 2C9 & 3A4
  - Half life – 1.5 hr
  - Urine 83%

Repaglinide (Prandin)

- Kinetics
  - Absorption – Rapid
  - Bioavailability – 56%
  - Protein binding – 98%
  - Duration – 4-6 hours
  - Metabolism – CYP 2C8 & 3A4
  - Half life – 1 hr
  - Feces 90 %

Meglitinides – Short-acting Secretagogues

- ADRs
  - Hypoglycemia
  - Weight gain
- Drug interaction
  - CYP enzyme inducers/inhibitors
    - 2C9 – nateglinide
    - 2C8 – repaglinide
    - 3A4 – both
- Dosing – TID with meals
  - PATIENTS DO NOT TAKE THIS DRUG IF THEY SKIP A MEAL

Thiazolidinediones - Pioglitazone

- Falling out of favor – some pulled off market
- MOA
  - Increase sensitivity to insulin
    - Must produce insulin in order to work
- Kinetics
  - Bioavailability – 80%
  - Peak concentrations – 1-2 hrs (slowed by food)
  - Distribution – Low (highly protein bound)
  - Metabolized – CYP2C8
  - Half life – 3-5 hrs
    - Duration – longer due to gene expression
  - Excretion – Urine and feces

Thiazolidinediones - Pioglitazone

- ADRs
  - Weight gain
  - Bone fracture
  - Edema – Avoid in CHF
    - Use with spironolactone
  - Hepatotoxicity
  - Heart attack and stoke
- Lawsuits against Avandia - Rosiglitazone

Dipeptidyl peptidase IV (DPP IV) inhibitors

- Incretins
  - Hormones in the body that:
    - Stimulates insulin secretion in response to meals
    - Inhibits glucagon secretion
    - Inhibits gastric emptying – makes you feel full (causes satiety)
    - VERY SHORT HALF LIFE – 2 MINUTES
  - Broken down by dipeptidyl peptidase IV
    - So, we created DPP IV inhibitors

Dipeptidyl peptidase IV (DPP IV) inhibitors

- Januvia (sitagliptin), Onglyza (saxagliptin), Trajenta (linagliptin)
- MOA
  - Inhibits the break down of incretin hormones
-

Kinetics	Sitagliptin	Saxagliptin	Linagliptin
Bioavailability	87%	75%	30%
Distribution	200 L	200 L	1100 L
Protein binding	40%	None	80-99%
Half life	8-12 hours	2-3 hours	> 100 hours
Excretion	Urine (unchanged)	Urine (metabolites)	Feces (unchanged)

  - Monitor renal function, caution with renal impairment

Dipeptidyl peptidase IV (DPP IV) inhibitors

- ADRs
  - Diarrhea
  - Constipation
  - Nausea
  - Hypoglycemia
  - Peripheral edema
  - Upper respiratory infection
- Drug interactions
  - Strong inhibitors/inducers of CYP3A4 for saxagliptin and linagliptin

Bile Acid Sequestrant - BAR

- Colesevelam – Lipids….
  - Decrease cholesterol reabsorption
  - Increase LDL loss in feces
- Used as an adjunct
  - Improve cholesterol
  - Slight decrease in blood glucose
- Interacts with many medications
  - Absorption

Sodium-glucose co-transporter 2 (SGLT 2) inhibitors

- empagliflozin, canagliflozin (Invokana), dapagliflozin, ipragliflozin
- MOA
  - Decrease glucose reabsorption in the kidney, increase glucose excretion in the urine
  - Increased insulin sensitivity
  - Decreased gluconeogenesis
  - Increased insulin release “first phase”

Sodium-glucose co-transporter 2 (SGLT 2) inhibitors - Invokana

- Kinetics
  - Onset – within 24 hours
  - Duration – throughout 24 hour dosing interval
  - Absorption – not affected by food, given prior to first meal may decrease intestinal absorption of glucose and further decrease post prandial blood glucose
  - Distribution – Vd 119 L
  - Protein binding – 99%
  - Metabolism – Hepatic, glucuronidation
  - Bioavailability – 65%
  - Half life – 10-13 hours
  - Time to peak – 1-2 hours
  - Excretion - ~40% feces, ~33% urine

Sodium-glucose co-transporter 2 (SGLT 2) inhibitors - Invokana

- ADRs
  - Hyperkalemia
  - Genitourinary infection, UTI
  - Renal insufficiency
  - Angioedema
  - Fatigue
  - Hypoglycemia
- Drug interactions
  - Drugs with mechanisms in the kidney (ACEI, ARBs, aliskirin) & potassium-sparing diuretics

Questions