4.1: Pathology

Diabetes mellitus is a condition that occurs when there is an elevated concentration of glucose in the blood. Glucose is the principal type of carbohydrate that the body uses for energy, and carbohydrates are one of the three macronutrients (along with proteins and lipids). In contrast to hyperlipidemia where there is a high concentration of hydrophobic lipids in the blood, in diabetes mellitus the situation is somewhat reversed. There is a high concentration of sugars in the blood, which are highly polar due to the multiple hydroxyl groups on each sugar molecule. This can lead to the blood becoming very 'sticky' and viscous. This can become more serious in organs with tiny blood vessels such as the eyes, kidneys and other extremities as it becomes challenging for the blood to reach these locations and deliver necessary components or immune cells. Therefore, it is very important to maintain appropriate concentrations of blood sugar.

Diabetes mellitus is a chronic condition and there are three different types: Type 1, 2, and gestational diabetes. Type 1 diabetes is generally thought of as a genetic condition, with early onset and lower frequency (~10% of diabetes cases). Type 2 diabetes may also have a genetic component but is largely driven by lifestyle and has a late onset. Gestational diabetes can occur when the patient is pregnant, and usually resolves naturally following the pregnancy term.

The incidence of diabetes in Canada has been increasing over the past two decades (4.7% of the population in 2001, compared to 8.1% in 2017), which may be attributed to changes in diet and lifestyle. Carbohydrates represent the most accessible form of energy for body, and form a large part of the natural human diet. They are digested and absorbed by different organs of the body, which provides a foundation for medicinal chemistry efforts to treat diabetes.

Carbohydrate Digestion – Mouth and Stomach

Carbohydrate digestion begins in the mouth. Although the mechanical action of chewing helps to physically separate carbohydrates, the enzyme salivary amylase starts hydrolyzing some of the complex sugars. Approximately 5% of carbohydrate digestion occurs in the mouth. These enzymes are inactivated by the gastric acid of the stomach. The mechanical action of the stomach coupled to the acidic conditions may help to further separate carbohydrates, but these are not the predominant sites of carbohydrate digestion.

Carbohydrate Digestion – Small Intestine

The stomach empties the mixture of food (now called chyme) into the small intestine, where several enzymes become involved. There is a different type of amylase (**pancreatic amylase**) that continues breaking down larger sugars. Another enzyme, **α-glucosidase**, breaks down polymer sugar molecules into monomers, such as glucose or fructose. These monomers can now be absorbed by different transporters. Proteins in cells of the small intestine are expressed asymmetrically on the cell membrane. (Figure 4.1) For example, **SGLT1** (sodium glucose transporter) enables glucose transport into the cells from the small intestine lumen. **GLUT2** (glucose transporter) faces the blood vessel lumen and deposits glucose in the blood stream. Both of these transporters are important and part of larger families of carbohydrate transporters and have different tissue expression throughout the body. SGLT1 is one of twelve members of the SLC5A (solute carrier family member 1) proteins. GLUT transporters represent a family of fourteen transporters with different affinities for glucose or other carbohydrate monomers (for example GLUT5 absorbs fructose).

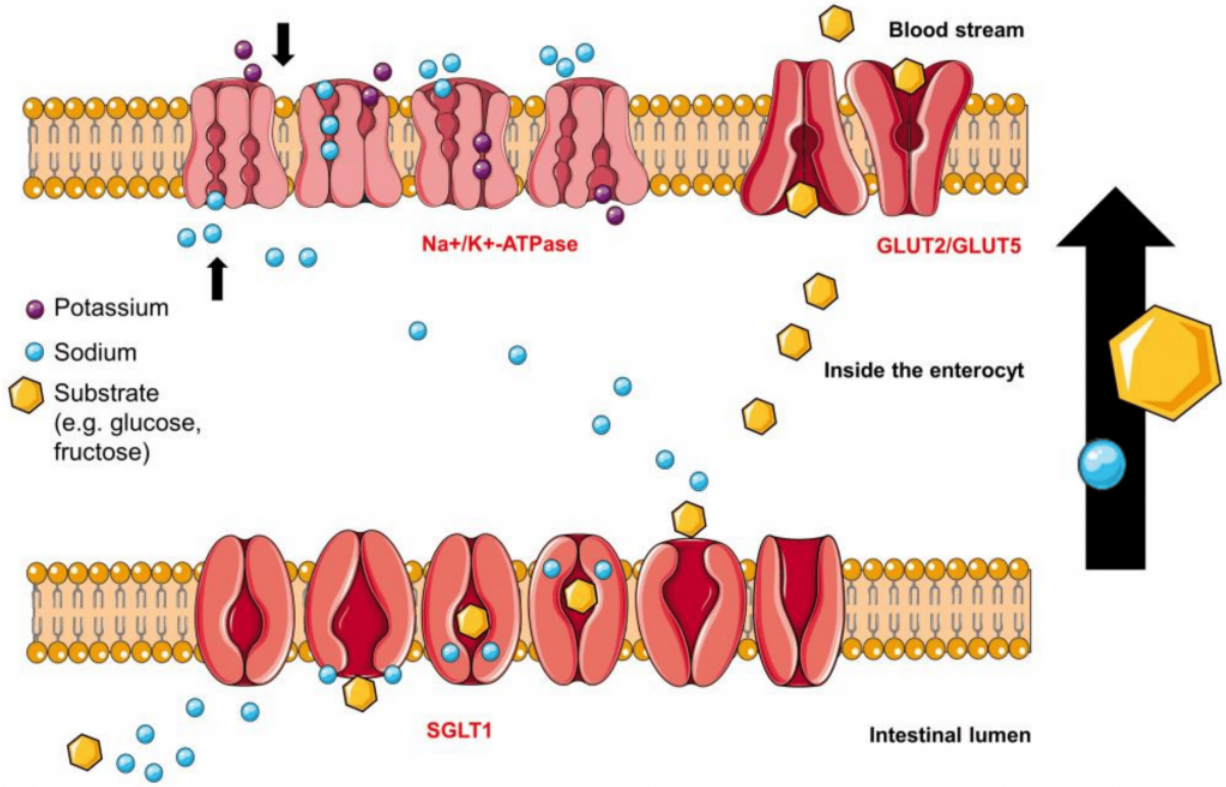

Figure 4.1 Glucose uptake in the small intestine occurs via different protein transporters. Image Source: (Fig 5) by Katharina Schreck and Matthias F. Melzig is used under a CC-BY 4.0 license.

As soon as chyme is released into the small intestine, it also triggers the release of hormones called **incretins**. (Figure 4.2) There are two incretins that are very important called glucagon-like peptide 1 (**GLP1**) and glucose-dependent insulinotropic peptide (**GIP1**). These are polypeptides that are secreted by specific cells of the upper and lower intestine that travel to the pancreas and help prepare it for the incoming spike in blood sugar. In this way, the action of incretins occurs even before any glucose enters the blood stream.

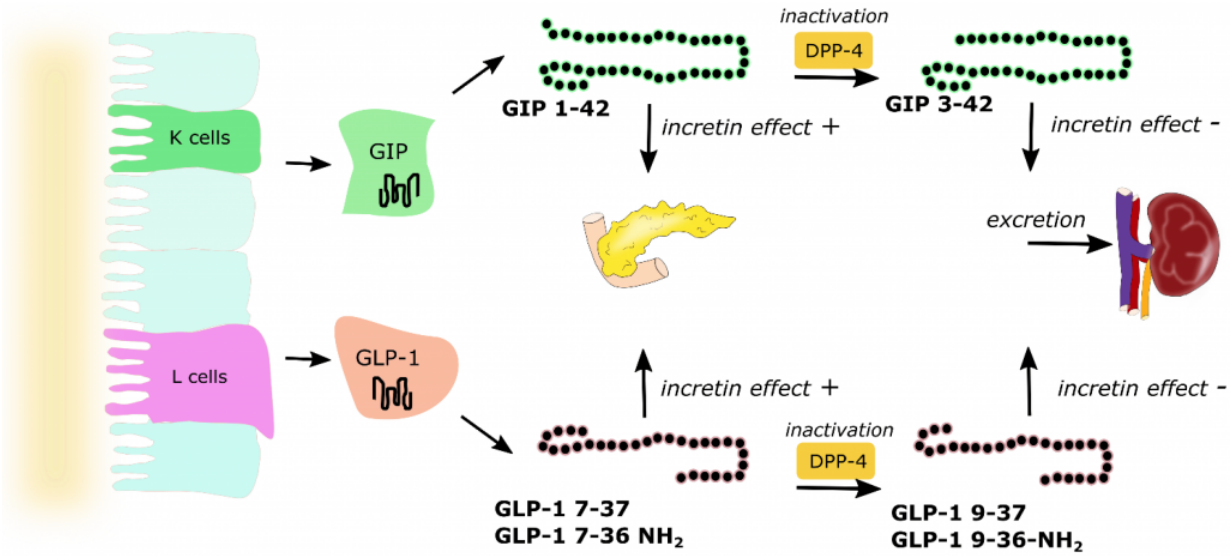

Figure 4.2 Incretin signalling in the small intestine. Image Source: (Fig 3) by Joanna Michałowska, Ewa Miller-Kasprzak and Paweł Bogdański is used under a CC-BY 4.0 license.

GIP has multiple roles including promoting insulin secretion, suppressing glucagon release, and retarding gastric emptying to provide additional time for digestion thereby softening large peaks in glucose levels. Incretins also provide a feeling of satiety,

which reduces food consumption. Incretins are rapidly deactivated by a set of enzymes called DDP-4 (dipeptidyl peptidase) in the blood stream and incretins are only active for a few minutes.

Carbohydrate Digestion – Pancreas

The pancreas is one of the most important organs for regulating blood glucose levels. (Figure 4.3) Once glucose enters the blood stream via the small intestine, multiple organs within the body start to respond. The pancreatic cells harbour GLUT2 transporters (similar to the small intestine) and these transporters uptake the glucose from the blood (specifically the pancreatic β-cells). The increased of intracellular glucose concentrations triggers ATP generation (via glycolysis, Krebs/TCA cycle, etc.) which leads to a high [ATP] state. ATP binds to K_{ATP} channels (ATP sensitive potassium channels) which causes the potassium channels to close, leading to a change in membrane polarization. This change triggers opening of voltage gated Ca^{2+} channels. The increase in Ca^{2+} ion content triggers secretion of **insulin** from the β-cells into the blood stream. Insulin is a critical hormone in carbohydrate digestion, and is responsible for making cells more permeable to glucose, which ultimately reduces glucose concentrations in the blood.

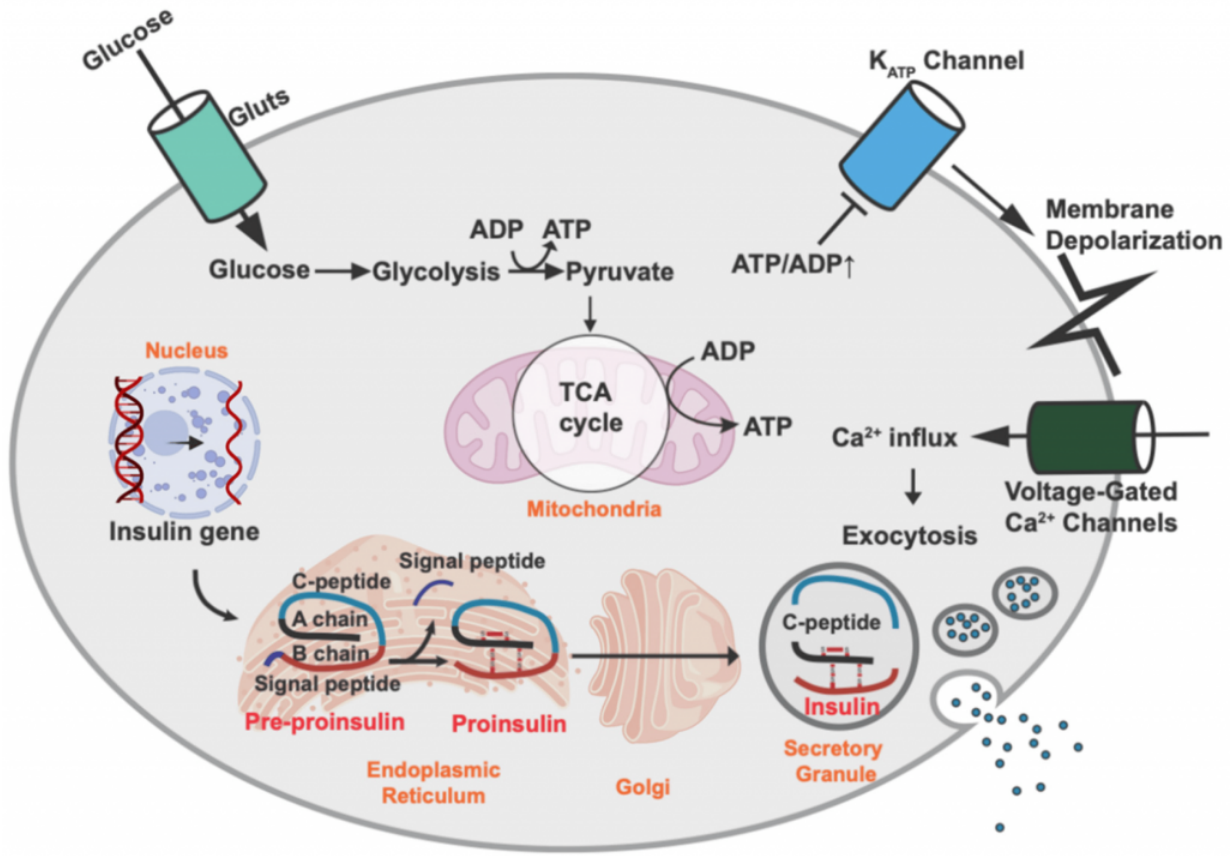

Figure 4.3 Release of insulin from pancreatic β-cells following glucose stimulation. Image Source: (Fig 1) by Ji-Hye Lee and Jaemin Lee is used under a CC-BY 4.0 license.

Insulin will travel through the blood stream and bind to insulin receptors on different types of cells. The binding event initiates a signal cascade inside the cell with a net result of glucose transporters translocating to the cell surface. The glucose transporters on skeletal and cardiac muscle are insulin expression dependent GLUT4 (whereas the transporters in the pancreas and small intestine are insulin independent GLUT2 proteins). The presence of these transporters enables the uptake of glucose from the blood providing an energy source to the cells and restoring normal glucose levels.

In cases where energy is required but food intake is not occurring, blood sugar levels can start to fall. The α-cells of the pancreas sense lowering of blood sugar levels and release the polypeptide, glucagon. **Glucagon** is the complementary hormone to insulin, and it signals the liver to release glucose (which is stored in the liver in a polymer called glycogen). The release of glucose will correspondingly raise blood sugar levels, and in this way, the interplay between the pancreas and liver by way of the hormones, insulin and glucagon, regulates homeostasis in the body. (Figure 4.4)

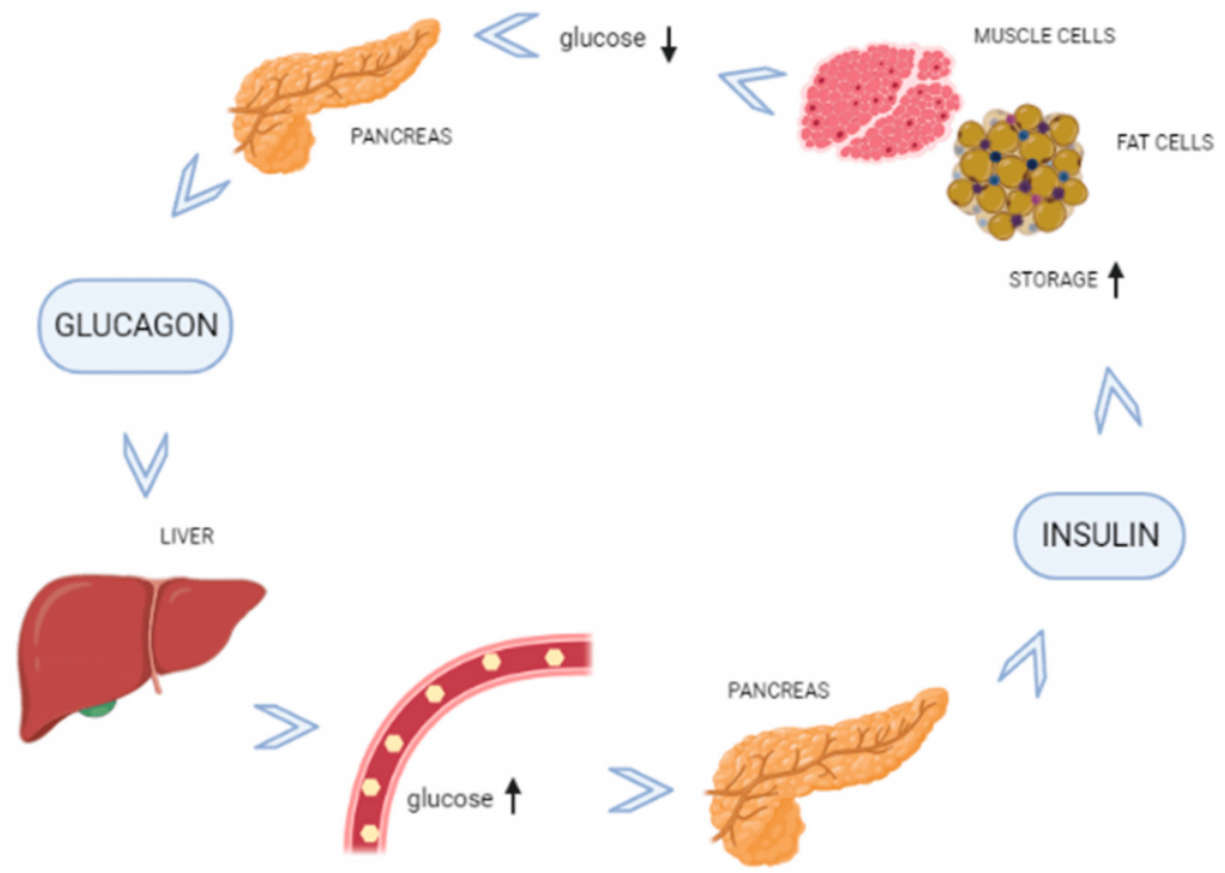

Figure 4.4 Regulation of blood glucose homeostasis by hormone signaling between the pancreas and liver. Image Source: (Fig 1) by Selvaraj Jayaraman, Anitha Roy, Srinivasan Vengadassalapathy, Ramya Sekar, Vishnu Priya Veeraraghavan, Ponnulakshmi Rajagopal, Gayathri Rengasamy, Raktim Mukherjee, Durairaj Sekar and Reji Manjunathan is used under a CC-BY 4.0 license.

Carbohydrate Digestion – Liver

The liver is critical in maintaining blood sugar levels. The liver stores excess glucose in the form of **glycogen** (a massive polymer of glucose). The pancreas and liver work in lockstep to ensure blood glucose levels remain constant throughout the daily demands and resources available to the body. Therefore, when the body has extra glucose, the pancreas releases insulin which causes the liver to starting storing glucose, and during periods where blood glucose levels fall, the pancreas releases glucagon which causes the liver to start breaking down glycogen to release glucose in the blood stream.
