Mathematical Modeling of Diabetes

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Overview

Role of Glucose

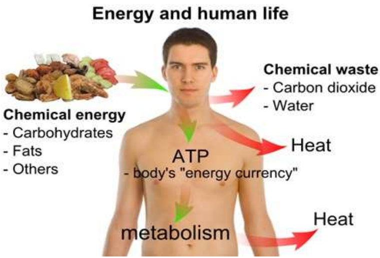
Homeostasis

Glucose Regulation

Diabetes and Its Types

Detection of Diabetes

Body's principle fuels: Glucose



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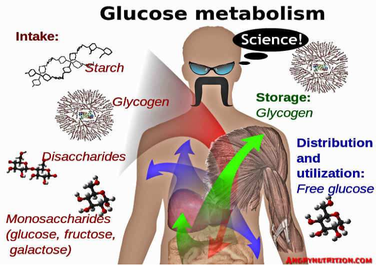
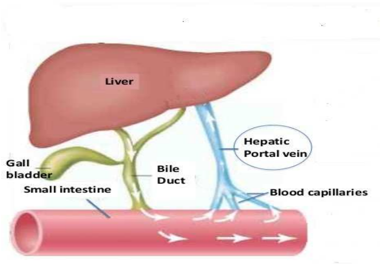


(b)

- Glucose: from starch (a chain of glucose molecule)-rich foods such as potatoes, rice, bread and pasta
- Andenosine triphosphate (ATP): produce from glucose broken down in our cells.
- Metabolism: biochemical reactions within a living organism in order to maintained life is powered by ATP (small packet of chemical energy).

Auto-regulatory of Blood glucose



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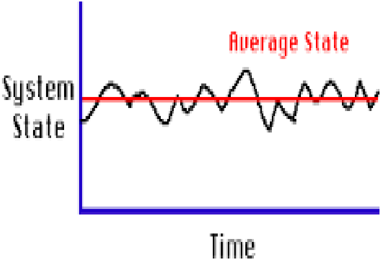
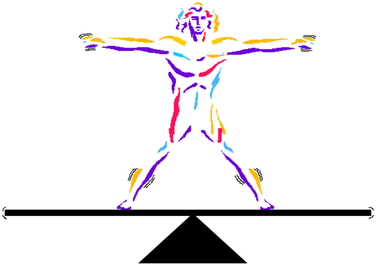


(d)

- **In the small intestine, glucose is absorbed into the blood and travel to the liver via the hepatic portal vein.**
- **This stored glucose can be reconverted when blood-glucose levels falls.**

Homeostasis



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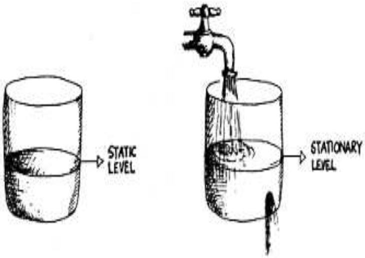


(f)

- Homeostasis: maintenance of a steady internal state, despite changes in external or internal conditions.
- Role: maintains **a steady but not static** internal state within organisms.
- Advantage: Individual can quickly adapt to their environment so that normal health is not disturbed.

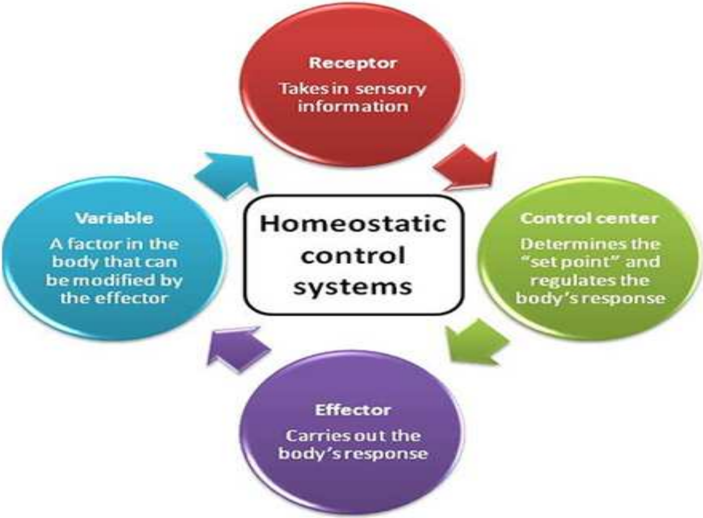
Examples of Homeostasis

Many variables are maintained by Homeostasis

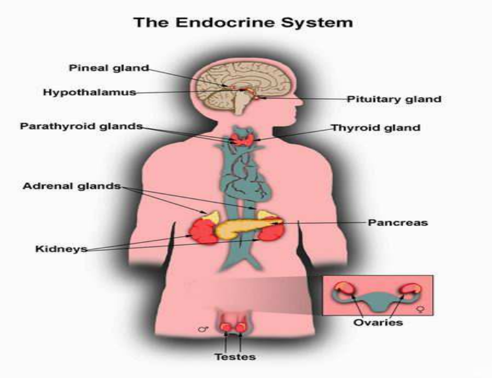
- **Temperature**
- **Blood pH**
- Blood sugar
- **Water balance**
- **Blood pressure**
- **Ion balance**

In this lecture I am going to focus on regulation of blood sugar.

Homeostatic Control Mechanisms

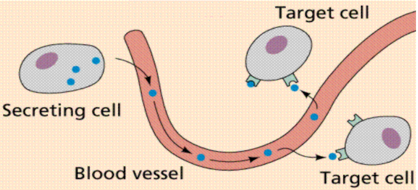


Regulation in Healthy Systems



The endocrine system is made up of glands that produce and secrete hormones, chemical substances produced in the body that regulate the activity of cells or organs.

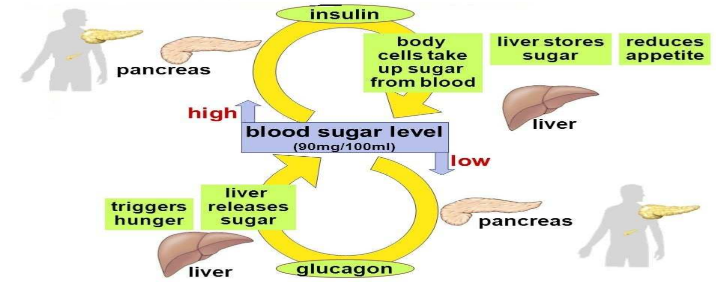
Hormones



Hormones

- Hormones are chemical messengers created by the body.
- They transfer information from one set of cells to another (via blood vessel) to coordinate the functions of different parts of the body.
- Hormones regulate the body's growth, metabolism (the physical and chemical processes of the body), and sexual development and function.

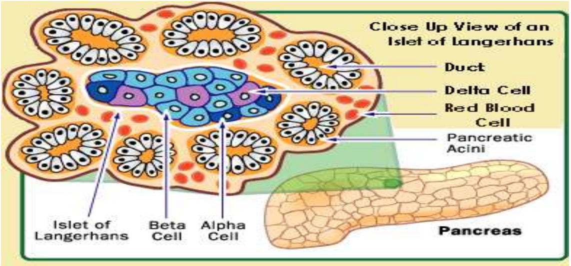
Glucose Regulation from a Biological Perspective



Key Organs and Hormones

- **Key organs that control blood glucose:** **the pancreas and the liver**
- **Key hormones:** **insulin and glucagon**

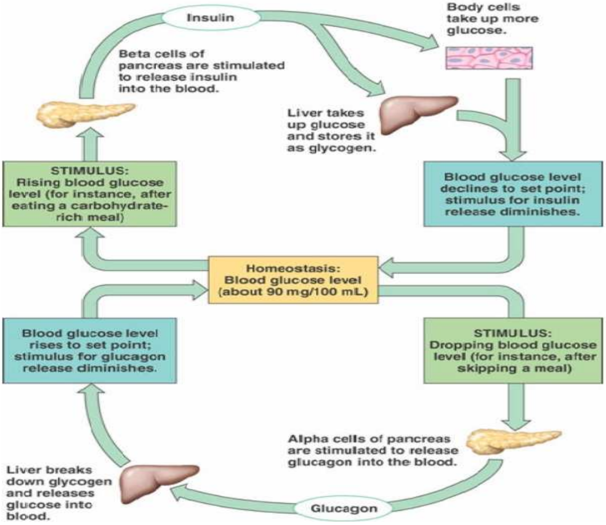
Pancreas



Clusters of endocrines cells

- α-**cells: produce glucagon**
- β-**cells: produce insulin**

Role of Insulin and Glucagon in Regulation



Diabetes and its Types

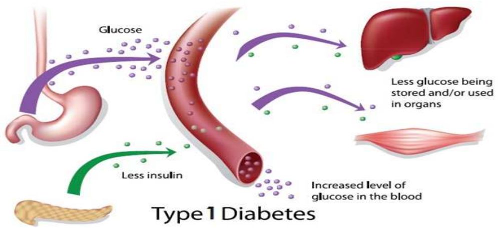
Diabetes:

- **It is a disease of metabolism which is characterized by too much sugar in the blood and urine.**
- In diabetes, the body is unable to burn of all its sugars, starches, and carbohydrates because of an insufficient supply of insulin.
- Diabetes in usually diagnosed by means of a glucose tolerance test (GTT).

Types:

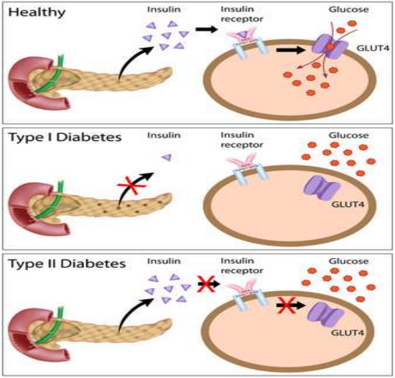
- **Type I Diabetes: an endocrine disorder caused by a deficiency of insulin**
- **Type II Diabetes: caused by a decreased response to insulin in target tissues**

Type I: insulin-dependent diabetes



- **It is an autoimmune disorder in which the immune system destroys the β-cells of the pancreas.**
- **As a result, the persons ability to produce insulin is greatly inhibited.**
- It is treated with insulin injections.

Type II: insulin-independent diabetes



- It is caused by a reduced responsiveness of insulin target cells due to some change in the insulin receptors.
- Heredity can play a role, but research indicates that excess body weight and lack of exercise significantly increases risk.

Mathematical Model for the Detection of Diabetes

The basic model to described insulin-glucose interactions

$$\frac{dG}{dt} = F_1(G, H) + J(t)$$
$$\frac{dH}{dt} = F_2(G, H)$$

- $G :=$ concentrations of glucose in the blood
- $H :=$ net hormonal concentrations
- F_1 and F_2 changes in G and H
- $J(t) :=$ external rate at which the blood glucose concentration being increased

Deviations of G and H from their optimal values

- We assume that G and H have achieved optimal values G_0 and H_0 by the time the fasting patient has arrived at the hospital.
- This implies that

$$F_1(G_0, H_0) = 0 \quad \text{and} \quad F_2(G_0, H_0) = 0.$$

Since we are interested here in the deviations of G and H from their optimal values, we make the substitution

$$g := G - G_0, \quad h := H - H_0.$$

Then

$$\frac{dg}{dt} = F_1(G_0 + g, H_0 + h) + J(t)$$
$$\frac{dh}{dt} = F_2(G_0 + g, H_0 + h)$$

Linearization

Now observer that

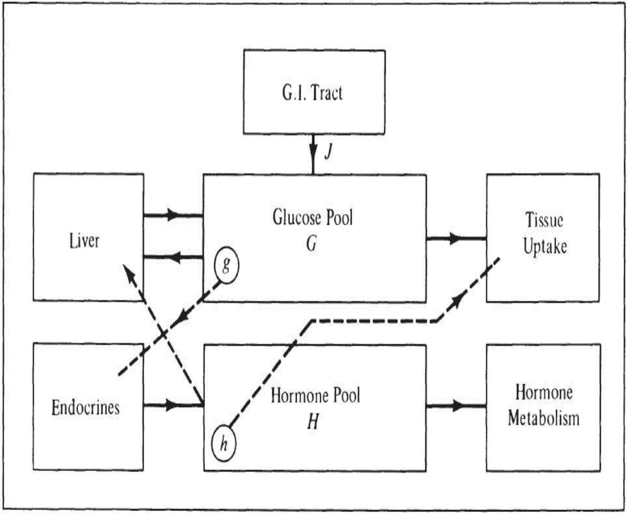
$$F_1(G_0+g, H_0+h) = F_1(G_0, H_0) + \frac{\partial F_1(G_0, H_0)}{\partial G} g + \frac{\partial F_1(G_0, H_0)}{\partial H} h + e_1$$
$$F_2(G_0+g, H_0+h) = F_2(G_0, H_0) + \frac{\partial F_2(G_0, H_0)}{\partial G} g + \frac{\partial F_2(G_0, H_0)}{\partial H} h + e_2$$

where e_1 and e_2 and very small compared to g and h.

Assuming that G and H deviate only slightly from G_0 and H_0

$$\frac{dg}{dt} \approx \frac{\partial F_1(G_0, H_0)}{\partial G} g + \frac{\partial F_1(G_0, H_0)}{\partial H} h + J_1$$
$$\frac{dh}{dt} \approx \frac{\partial F_2(G_0, H_0)}{\partial G} g + \frac{\partial F_2(G_0, H_0)}{\partial H} h$$

Simplified model of the blood glucose regulatory system



Sign determination

- dg/dt is negative for $g > 0$ and $h = 0$, since the blood glucose concentration will be decreasing through tissue uptake of glucose and the storing of excess glucose in the liver in the form of glycogen. Consequently $\partial F_1(G_0, H_0)/\partial G$ must be negative.
- Similarly, $\partial F_1(G_0, H_0)/\partial H$ is negative since a positive value of h tends to decrease blood glucose levels by facilitating tissue uptake of glucose and by increasing the rate at which glucose is converted to glycogen.
- The number $\partial F_2(G_0, H_0)/\partial G$ must be positive since a positive value of g causes the endocrine glands to secrete those hormones which tend to increase H.
- Finally, $\partial F_2(G_0, H_0)/\partial H$ must be negative, since the concentration of hormones in the blood decreases through hormone metabolism.

Mathematical Model

We can write

$$\frac{dg}{dt} = -m_1 g - m_2 h + J_1$$
$$\frac{dh}{dt} = -m_3 h + m_4 g$$

where m_1, m_2, m_3 and m_4 are positive constants.

- **Since we only measure the concentration of glucose in the blood, we would like to remove the variable h.**

Differentiating first equation w.r.t time and substituting dh/dt

$$\frac{d^2g}{dt^2} = -m_1\frac{dg}{dt} - m_2\frac{dh}{dt} + \frac{dJ}{dt}$$
$$= -m_1\frac{dg}{dt} + m_2 m_3 h - m_2 m_4 g + \frac{dJ}{dt}$$

Mathematical Model Continued...

Substituting $m_2 h = (-dg/dt) - m_1 g + J(t)$ in last equation, one can write

$$\frac{d^2 g}{dt^2} + (m_1 + m_3)\frac{dg}{dt} + (m_1 m_3 + m_2 m_4) g = m_3 J + \frac{dJ}{dt}$$

We rewrite this equation in the form

$$\frac{d^2 g}{dt^2} + 2\alpha \frac{dg}{dt} + \omega_0^2 g = S(t)$$

where $\alpha = (m_1 + m_3)/2, \omega_0^2 = m_1 m_3 + m_2 m_4$ and $S(t) = m_3 J + dJ/dt$.

Analysis of Mathematical Model

- **Notice that the right-hand side of last equation is identically zero except for the very short time interval in which the glucose load is being ingested.**
- Therefore, for $t \geq 0$, we can get

$$\frac{d^2 g}{dt^2} + 2\alpha \frac{dg}{dt} + \omega_0^2 g = 0$$

Solution of above differential equation is

$$g(t) = Ae^{-\alpha t}\cos(\omega t - \delta), \quad \omega^2 = \omega_0^2 - \alpha^2$$

- Consequently, $G(t) = G_0 + Ae^{-\alpha t}\cos(\omega t - \delta)$
- **Conclusion: Thus our model certainly conforms to reality in predicting that the blood glucose concentration tends to return eventually to its optimal concentration.**

Determination of parameters of analytical solution

- There are five unknowns in $G(t) = G_0 + Ae^{-\alpha t}\cos(\omega t - \delta)$

One way of determining them is as follows.

- The patient's blood glucose concentration before the glucose load is ingested is G_0.
- Hence, we can determine G_0 by measuring the patient's blood glucose concentration immediately upon his arrival at the hospital.
- Next, if we take four additional measurements G_1, G_2, G_3, and G_4 of the patient's blood glucose concentration at times t_1, t_2, t_3, and t_4, then we can determine A, α, ω_0, and δ from the four equations

$$G_j = G_0 + Ae^{-\alpha t_j}\cos(\omega t_j - \delta), \quad j = 1, \cdots, 4$$

- Note: **Natural period of differential equation** $T_0 = 2\pi/\omega_0$.

Concluding Remarks

- **The remarkable fact is that data from a variety of sources indicated that a value of less than four hours for $T_0 = 2\pi/\omega_0$ indicated normalcy, while appreciably more than four hours implied mild diabetes.**

The End