Simulating Treatment for Obesity-Induced Type II Diabetes with GLP-1 Agonist Drugs

By Eli Bullock-Papa

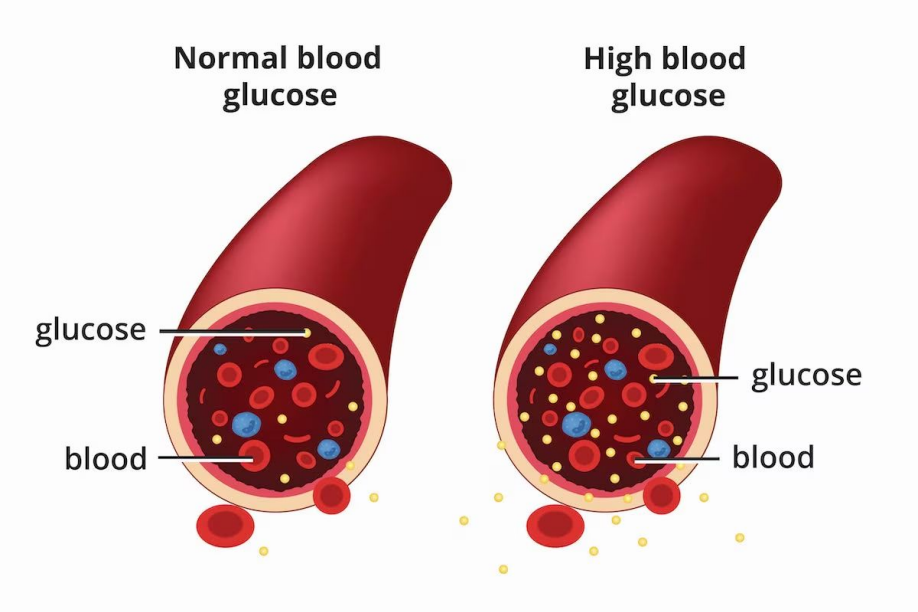
In this presentation:

1. What is diabetes
2. Overview of how it forms
3. A more complete model (we'll breeze through it this time)
4. My Work

What is Diabetes?

Diabetes Overview

Complex condition **diagnosed** by having **too much glucose in your blood**



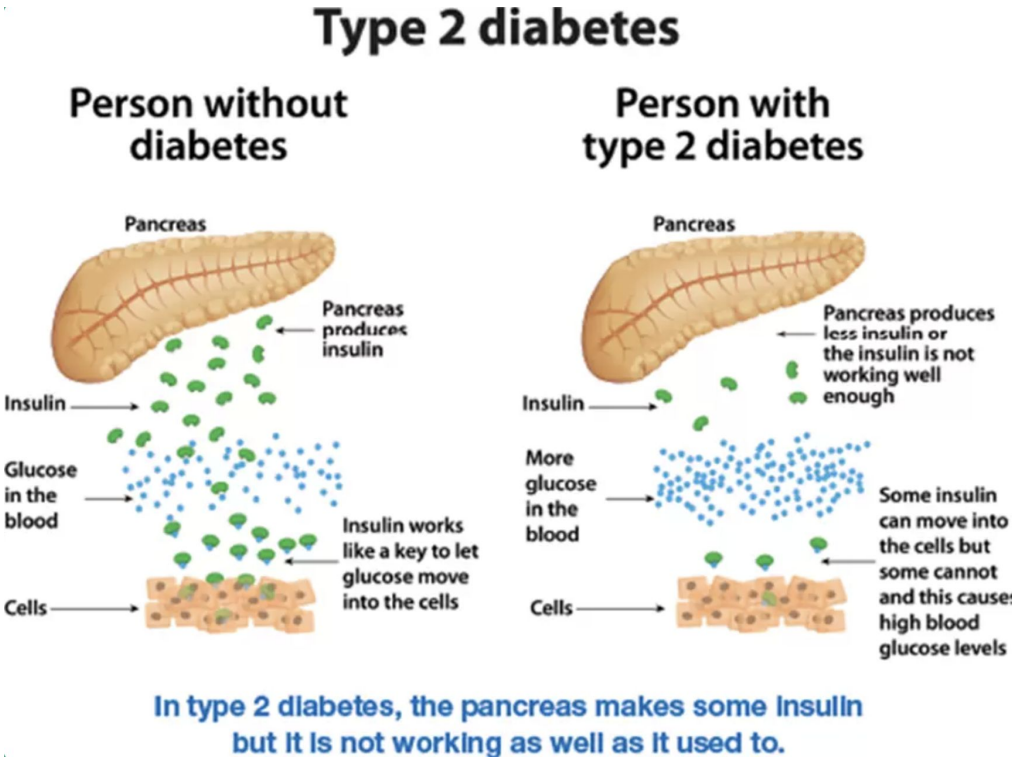
Major Components Overview

Blood Glucose: sugar your body produces when you eat.

Insulin: a hormone produced to tell cell they should absorb glucose from the bloodstream.

Beta cells: cells in the pancreas that produce insulin.

Type 2 Diabetes



How does it develop?

Diabetes Development and Obesity

Views have **changed over time** but this is the modern overview of **how we think Type 2 Diabetes (T2D) is developed in youth** (people under 40):

1. Due to the combination of diet and lack of exercise, a person starts to **gain excessive weight**, potentially leading to obesity.
2. In response to high blood sugar levels, the **pancreas produces more insulin** than normal to try to lower blood sugar levels.

Diabetes Development and Obesity

3. The body **begins to develop insulin resistance as a protective response**. It's theorized that this resistance helps shield the body's cells from excessive sugar intake and the stress of high insulin levels
4. The insulin resistance means that cells aren't taking up all of the blood glucose, and **blood sugar remains high** even with high insulin levels.
5. High blood sugar levels **keep beta cells producing insulin levels in overdrive**.
6. Over long stretches of time, this overwork causes **beta cells to begin dysfunctioning or even die**.
7. This plus continued insulin resistance means **blood glucose levels continue to spiral upwards**

A more complete model

Model source:

iScience. 2023 Nov 17; 26(11): 108324.
Published online 2023 Oct 23. doi: 10.1016/j.isci.2023.108324

PMCID: PMC10665812
PMID: 38026205

Journal Article

A data-driven computational model for obesity-driven diabetes onset and remission through weight loss

Vehpi Yildirim,[1,2,9,*] Vivek M. Sheraton,[2,3,4] Ruud Brands,[5,6] Loes Crielaard,[1,2] Rick Quax,[2,3] Natal A.W. van Riel,[7,8] Karien Stronks,[1,2] Mary Nicolaou,[1,2] and Peter M.A. Sloot[2,3]

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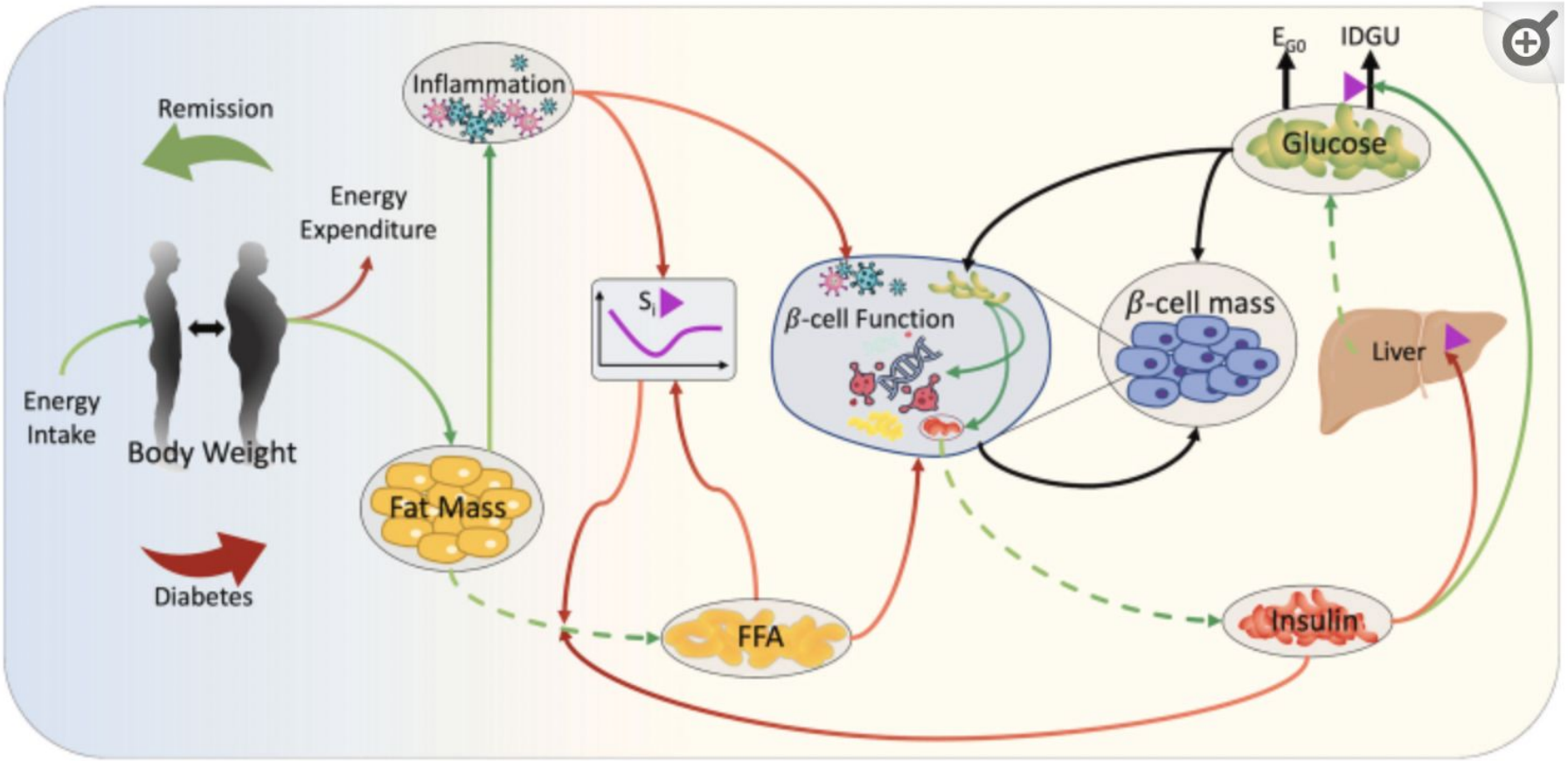
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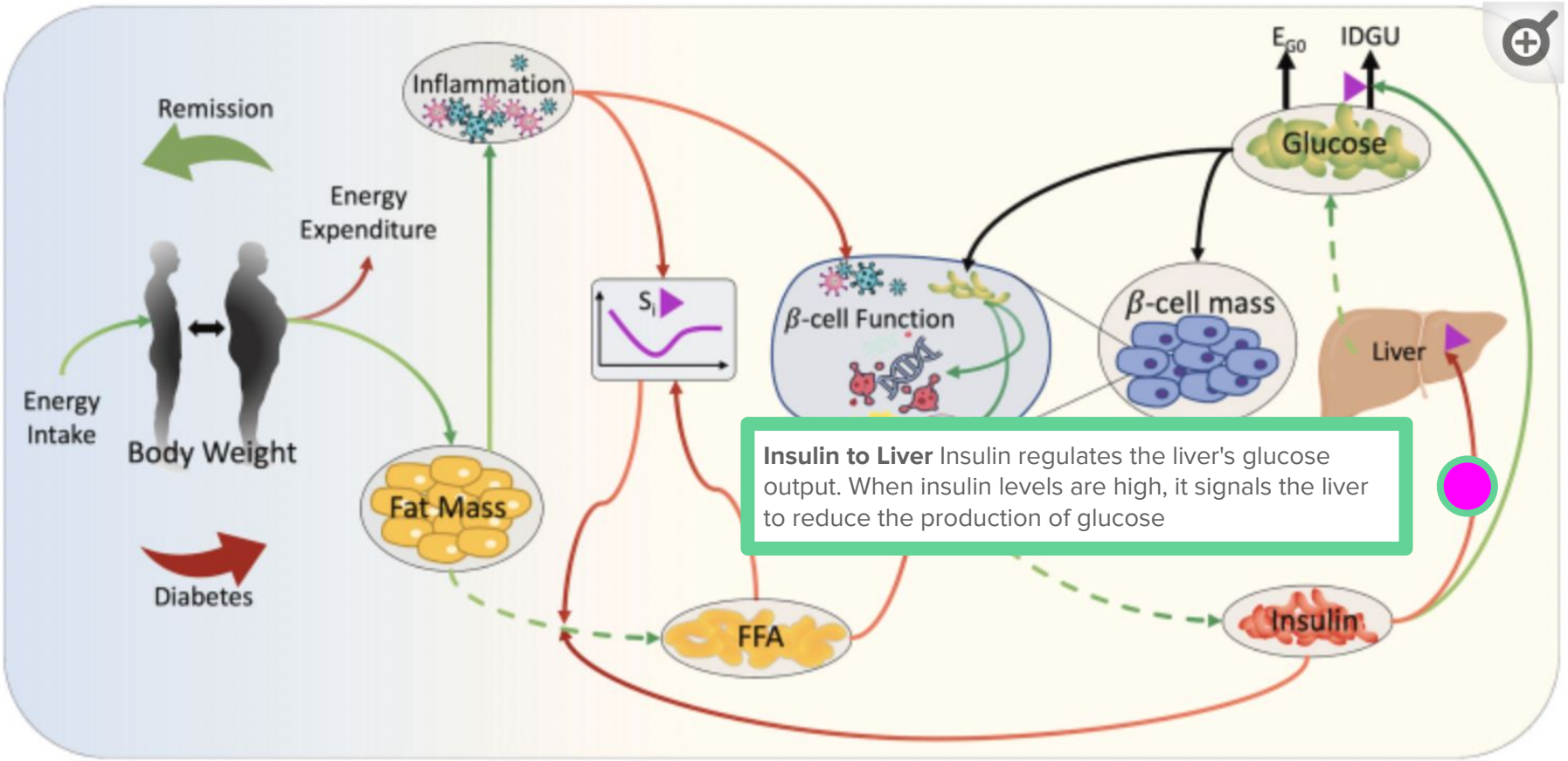
β-cell Function
β-cell mass
Liver
Energy Intake
Body Weight
Fat Mass
Diabetes
FFA
Insulin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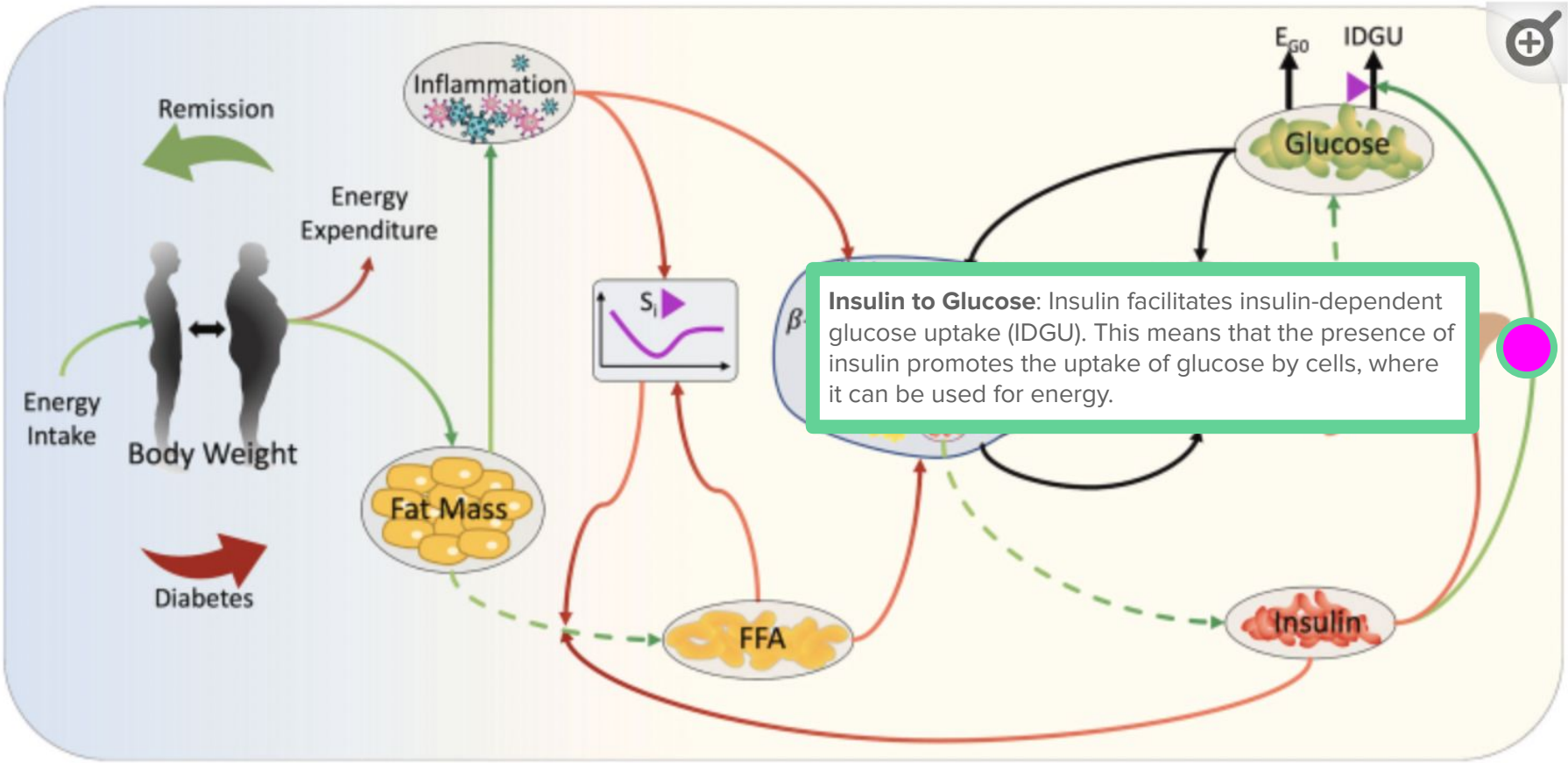
Insulin to Liver Insulin regulates the liver's glucose output. When insulin levels are high, it signals the liver to reduce the production of glucose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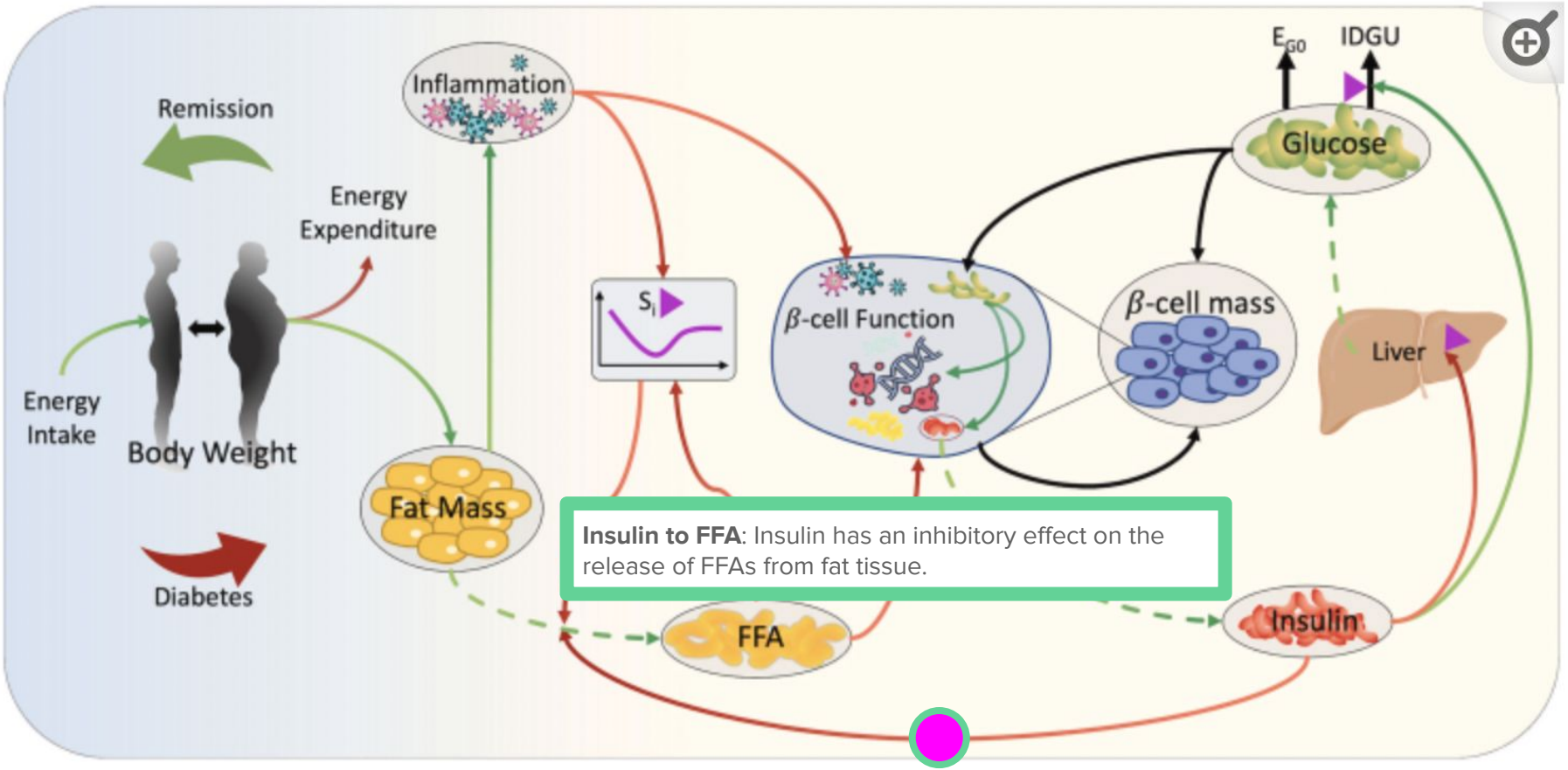
Insulin
Insulin to Glucose: Insulin facilitates insulin-dependent glucose uptake (IDGU). This means that the presence of insulin promotes the uptake of glucose by cells, where it can be used for energy.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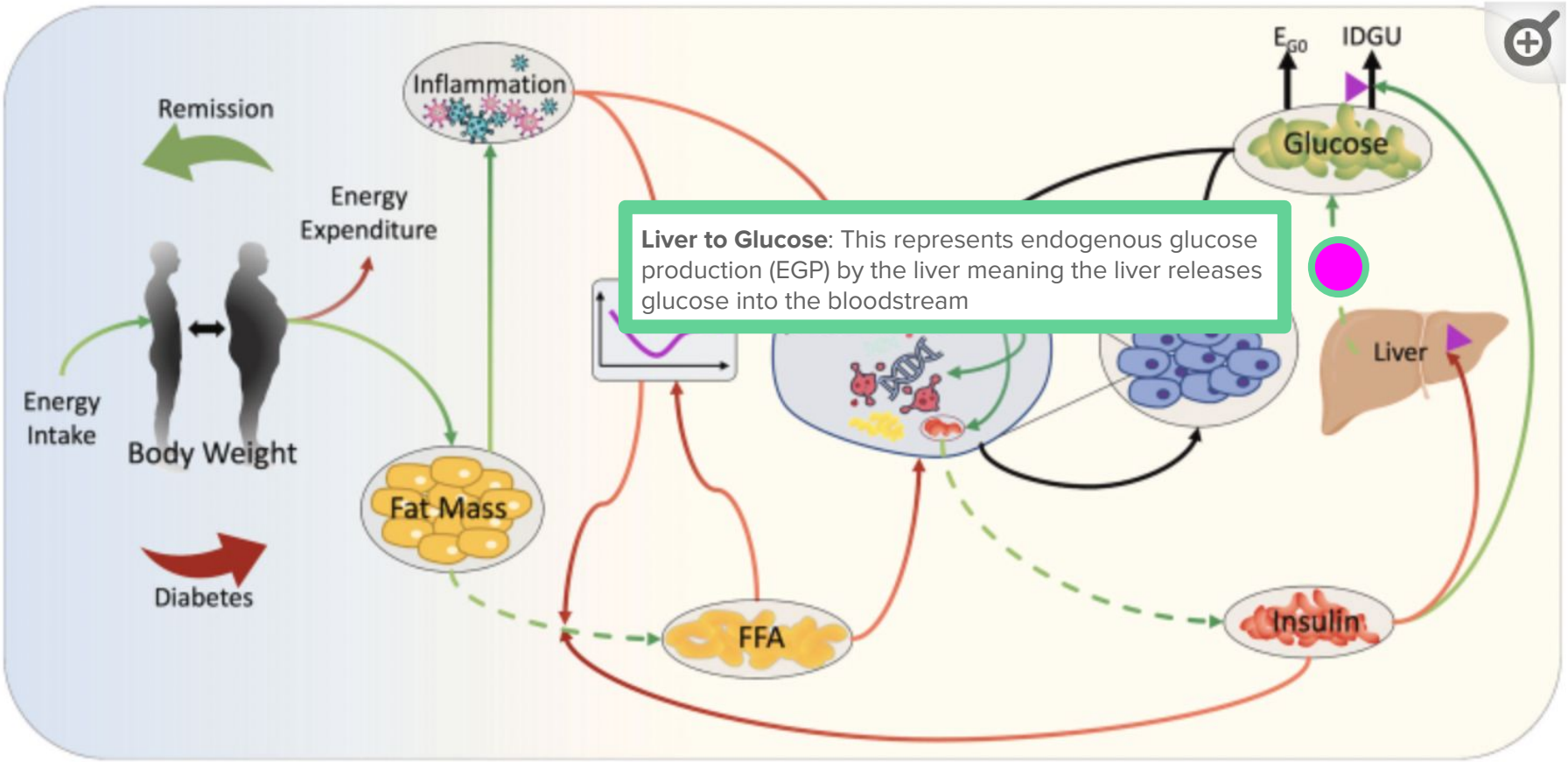
Insulin to FFA: Insulin has an inhibitory effect on the release of FFAs from fat tissue.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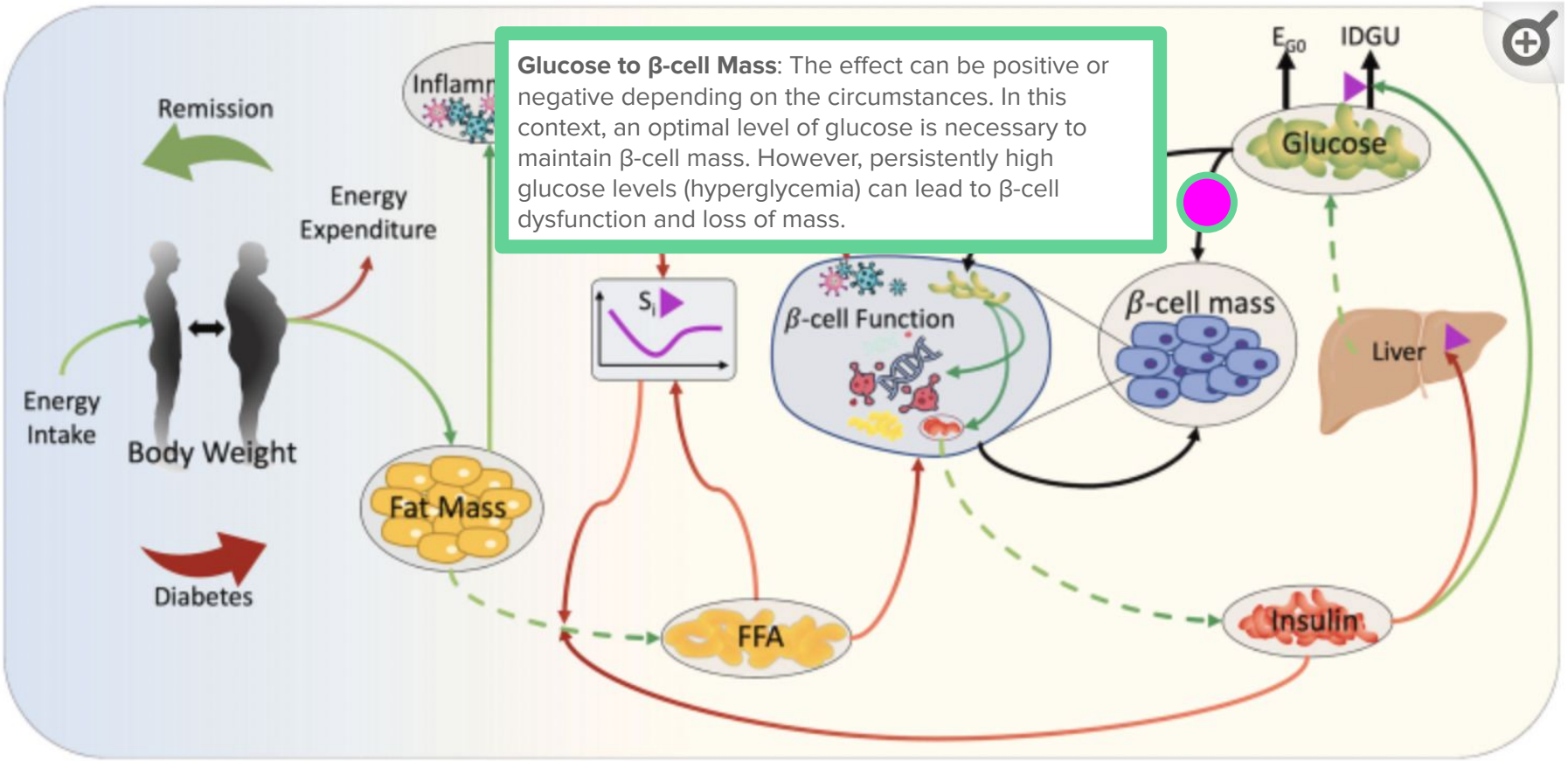
Liver to Glucose: This represents endogenous glucose production (EGP) by the liver meaning the liver releases glucose into the bloodstream


Glucose to β-cell Mass: The effect can be positive or negative depending on the circumstances. In this context, an optimal level of glucose is necessary to maintain β-cell mass. However, persistently high glucose levels (hyperglycemia) can lead to β-cell dysfunction and loss of mass.
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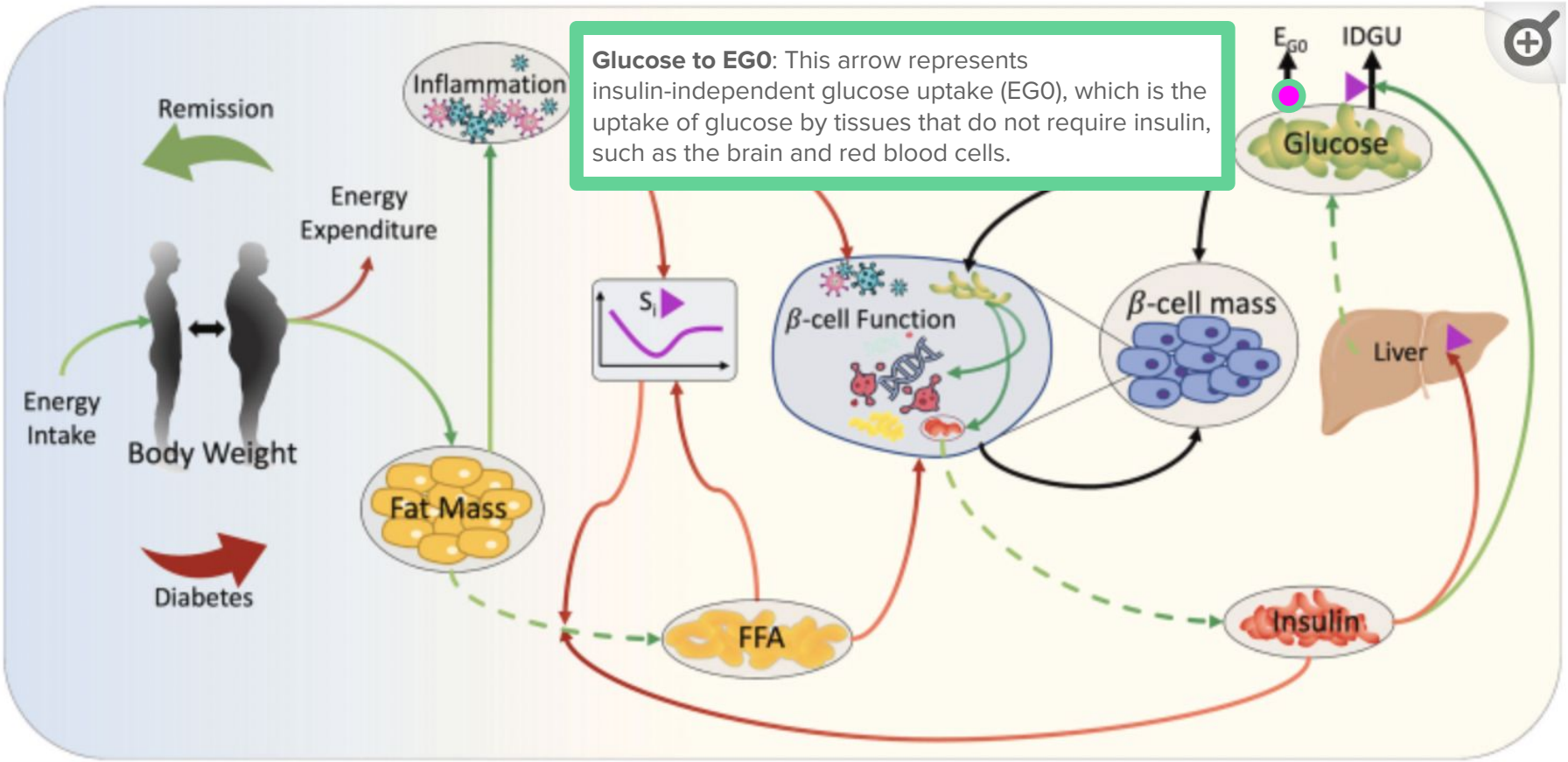
Glucose to EG0: This arrow represents insulin-independent glucose uptake (EG0), which is the uptake of glucose by tissues that do not require insulin, such as the brain and red blood cells.
Remission
Inflammation
Energy Expenditure
Energy Intake
Body Weight
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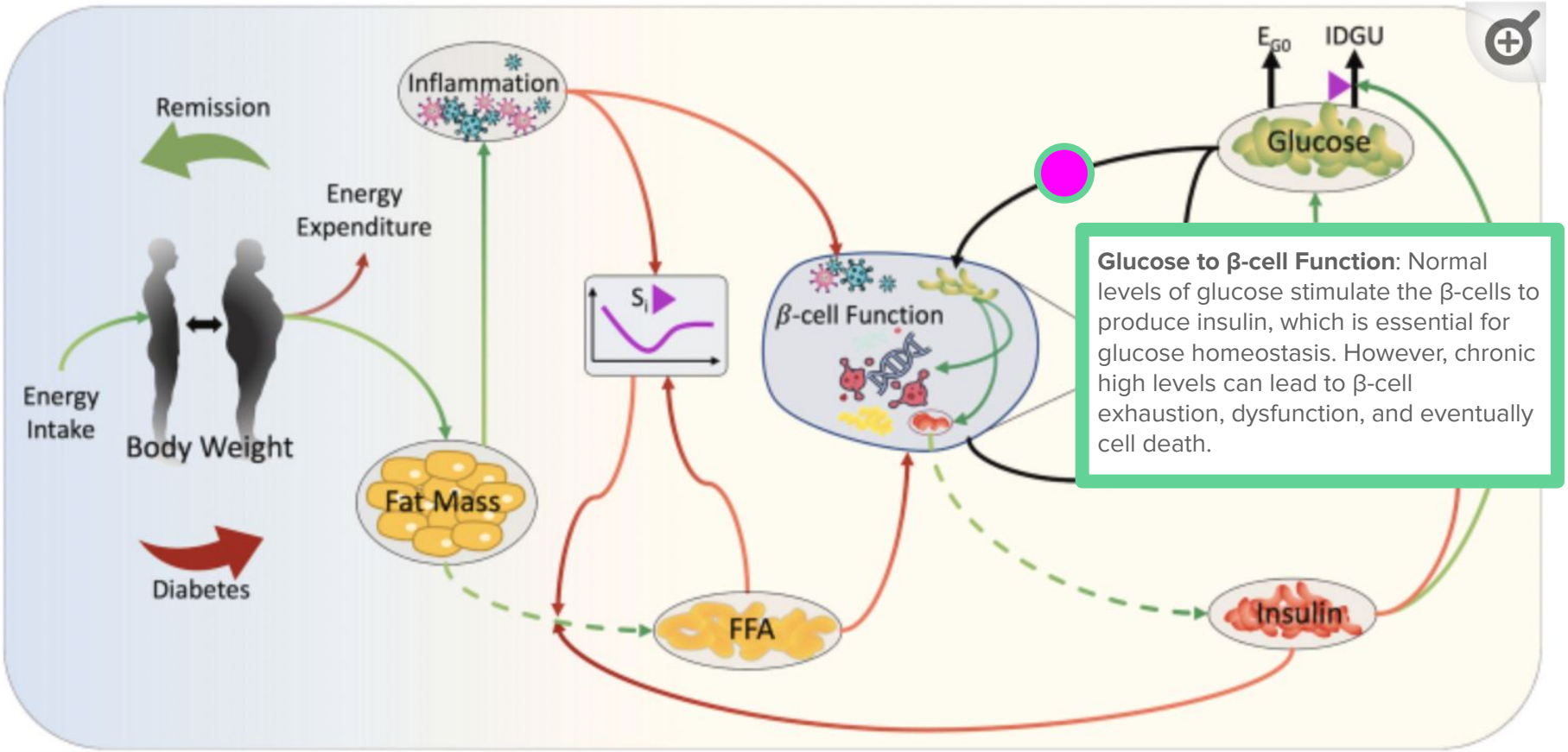
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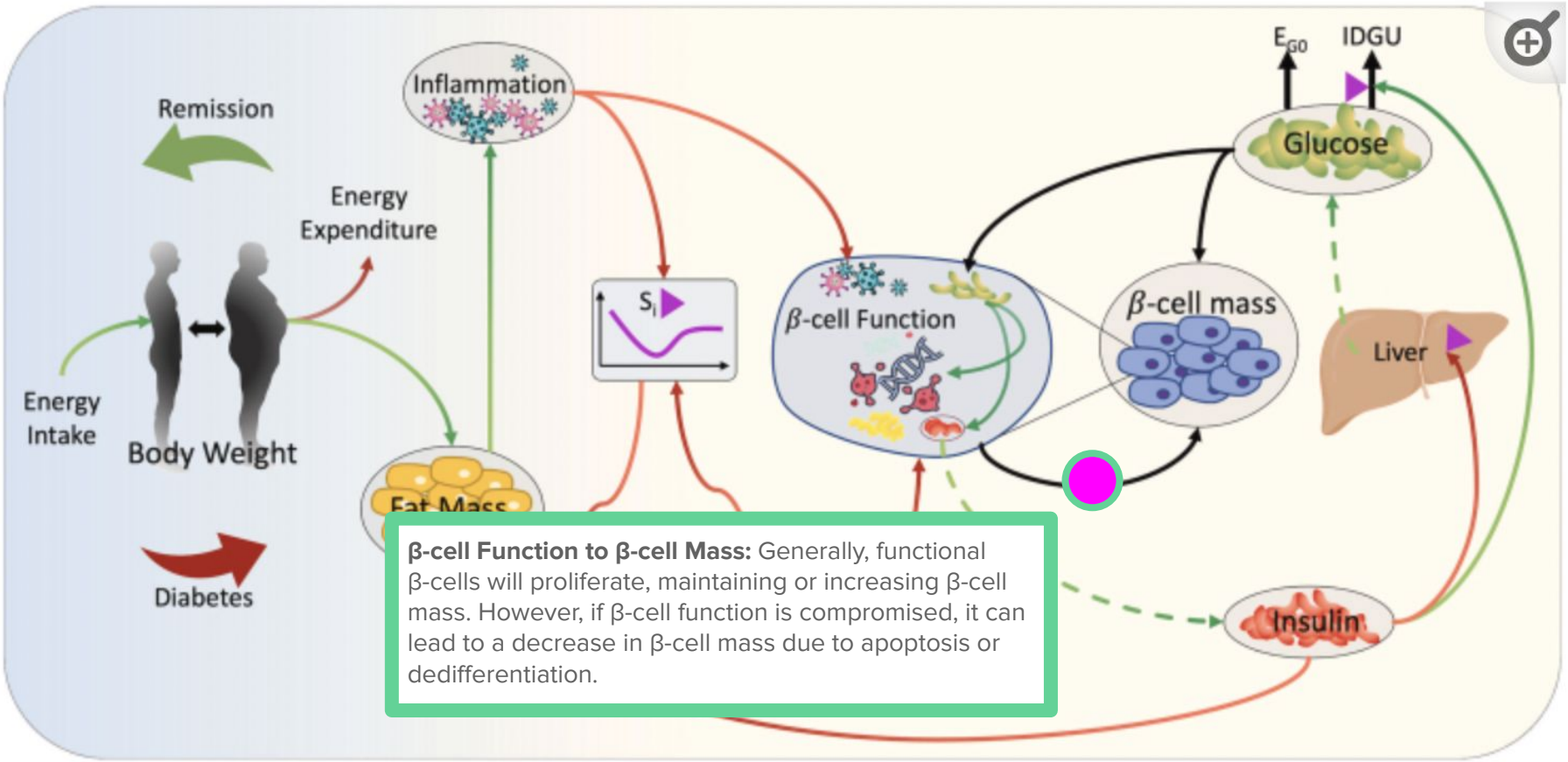
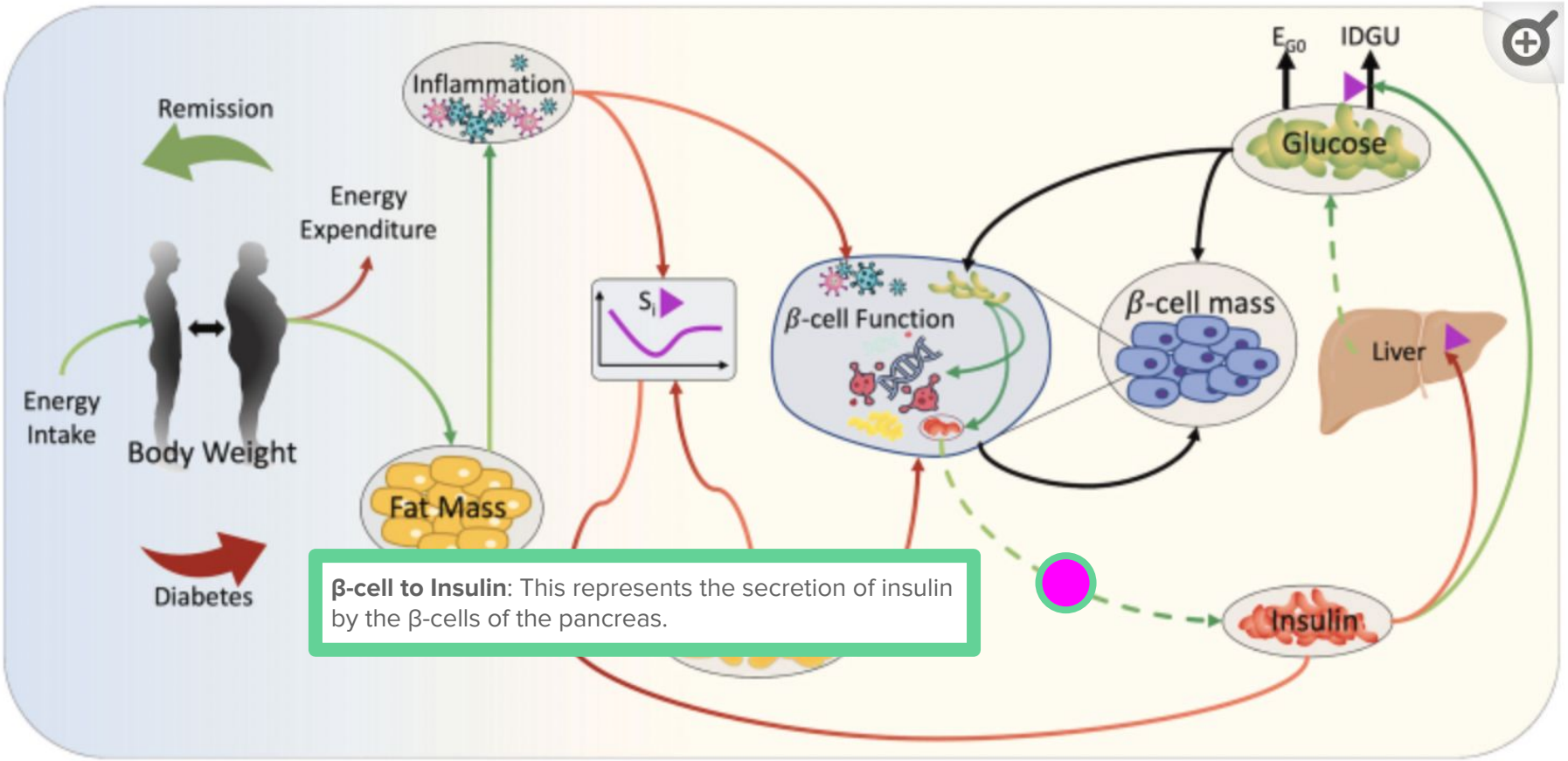
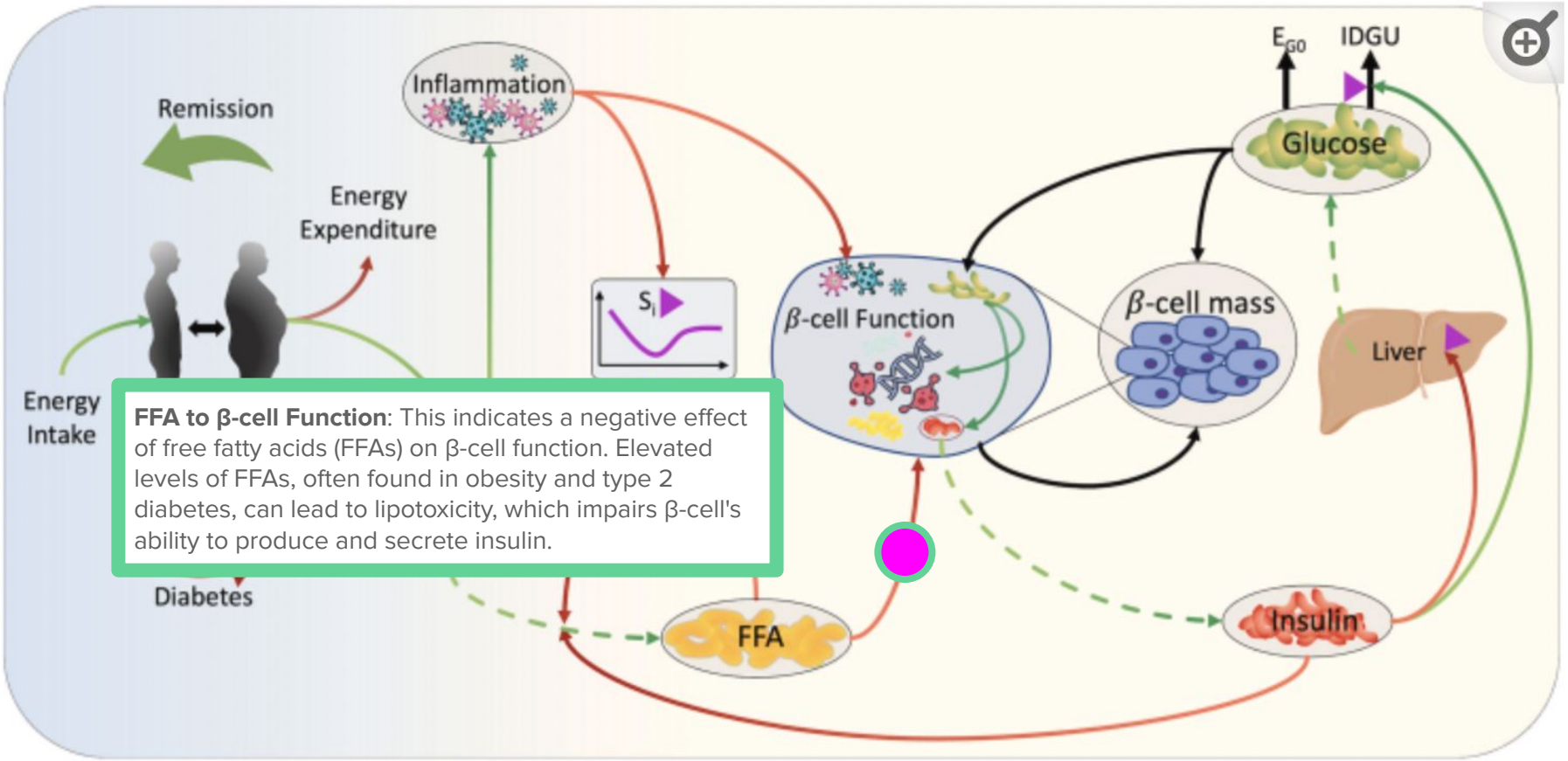
Glucose to β-cell Function: Normal levels of glucose stimulate the β-cells to produce insulin, which is essential for glucose homeostasis. However, chronic high levels can lead to β-cell exhaustion, dysfunction, and eventually cell death.



β-cell Function to β-cell Mass: Generally, functional β-cells will proliferate, maintaining or increasing β-cell mass. However, if β-cell function is compromised, it can lead to a decrease in β-cell mass due to apoptosis or dedifferentiation.



β-cell to Insulin: This represents the secretion of insulin by the β-cells of the pancreas.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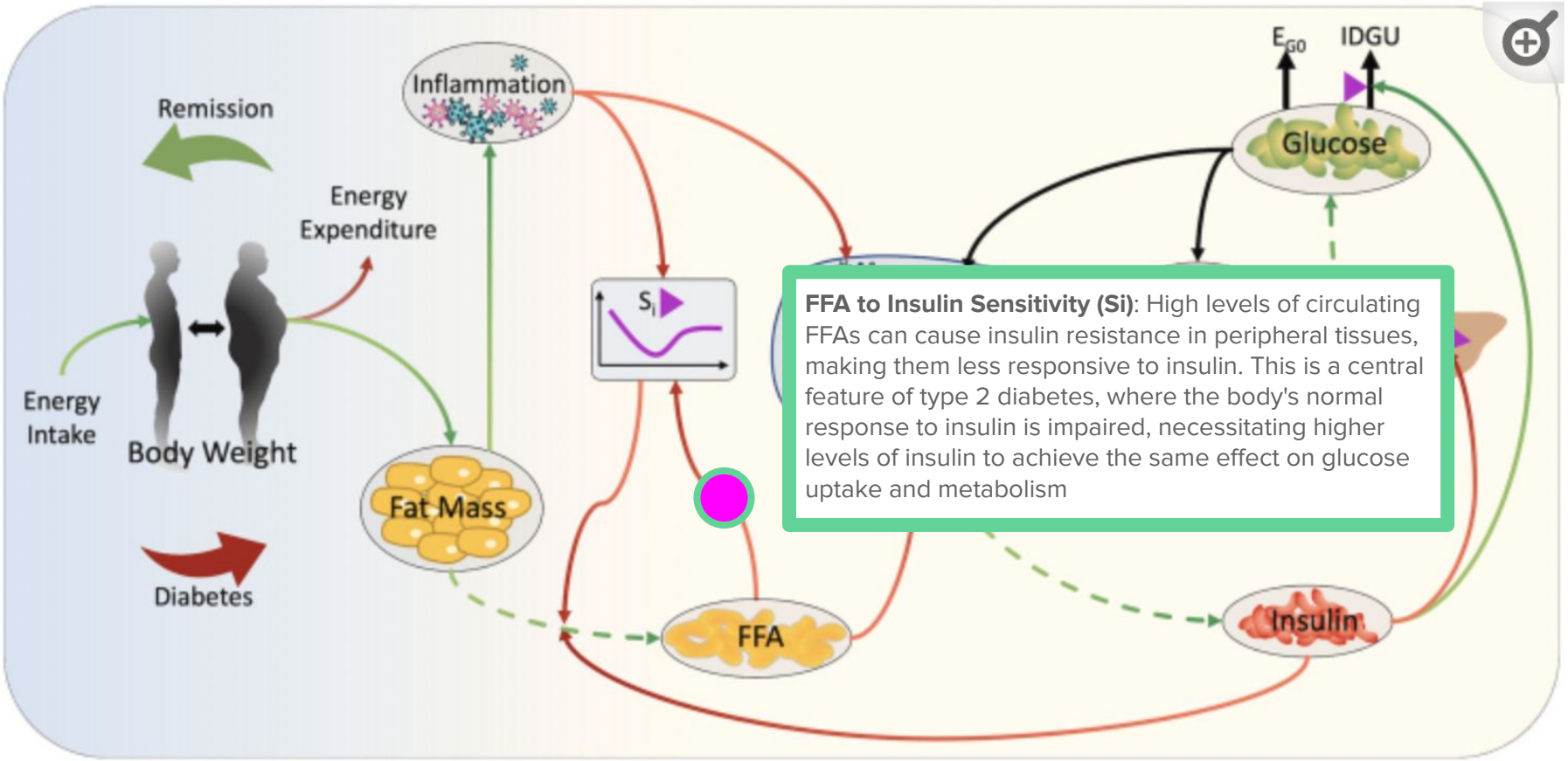
FFA to β-cell Function: This indicates a negative effect of free fatty acids (FFAs) on β-cell function. Elevated levels of FFAs, often found in obesity and type 2 diabetes, can lead to lipotoxicity, which impairs β-cell's ability to produce and secrete insulin.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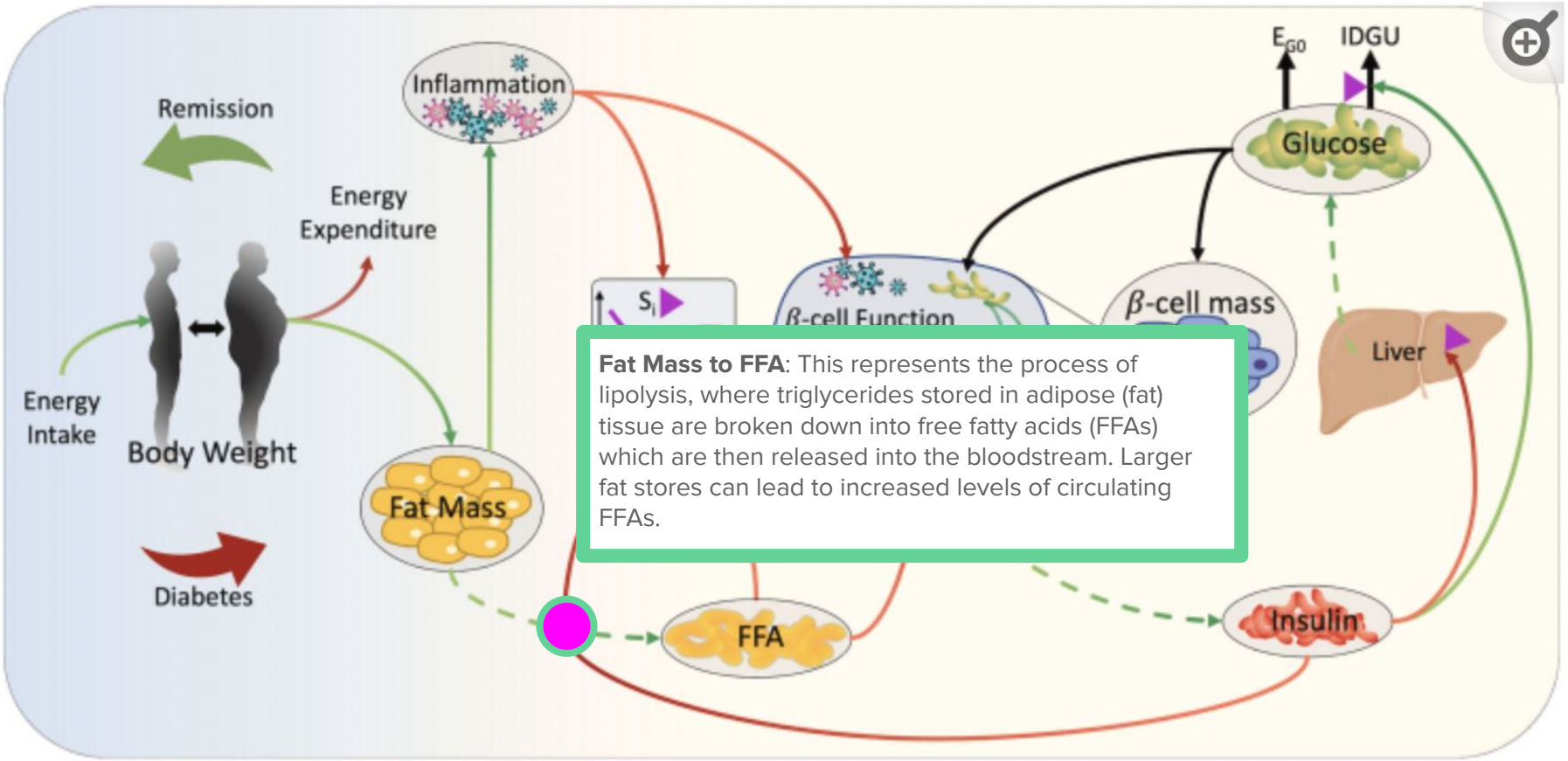
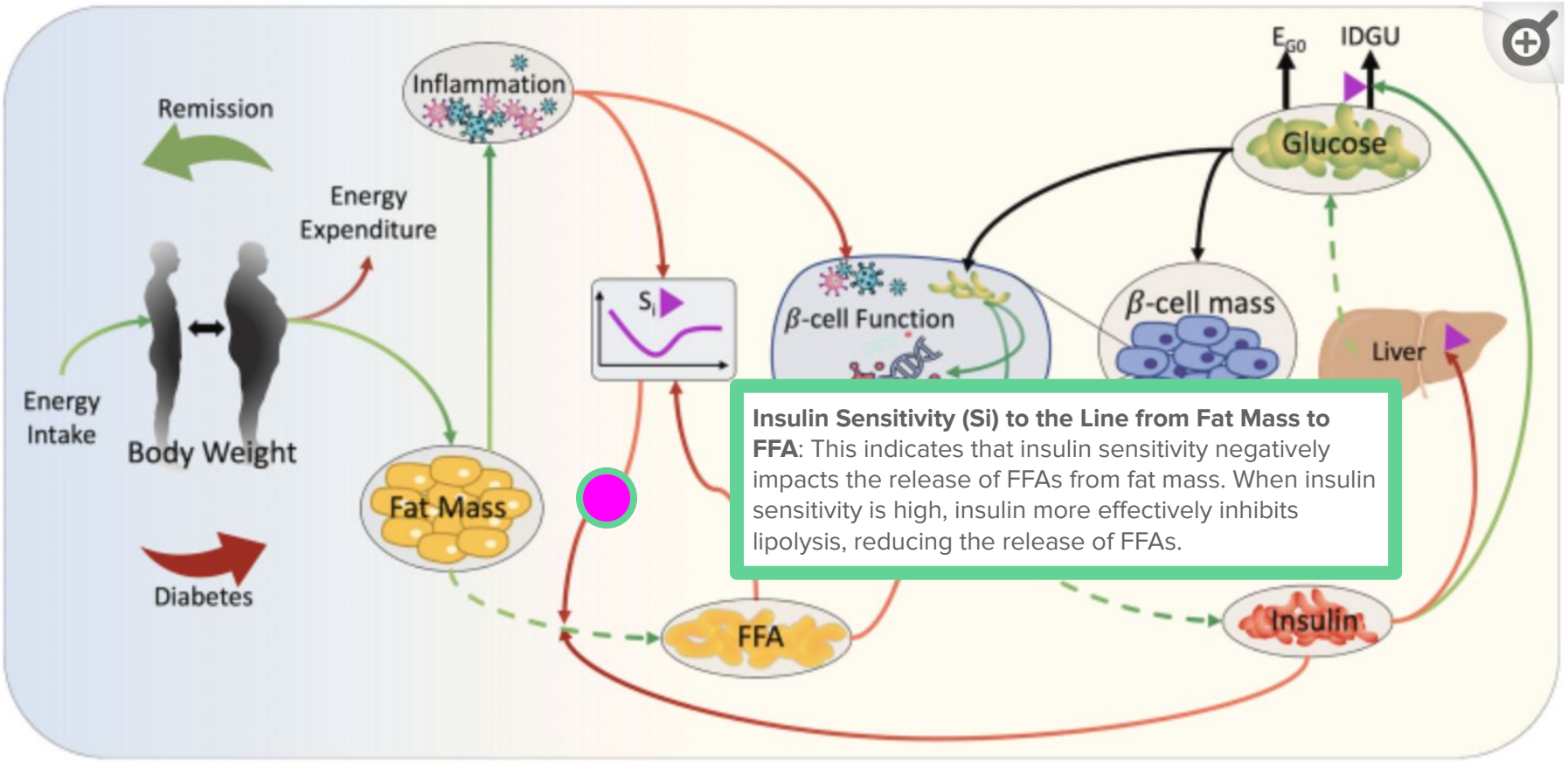
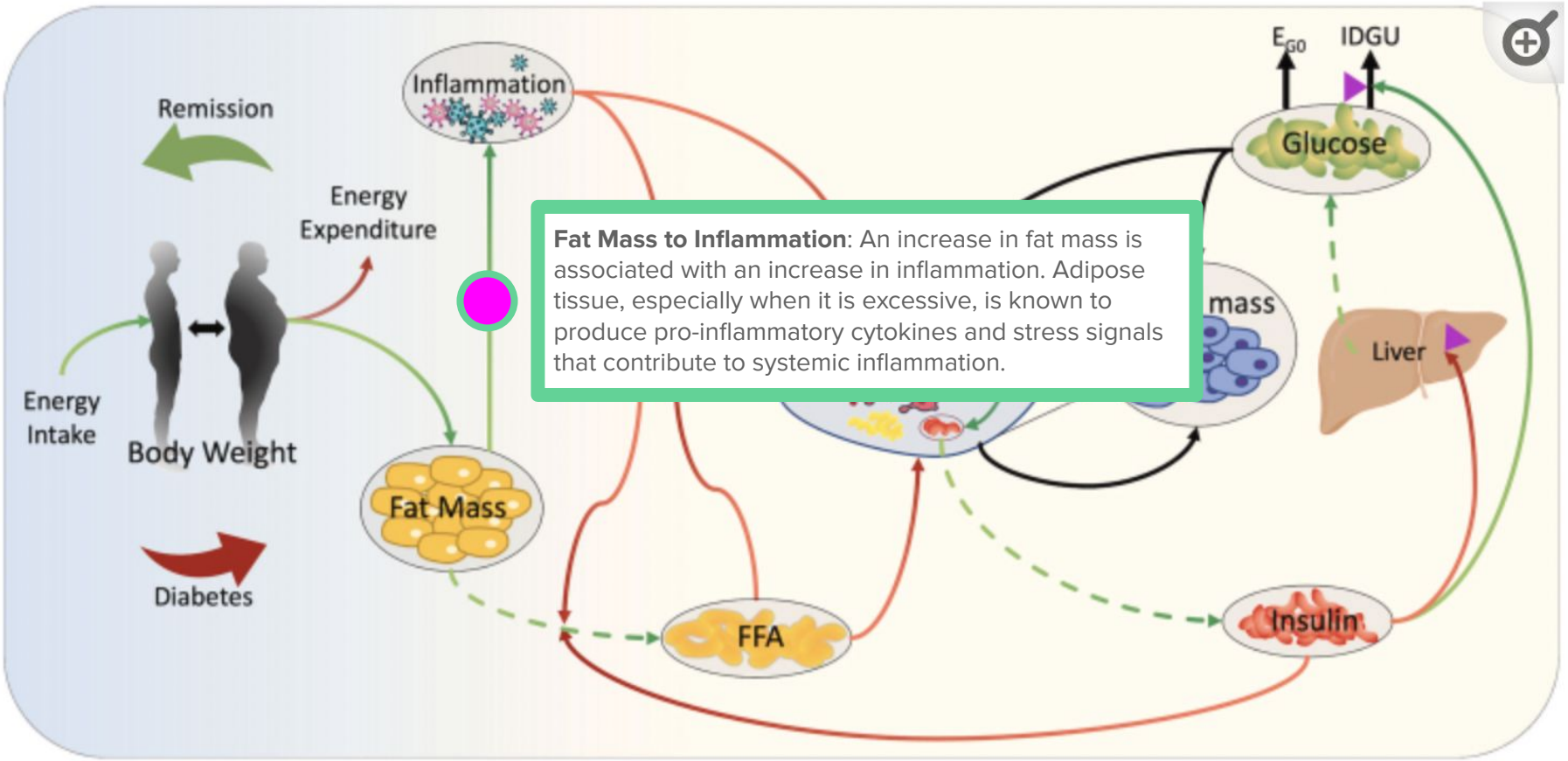
FFA to Insulin Sensitivity (Si): High levels of circulating FFAs can cause insulin resistance in peripheral tissues, making them less responsive to insulin. This is a central feature of type 2 diabetes, where the body's normal response to insulin is impaired, necessitating higher levels of insulin to achieve the same effect on glucose uptake and metabolism



Fat Mass to FFA: This represents the process of lipolysis, where triglycerides stored in adipose (fat) tissue are broken down into free fatty acids (FFAs) which are then released into the bloodstream. Larger fat stores can lead to increased levels of circulating FFAs.



Insulin Sensitivity (Si) to the Line from Fat Mass to FFA: This indicates that insulin sensitivity negatively impacts the release of FFAs from fat mass. When insulin sensitivity is high, insulin more effectively inhibits lipolysis, reducing the release of FFAs.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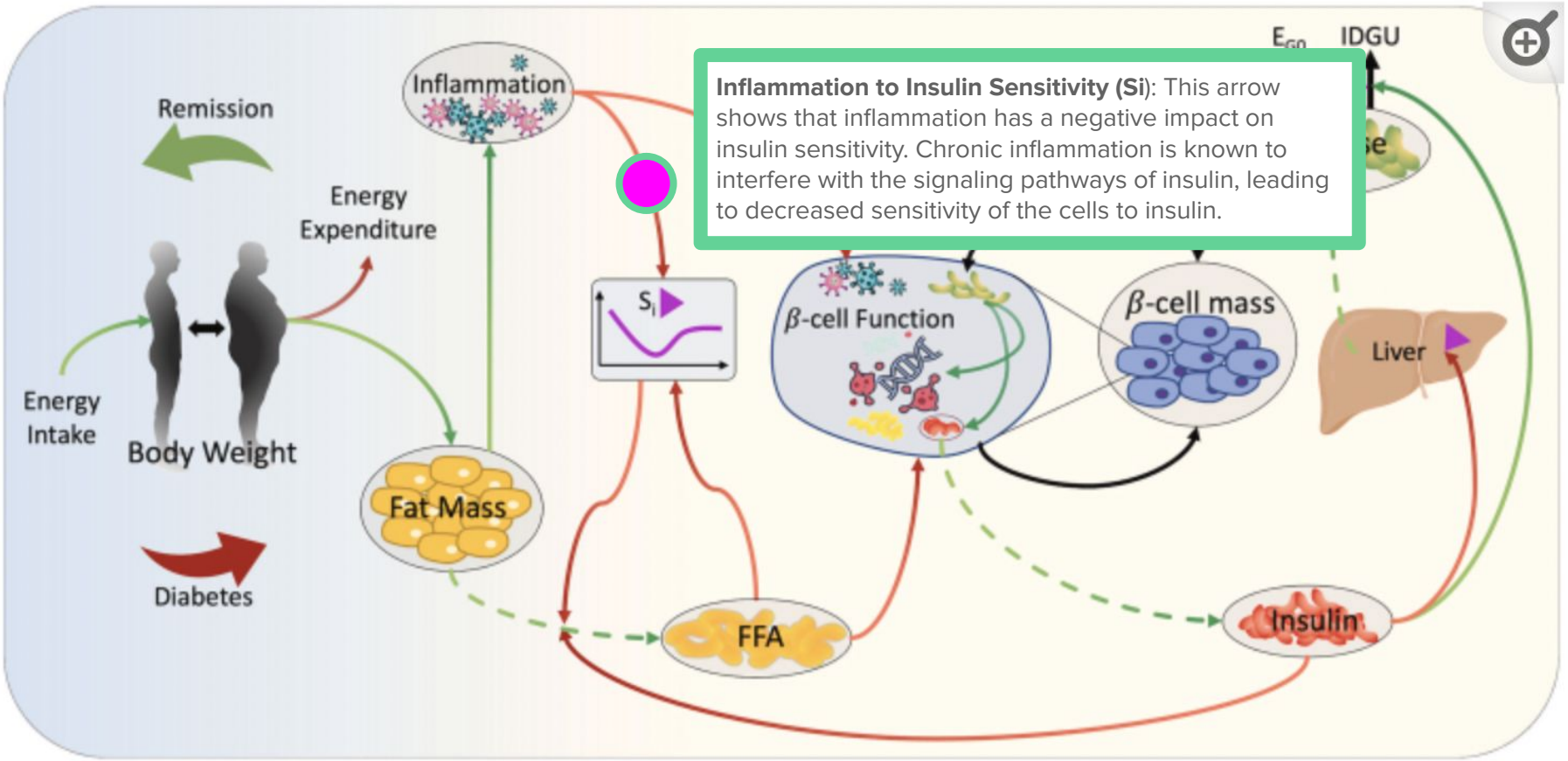
Liver
Fat Mass to Inflammation: An increase in fat mass is associated with an increase in inflammation. Adipose tissue, especially when it is excessive, is known to produce pro-inflammatory cytokines and stress signals that contribute to systemic inflammation.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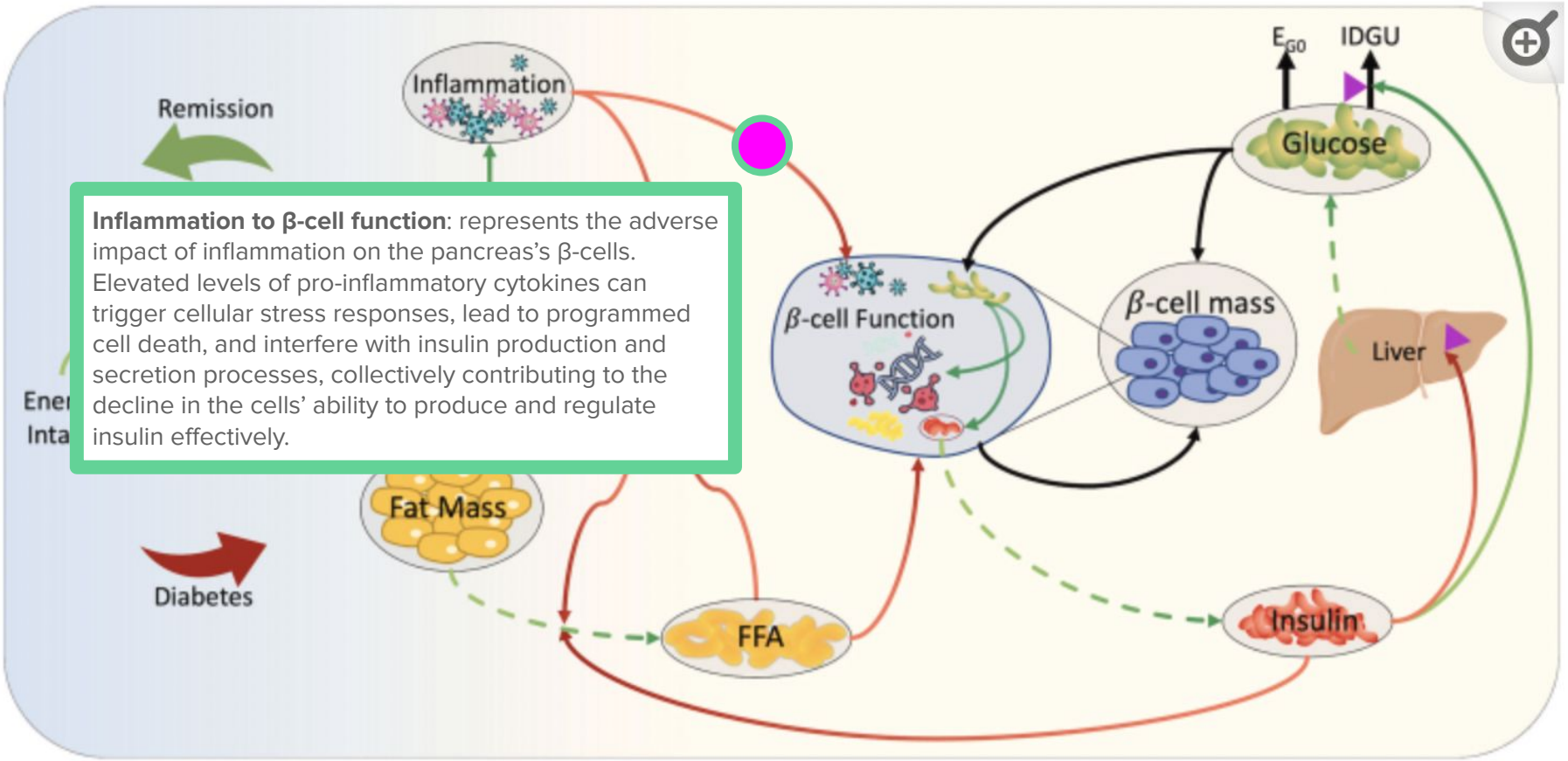
Inflammation to Insulin Sensitivity (Si): This arrow shows that inflammation has a negative impact on insulin sensitivity. Chronic inflammation is known to interfere with the signaling pathways of insulin, leading to decreased sensitivity of the cells to insulin.



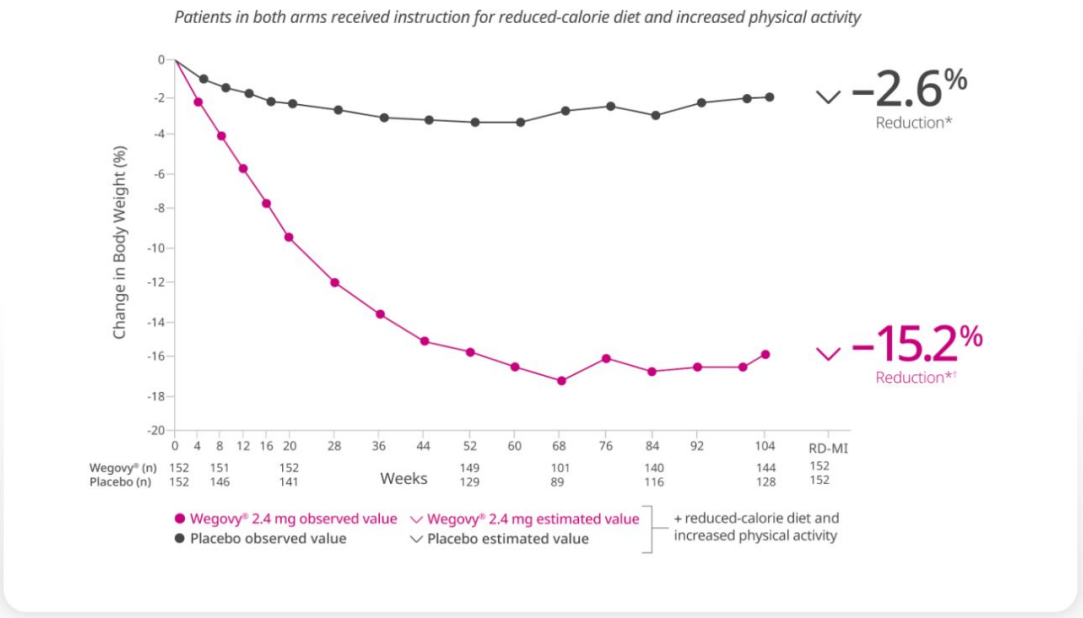
Inflammation to β-cell function: represents the adverse impact of inflammation on the pancreas's β-cells. Elevated levels of pro-inflammatory cytokines can trigger cellular stress responses, lead to programmed cell death, and interfere with insulin production and secretion processes, collectively contributing to the decline in the cells' ability to produce and regulate insulin effectively.

My work

Understanding and labeling the source code

```
pars={}
pars['eg0'] = 24.48  # Endogenous glucose production rate (mg/dl)
pars['k'] = 700  # Glucose elimination constant or sensitivity (dimensionless)
pars['bv'] = 5  # Blood volume (liters) assumed for the insulin and glucose distribution
pars['mmax'] = 1  # Maximum metabolic rate (mg/dl/day)
pars['alpha_m'] = 140  # Half-saturation constant for glucose effect on metabolic rate (mg/dl)
pars['km'] = 2  # Hill coefficient for glucose effect on metabolic rate (dimensionless)
pars['alpha_isr'] = 1.2  # Insulin secretion rate modulation factor (dimensionless)
pars['kisr'] = 2  # Insulin secretion rate sensitivity to metabolic rate changes (dimensionless)
pars['pmax'] = 4.55  # Maximum rate of beta-cell proliferation (mg/day)
pars['kp'] = 4  # Sensitivity parameter for insulin's effect on beta-cell proliferation (dimensionless)
pars['alpha_p'] = 35  # Half-saturation constant for insulin effect on beta-cell proliferation (uU/ml)
pars['p_b'] = 0  # Baseline beta-cell proliferation rate when insulin is minimal (mg/day)
pars['amax'] = 5  # Maximum rate of beta-cell apoptosis (mg/day)
pars['alpha_a'] = 0.37  # Half-saturation constant for glucose effect on beta-cell apoptosis (mg/dl)
pars['ka'] = 6  # Hill coefficient for glucose effect on beta-cell apoptosis (dimensionless)
pars['a_b'] = 0.9  # Baseline apoptosis rate of beta-cells when glucose is minimal (mg/day)
pars['tau_b'] = 1800  # Time constant for beta-cell mass dynamics (days)
pars['height'] = 1.8  # Subject's height (meters)
pars['age_b'] = 30  # Baseline age of the subject (years)
pars['sex'] = 1  # Sex of the subject (1 for male, 0 for female)
pars['cage'] = 0  # Age change coefficient, for dynamic aging effects (dimensionless)
pars['target_si'] = 1.4  # Target whole body insulin sensitivity (uU/ml/day)
pars['tau_si'] = 1  # Time constant for insulin sensitivity dynamics (days)
pars['bmi_h'] = 25  # Threshold BMI for health risk assessment (kg/m^2)
pars['mffa'] = 0.8  # Modulation factor for FFA's effect on insulin sensitivity (dimensionless)
pars['ksi_infl'] = 1.8  # Inflammatory status modulation constant for insulin sensitivity (dimensionless)
```

Experimental data on GLP-1 agonist Wegovy



Data issues

The published drug test results do not show how many calories participants ate, instead they focused on weight as an endpoint. Therefore, I can't get experimental information on calorie reduction (or an accompanying timeline).

Therefore, I had to estimate calorie reductions in order to replicate the weight findings

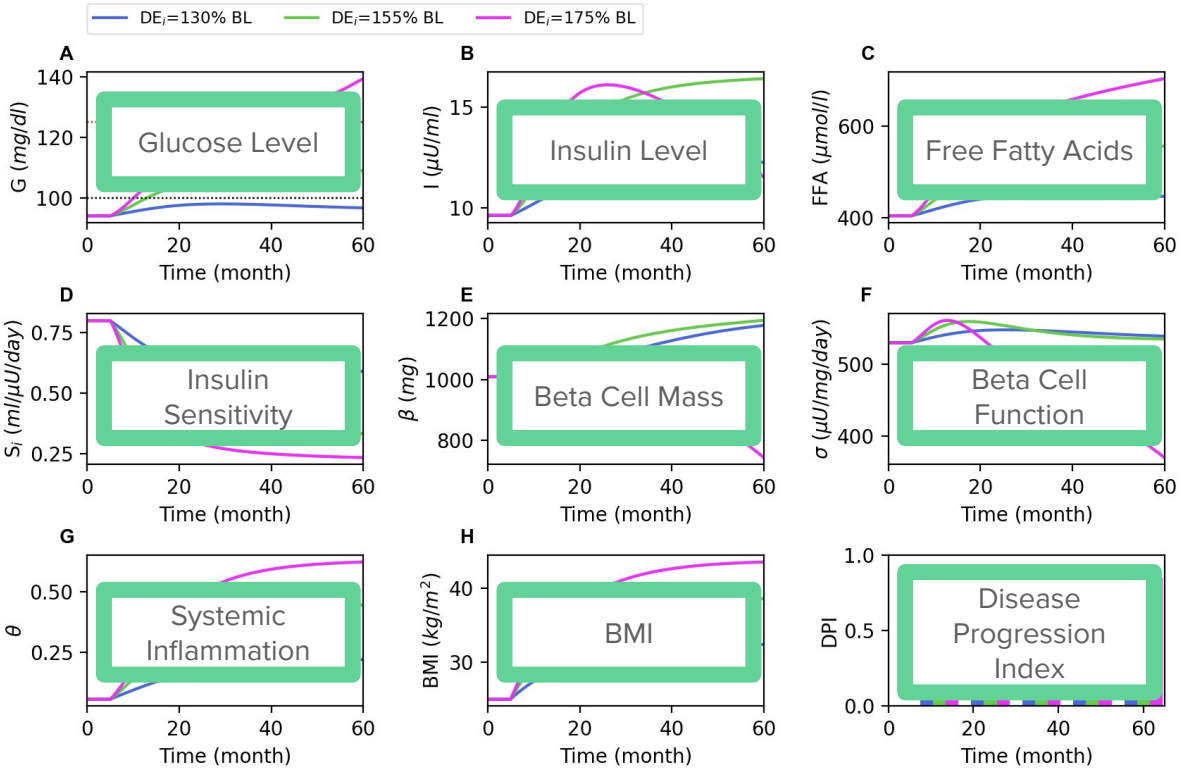
Defining a function to mimic GLP-1 Agonist treatment

```python
def adjust_for_wegovy(t, pars):
    if t > 365:  # Assuming drug introduction after one year, expressed in days
        ramp_duration = 180  # duration over which the drug effect ramps up in days
        ramp_factor = min((t - 365) / ramp_duration, 1)  # caps at 1 when the full effect is reached
        pars['inc_i1'] = max(pars['inc_i1'] - ramp_factor, pars['inc_i1'] - 0.15)   # Gradually apply the reduction in caloric intake
```

Important parts of this function

- Treatment start time (in this case 365 days)
- Ramp duration to increase to full dose (in this case 180 days)
- Minimum calorie intake (in this case 15% below the original amount)

Reproducing the results in the paper



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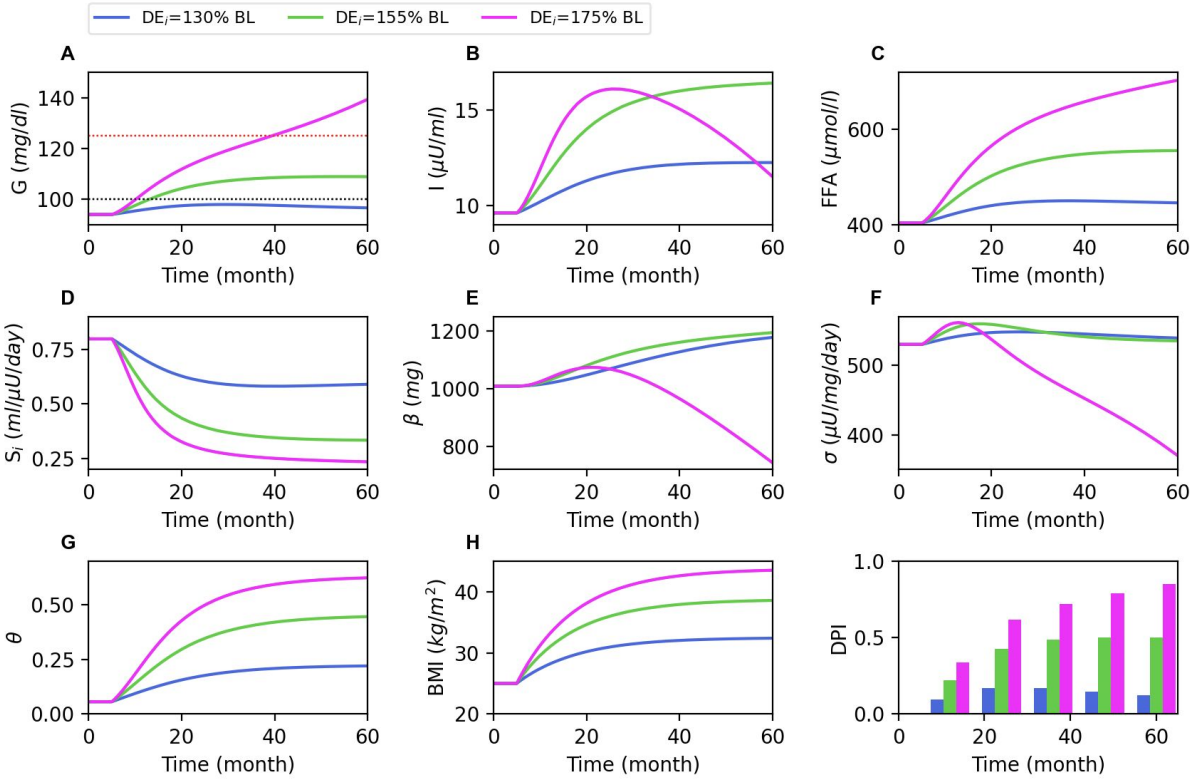
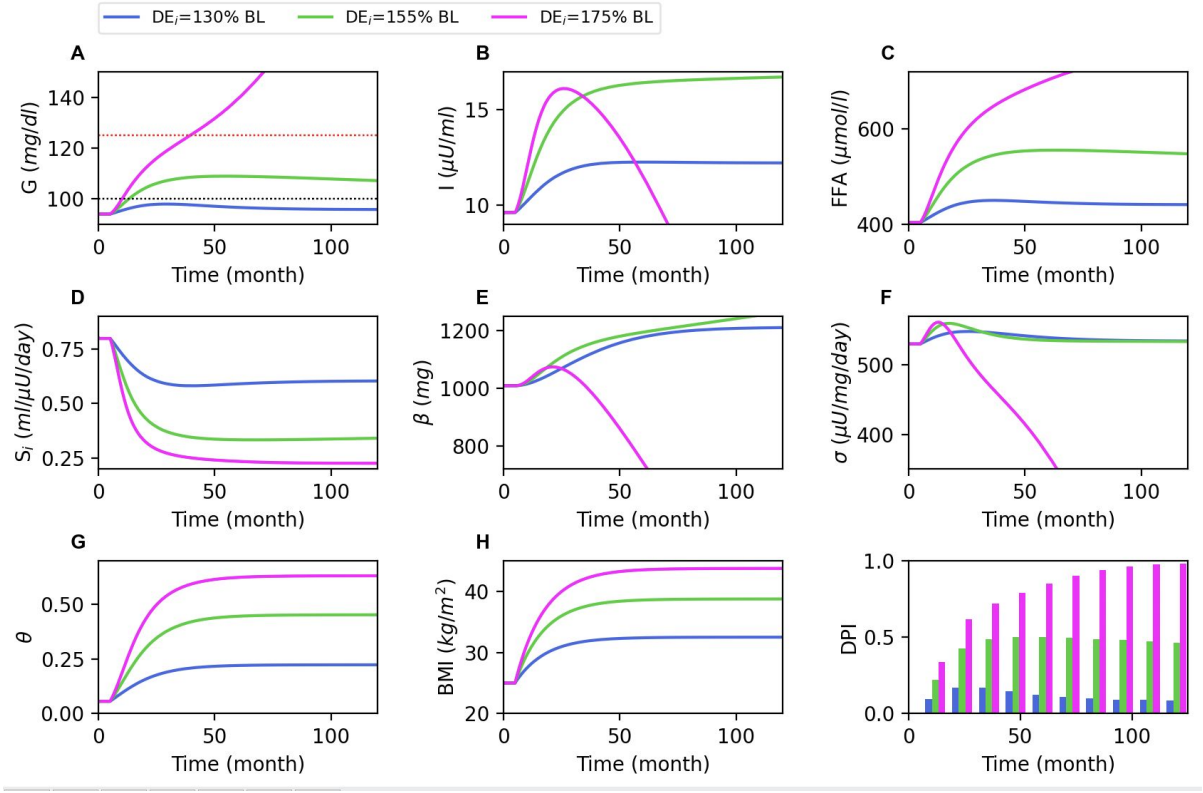
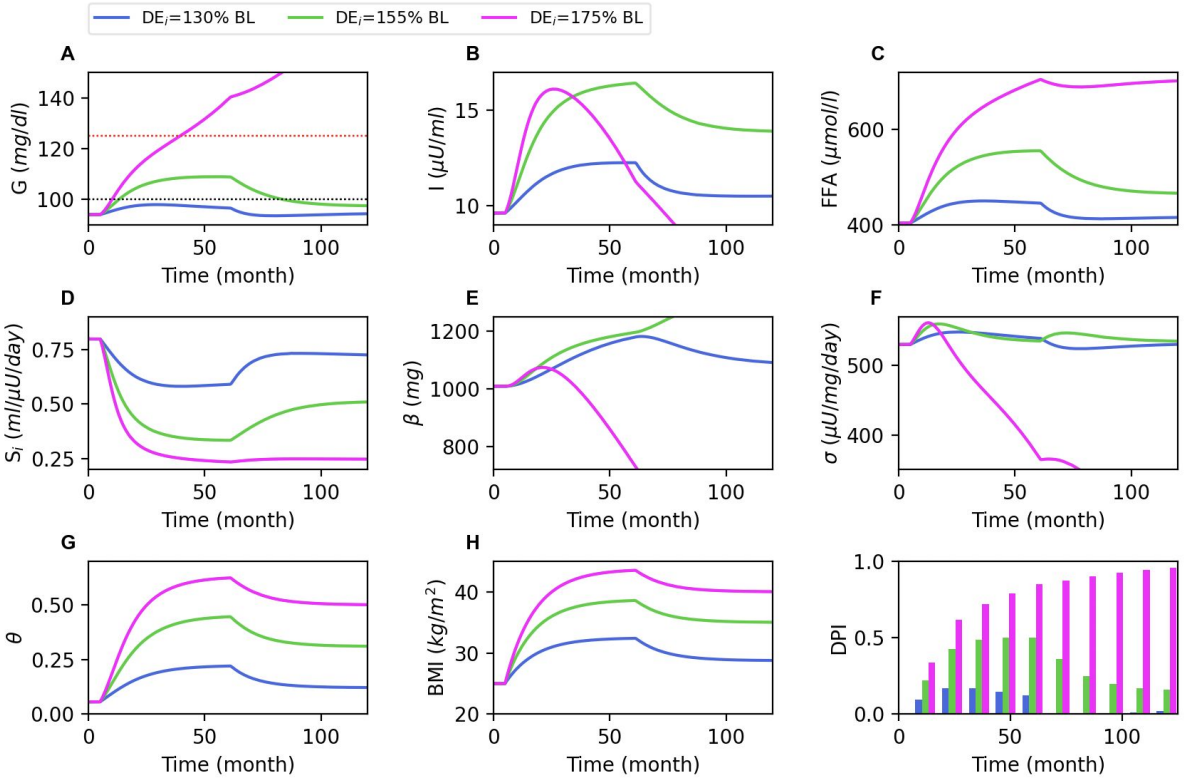


Extending the results in the paper



Doubled length of time to 10 years

Trying to replicate Wegovy medical trials

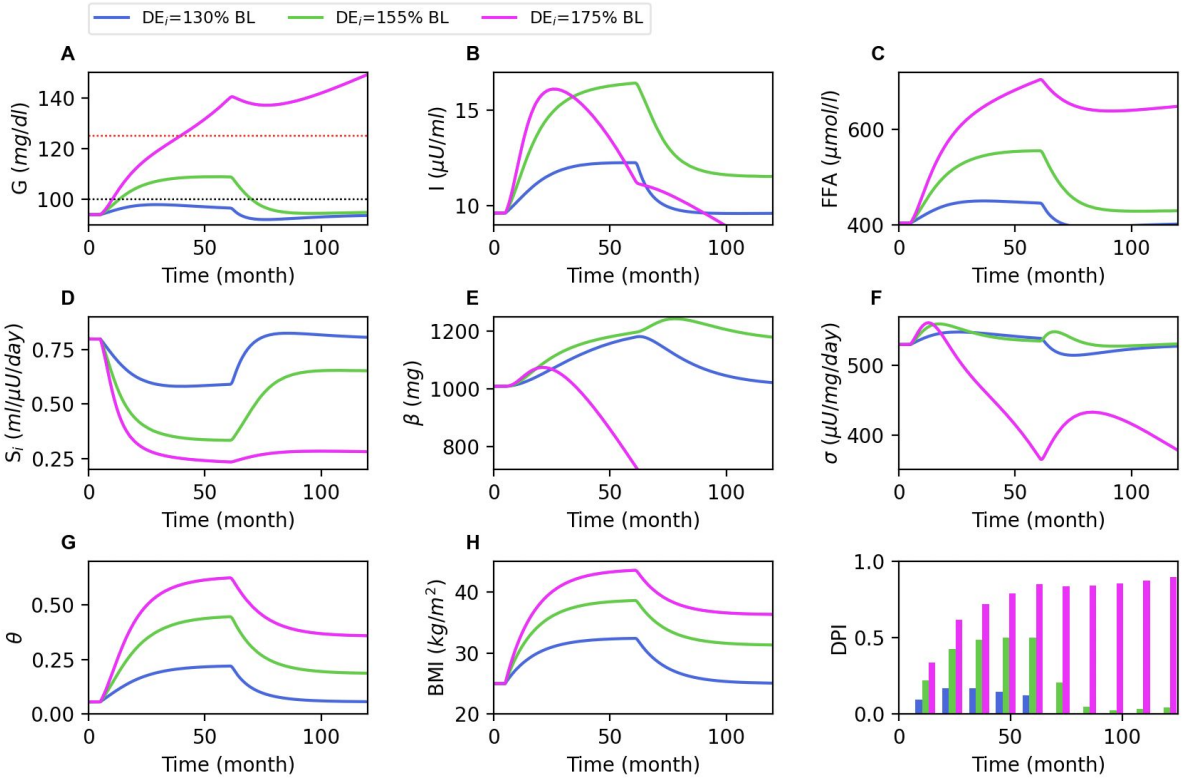


Treatment start time
- Year 5

Ramp duration
- 120 days

Ending calorie intake
- 15% less than what they've been eating for the past 5 years

Trying to replicate Wegovy medical trials

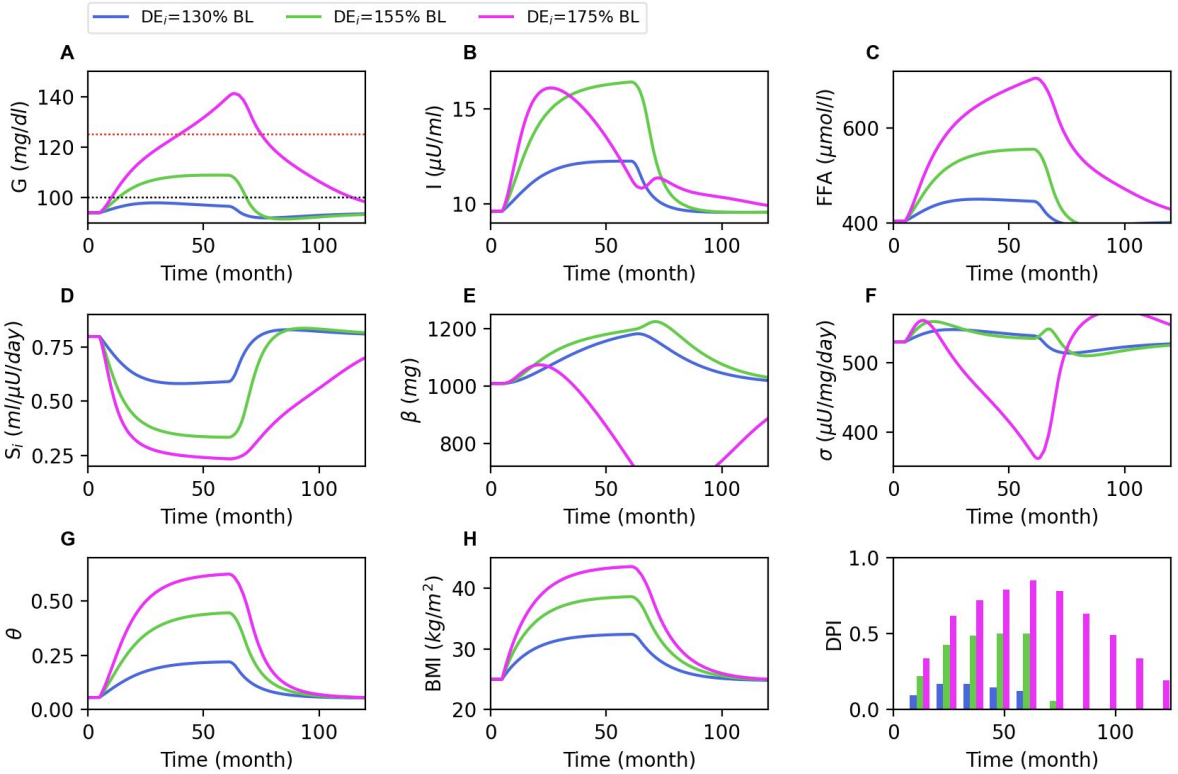


Treatment start time
- Year 5

Ramp duration
- 120 days

Ending calorie intake
- 30% less than what they've been eating for the past 5 years

Trying to replicate Wegovy medical trials



Treatment start time
- Year 5

Ramp duration
- 365 days

Ending calorie intake
- 1% calorie deficit below baseline needs based on height

Important Caveats

- Wegovy and other GLP-1 agonists have additional blood sugar controlling effects **independent** of weight loss effects.
- Anecdotally at least, people with **severe** diabetes (200mg/dl +) have seen their blood sugar lowered to more reasonable levels in less than a year

Any Questions?