

BCMB 8020
April 13, 2006

Glycogen

Most common storage form of glucose in animals, bacteria (yeast)

Branched polymer of α 1,4- & α 1,6-linked glucose

Similar to amylopectin; but with smaller and more frequent branching: branching every 8-12 residues

In animals glycogen is stored largely in the liver and muscle

In mammals glycogen can make up ~10% liver mass & 2% of muscle mass

Glycogen use in animals

Insulin

glucagon or adrenaline
(fasting) (flight or fight)

Excess Glucose \leftrightarrow GLYCOGEN \leftrightarrow replenished glucose
(i.e. after feeding)

glycogen synthesis

glycogenolysis

In vertebrates - 2/3 of dietary glucose is converted to glycogen

transported in blood

Food \rightarrow Glucose \rightarrow Intestine \rightarrow cells \rightarrow converted to Glc-6-P
absorbed hexokinase

liver (GLUT1)

muscle (*GLUT4, GLUT 1)

*=insulin stimulated

The stimulation of glycogen synthesis is one of the major physiological responses modulated by Insulin

The exact mechanism by which insulin stimulates glycogen synthesis is not known

Insulin:

- Controls uptake and transport of glucose (GLUT4)
- Regulates phosphorylation and activation state of glycogen biosynthetic and catabolic enzymes (glycogen synthase; glycogen phosphorylase)

Steps in Glycogen Synthesis

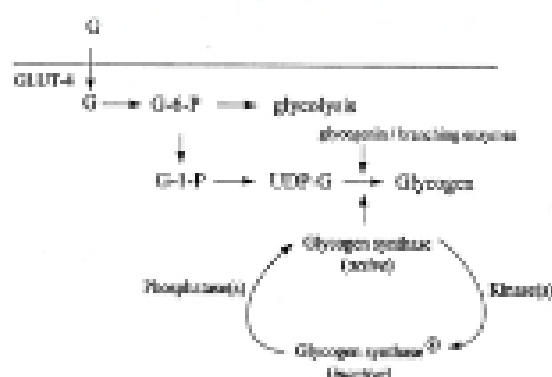
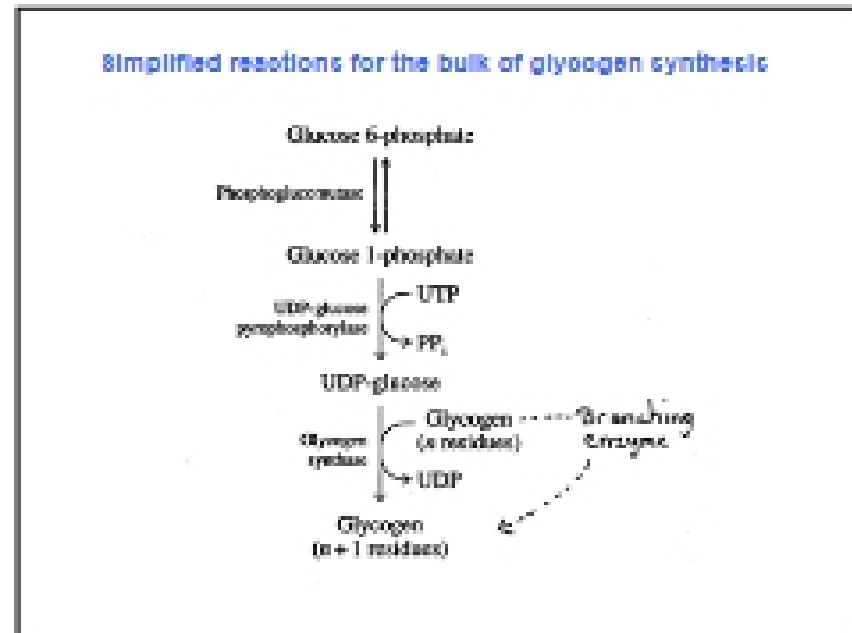
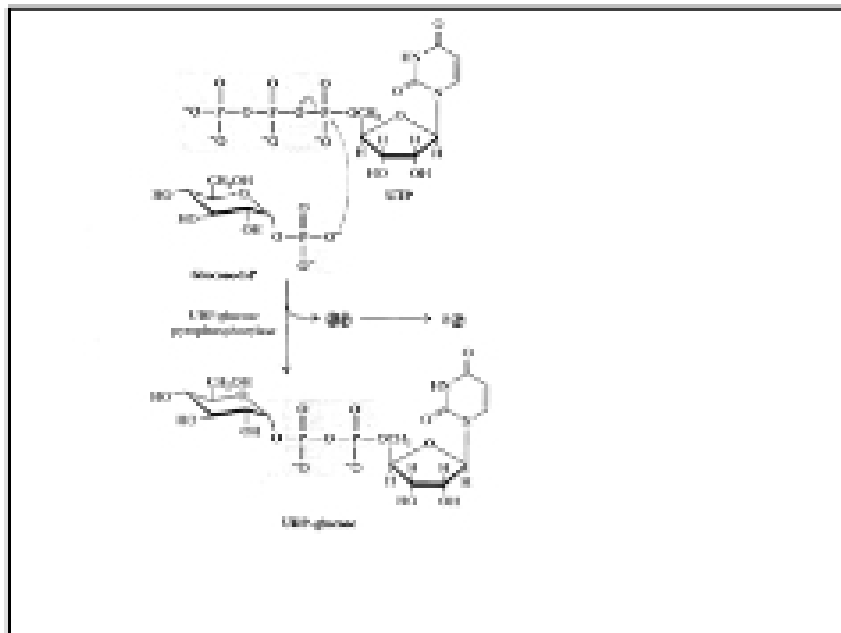


Fig. 1. In vertebrate cells the essential steps of glycogen synthesis. Glucose enters the cell in vertebrate animals through a facilitated transport system mediated by insulin-stimulated glucose transporters (GLUT 1-GLUT 4). Glucose is converted first to glucose-6-phosphate in response to insulin. Glucose-6-phosphate is converted to glucose-1-phosphate by hexokinase, which also catalyzes conversion of glucose-6-phosphate to 1,6-bisphosphoglycerate. Glucose-1-phosphate is converted to UDP-glucose by UDP-glucose pyrophosphorylase, which liberates glucose-6-phosphate as pyrophosphate. Glycogen synthase transfers the glucose units from UDP-glucose to the non-reducing ends of glycogen molecules. Glycogen-synthase activity is regulated by phosphorylation and dephosphorylation. Glycogen synthase activity is stimulated by insulin-stimulated phosphatases and inhibited by protein kinases that are activated in response to stress (e.g., glucagon).

Synthesis of the chemically activated substrate for glycogen synthesis, UDP-Glc, by UDP-Glc pyrophosphorylase

(Luis Leloir, discovered NDP-sugars)

The synthesis of UDP-Glc is driven by the subsequent hydrolysis of pyrophosphate



The question of how glycogen synthesis was initiated remained open for many years. It is now known that glycogen synthesis begins by the Mn⁺⁺-dependent self-glycosylation of glycogenin on Tyr184 to form a glycogenin with an average glucose chain of DP 8 (maltooctose).

Steps in glycogen synthesis

Self-glycosylation of glycogenin (~37 kD) on Tyr-184 in a glycosidic linkage

UDP-Glc + Proglycogen Synthase + Branching Enzyme → **Proglycogen** (~ 400,000 daltons; ~DP 3470)

Proglycogen + UDP-Glc + Macroglycogen Synthase + Branching Enzyme → Macroglycogen (~ 10⁷ daltons; ~DP 81,728)

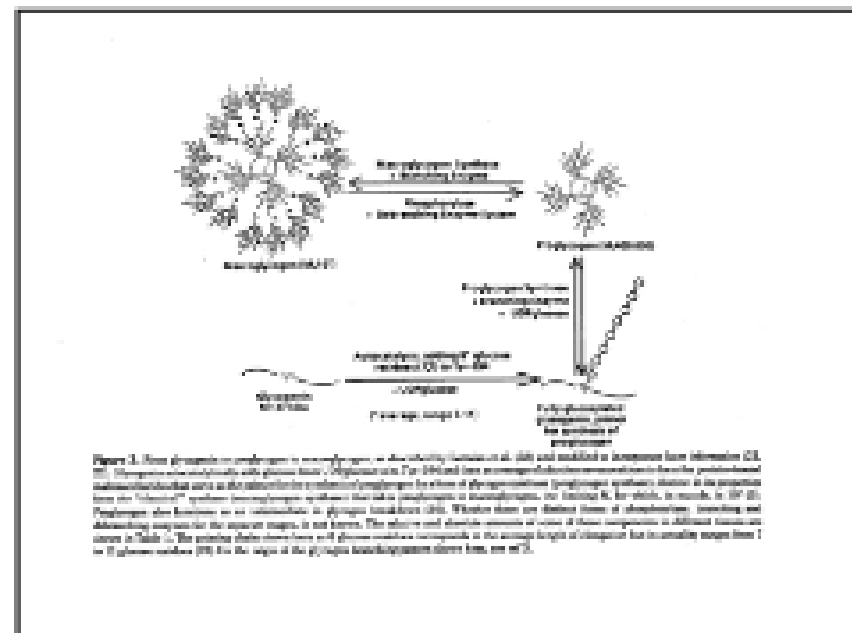


Figure 1. How glycogen synthesis is initiated. Glycogenin (37 kD) and modified tyrosine from molecule (2), (3). Glycogenin is covalently linked to glucose from UDP-glucose. The DP4000 proglycogen (400,000 daltons) is formed by the action of glycogen synthase on the maltooctose unit at the site of the tyrosine-glycosylation. The action of glycogen synthase on the proglycogen is shown in the reaction from the "Proglycogen" system. Glycogen synthase continues to add a glucose to the proglycogen, and, finally, it results in DP 3470. Proglycogen also functions as an intermediate in glycogen synthesis (2). Branching enzyme (4) cleaves the linear form of proglycogen, creating and allowing expansion of the glycogen granule in its form. The chain and branch points of some of these proglycogen in different positions are in (5). The specific data structure of these molecules correspond to the average length of proglycogen for a normally sized liver (1 × 10⁷ glucose residues (DP) for the size of the glycogen macromolecule shown here, see (6).

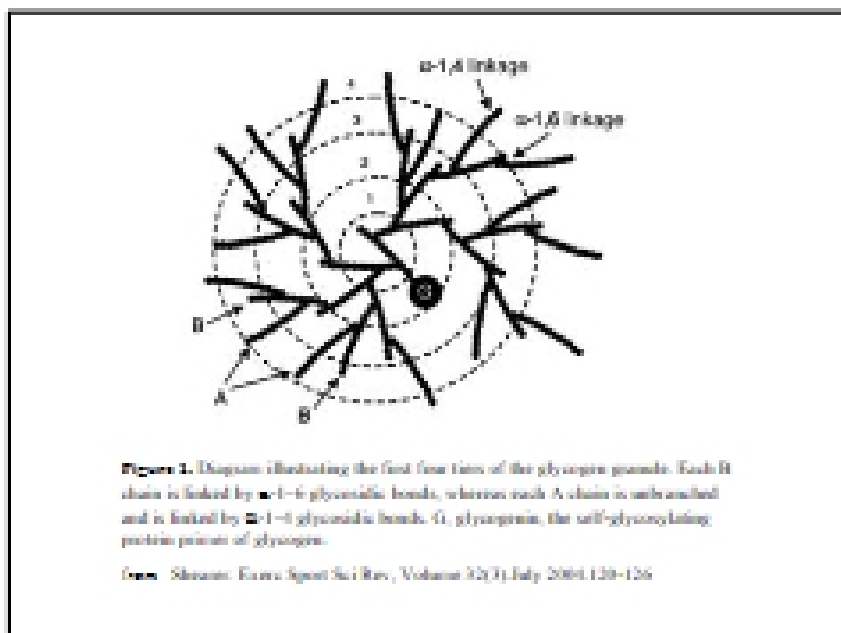


Figure 1. Diagram illustrating the first few lines of the glycogen granule. Each B chain is linked by α-1-4 glycosidic bonds, whereas each A chain is unbranched and is linked by α-1-6 glycosidic bonds. G, glycogenin, the self-glycosylating protein primer of glycogen.

From: Sheehan: *Exercise Sport Sci Res*, Volume 32(3), July 2004, 120-126

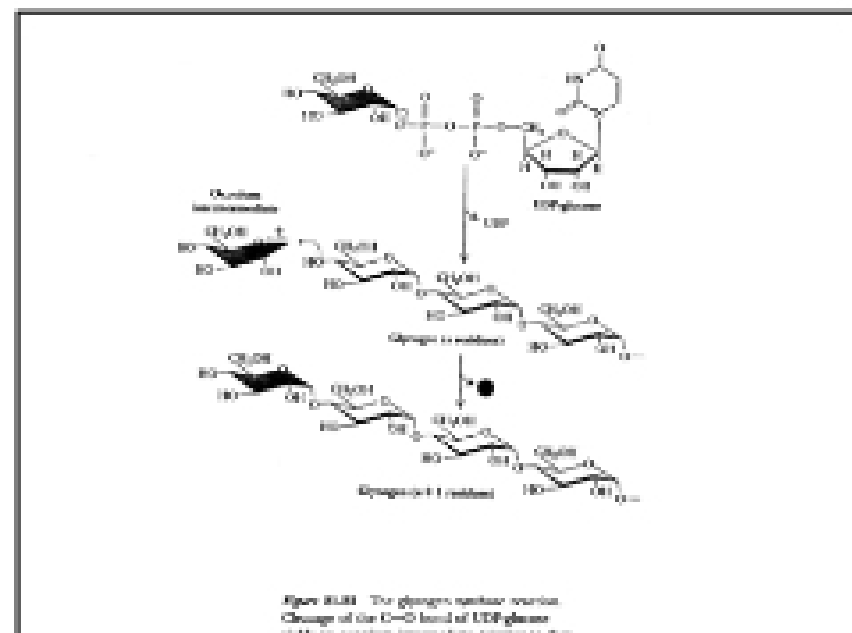


Figure 1(B). The glycogen synthase reaction. Change of the C-2 bond of UDP-glucose (4) to a glucose unit on the glycogen chain.

