Insulin controls glucose uptake

Adipose tissue and muscles contain a passive glucose transporter GluT4 which takes up glucose from blood. (This is not driven by Na\(^+\) symport, the process that intestinal cells use to absorb glucose from the gut.)

After a glucose rich meal, blood glucose rises above the normal 5 mM, and this stimulates insulin release from the pancreas. Insulin in turn stimulates glucose uptake in these tissues, to be stored as glycogen in muscle or used for fatty acid biosynthesis in adipose tissue.

After exposure to insulin, \(V_{\text{max}}\) for glucose uptake goes up 10-12 fold, while \(K_{\text{M}}\) stays constant. When insulin levels decline, the glucose transport rate decreases to the original value over about 2 h. Changes in \(V_{\text{max}}\) often reflect change in the amount of enzyme, but the insulin stimulated increase is observed even when no new protein synthesis occurs.

The GluT4 transporter is held internally in the membrane of storage vesicles. After insulin stimulation, which involves a protein tyrosine kinase cascade, the vesicles undergo exocytosis and fuse with the plasma membrane, where they are now available to transport glucose. In the absence of insulin, the GluT4 molecules are taken back into storage by endocytosis.

The N-terminal end of GluT4 is recognized by an as yet unknown mechanism. If the N-terminal is removed, GluT4 transports glucose normally, but does not undergo endocytosis, so the modified GluT4 is always available.
An elaborate system of transporters links cytoplasm and mitochondrion

**H⁺ symporters:** Both pyruvate and inorganic phosphate are brought into mitochondria by symporters linked to H⁺. Both symport systems are neutral with respect to charge, so only the ΔpH component of the H⁺ gradient is used.

\[
\text{H}^+:\text{pyruvate}^- \text{translocator} \\
\text{Pyruvate}^-_{\text{out}} + H^+_{\text{out}} \rightarrow H^+_{\text{in}} + \text{pyruvate}^-_{\text{in}}
\]

\[
\text{H}^+:\text{phosphate}^- \text{translocator} \\
H_2\text{PO}_4^-_{\text{out}} + H^+_{\text{out}} \rightarrow H^+_{\text{in}} + H_2\text{PO}_4^-_{\text{in}}
\]

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The tricarboxylate carrier links TCA cycle and FA biosynthesis

The proton gradient of oxidative phosphorylation helps drive pyruvate into the mitochondrion.

Citrate export by the tricarboxylate carrier is actually opposed by the H⁺ gradient, so that citrate export only occurs with a large citrate build up.

This occurs if [ADP] is low, so that TCA cycle oxidation reactions slow down. Export of citrate to the cytoplasm bypasses most of the oxidative reactions of the TCA cycle. Malate generated in the cytoplasm balances citrate export, ensuring that substrate to generate new citrate is maintained.

Secondary NADPH generating reactions also require citrate or isocitrate export

Isocitrate can also be transported by the tricarboxylate carrier in exchange for malate.

This provides substrate for the cytoplasmic NADP⁺ dependent isozyme of isocitrate dehydrogenase.

α-Ketoglutarate that accumulates in the cytoplasm can return to the mitochondrion via the α-ketoglutarate carrier in exchange for malate, and then can continue in the TCA cycle. Since malate is also the substrate exchanged for isocitrate, the same amount of malate is used in each direction, so there is no net gain or loss of malate from either compartment.
Acyl carnitine transporter

Long chain acyl-CoA from fat breakdown has to enter the mitochondrion for \( \beta \)-oxidation. The process carries the acyl group in, but leaves the cytoplasmic HSCoA in the cytoplasm. The acyl chain is transferred to a molecule called carnitine internally within carnitine acyltransferase I.

Acyl carnitine exchanges across the membrane for free carnitine via an antiport carrier, and then on the mitochondrial side carnitine acyl transferase II transfers the acyl group back onto a mitochondrial molecule of HSCoA (Lehninger p. 603).

Carnitine acyltransferase I is inhibited by the presence of malonyl-CoA in the cytoplasm; if condition are suitable for fatty acid synthesis, fatty acids are not brought into the mitochondrion.

The malate-aspartate shuttle transfers NADH into mitochondria by an indirect mechanism

There is no direct translocator for NADH or NAD\(^+\) in the mitochondrial membrane.

Instead, cytoplasmic NADH produced by glycolysis is used to reduce oxaloacetate to malate in the cytoplasm.

Malate is then transported into the mitochondrion

Once inside, malate is reoxidized to oxaloacetate, so that an equivalent molecule of NADH is generated inside the mitochondria, where it has access to the oxidative phosphorylation system.

But oxaloacetate is not a transport substrate, so where does cytoplasmic oxaloacetate come from? What balances the malate transport?
Oxaloacetate can also be produced from aspartate by the action of aspartate aminotransferase (also known as transaminase).

Aspartate can be transported by a specific aspartate:glutamic acid antiporter.

This still leaves open the question of balancing substrates for the transporters and for the aminotransferases. These are provided by an opposite cycle made up of glutamic acid and α-ketoglutarate. The complete circuit of two antiports and the opposing cycles of C₄ and C₅ compounds is called the malate-aspartate shuttle (Lehninger p. 685).

Conversion of α-ketoglutarate to glutamic acid recycles the aminotransferase coenzyme pyridoxamine phosphate (PMP) back to pyridoxal phosphate (PLP) in the cytoplasm. The opposite happens inside the mitochondrion.

α-Ketoglutarate exchanges with malate on the α-ketoglutarate carrier. Glutamic acid exchanges for aspartate on their own antiporter.

The aspartate:glutamic acid antiporter exchanges neutral glutamic acid for negative aspartate, making the process electrogenic, driven by the membrane potential $\Delta\psi$ of the mitochondrial membrane. Export of aspartate$^-$ to the positive side of the membrane is favoured. This sets the direction for the whole cycle.