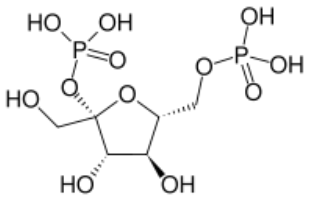
Fructose 2,6-bisphosphate



Fructose 2,6-bisphosphate, is a metabolite that allosterically affects the activity of the enzymes phosphofructokinase 1 (PFK-1) and fructose 1,6-bisphosphatase (FBPase-1) to regulate glycolysis and gluconeogenesis.

F-2,6-BP is synthesized and broken down by the **bifunctional enzyme** phosphofructokinase 2/fructose-2,6-bisphosphatase (PFK-2/FBPase-2).
The synthesis of F-2,6-BP is performed through the phosphorylation of fructose 6-phosphate using ATP by the PFK-2 portion of the enzyme.
The breakdown of F-2,6-BP is catalyzed by dephosphorylation by FBPase-2 to produce Fructose 6-phosphate and P_i.

F-2,6-BP strongly activates glucose breakdown in glycolysis through **allosteric modulation of phosphofructokinase 1** (PFK-1).
Elevated expression of F-2,6-BP levels in the liver allosterically activates phosphofructokinase 1 by increasing the enzyme's affinity for fructose 6-phosphate, while decreasing its affinity for inhibitory ATP and citrate. At physiological concentration, PFK-1 is almost completely inactive, but interaction with F-2,6-BP activates the enzyme to stimulate glycolysis and enhance breakdown of glucose.

The concentration of F-2,6-BP in cells is controlled through regulation of the synthesis and breakdown by PFK-2/FBPase-2. The primary regulators of this are the hormones insulin, glucagon, and epinephrine, which affect the enzyme through phosphorlyation/dephosphorylation reactions.

Release of the hormone **glucagon** triggers production of cyclic adenosine monophosphate (cAMP), which activates a cAMP-dependent protein kinase A. This kinase phosphorylates the PFK-2/FBPase-2 enzyme at an NH_2-terminal Ser residue with ATP activating the FBPase-2 activity and inhibit the PFK-2 activity of the enzyme, thus reducing levels of F-2,6-BP in the cell. (PFK-1 inhibited, glycolysis slows down, gluconeogenesis accelerates).

Insulin triggers the opposite response. As a phosphoprotein phosphatase, insulin dephosphorylates the enzyme, thus activating the PFK-2 and inhibiting the FBPase-2 activities. With additional F-2,6-BP present, activation of PFK-1 occurs to stimulate glycolysis while inhibiting gluconeogenesis.