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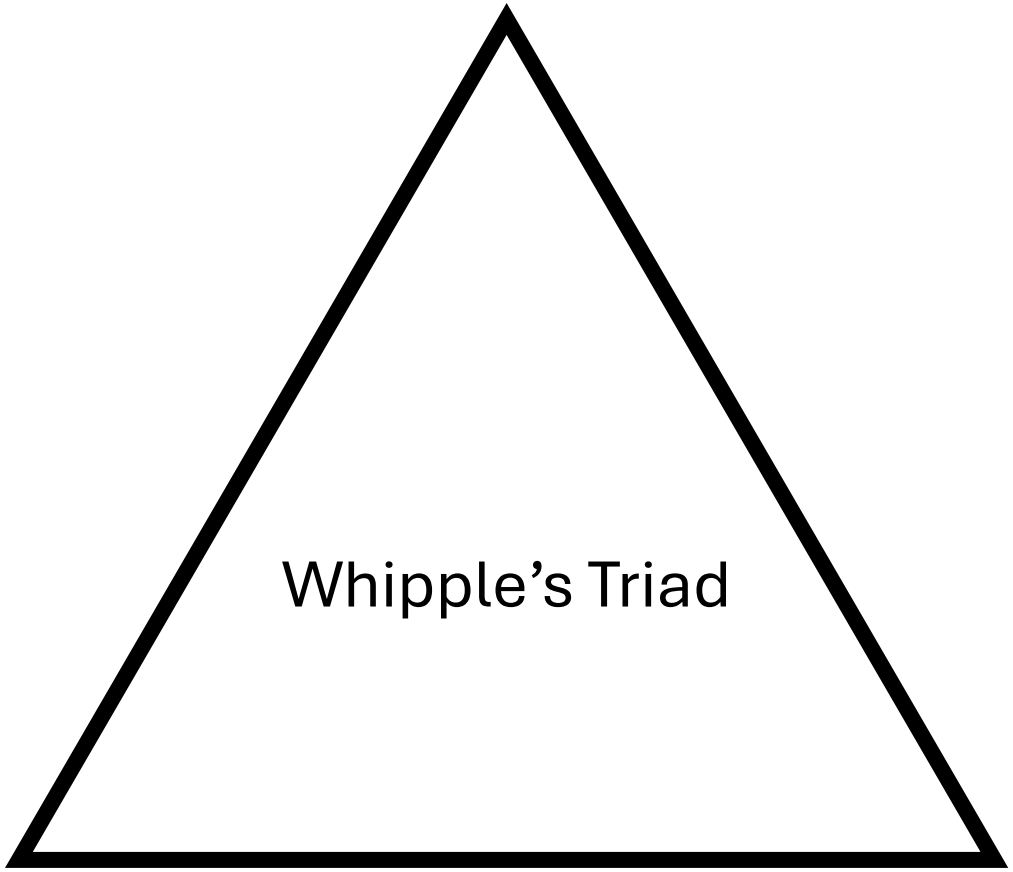
The Case

- 69M currently working on a small hobby farm is brought to the ED by his wife with sudden onset confusion, agitation and sweating
- 3 weeks prior experienced 3 weeks of flu-like symptoms with a persistent cough
- During this illness he experienced a similar episode of sweating and drowsiness which improved with sitting down for a cup of tea and a snack, which he attributed to recovering from his viral illness

The Case

- Past Medical History:
  - Hypercholesterolaemia
  - Solar keratoses
- Medications:
  - Aspirin for primary prevention
  - Magnesium supplementation
- Examination:
  - HR 60s SBP 126 RR 15 Sats >94% on RA Temp 35.6
  - VBG – pH 7.32 pCO2 59 Bicarb 30 BE 4 Na 136 K 3.3 Cl 98 AG 12 Ca 1.18 **Glucose 2.8** Lactate 1.4 Hb 125
  - **Ethanol <0.01**
  - Confused and disorientated
  - Examination after correction of hypoglycaemia was unremarkable

BSL ≤3.9mmol/l



Signs and symptoms of hypoglycaemia

Reversal of signs and symptoms when BSL is raised ≥4mmol/L

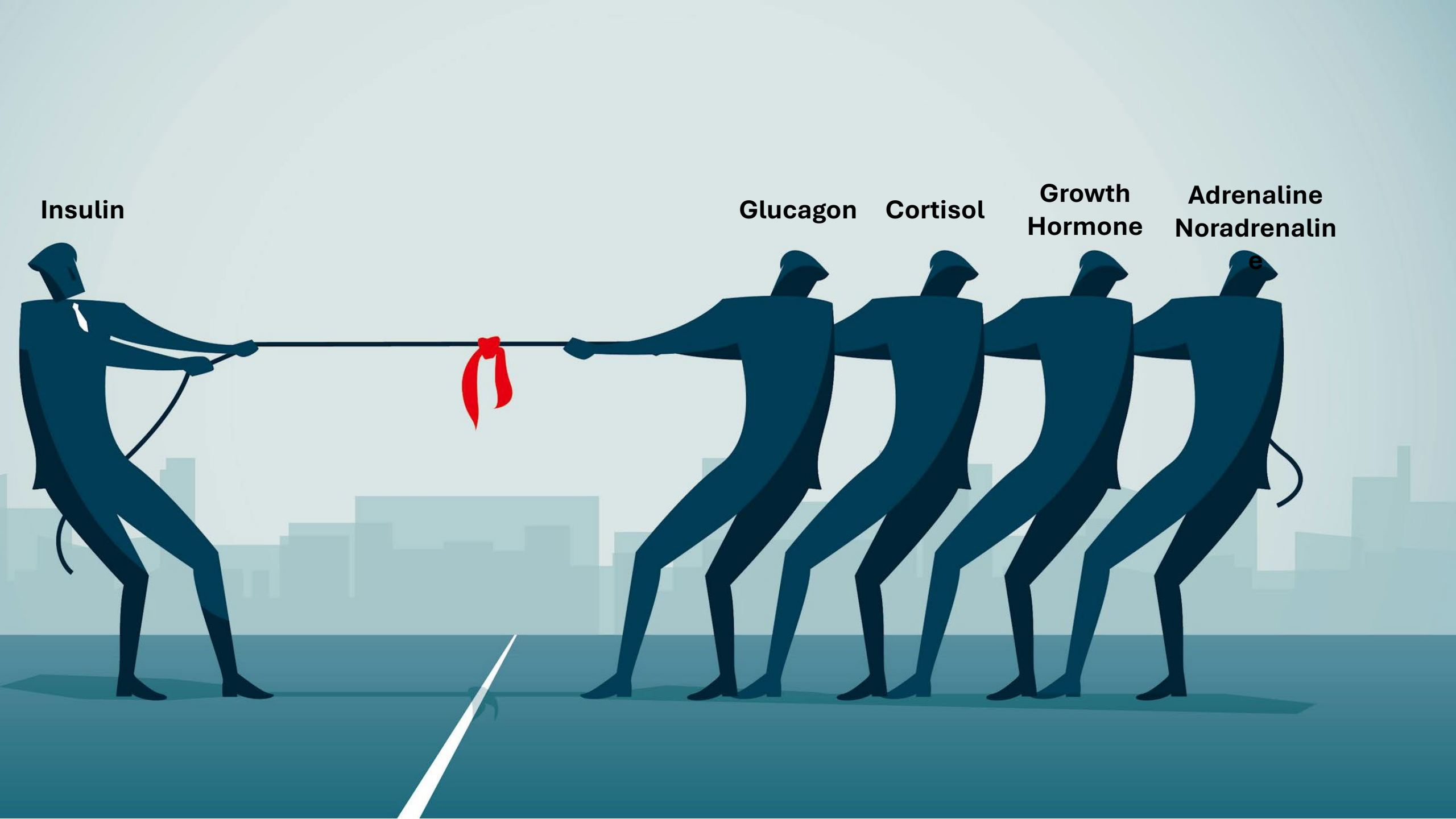
Causes of Hypoglycaemia

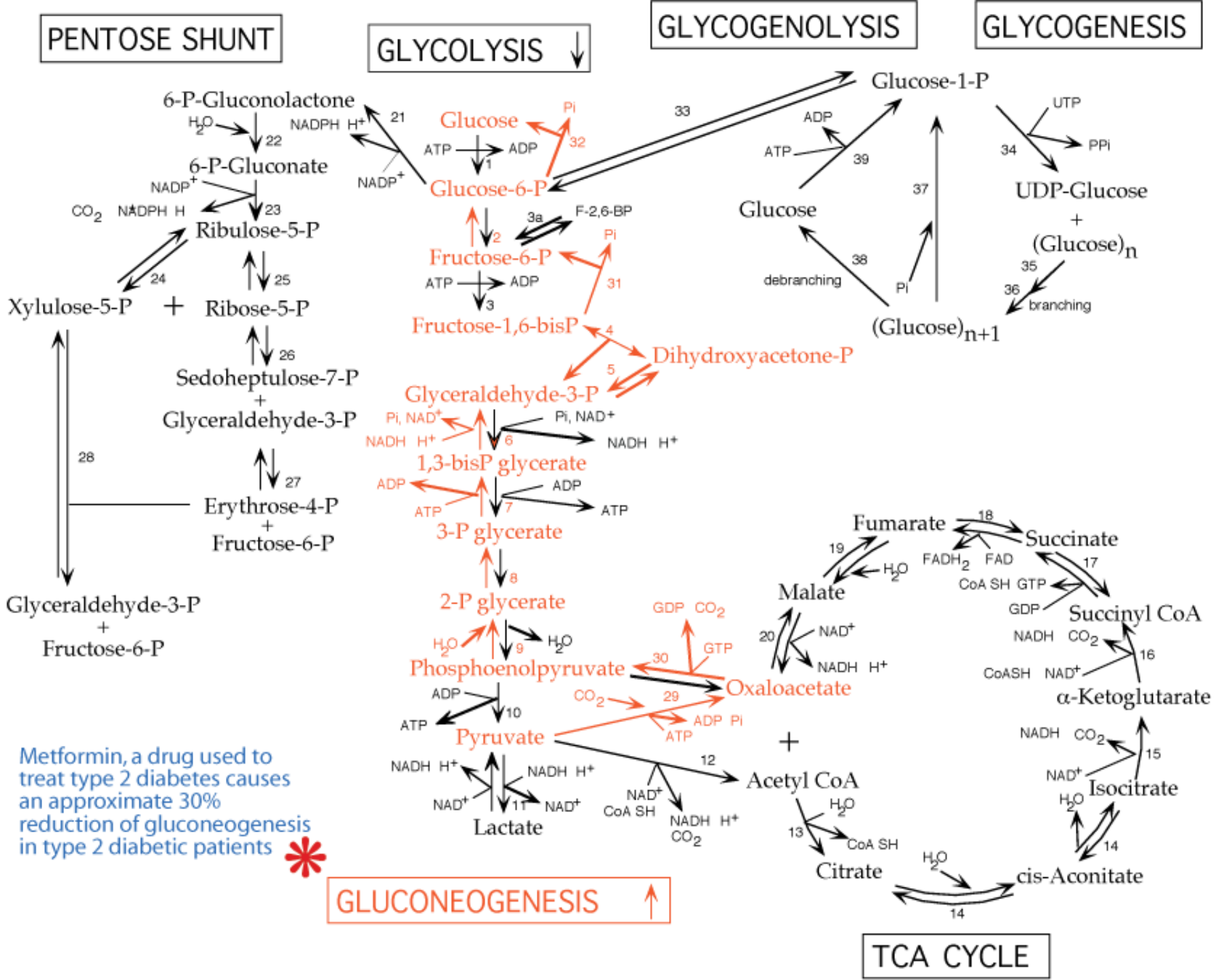
Hypoinsulinaemic Hypoglycaemia

- Alcohol induced hypoglycaemia
- Adrenal insufficiency
- GH deficiency
- Prolonged exercise
- Acute liver failure
- Renal failure
- Malnutrition
- Critical illness
- Paraneoplastic syndromes
- Fatty acid oxidation disorders
- Glycogen storage diseases
- Extreme carbohydrate restriction
- Inborn errors of metabolism
- Non-islet cell tumour hypoglycaemia
- Medications/Toxins

Hyperinsulinaemic Hypoglycaemia

- Exogenous insulin
- Insulinoma
- Non-Insulinoma Pancreatogenic Hypoglycaemia Syndrome
- Nesidioblastosis
- Sulfonylureas
- Dumping syndrome in pts with Hx of gastric bypass
- Insulin autoimmune syndrome/Hirata syndrome
- Type B insulin resistance
- “Reactive hypoglycaemia”

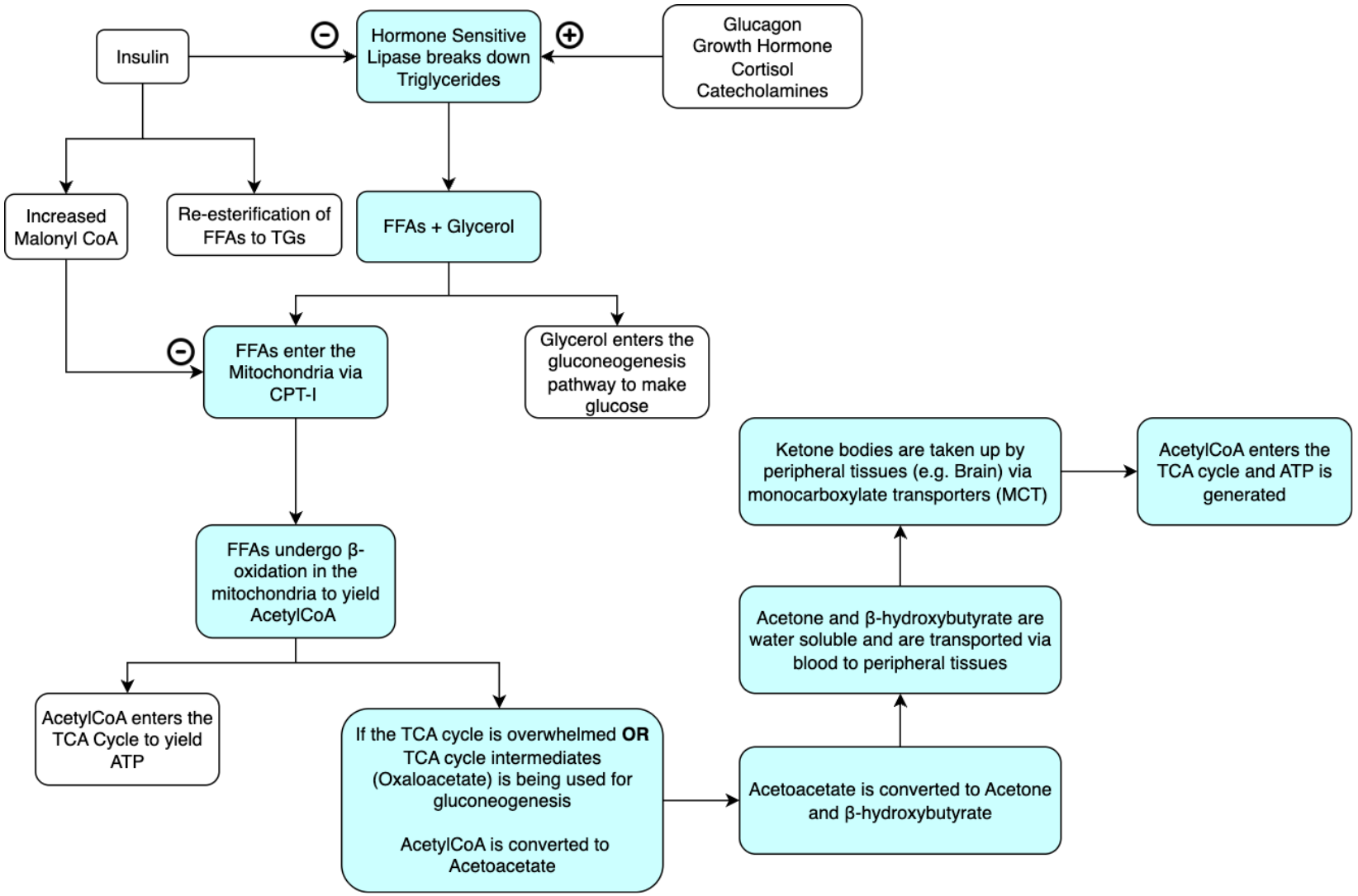

Insulin
Glucagon
Cortisol
Growth Hormone
Adrenaline Noradrenaline


PENTOSE SHUNT
GLYCOLYSIS
GLYCOGENOLYSIS
GLYCOGENESIS
6-P-Gluconolactone
6-P-Gluconate
Ribulose-5-P
Xylulose-5-P
Ribose-5-P
Sedoheptulose-7-P
Glyceraldehyde-3-P
Erythrose-4-P
Fructose-6-P
Glucose
Glucose-6-P
Fructose-6-P
Fructose-1,6-bisP
Dihydroxyacetone-P
Glyceraldehyde-3-P
1,3-bisP glycerate
3-P glycerate
2-P glycerate
Phosphoenolpyruvate
Pyruvate
Lactate
Acetyl CoA
Citrate
cis-Aconitate
Isocitrate
α-Ketoglutarate
Succinyl CoA
Succinate
Fumarate
Malate
Oxaloacetate
Glucose-1-P
UDP-Glucose
(Glucose)n
(Glucose)n+1
Metformin, a drug used to treat type 2 diabetes causes an approximate 30% reduction of gluconeogenesis in type 2 diabetic patients
GLUCONEOGENESIS
TCA CYCLE

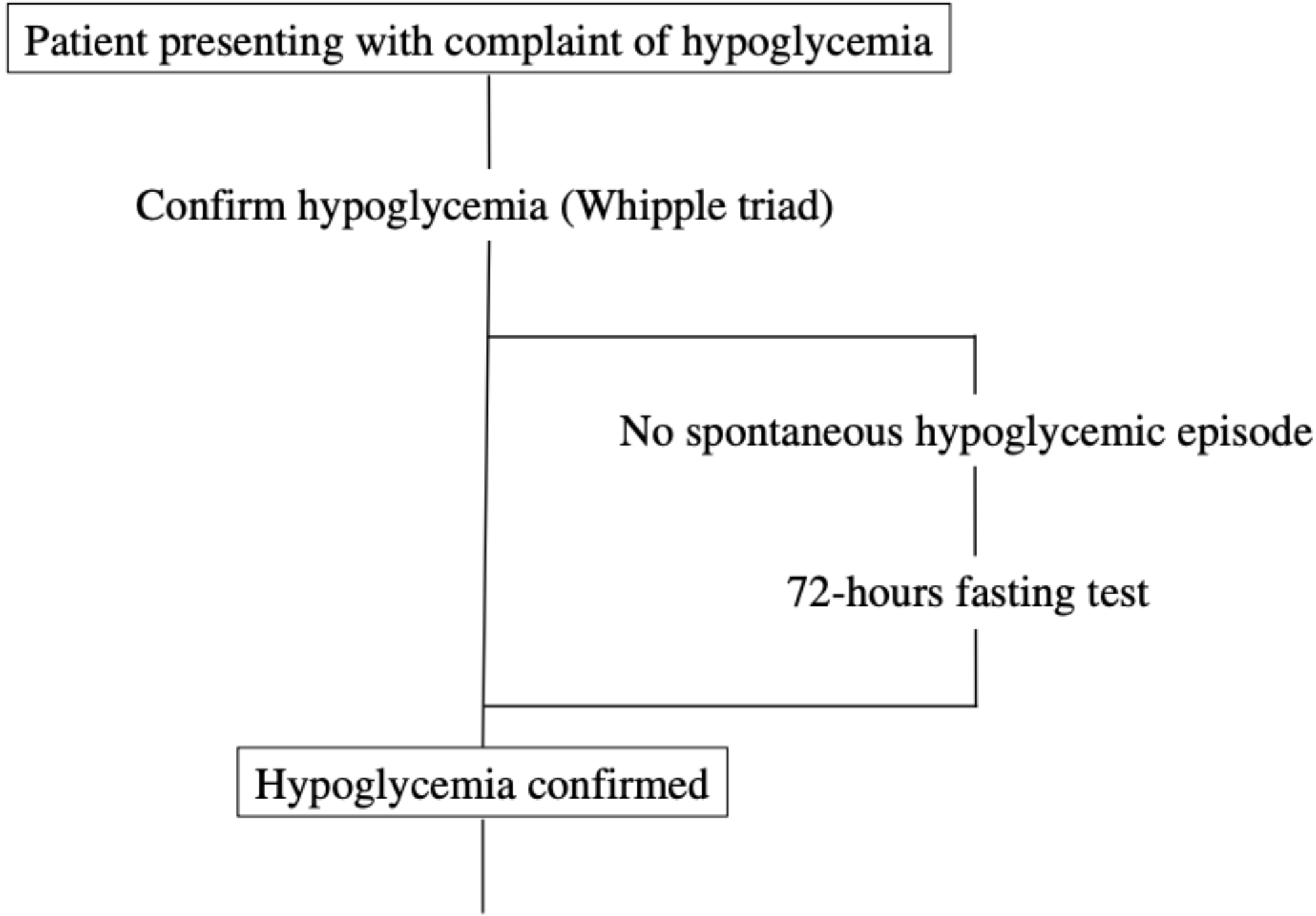
Keeping Glucose High

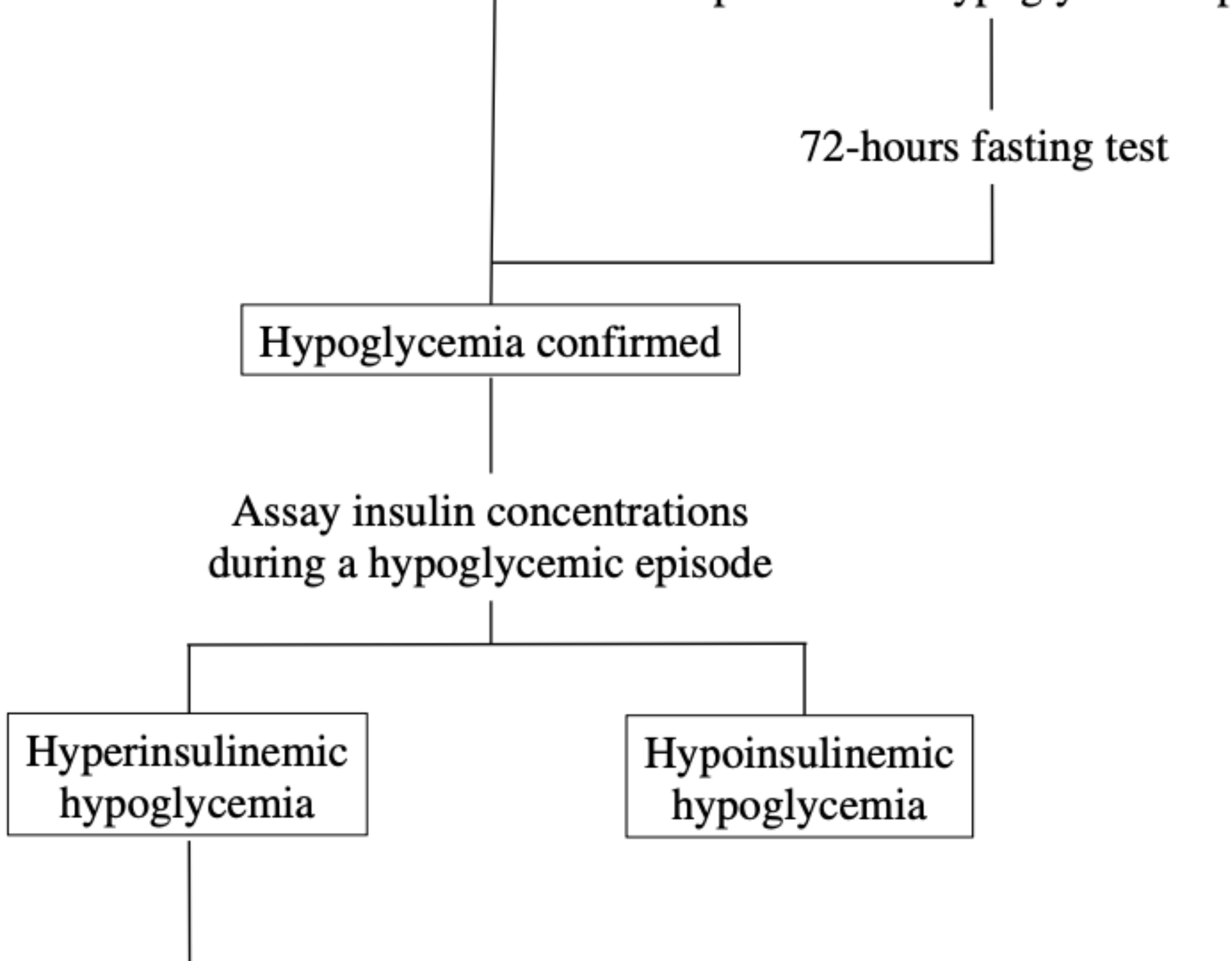
- Glycogenolysis
  - Polymers of glucose units branching off a core protein (glycogenin)
  - Found in the liver and skeletal muscle
  - Glycogenolysis → ↑ glucose
- Gluconeogenesis
  - Substrates include lactate, glycerol (from FFAs) and glucogenic amino acids, TCA cycle intermediates
  - Occurs predominantly in the liver and a small amount in the renal cortex

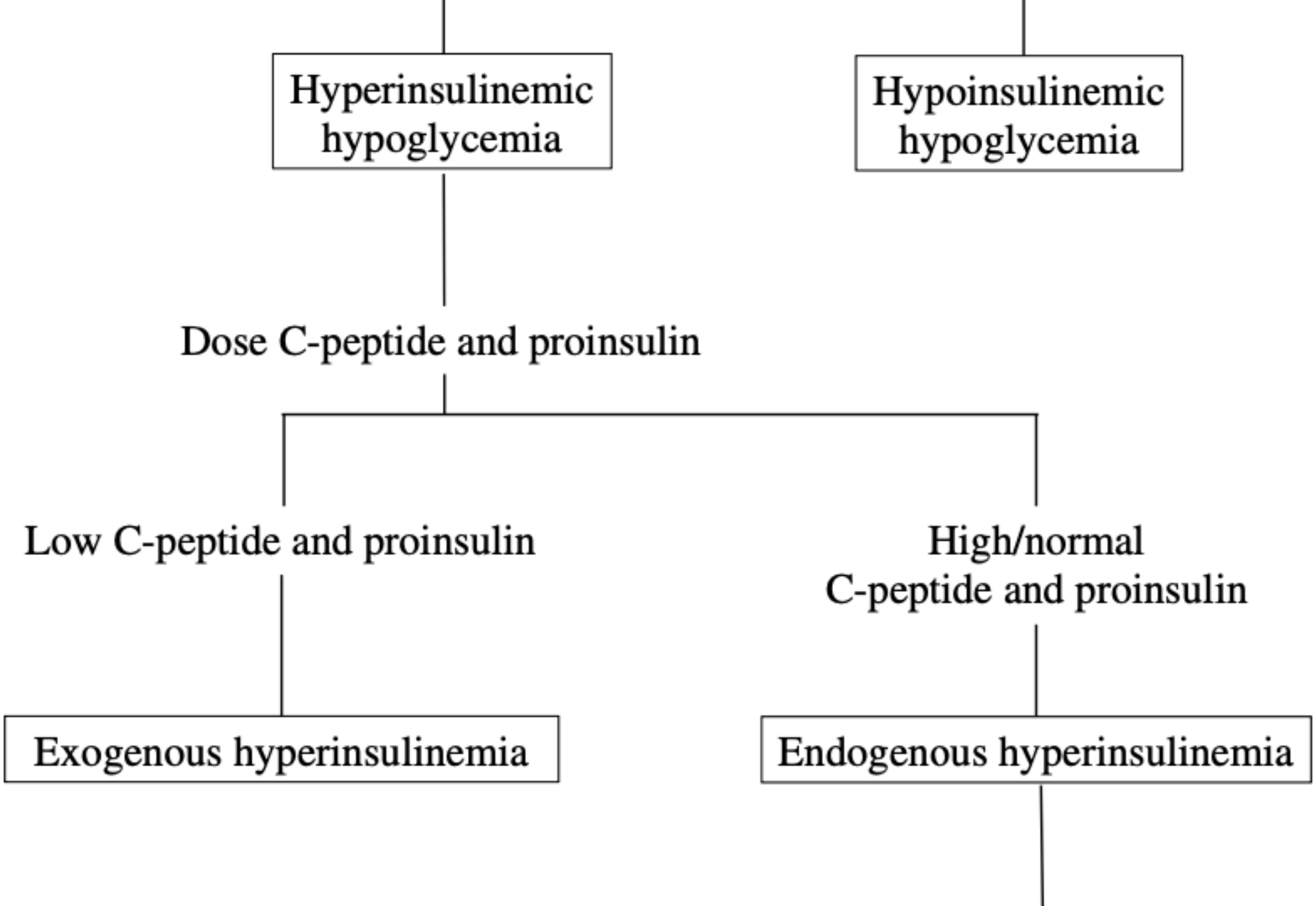
Ketogenesis

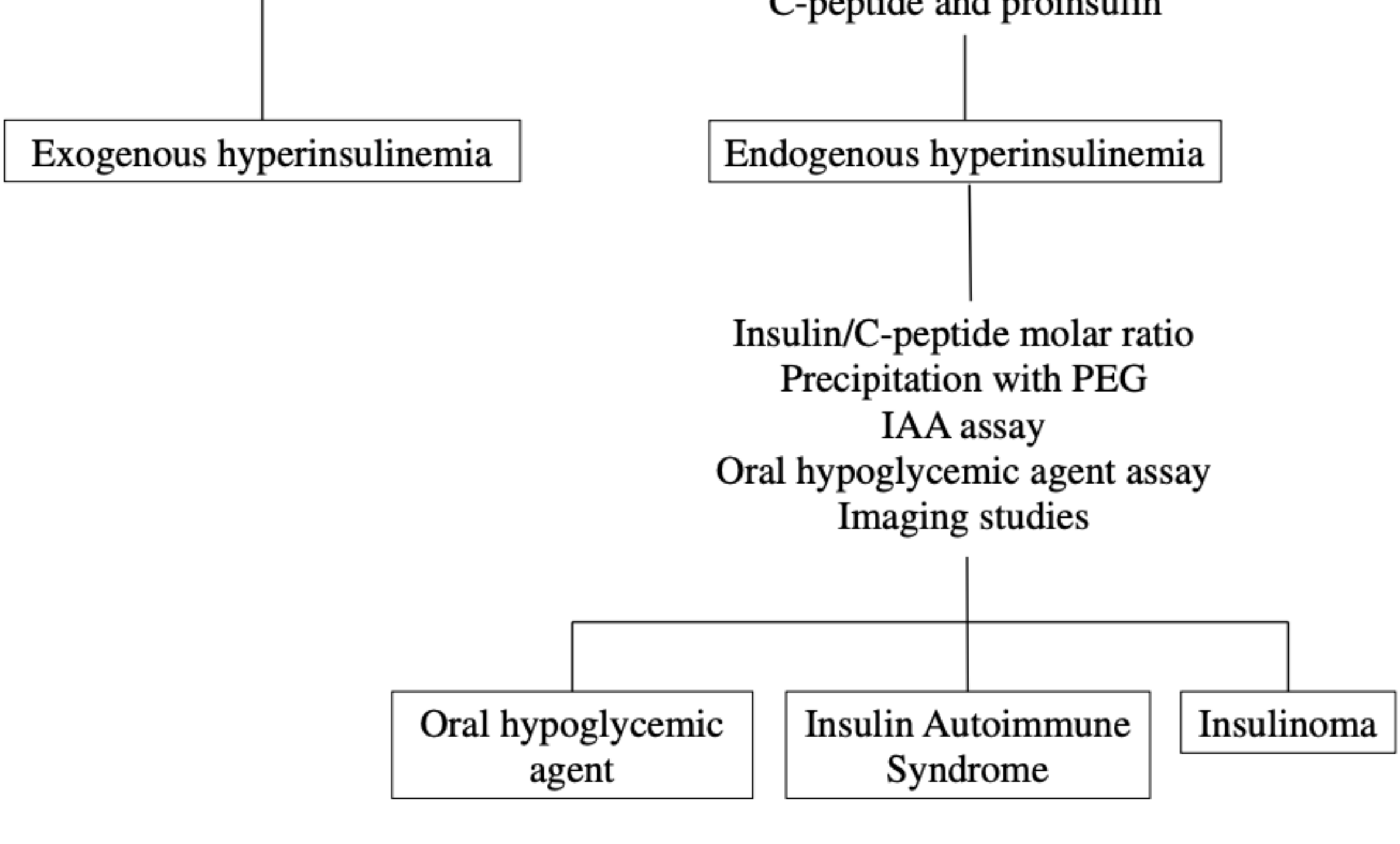


- Occurs primarily in the mitochondria of hepatocytes.
- Insulin is the key regulator (inhibitor) of the ketogenic pathway
- AcetylCoA produces 22 ATP per molecule in extrahepatic tissue


Patient presenting with complaint of hypoglycemia
Confirm hypoglycemia (Whipple triad)
No spontaneous hypoglycemic episode
72-hours fasting test
Hypoglycemia confirmed


72-hours fasting test
Hypoglycemia confirmed
Assay insulin concentrations during a hypoglycemic episode
Hyperinsulinemic hypoglycemia
Hypoinsulinemic hypoglycemia


Hyperinsulinemic hypoglycemia
Hypoinsulinemic hypoglycemia
Dose C-peptide and proinsulin
Low C-peptide and proinsulin
High/normal C-peptide and proinsulin
Exogenous hyperinsulinemia
Endogenous hyperinsulinemia


C-peptide and proinsulin
Exogenous hyperinsulinemia
Endogenous hyperinsulinemia
Insulin/C-peptide molar ratio
Precipitation with PEG
IAA assay
Oral hypoglycemic agent assay
Imaging studies
Oral hypoglycemic agent
Insulin Autoimmune Syndrome
Insulinoma

Investigations

- At time of presentation:
  - C Peptide **2.29 elevated**
  - Insulin **180 (<12)**
  - BSL **2.8mmol**
- Sulphonylurea screening negative on 3 separate occasions
- Anti-insulin antibodies pending

- Na **133** K **3.2** Bicarb 31 Urea 4.6 Cr 58 eGFR >90
- **ALT 60** otherwise LFTs NAD
- ESR and CRP normal
- Urine MCS and blood cultures negative
- Morning cortisol 280 TSH 0.89 T4 13
- HbA1c 5.9%
- QUEP and Free light chains normal

Hirata Syndrome
Insulin Autoimmune Syndrome

Spontaneous episodes of hyperinsulinemic hypoglycaemia due to the presence of insulin autoantibodies (IAA) in patients who have no islet cell abnormalities and have not previously exposed to exogenous insulin

Hirata Syndrome

- Originally described by Yukimasa Hirata (幸真平田) in 1970
- 380 cases were reported worldwide from 1970 to 2009
- The majority of confirmed cases have been in Japan, although the first Caucasian case was identified in 1972
- M=F
- Most common in the 6th decade of life
- Associated with:
  - Drugs
  - Graves disease
  - Viral infections - superantigens
  - Monoclonal gammopathies/plasma cell dyscrasias
  - Strongly associated with HLA-DR4 and specifically, with the DRB1*0406 (higher prevalence of HLA-DRB1*0406 in Asian populations thought to be the reason there is a higher incidence of IAS in Japan)

How do patients present?

Most patients present with post-prandial hypoglycaemic episodes which are preceded by transient hyperglycaemia

Occasionally patients can present with fasting hypoglycaemia and rarely spontaneous hypoglycaemia

Drugs associated with Hirata syndrome

- Methimazole and Alpha lipoic acid are the commonest drugs associated with IAS
- The mean onset time was 4-6 weeks after starting the drug
- Prevalence of drug-induced IAS is estimated to be between 43-50%
- Patients who develop IAS following methimazole exposure invariably carry the DRB1*0406 allele

- Most medications associated with IAS are sulphydryl and reducing compounds
- Proposed mechanism is that these drugs bind and cleave the sulphydryl bonds between the insulin chains A and B, leading to a conformational change that exposes previously unseen epitopes

Table 2 List of Medications Associated with the Development of Insulin Autoimmune Syndrome

Class	Medication	References	Strenght of the Association
Antithyroid drugs	Methimazole Carbimazole	[9,11,23,29,37–41] [42–47]	High Medium
Supplements	Alpha-lipoic acid Pyritinol Glutathione Methionine	[33–35,48–52] [53,54] [21] [55]	High Low Low Low
Antihypertensives	Captopril Hydralazine Procainamide Diltiazem	[22,36] [56,57] [56] [22]	Low Low Low Low
Antiplatelet drugs	Clopidogrel	[58,59]	Low
Oral antidiabetics	Tolbutamide Gliclazide	[22] [60]	Low Low
Anti-inflammatory drugs	Steroids Loxoprofen-sodium Diclofenac	[22] [61] [22]	Low Low Low
Muscle relaxants	Tolperisone hydrochloride	[22]	Low
Antibiotics	Penicillamine Imipenem Penicillin G Isoniazid	[62,63] [64] [65] [66]	Low Low Low Low
Proton pump inhibitors	Pantoprazole Omeprazole	[67] [68]	Low Low
Plasma proteins Orphan drugs	Albumin Tiopronin (Mercaptopropionyl glycine)	[69] [21,22]	Low Low

Notes: The strength of the association has been defined as low (less than 5 reports), medium (between 5 and 9 reports), or high (more than 10 reports).

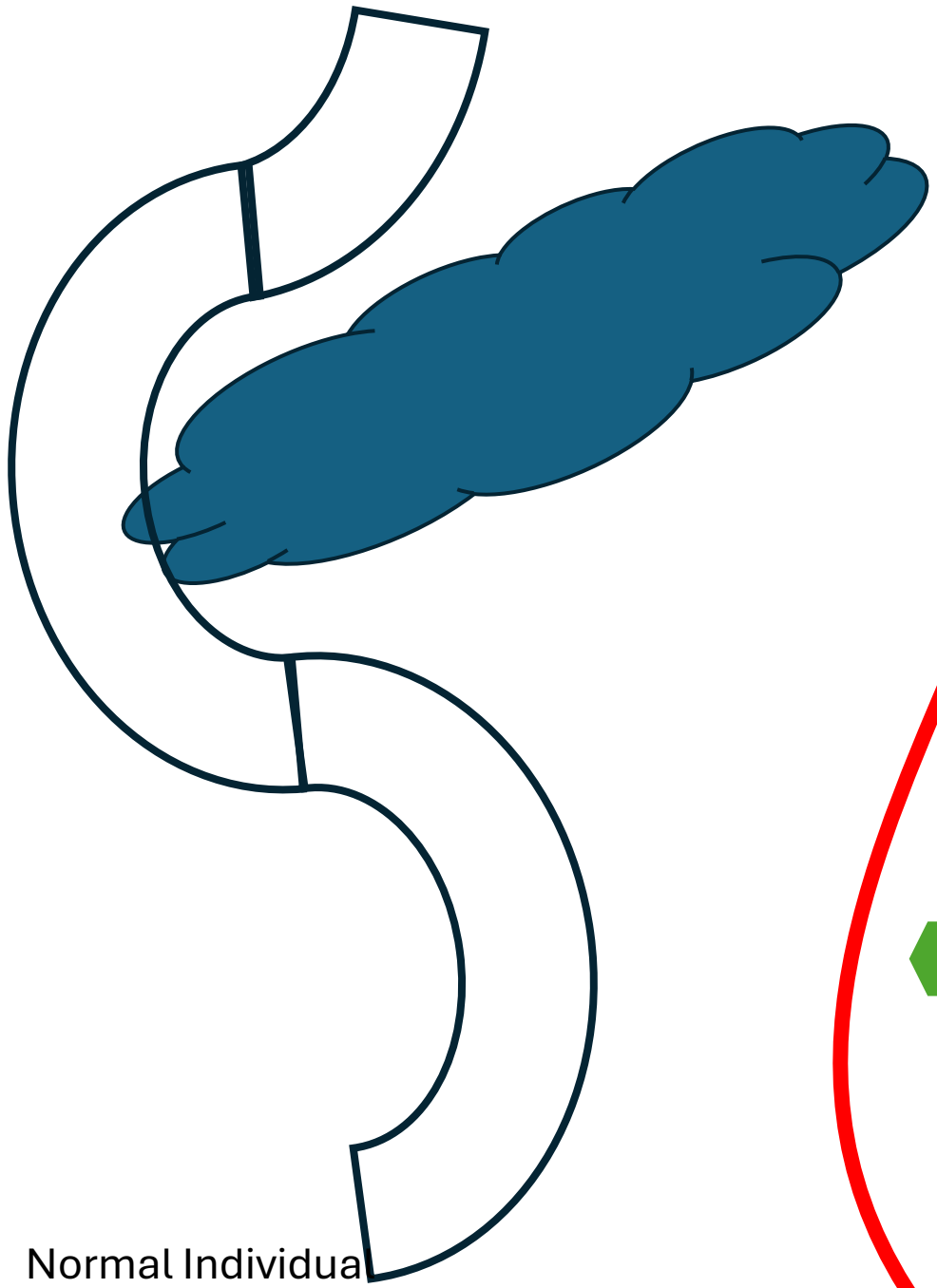
Le Chatelier's Principle

Free Insulin + Insulin Antibody ←→ Insulin-Antibody Complex

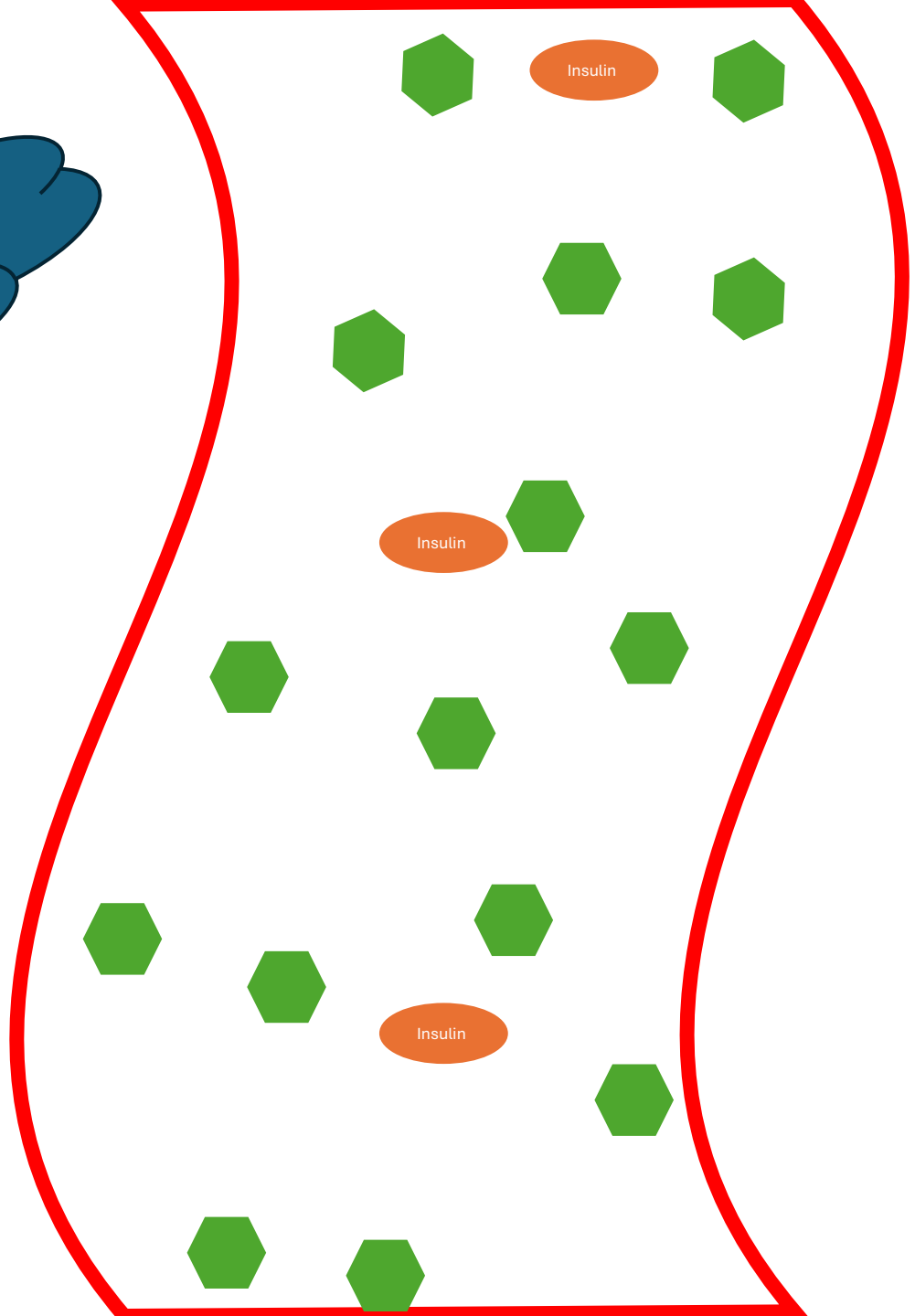
A system in equilibrium will adjust to counteract any change and restore equilibrium

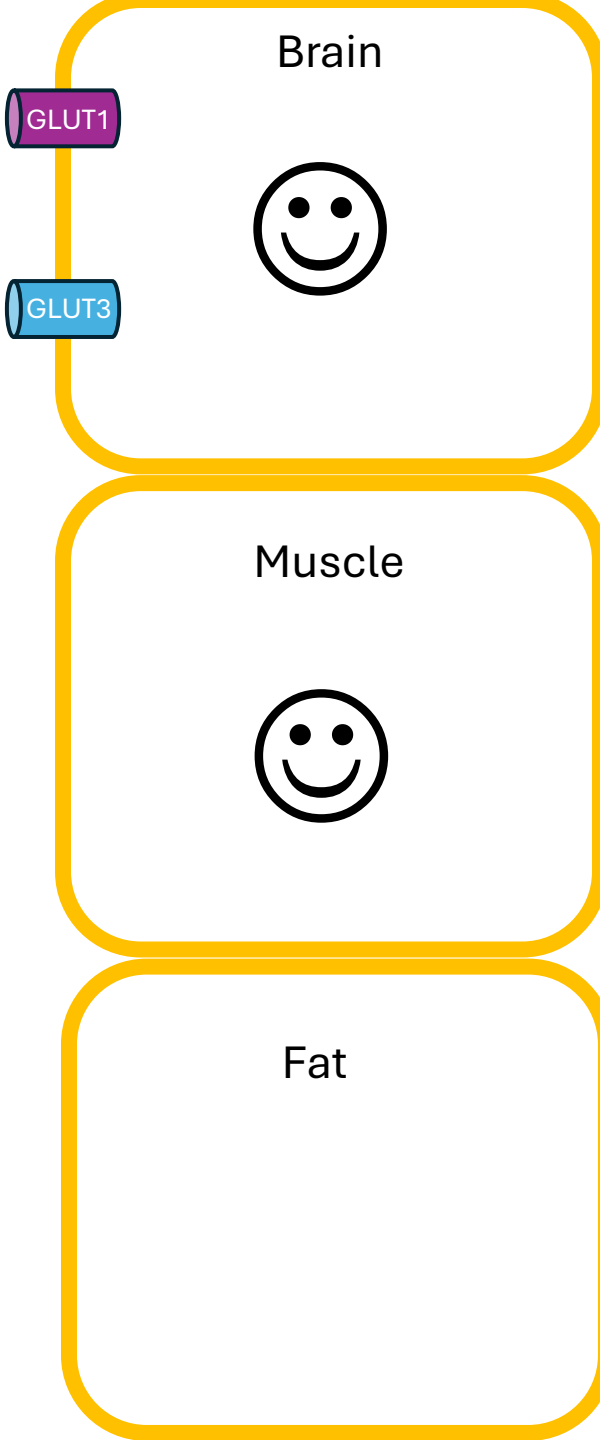
As free insulin is metabolised, the equilibrium shifts to the left and bound insulin is unbound

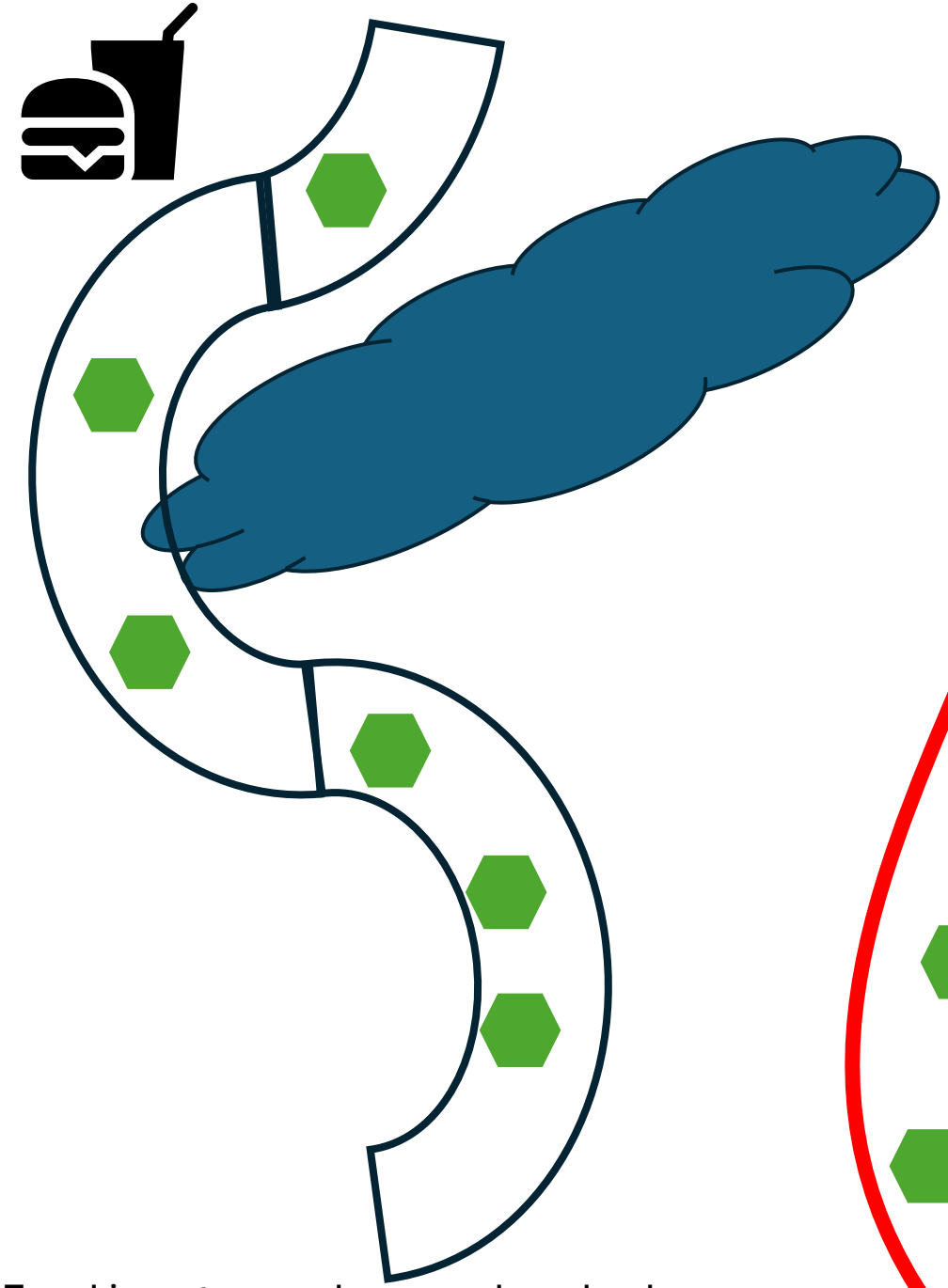
So how exactly do insulin autoantibodies produce hypoglycaemia?



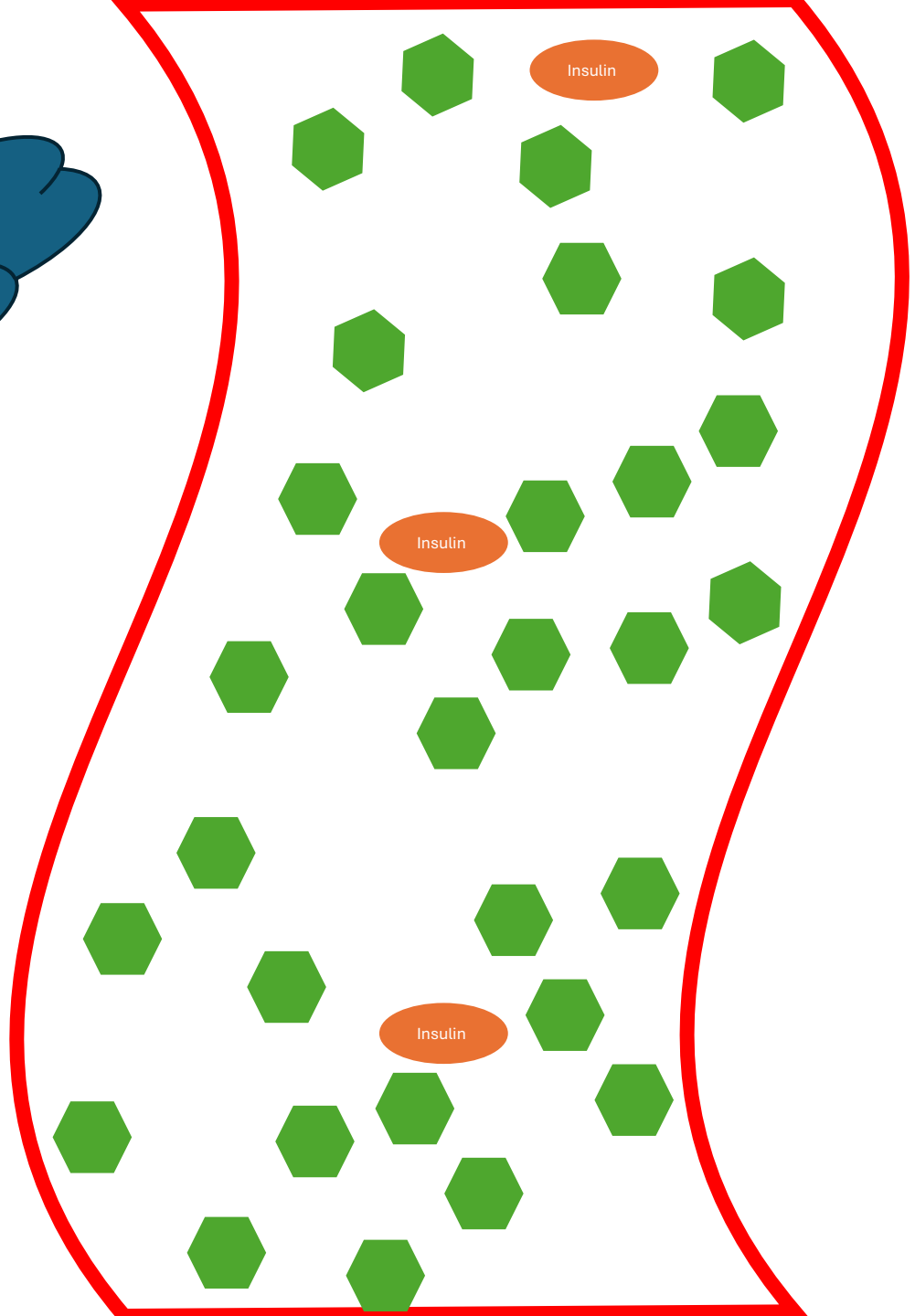
Normal Individua

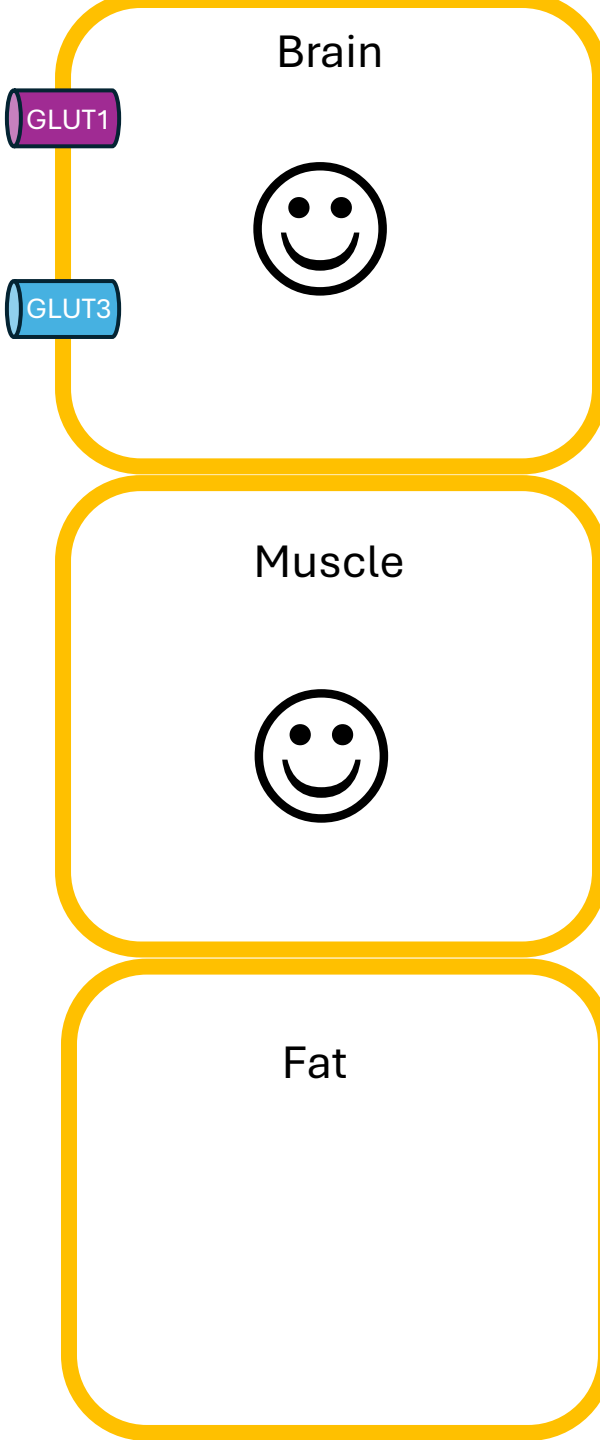


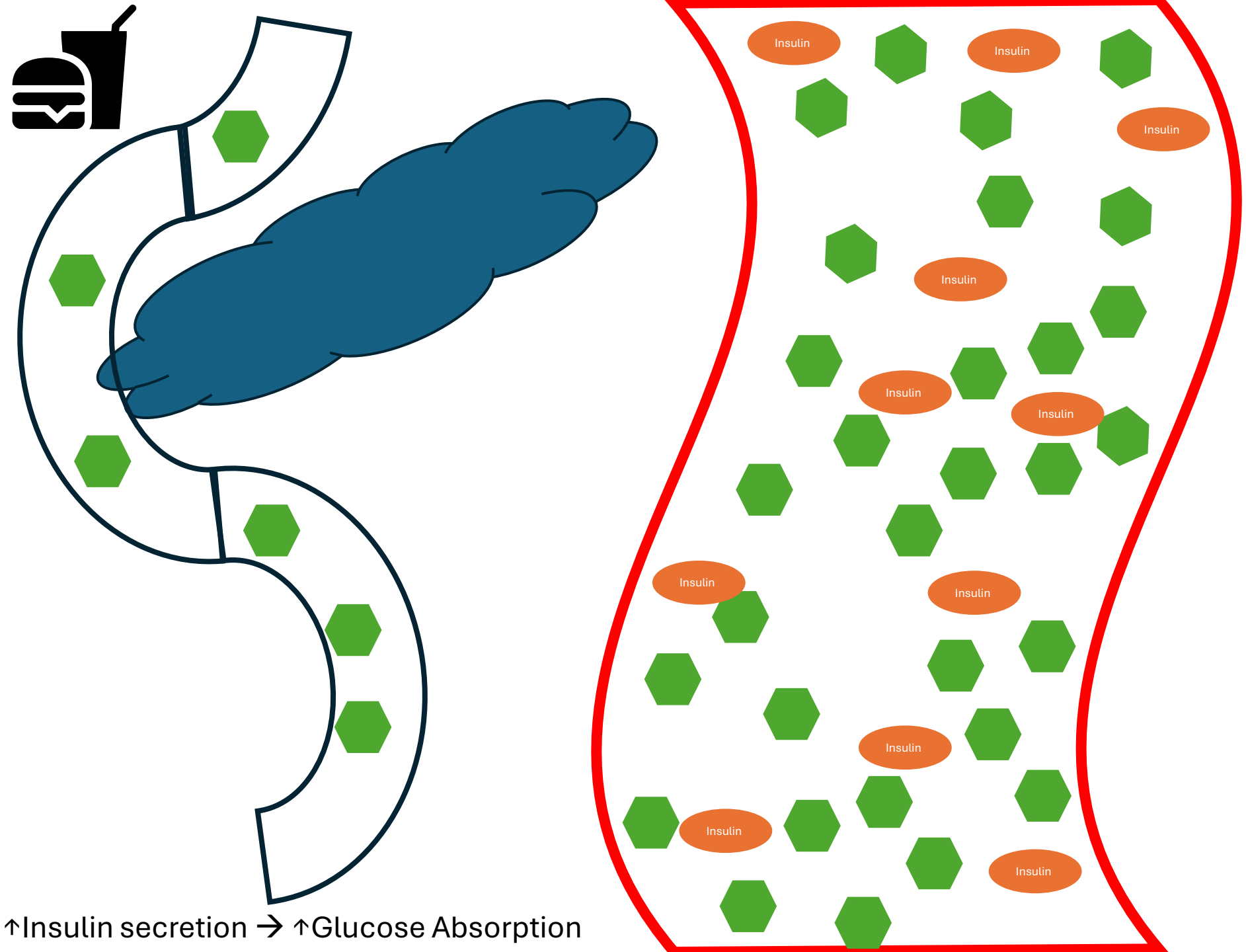


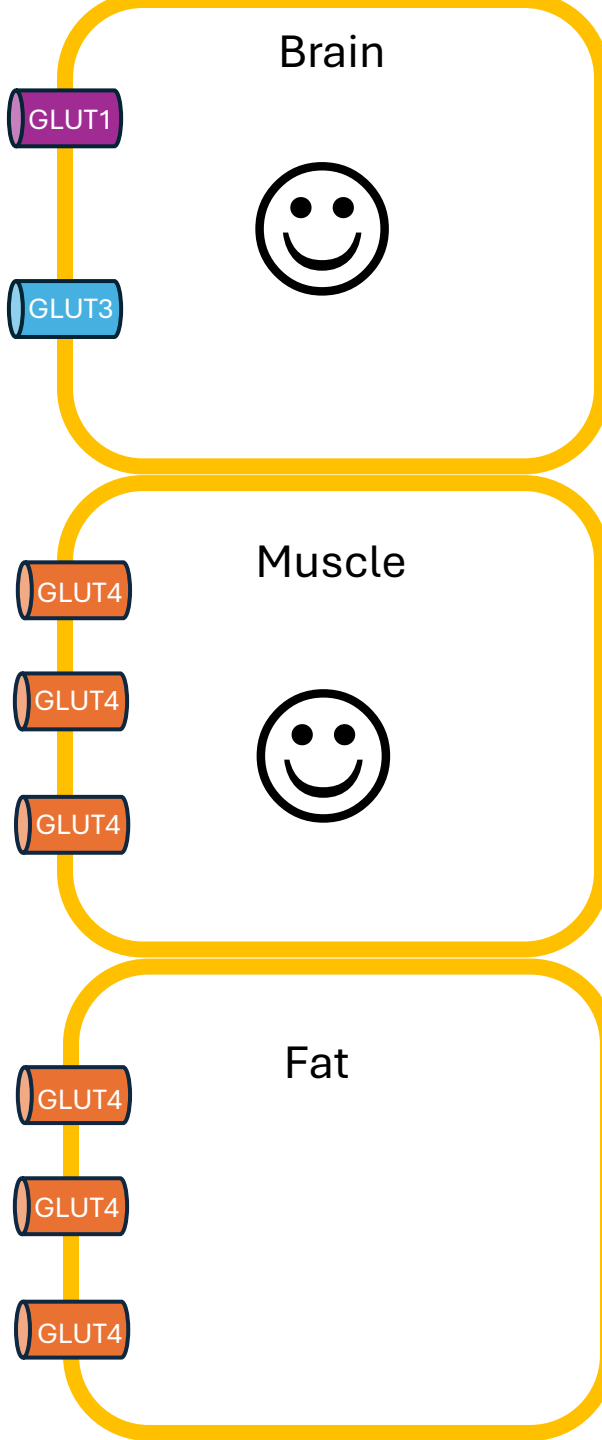


Food is eaten and sugar absorbed

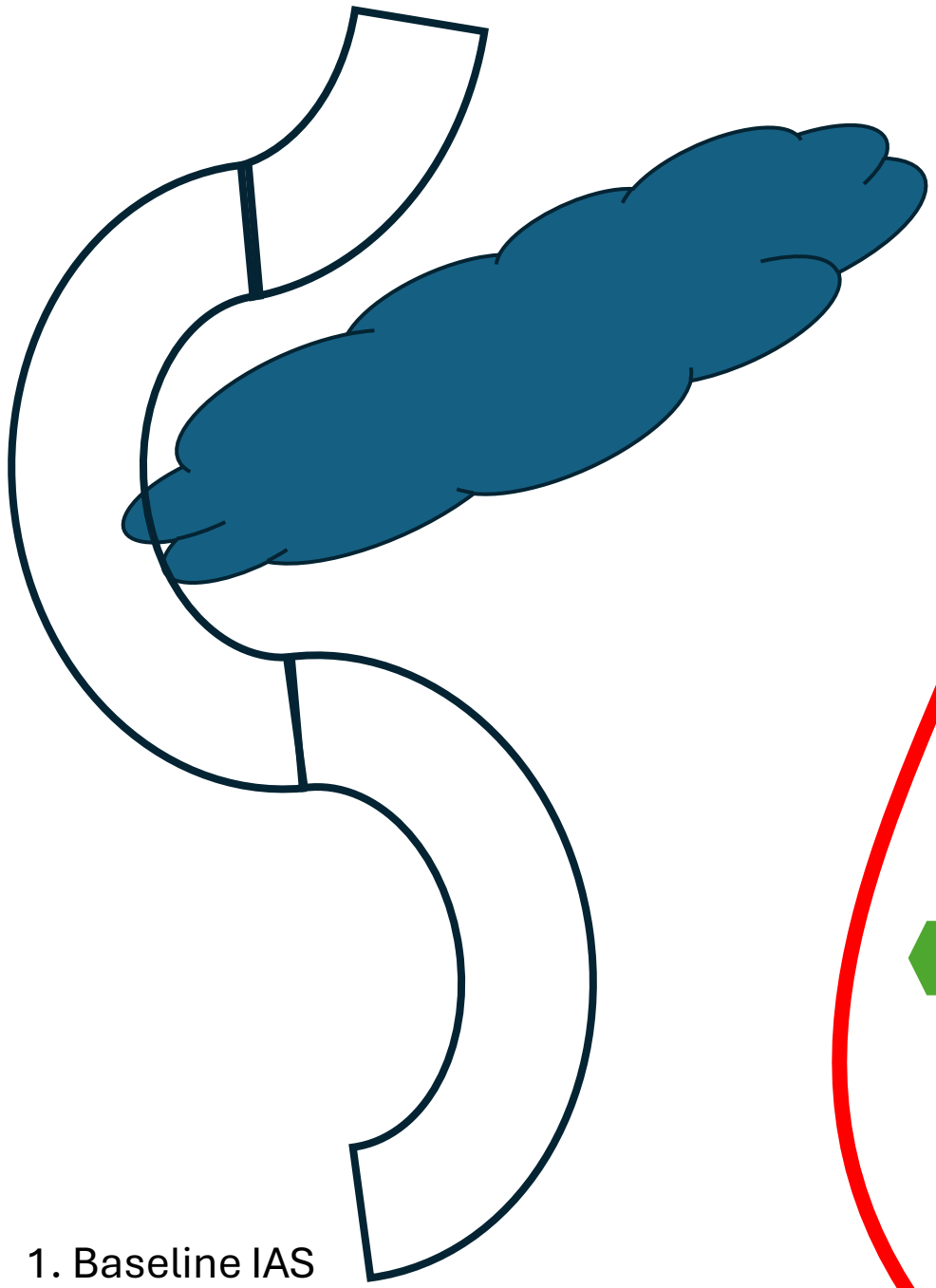




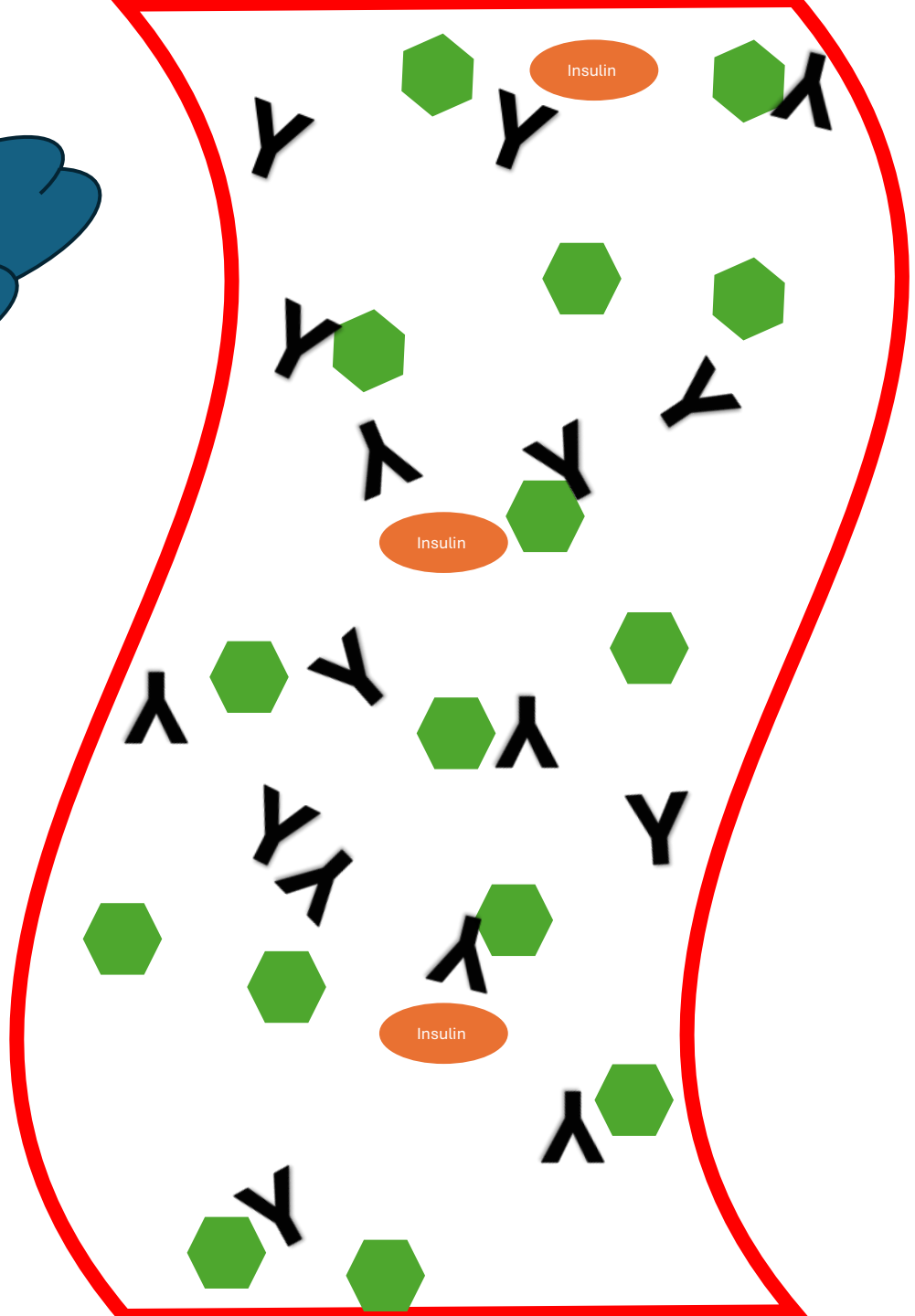


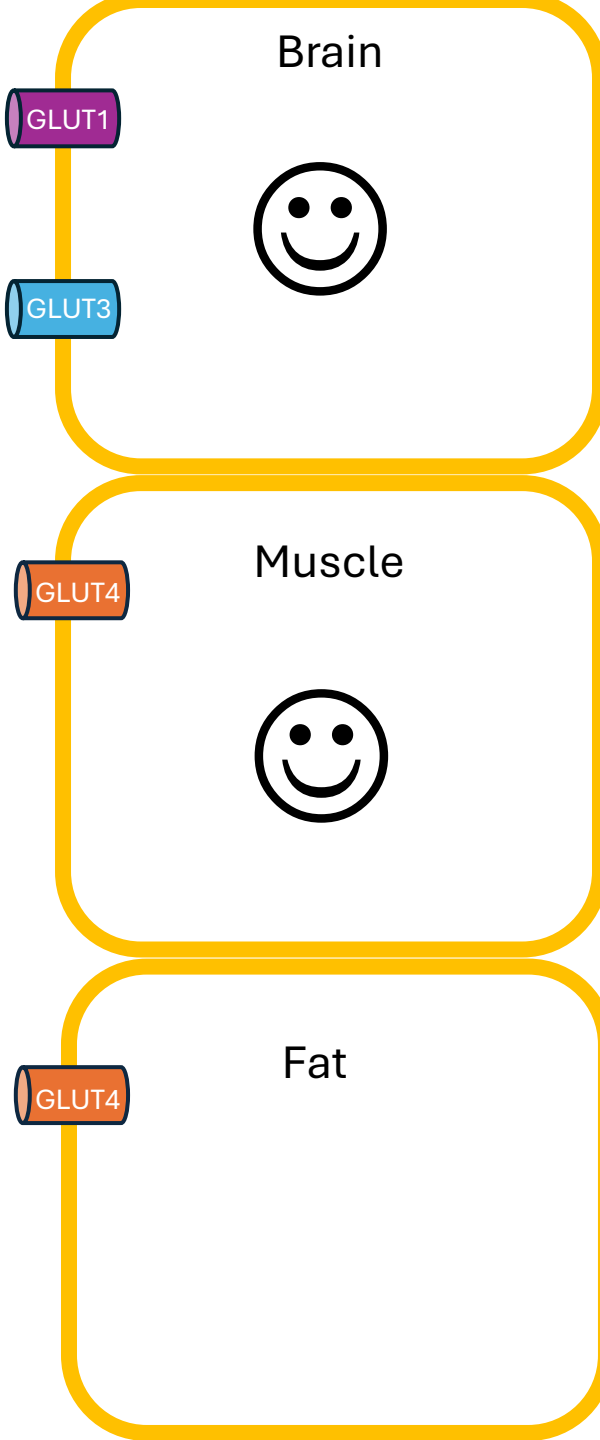


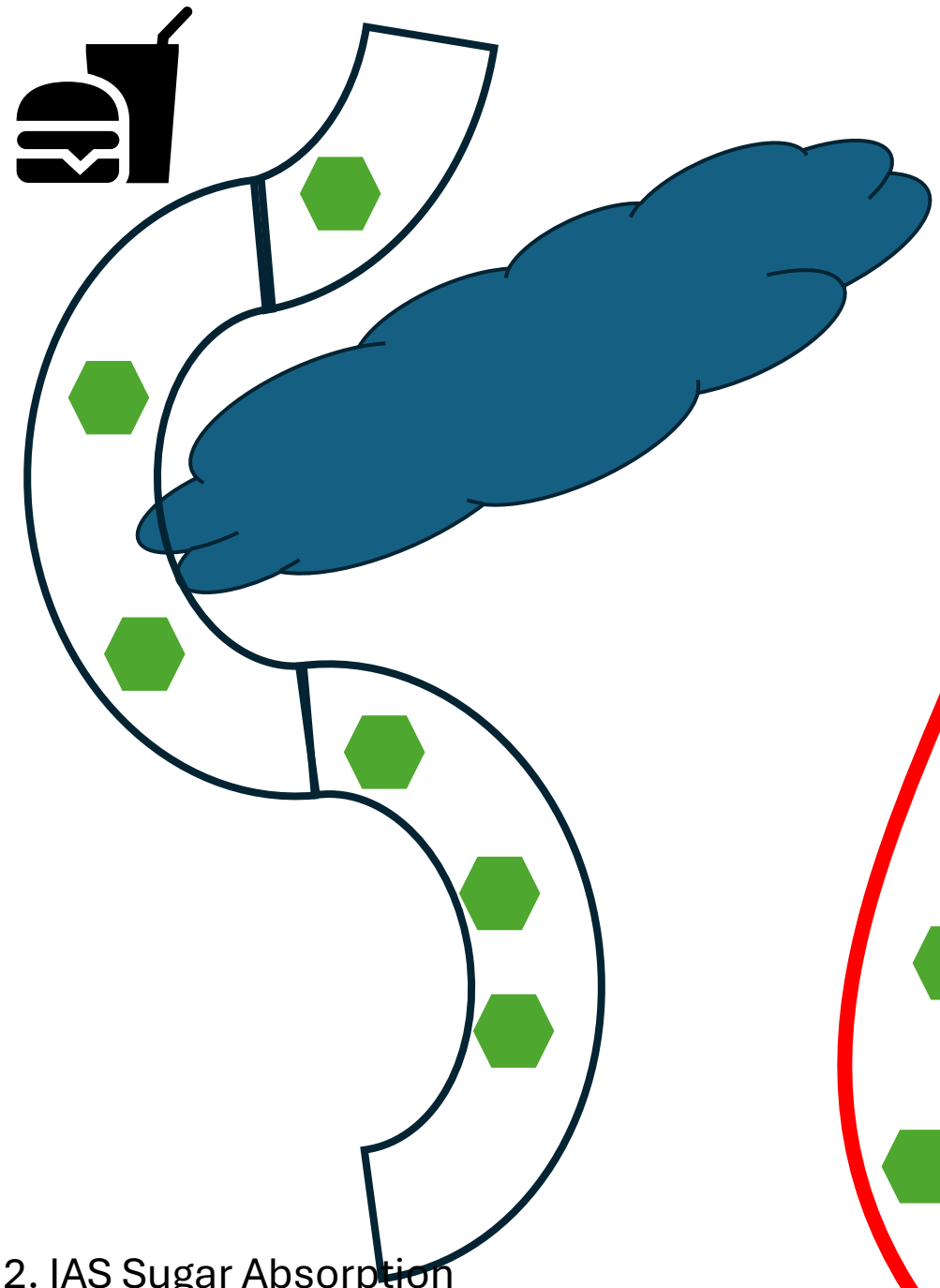
↑Insulin secretion → ↑Glucose Absorption

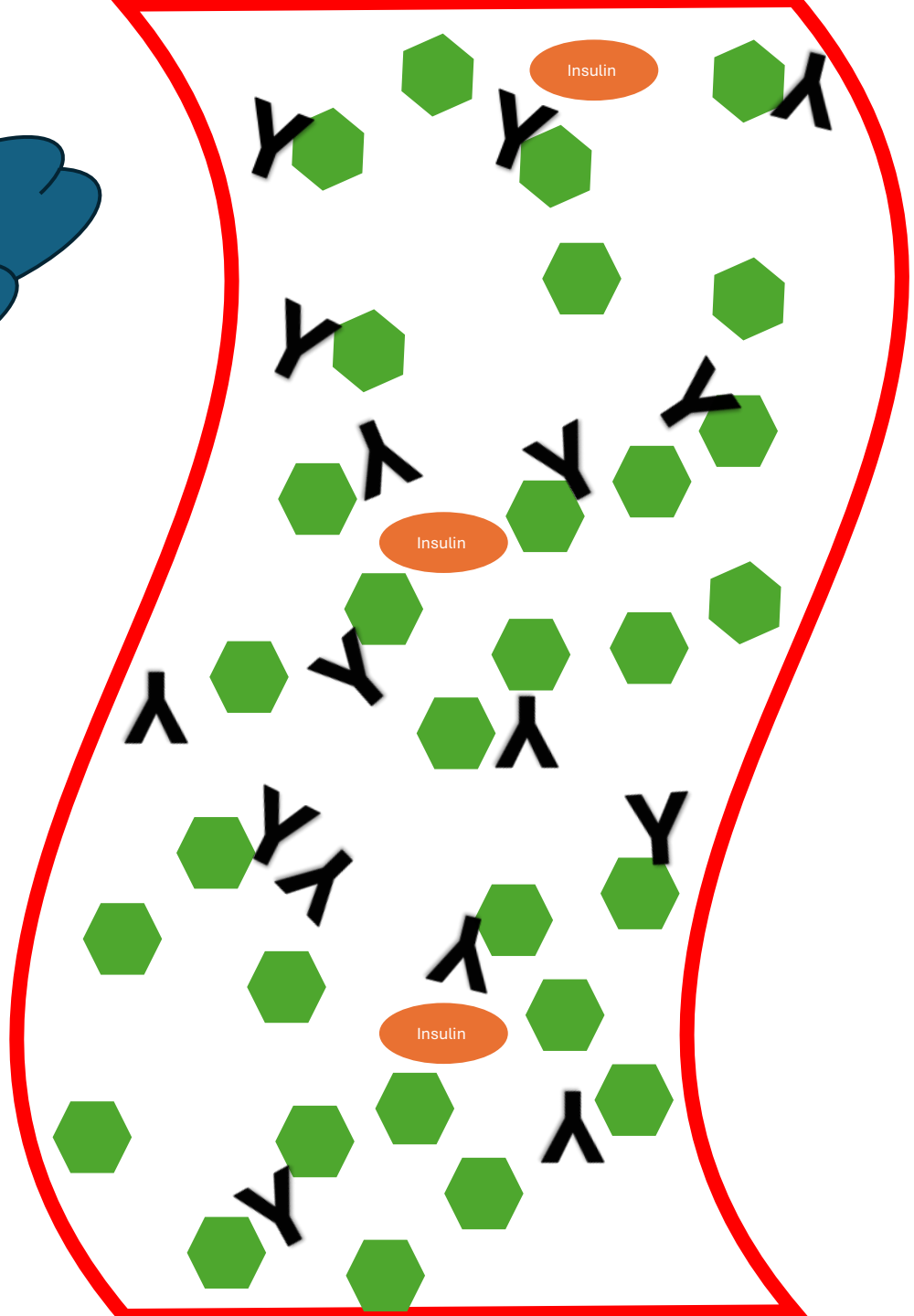


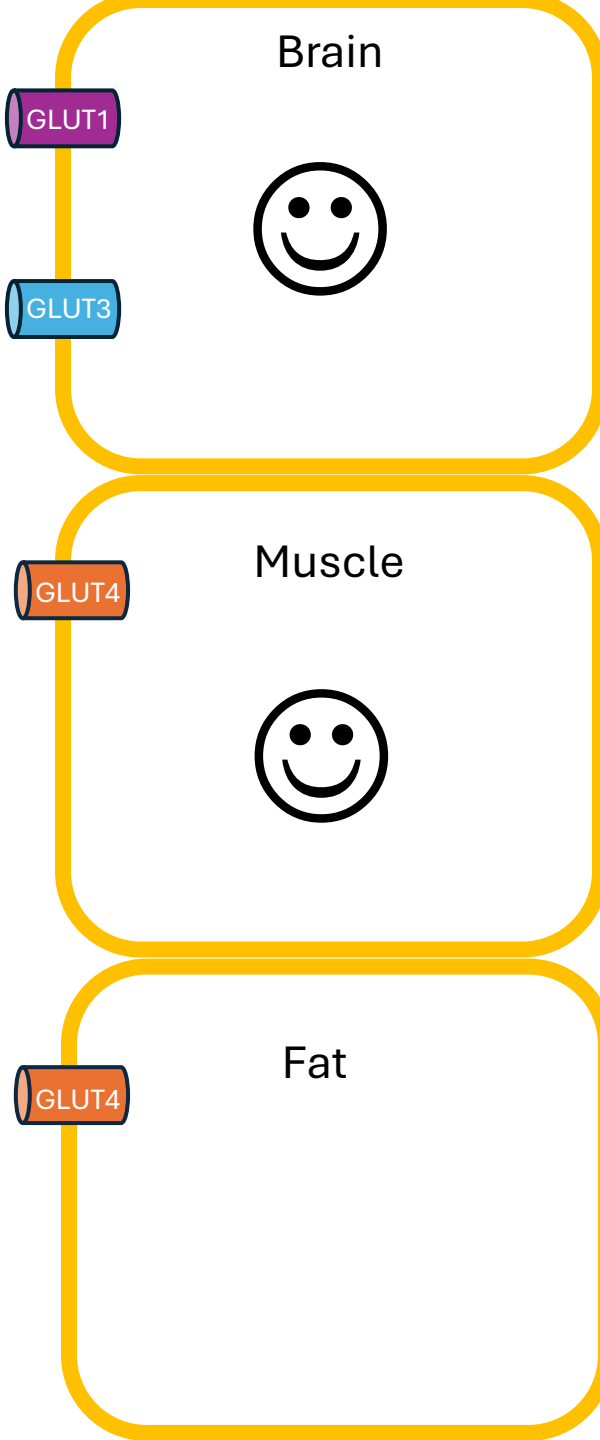
1. Baseline IAS



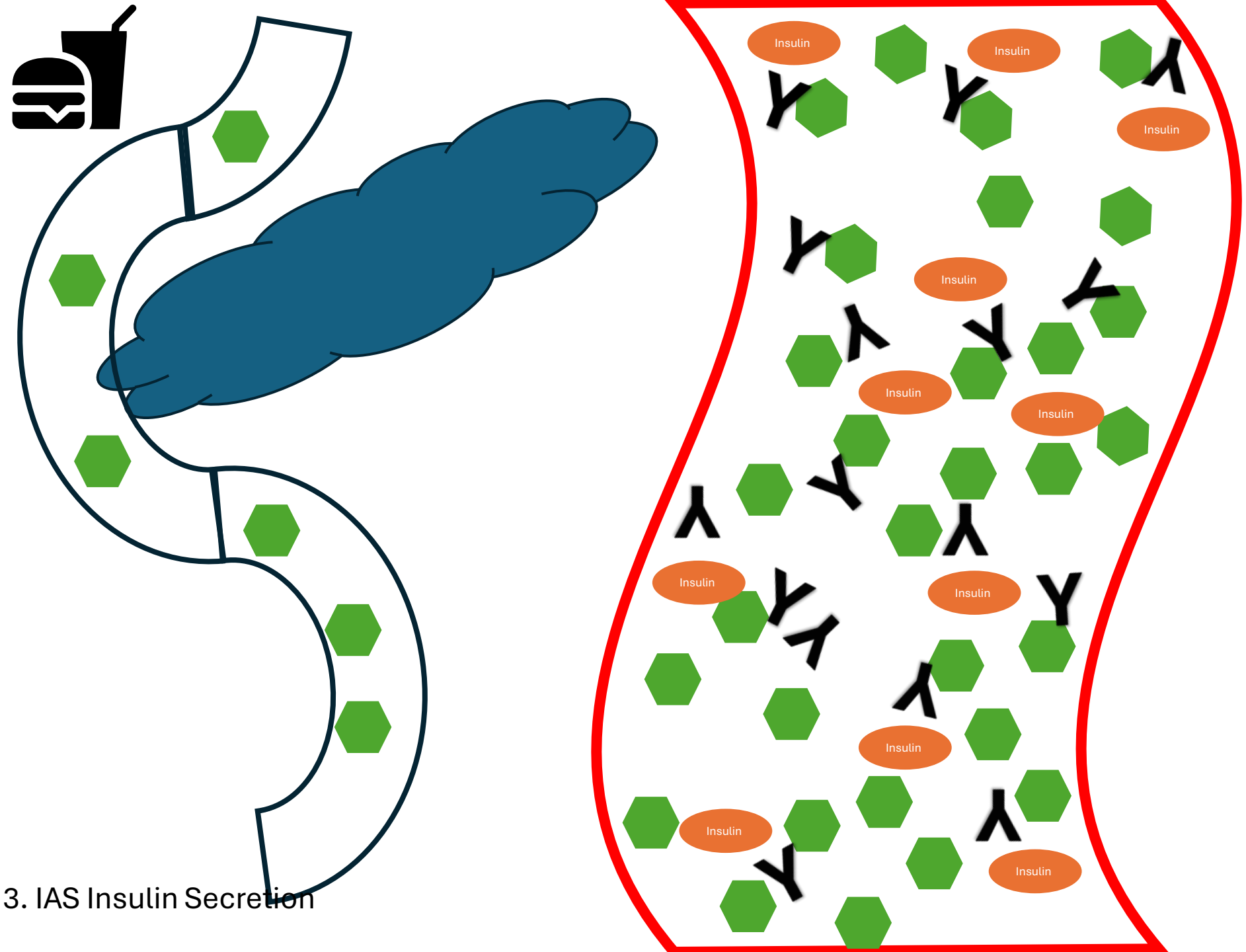


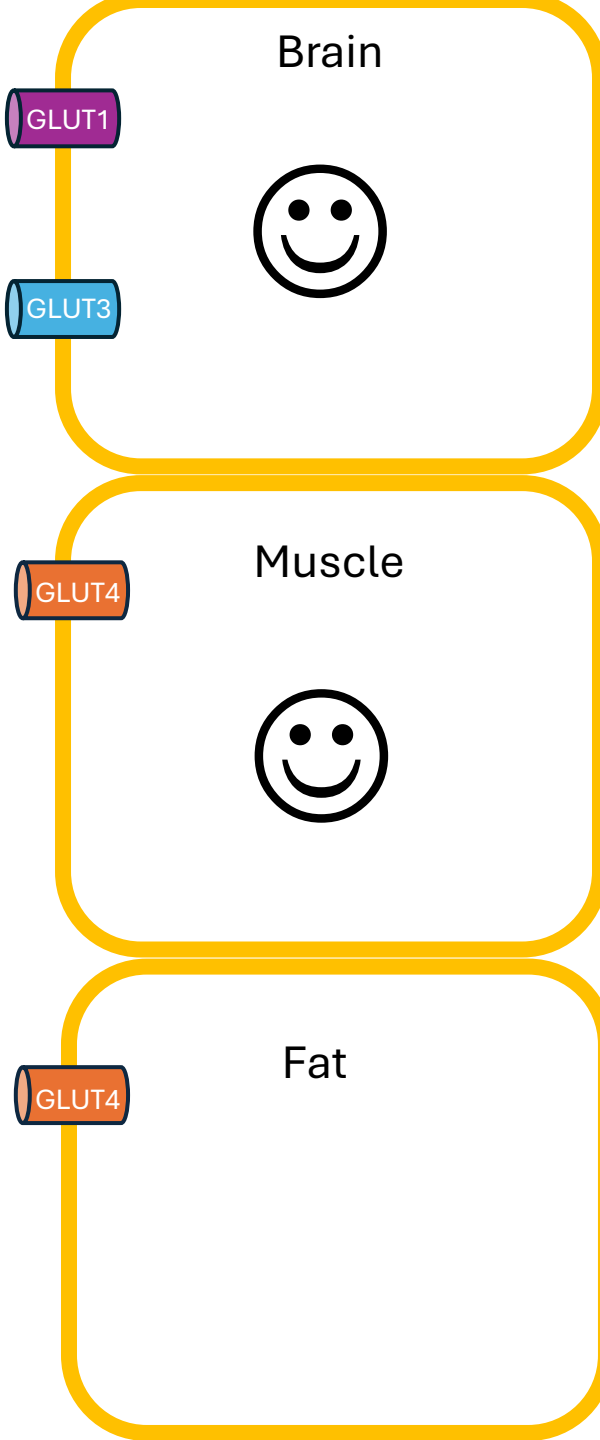




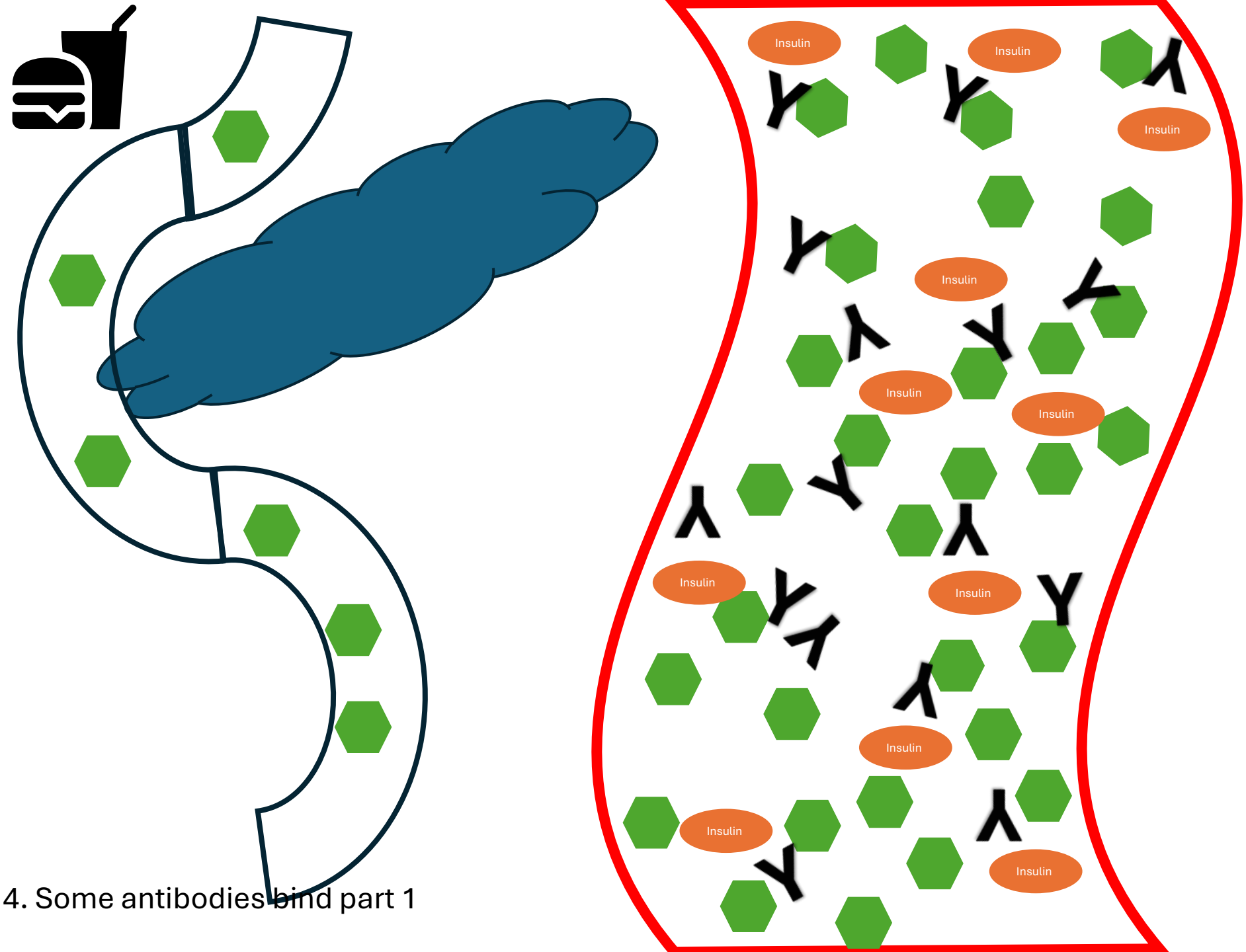


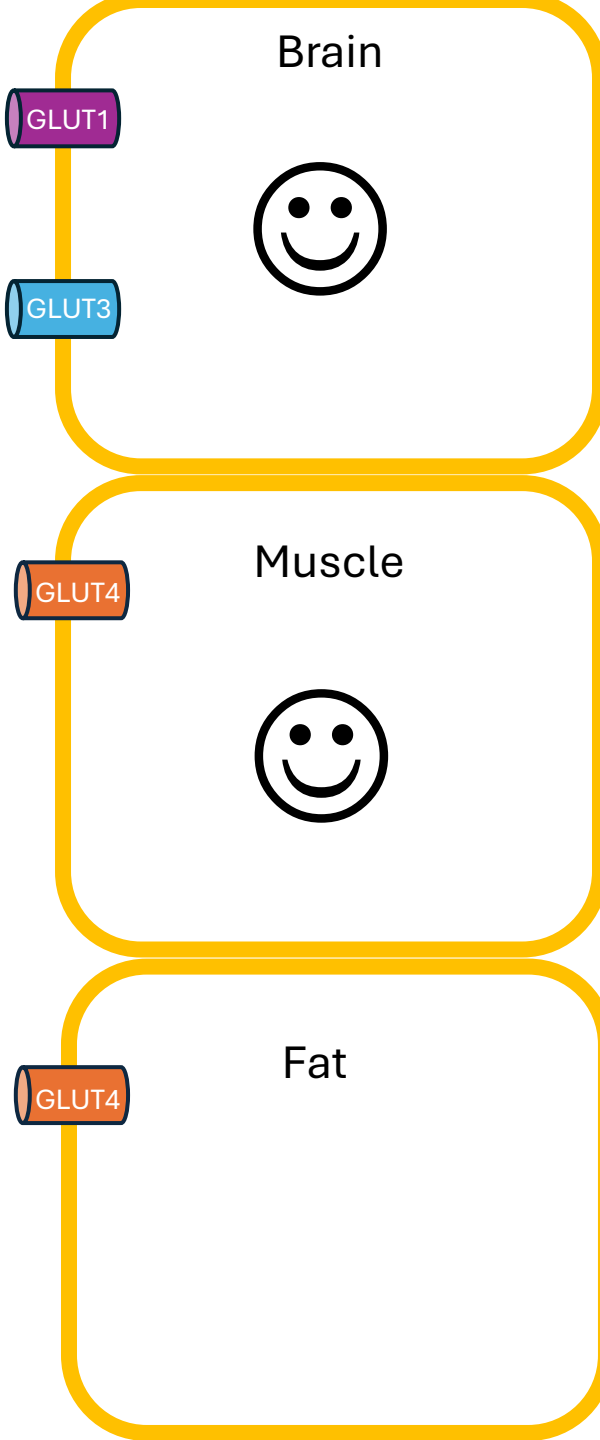
2. IAS Sugar Absorption



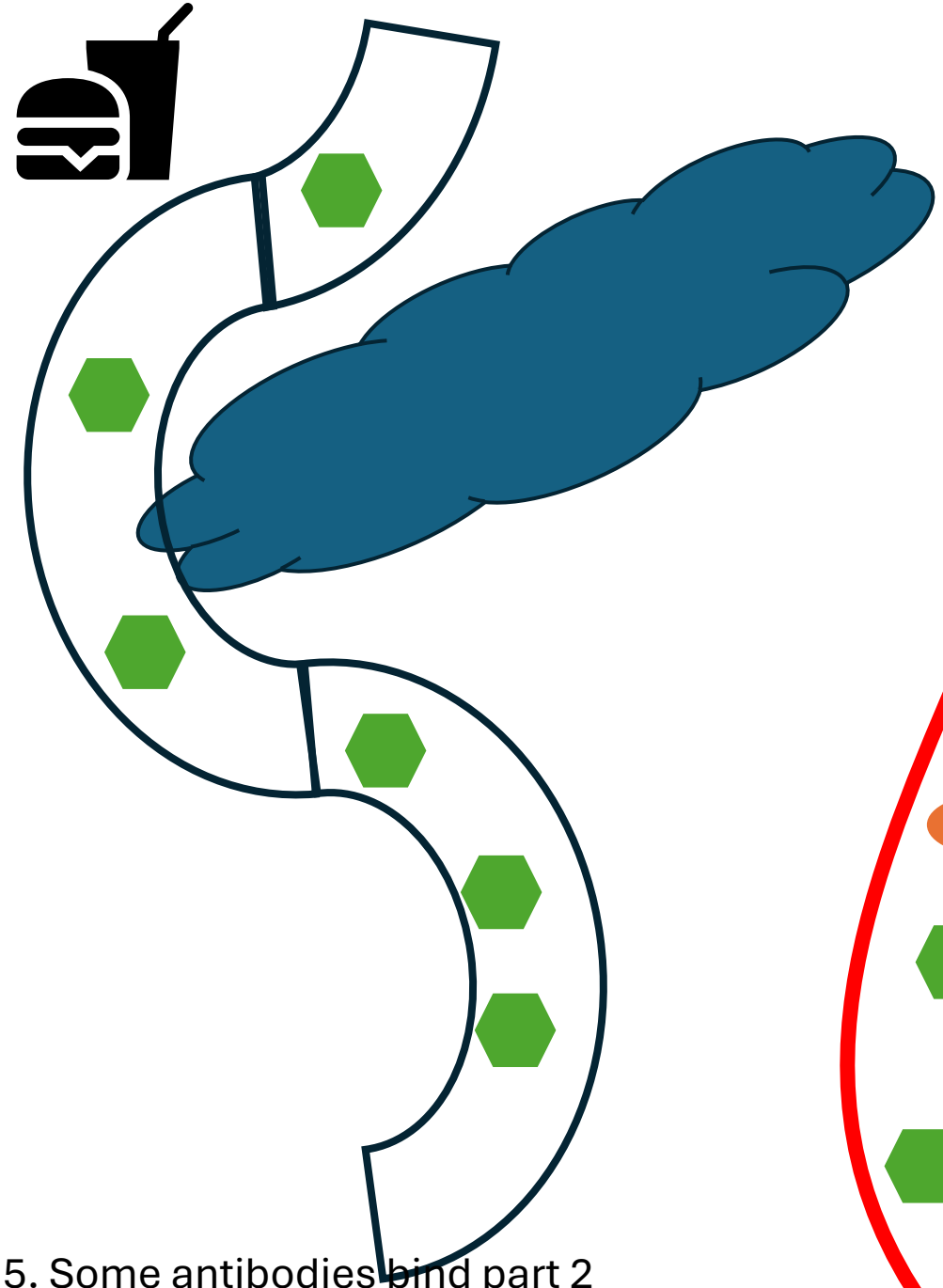


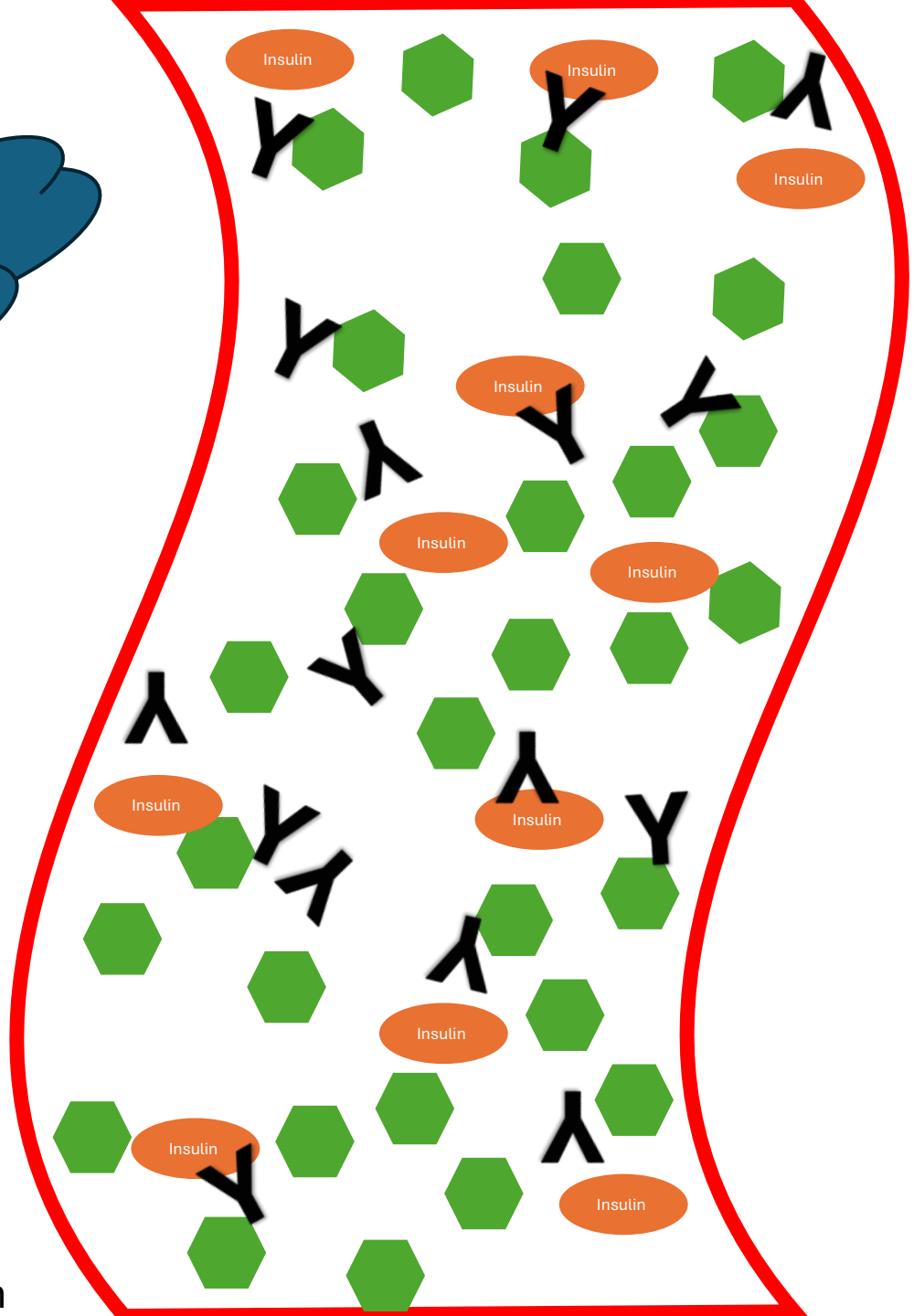
3. IAS Insulin Secretion

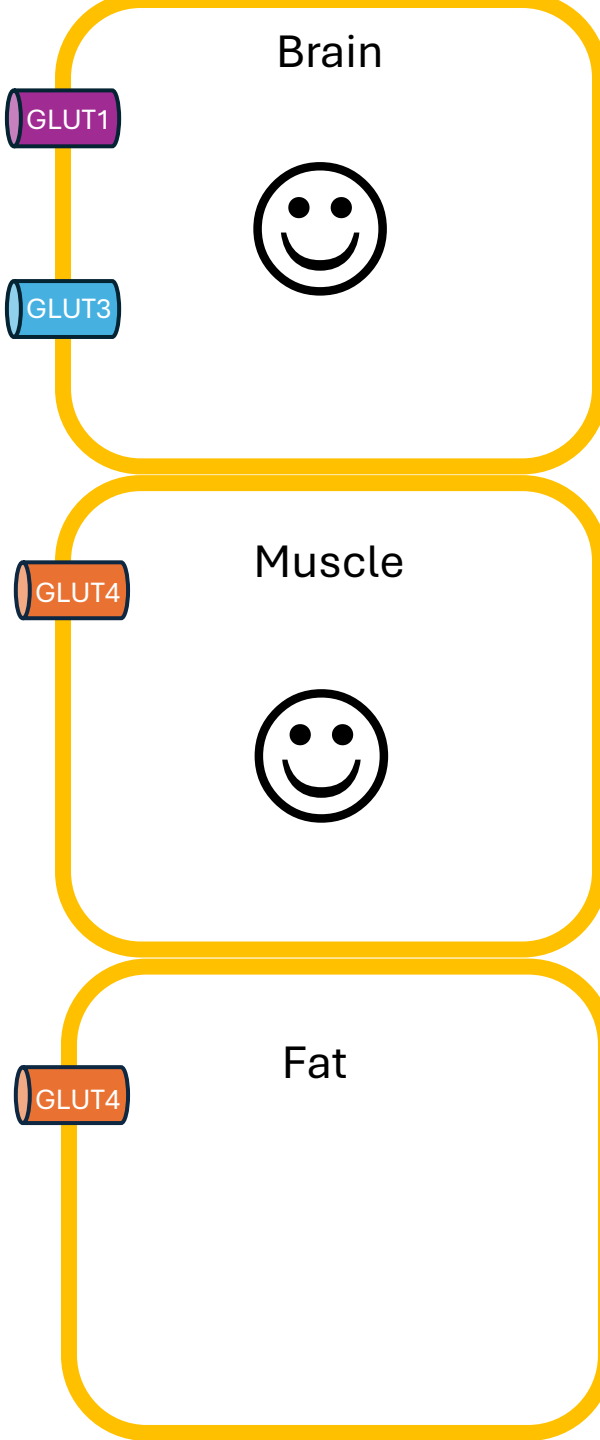




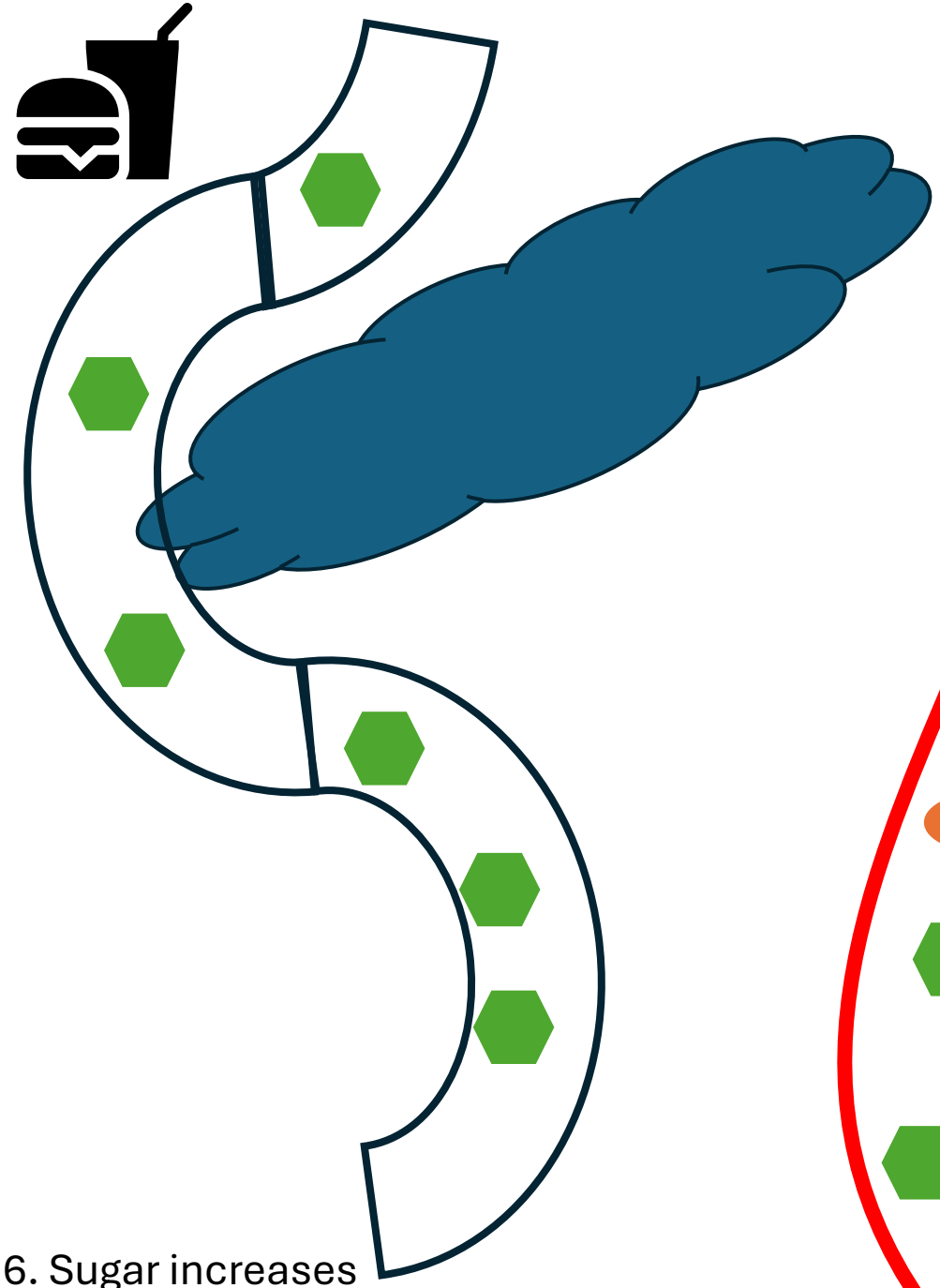
4. Some antibodies bind part 1



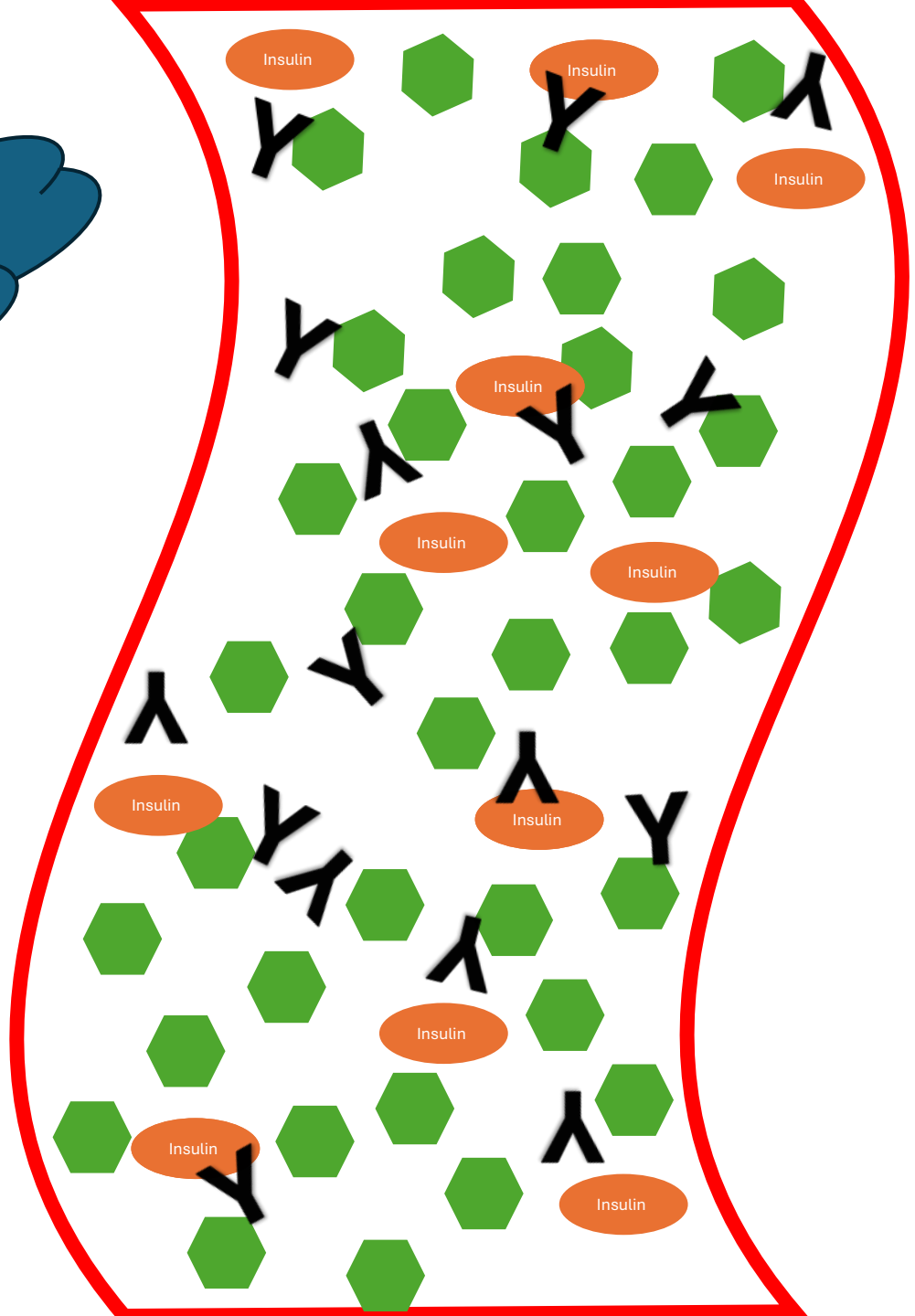


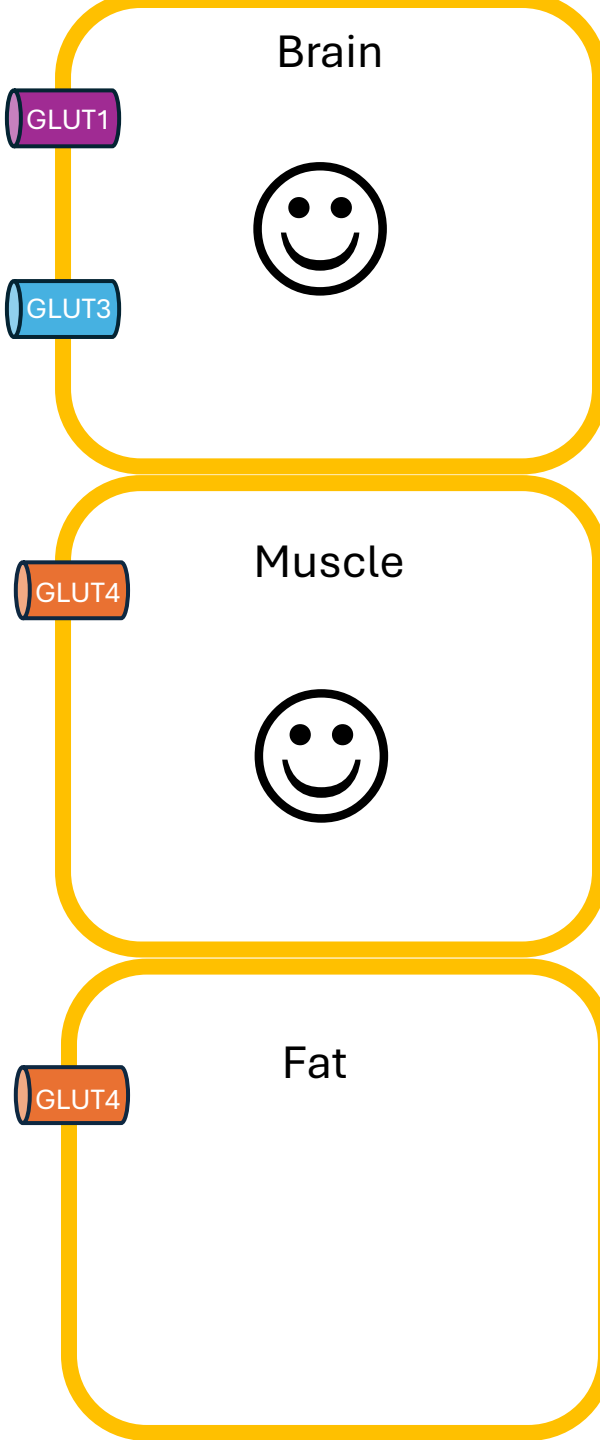


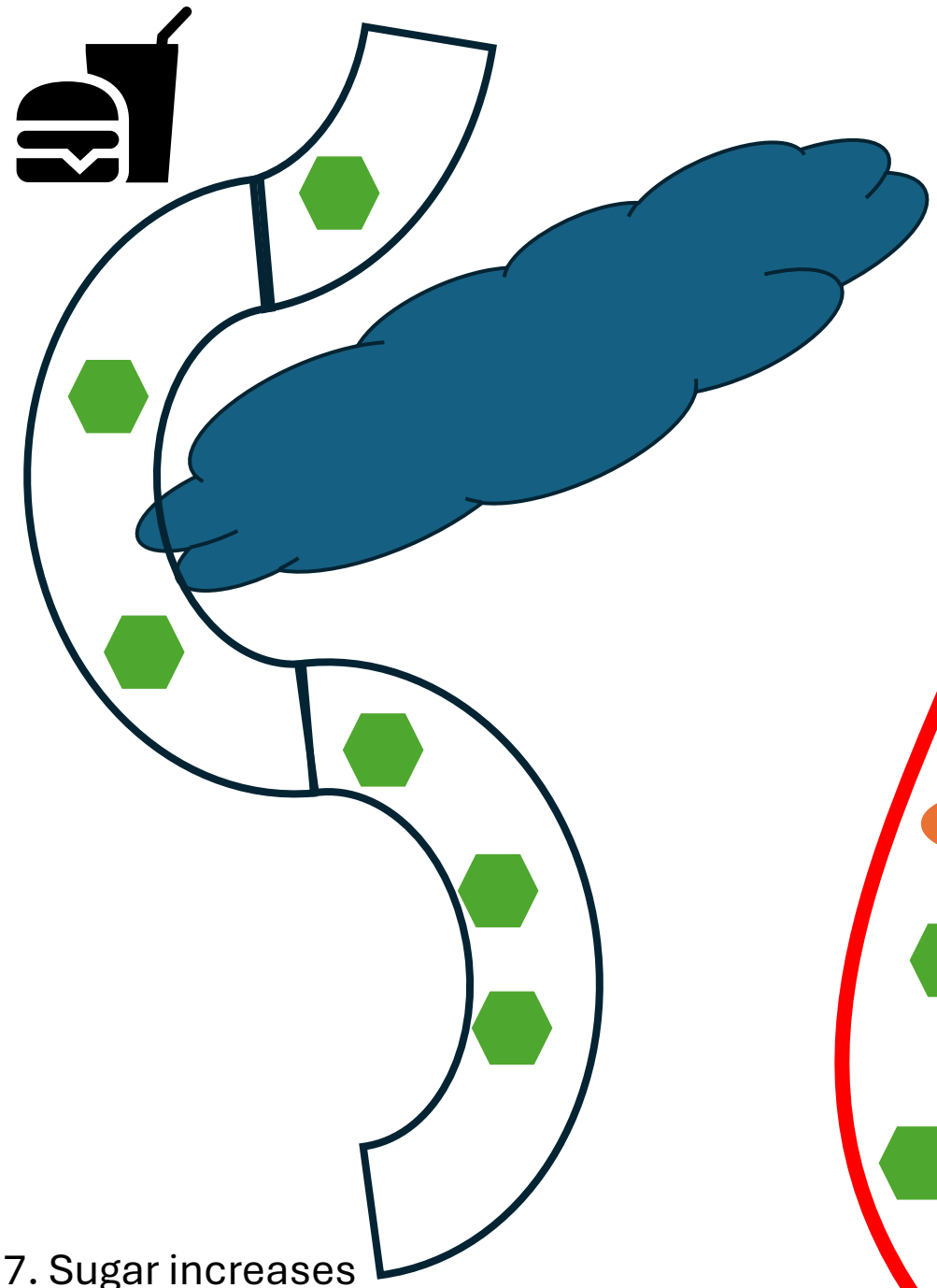
5. Some antibodies bind part 2
Sugar doesn't go anywhere so remains high

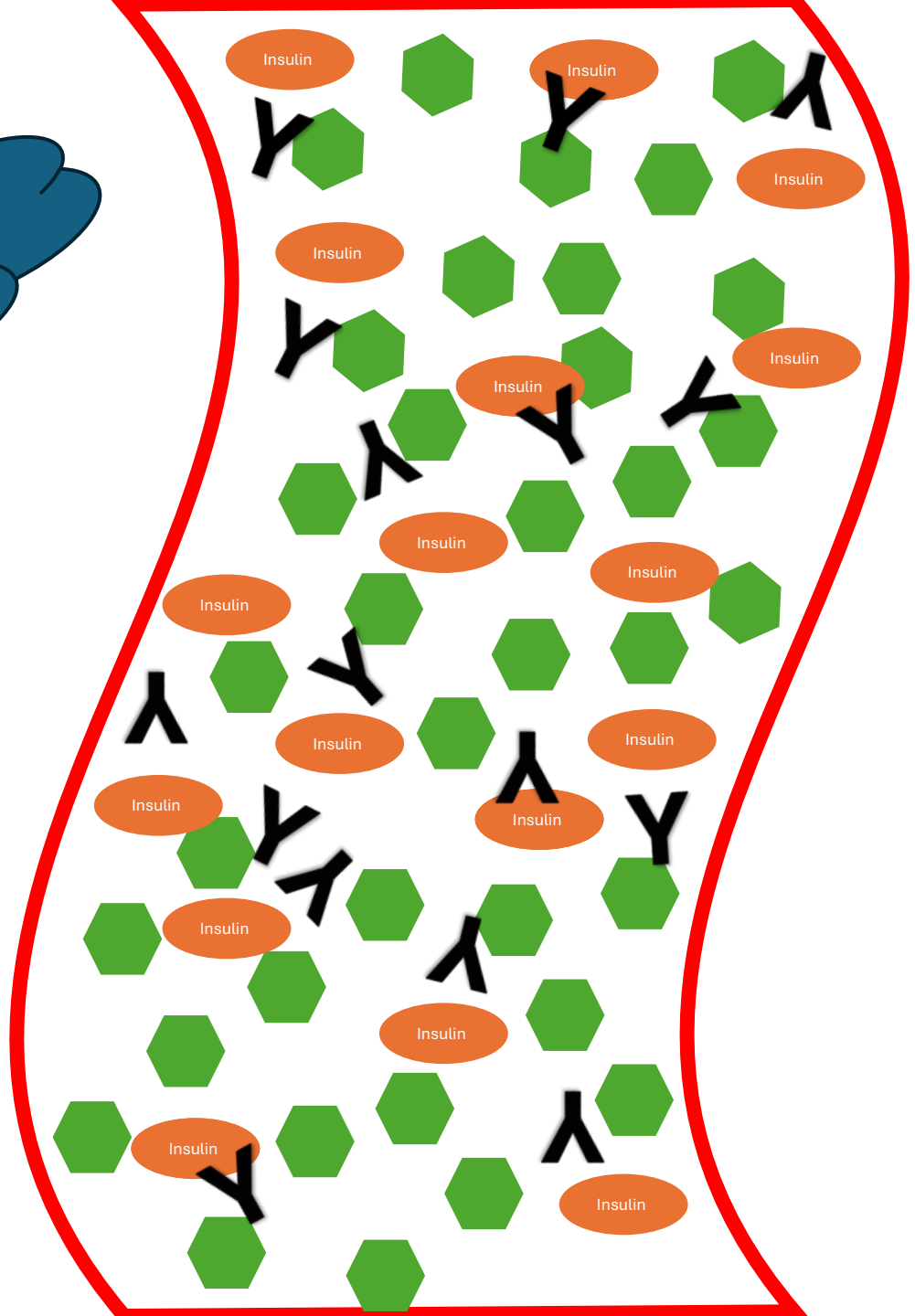


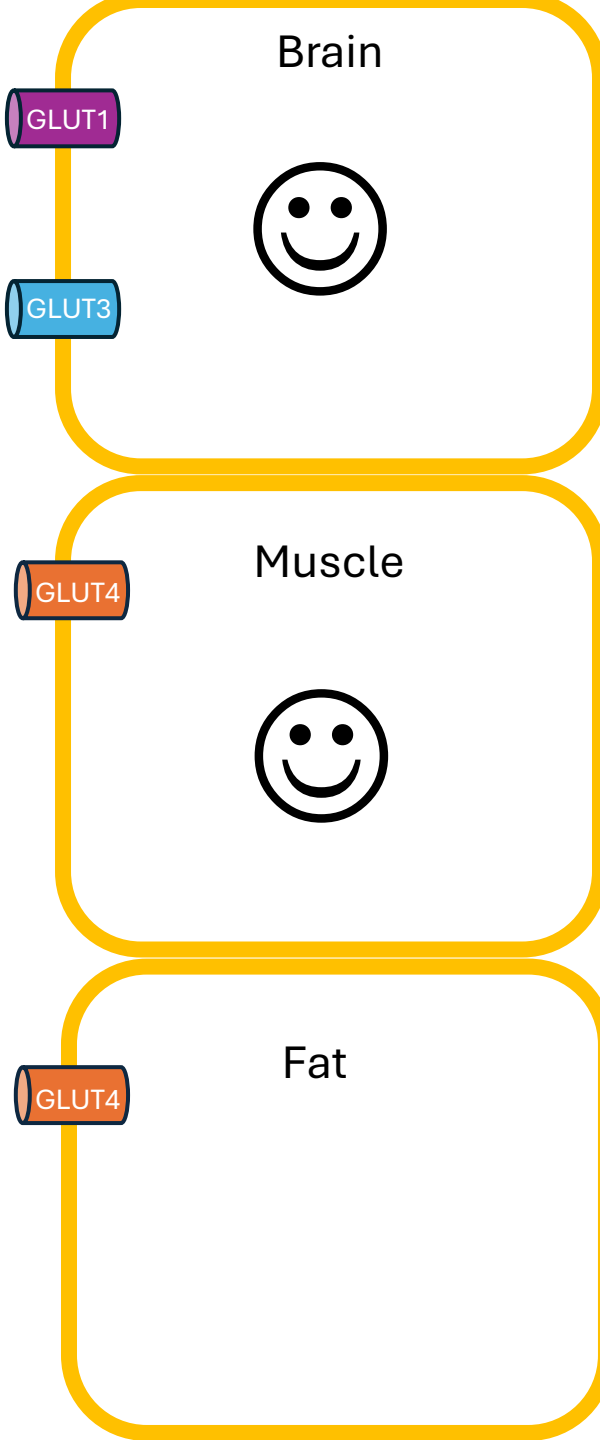
6. Sugar increases



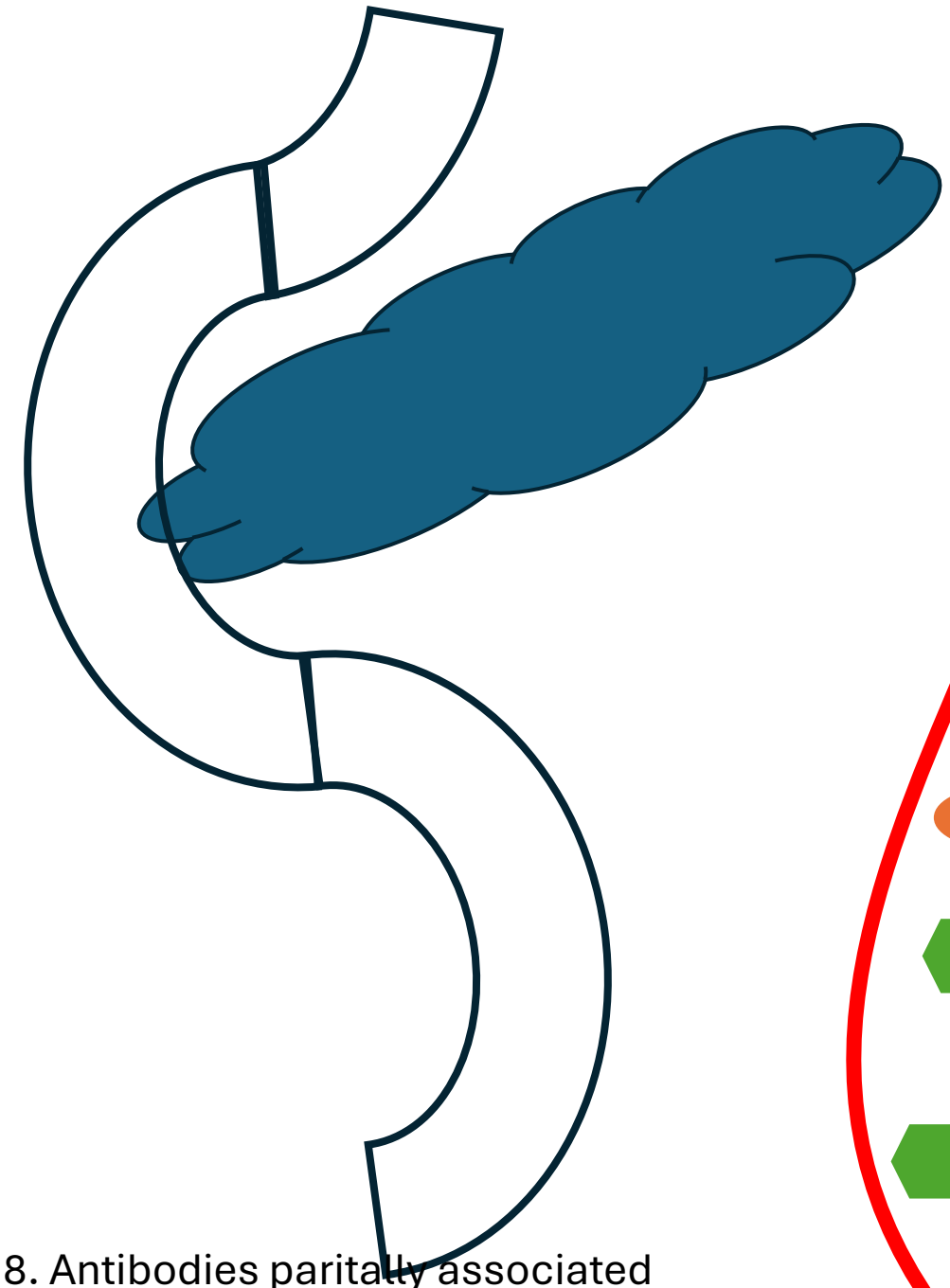


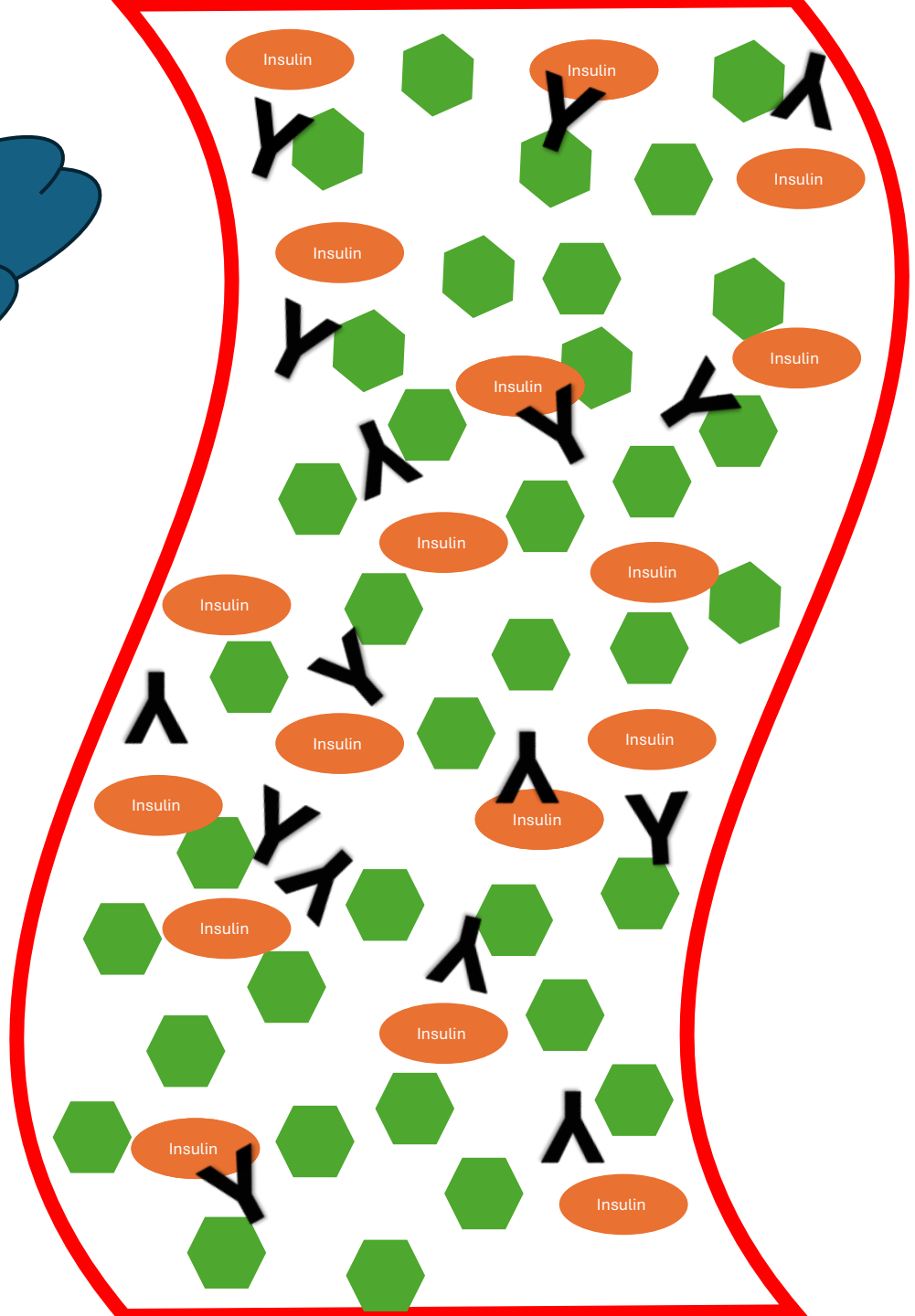


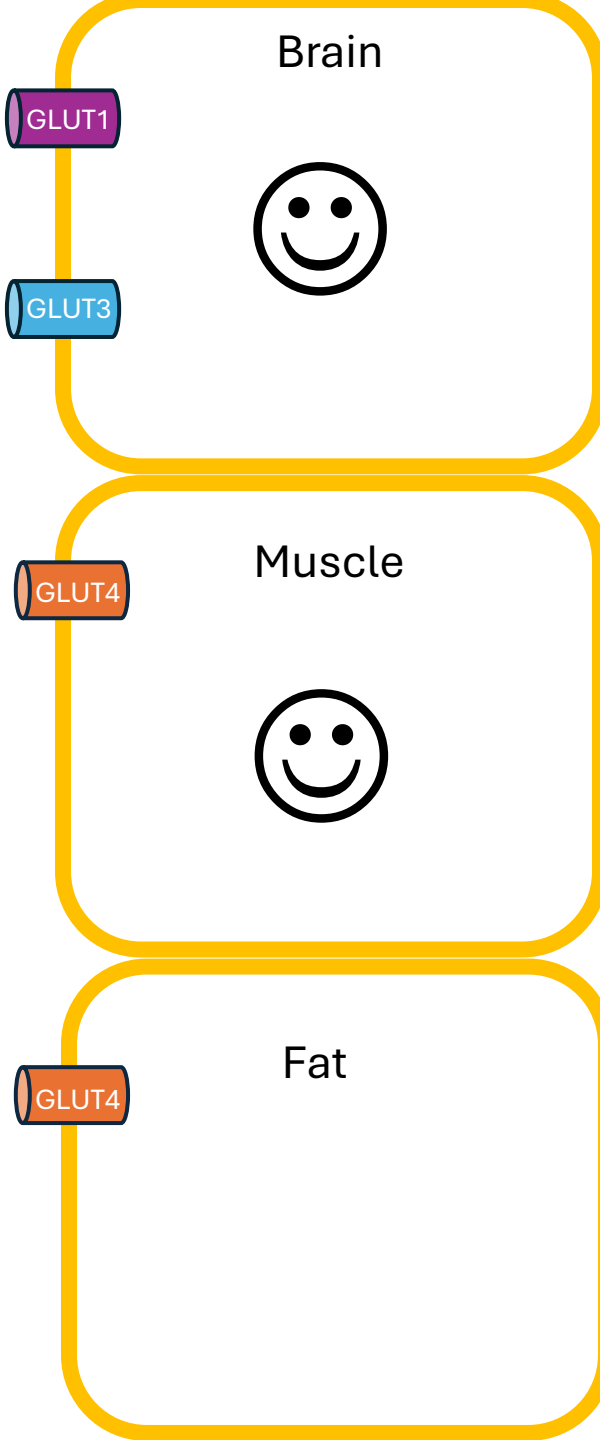




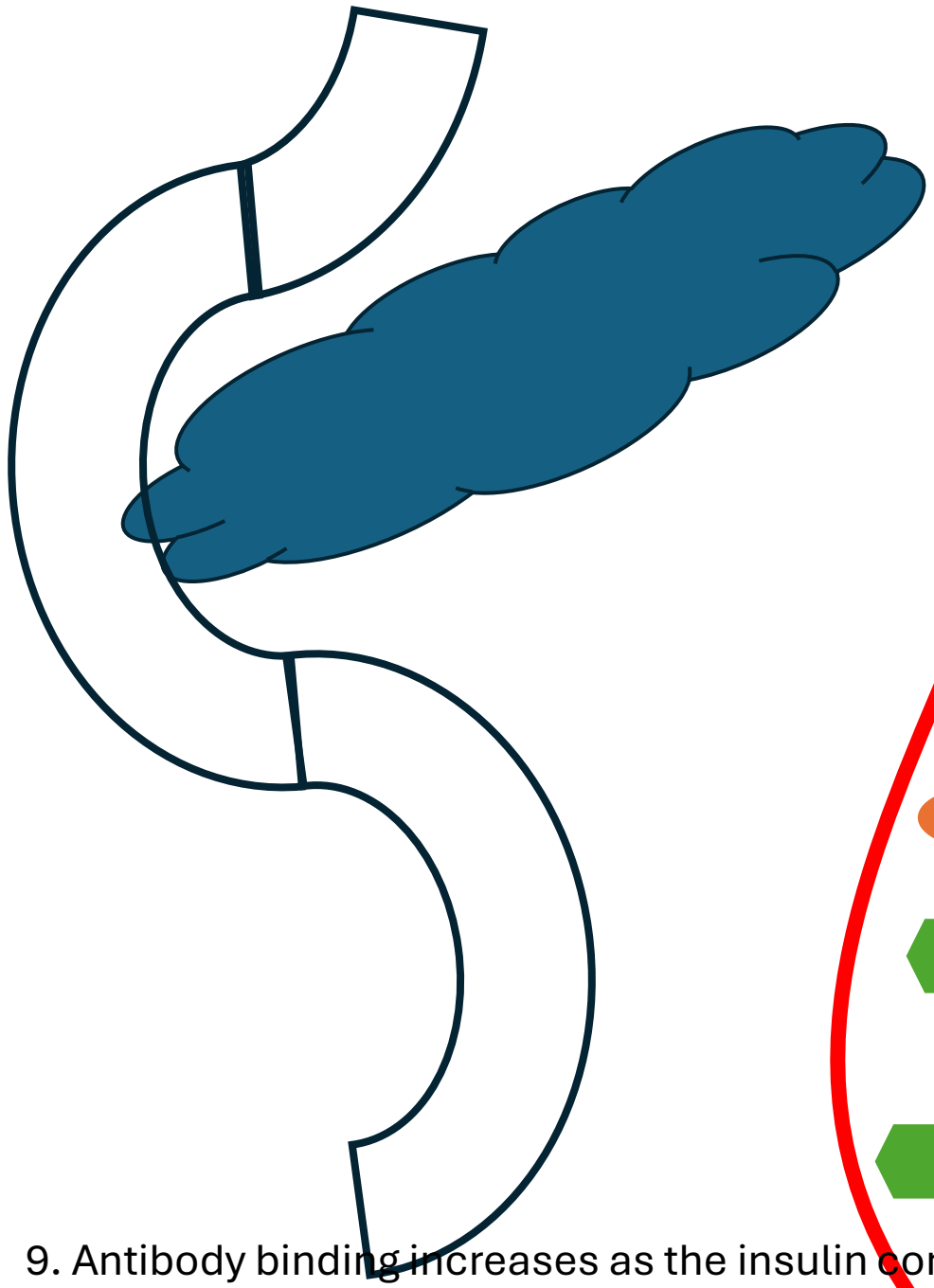
7. Sugar increases

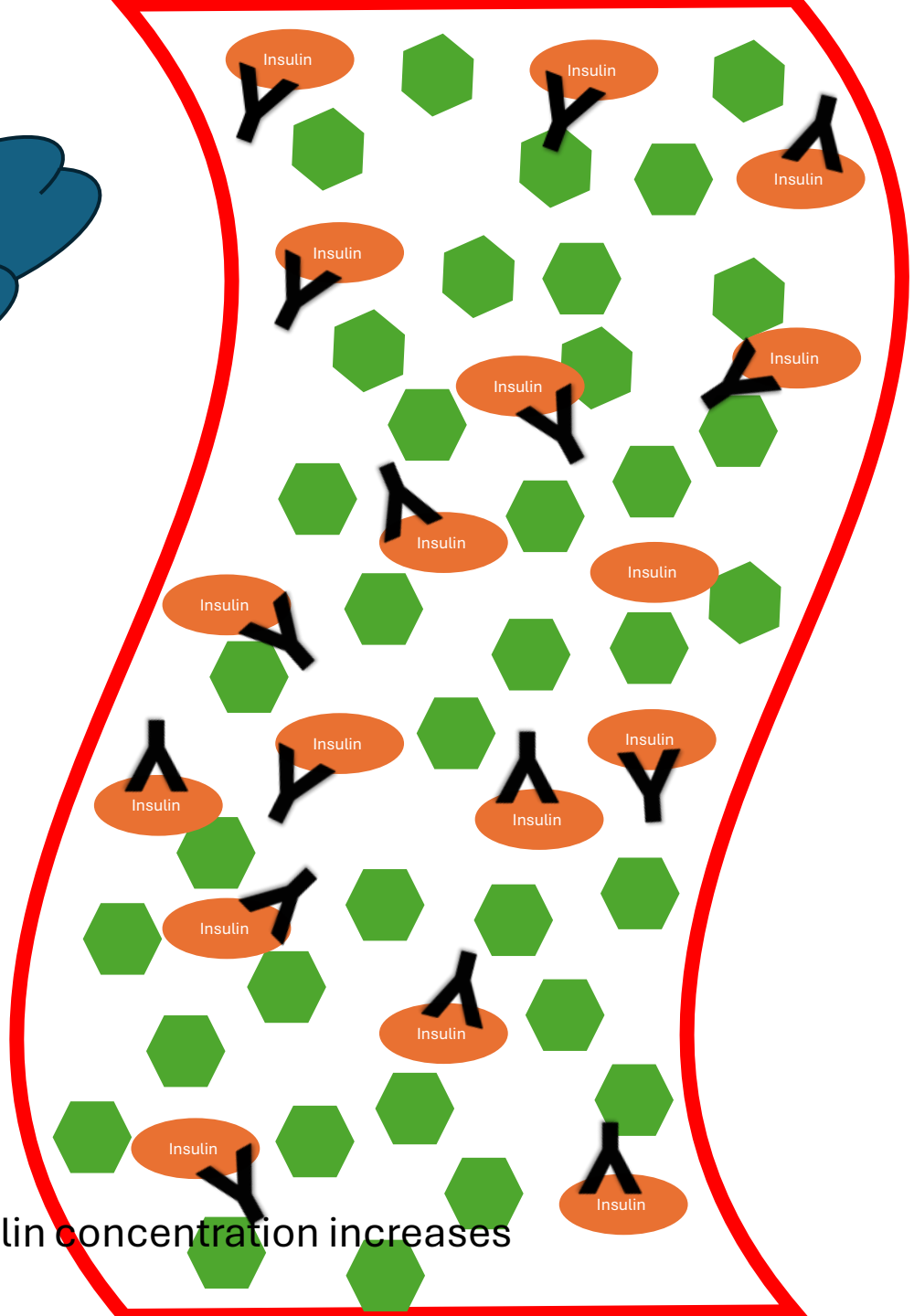


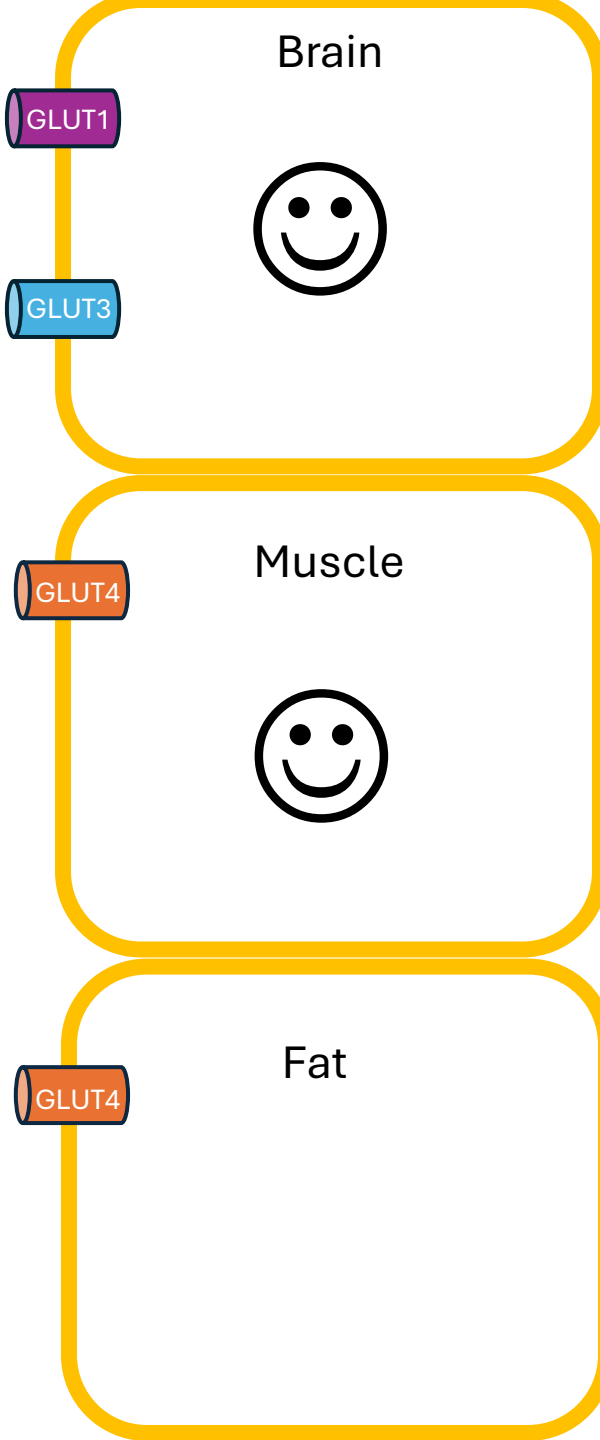




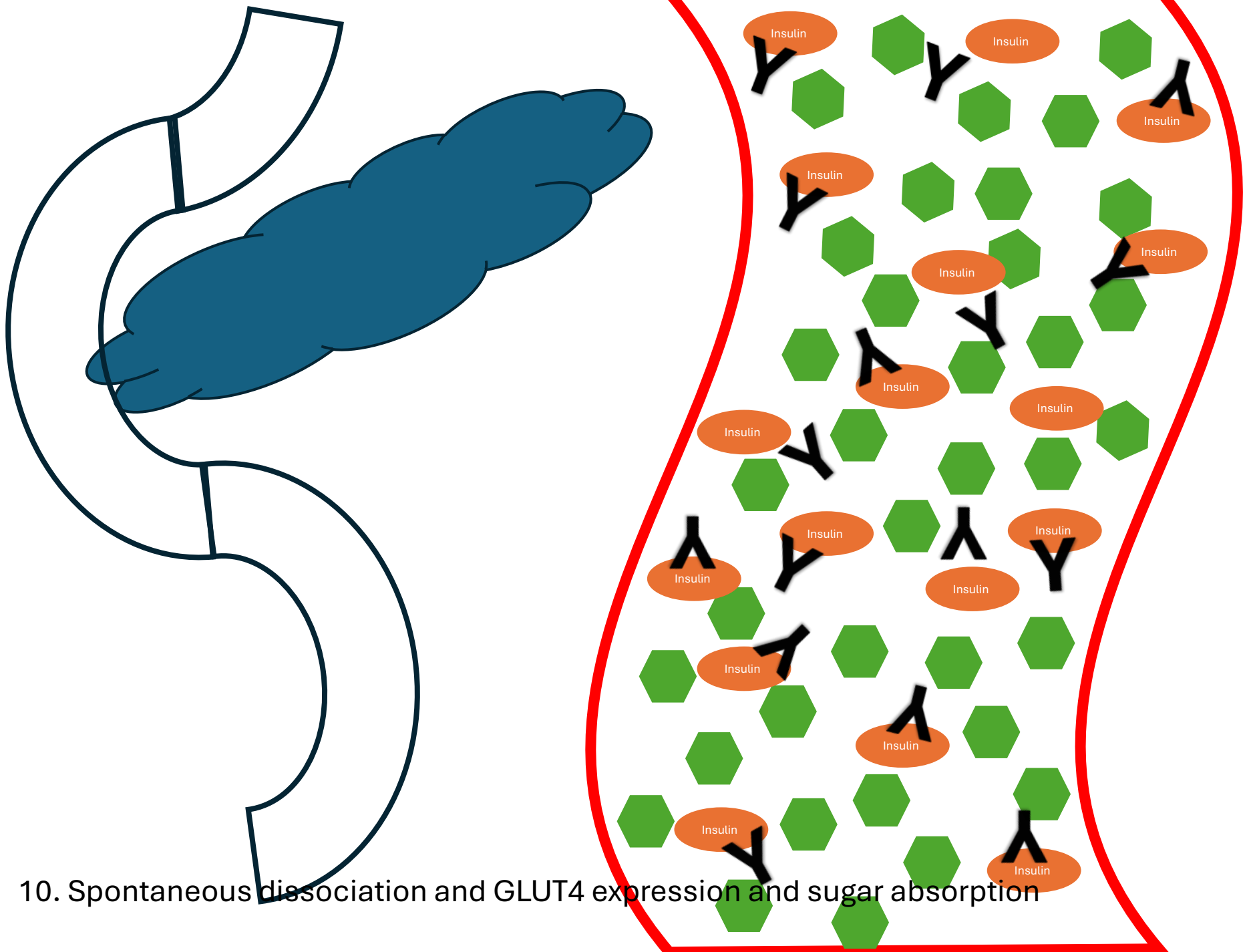
8. Antibodies paritally associated



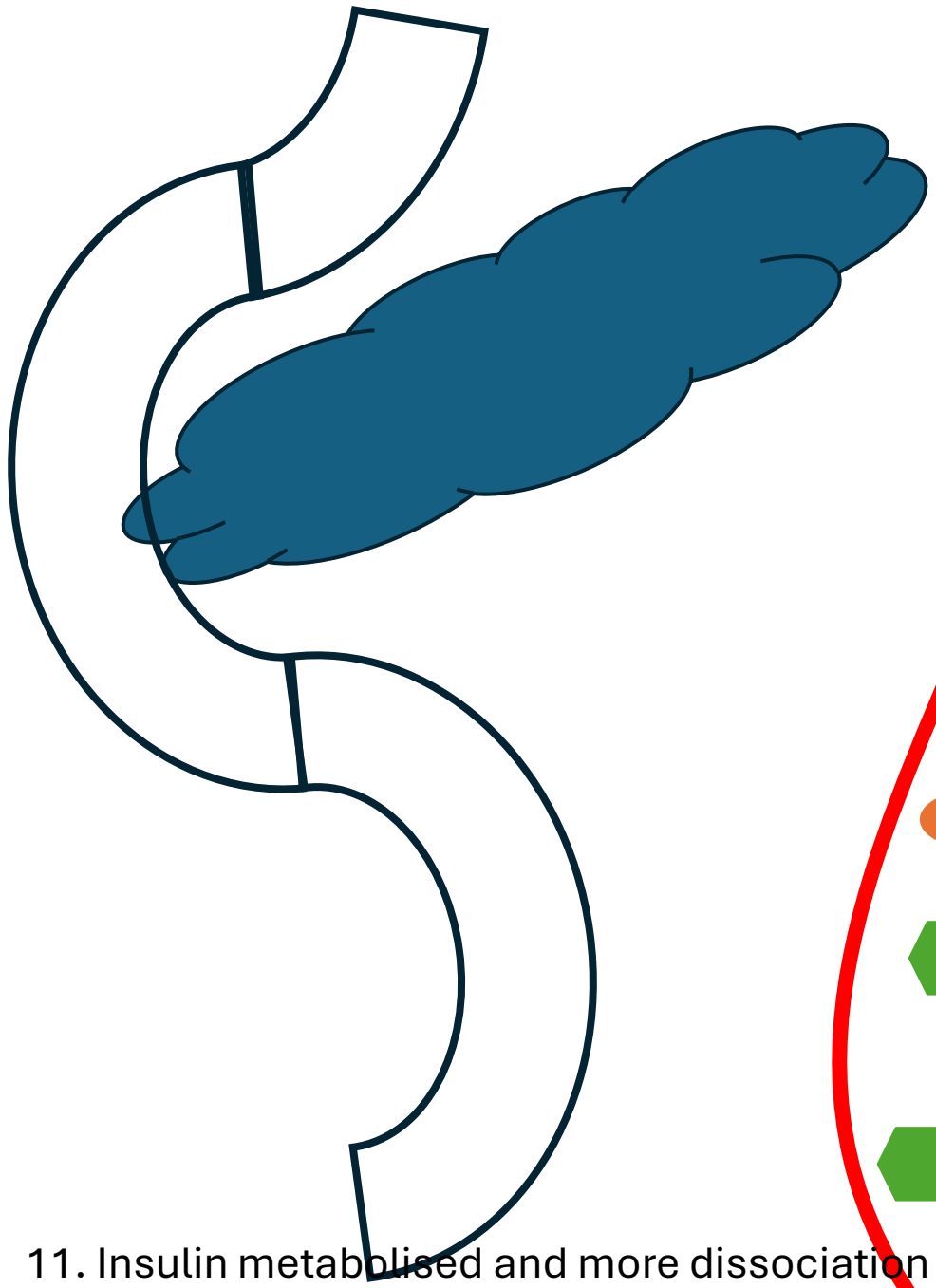


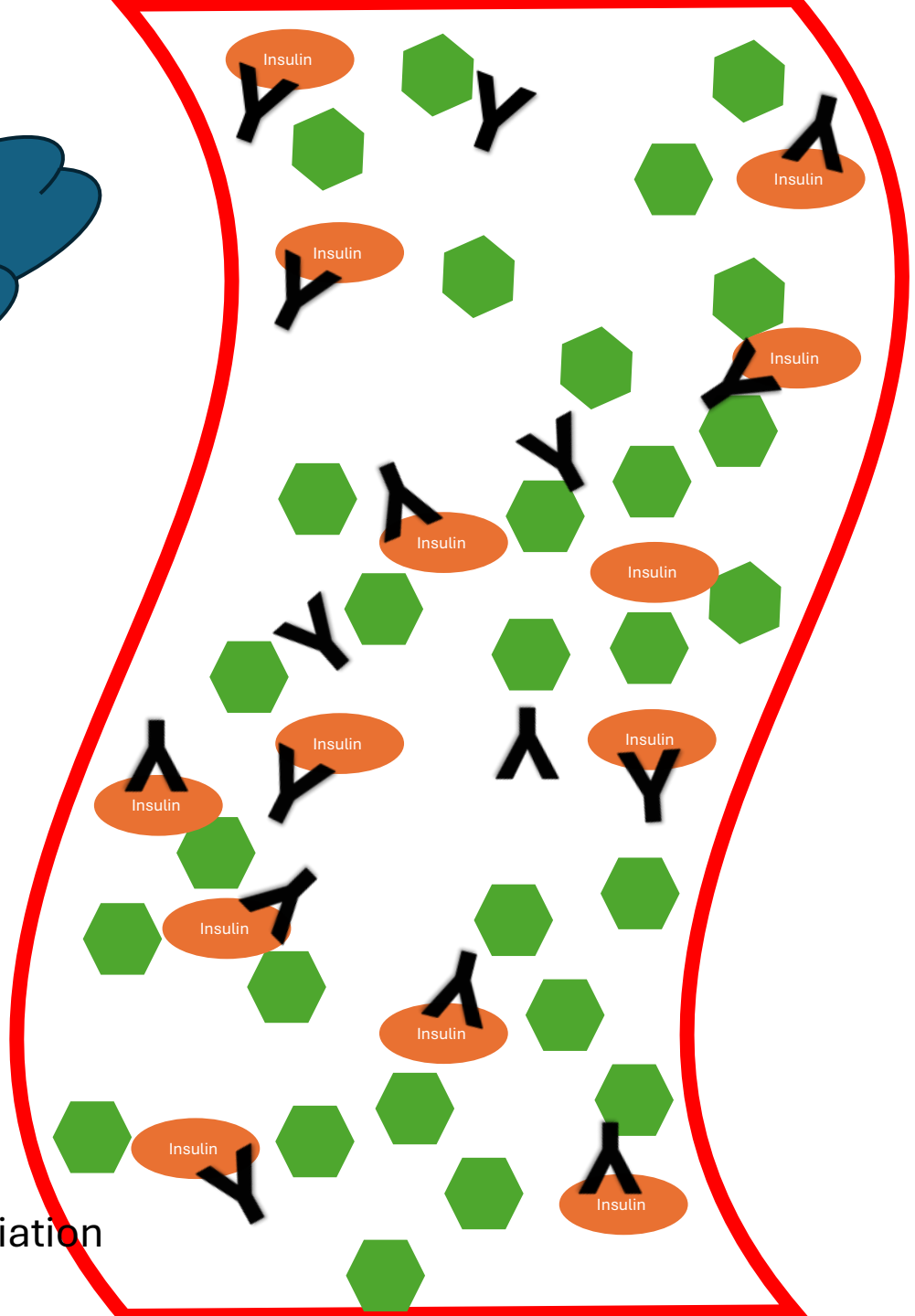


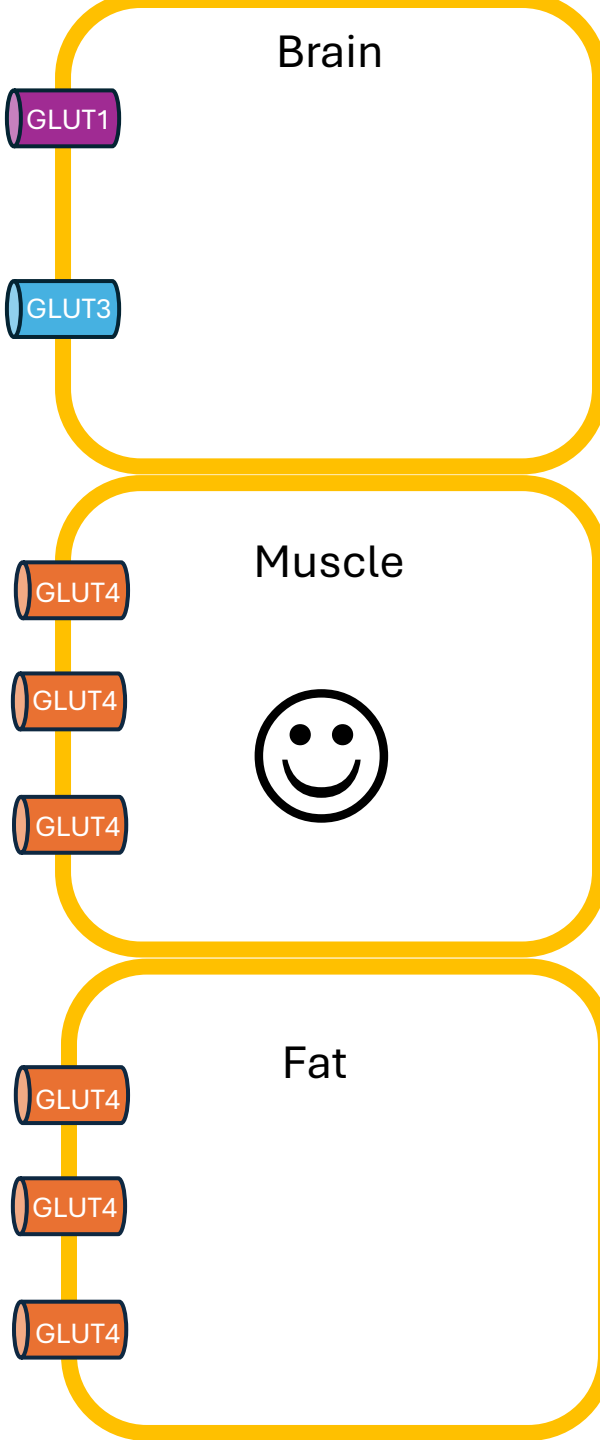
9. Antibody binding increases as the insulin concentration increases



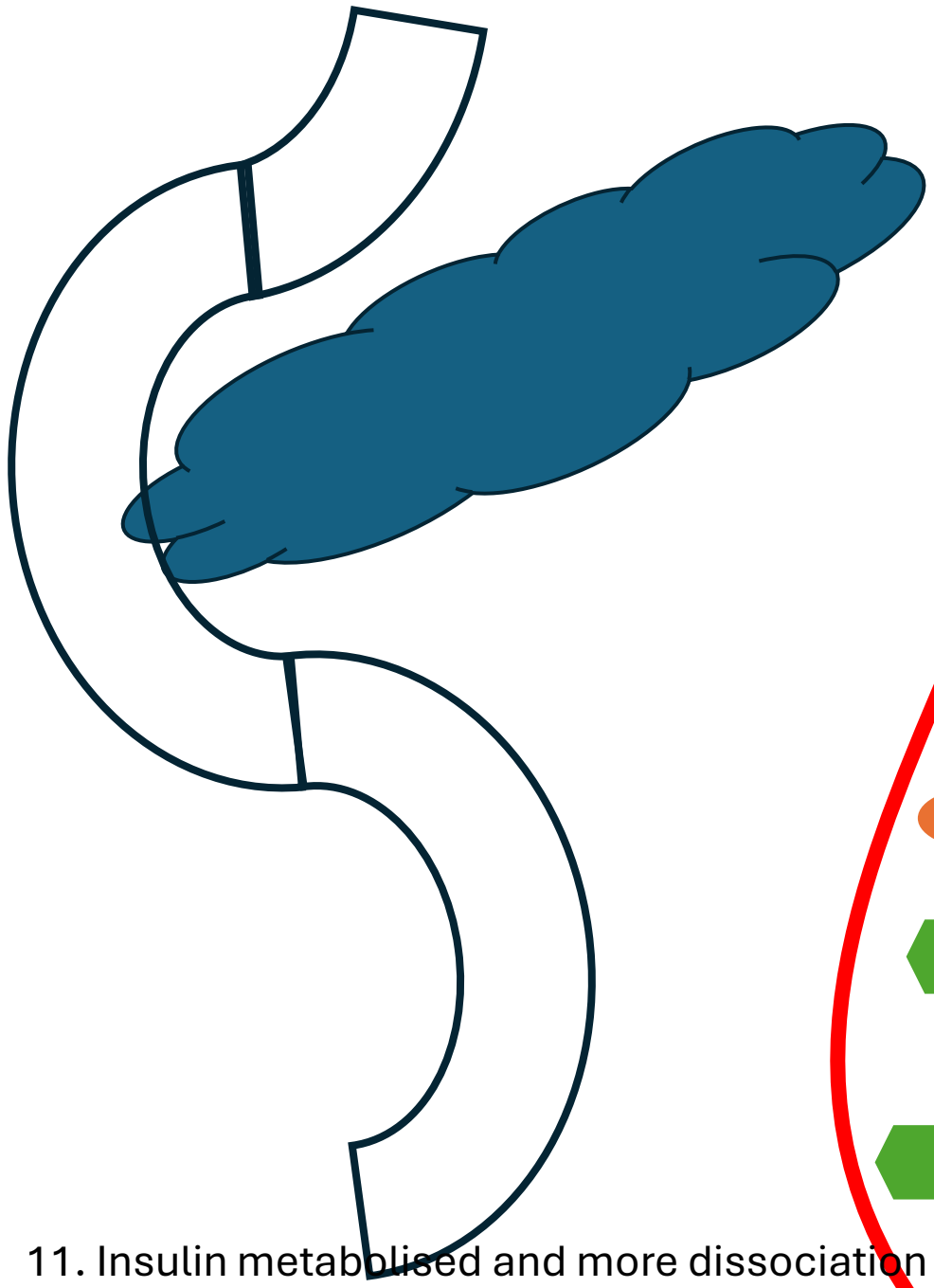
10. Spontaneous dissociation and GLUT4 expression and sugar absorption

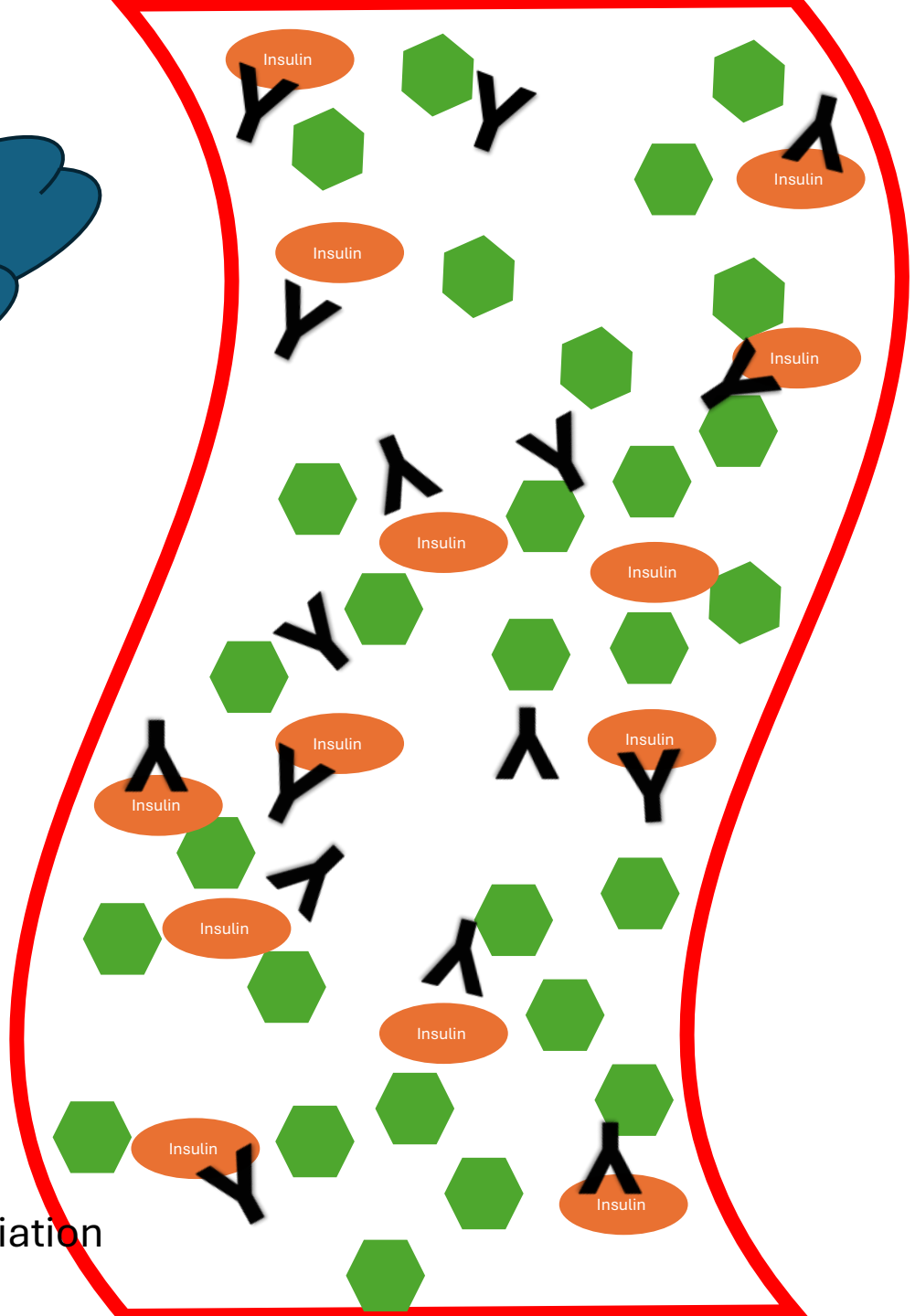


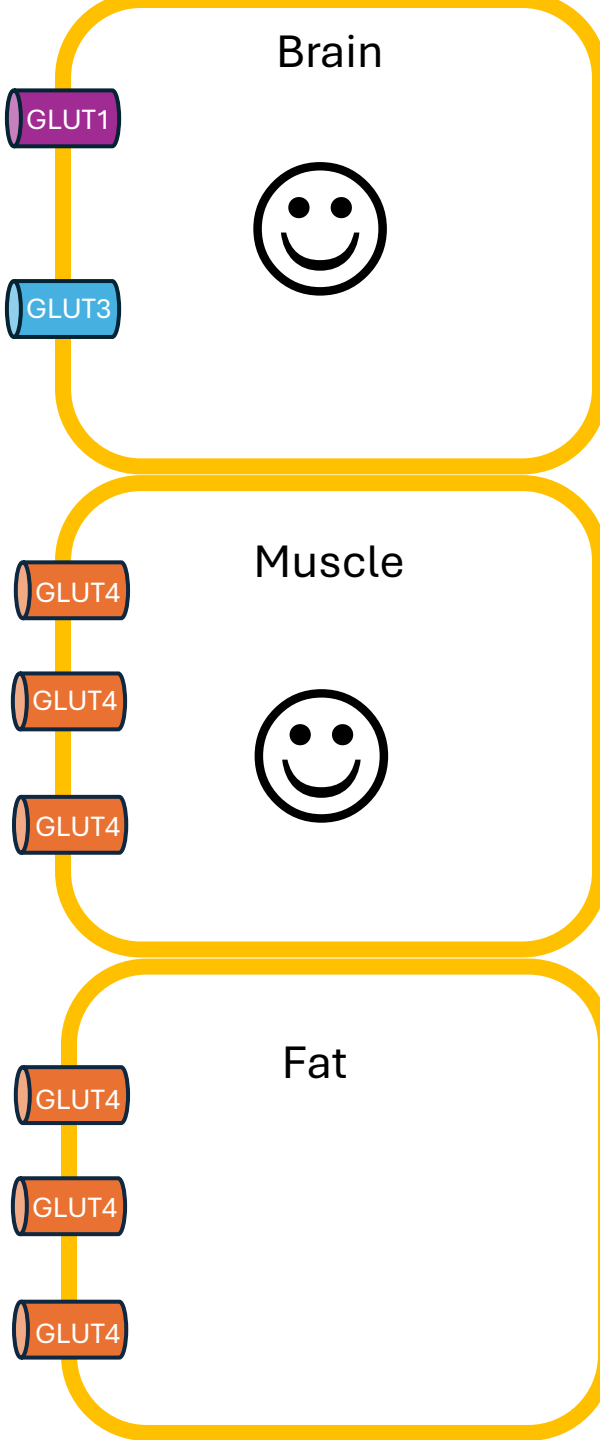




11. Insulin metabolised and more dissociation







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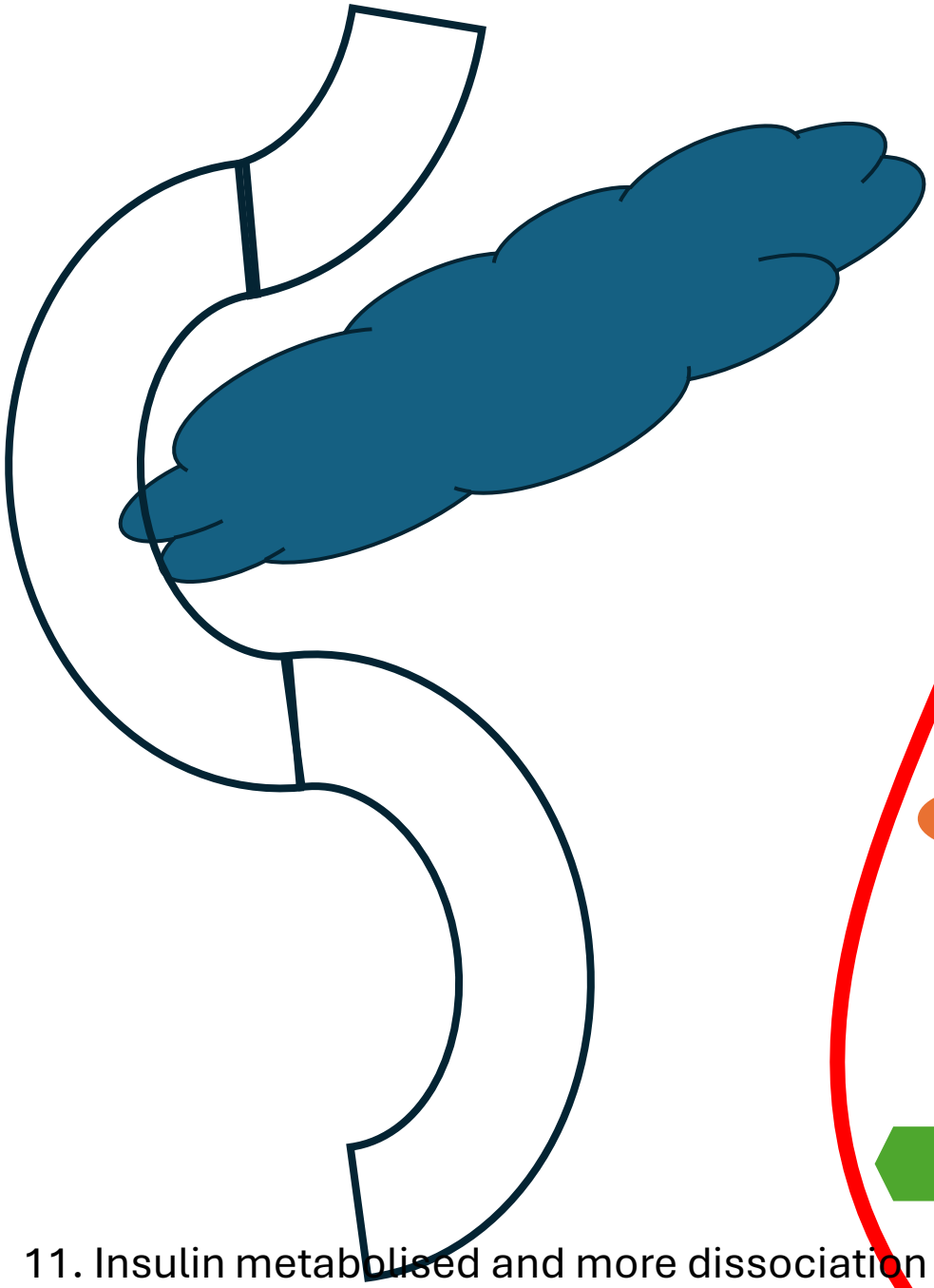
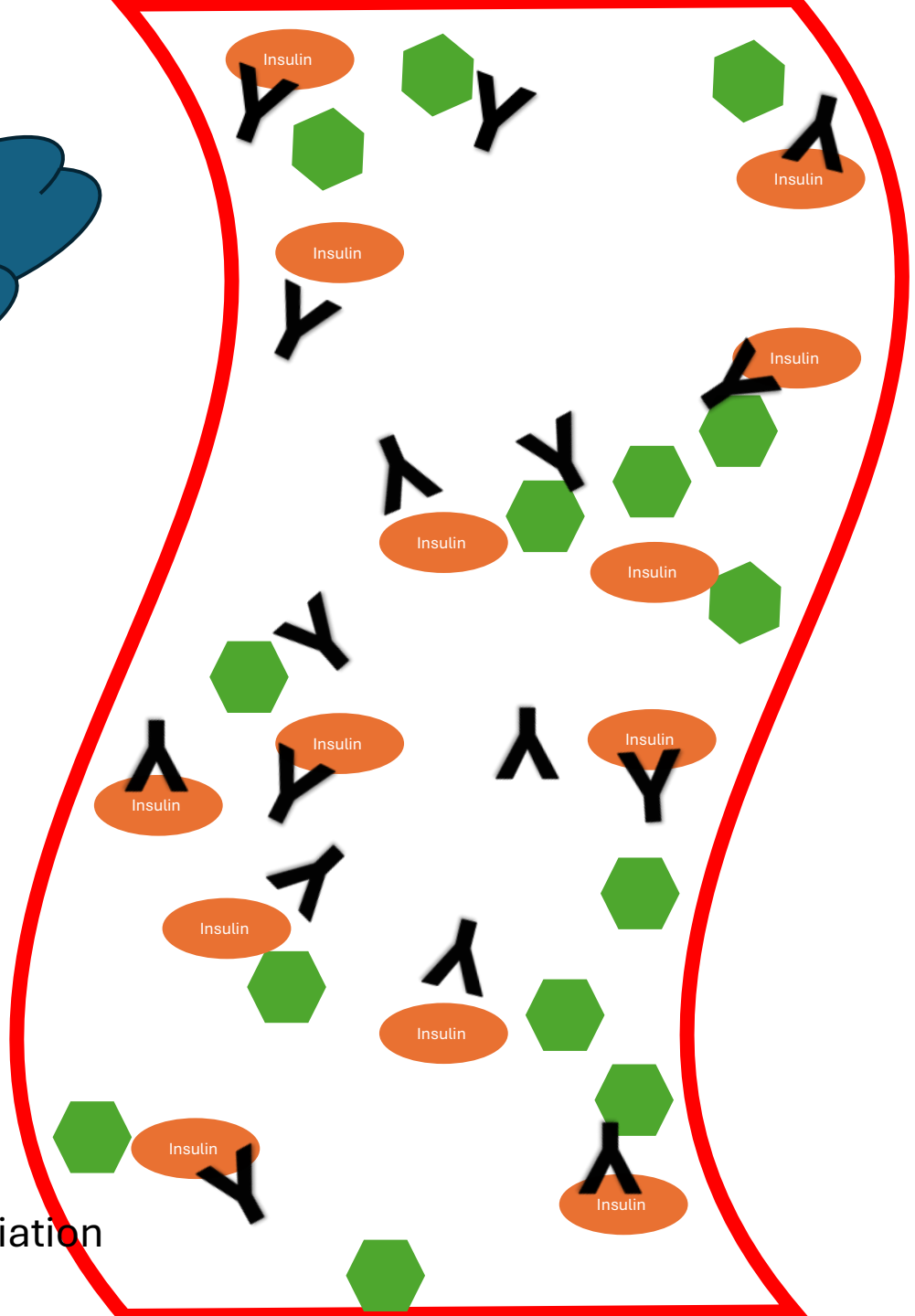
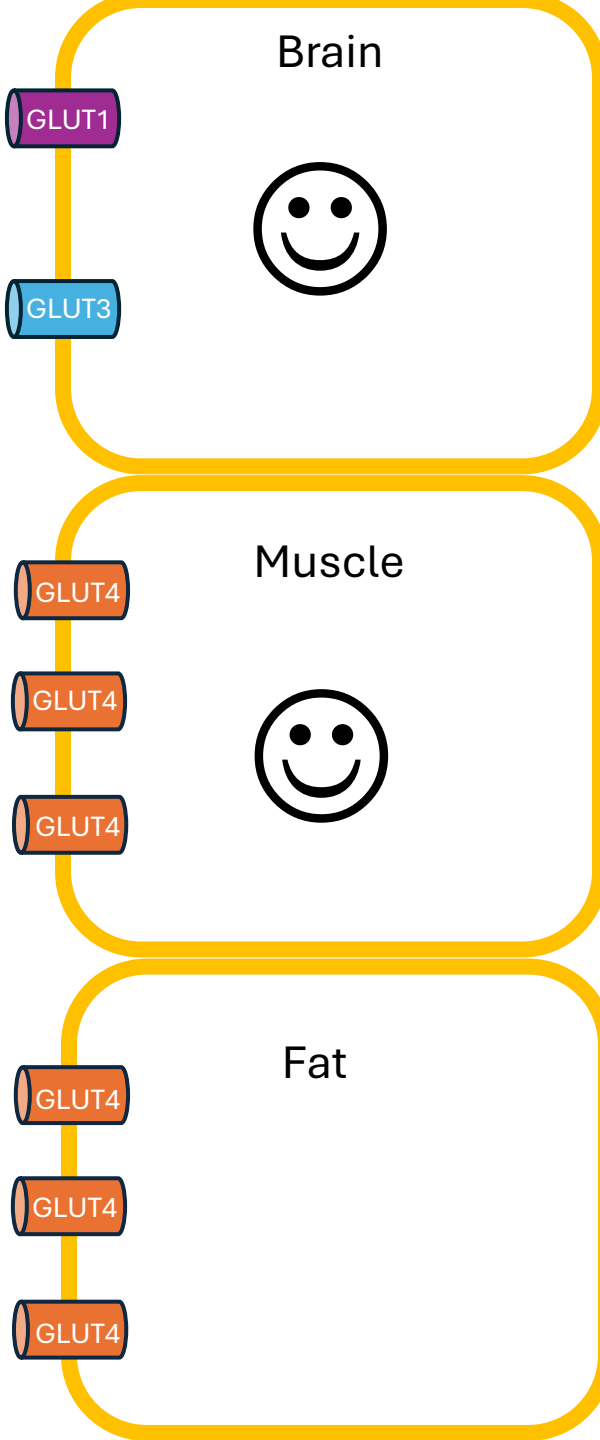
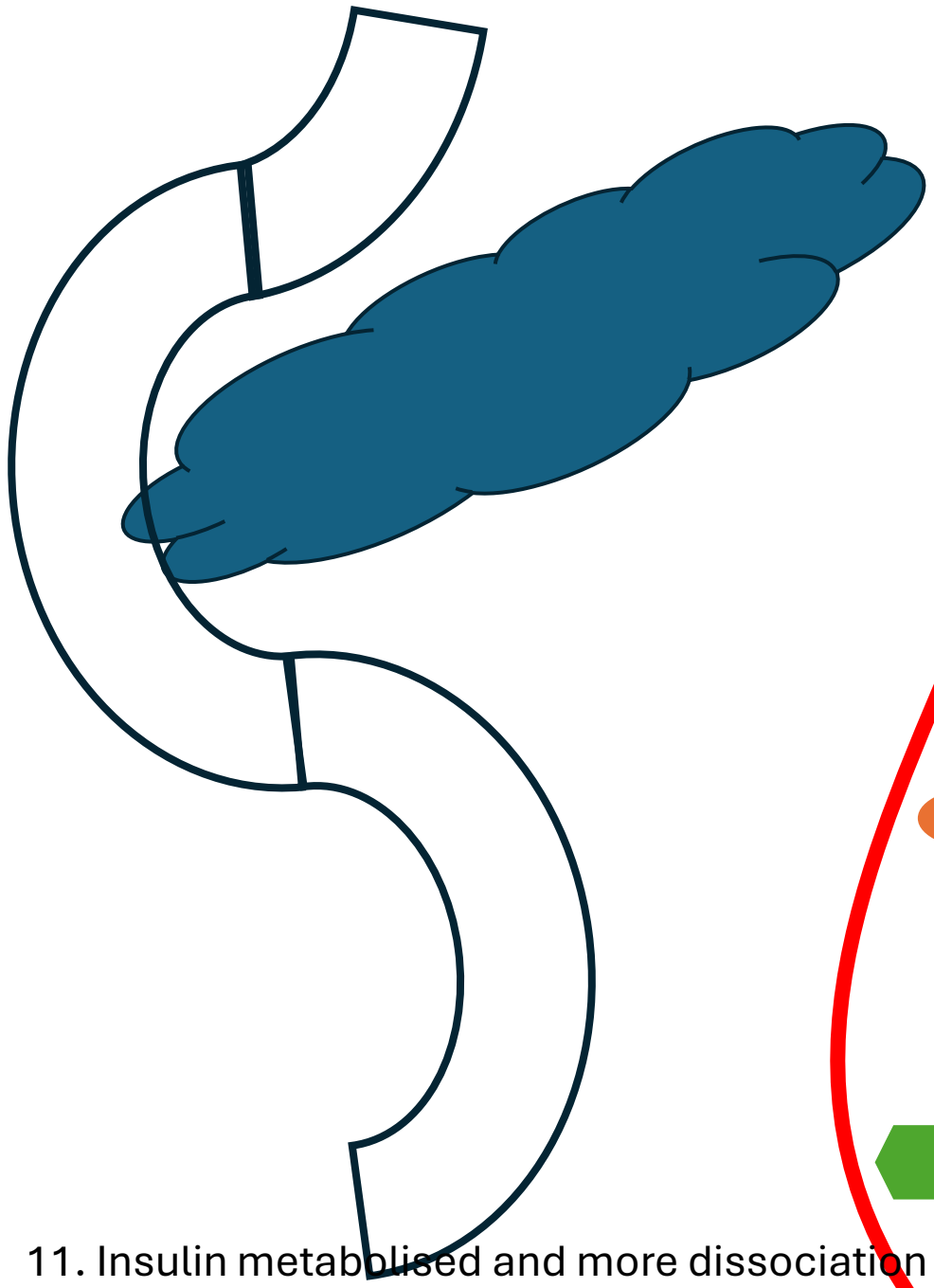
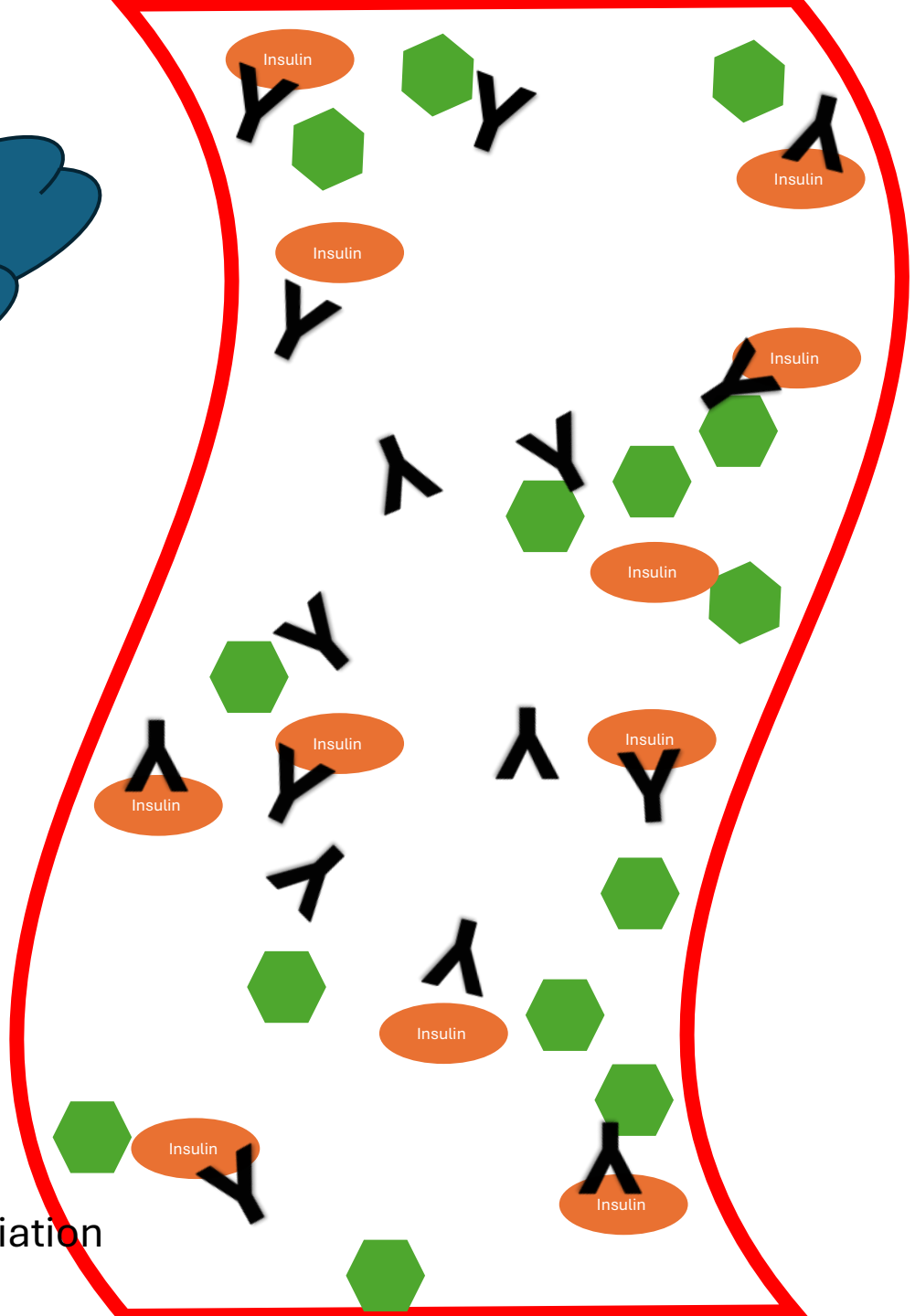


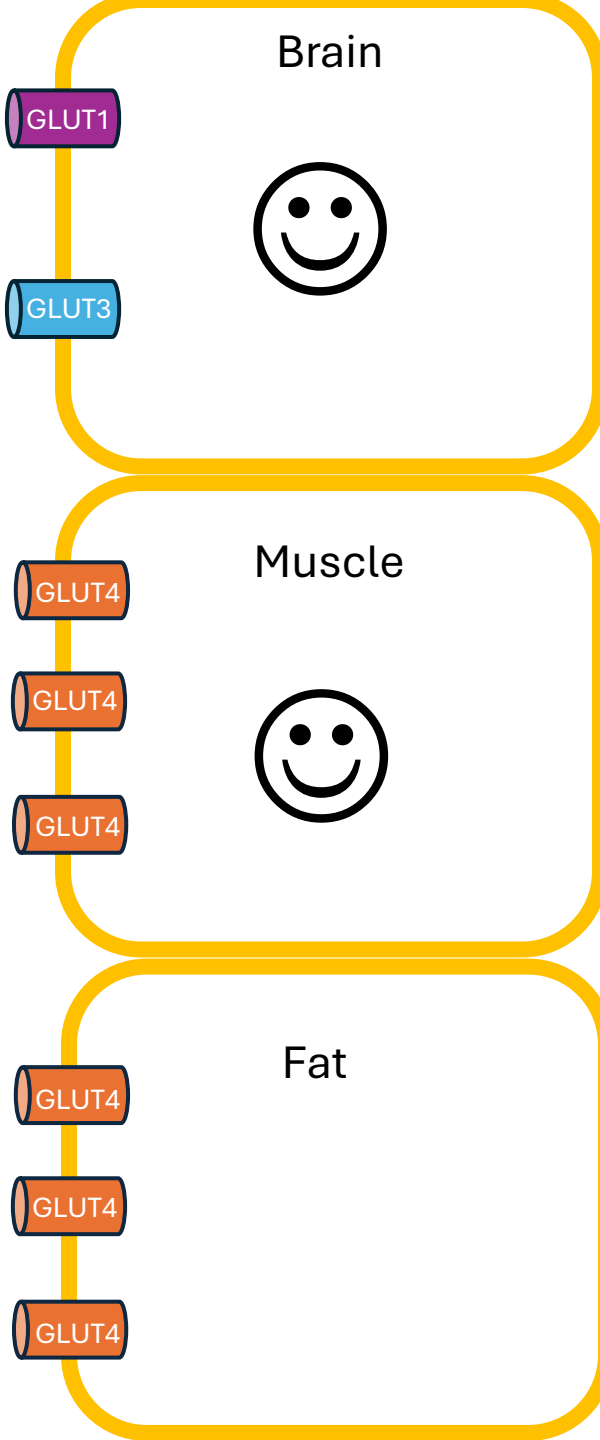




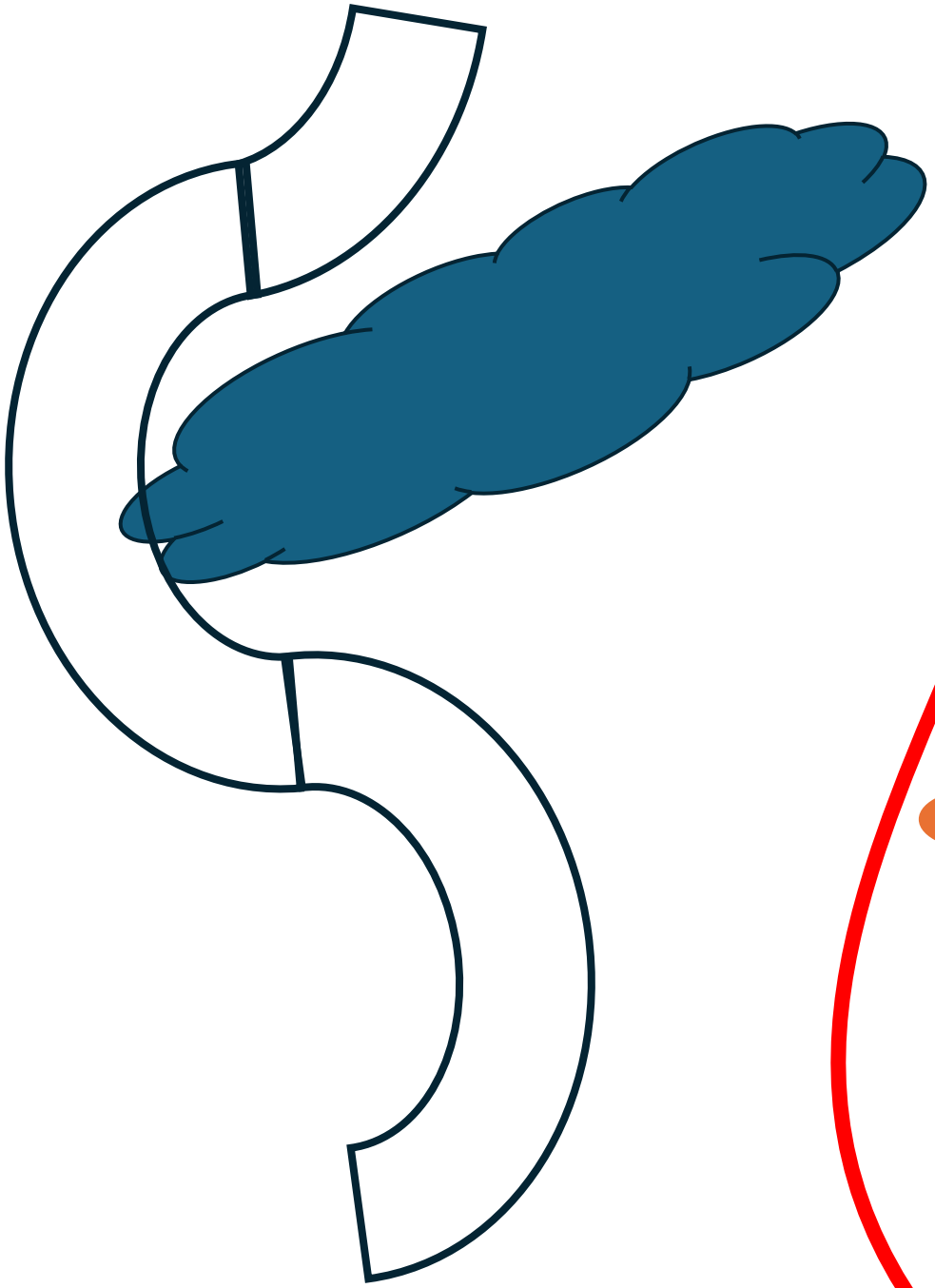
11. Insulin metabolised and more dissociation

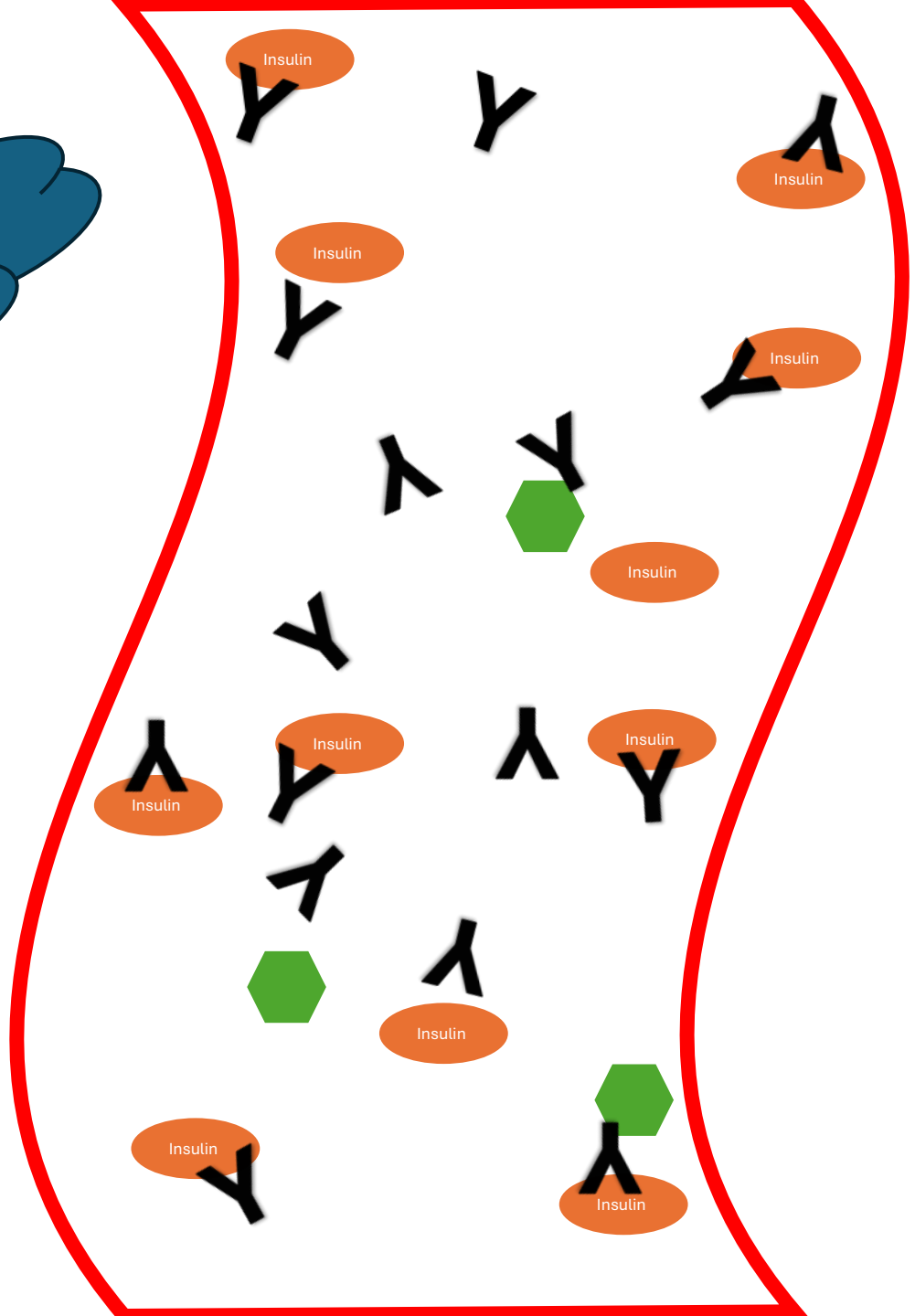


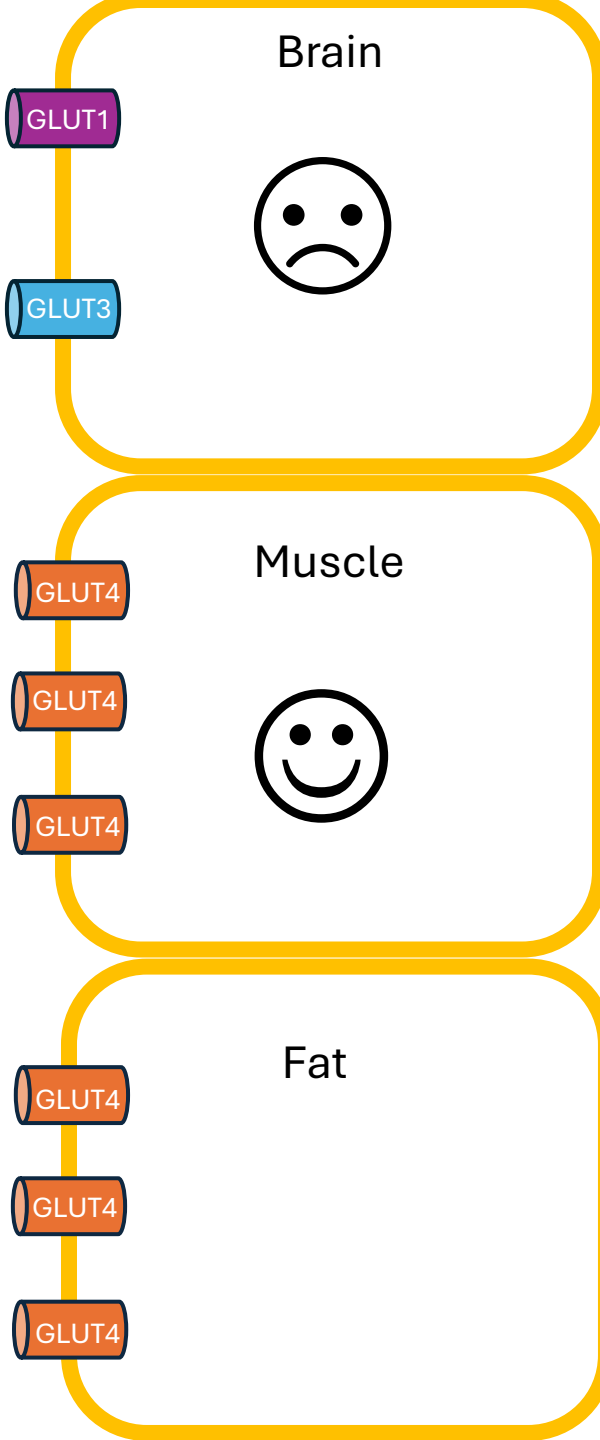




11. Insulin metabolised and more dissociation







↓ BSL → Symptomatic hypoglycaemia

So you've diagnosed IAS. Now what?

- IAS is usually a spontaneously remitting disease with up to 80% of confirmed cases resolving within 1-3 months
- Treatment:
  - Prevention of post-prandial hyperglycaemia to prevent delayed hypoglycaemia
    - Small frequent meals
    - Alpha-glucosidase inhibitors e.g. acarbose
  - Reduce antibody titres
    - Glucocorticoids
    - Azathioprine
    - Rituximab
    - Plasmapheresis
  - Reduce hyperinsulinaemia
    - Diazoxide
    - Somatostatin analogues
  - Close monitoring of BSLs
    - Continuous glucose monitors

Summary

- Insulin autoimmune syndrome is an extremely rare cause of hyperinsulinaemic hypoglycaemia
- Consider IAS in pts presenting with hypoglycaemia that have a history of recent drug changes and viral infections
- Zebras live amongst us, you just have to know how to look for them

Thank You

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