CONCEPT: INSULIN SIGNALING ON GLUCOSE METABOLISM

●Recall: Insulin affects *glucose metabolism* by: 1) ↑ _____ *expression* & 2) ↑ _____ *synthesis*.

□ Recall: both help to _____ [glucose] in the blood.

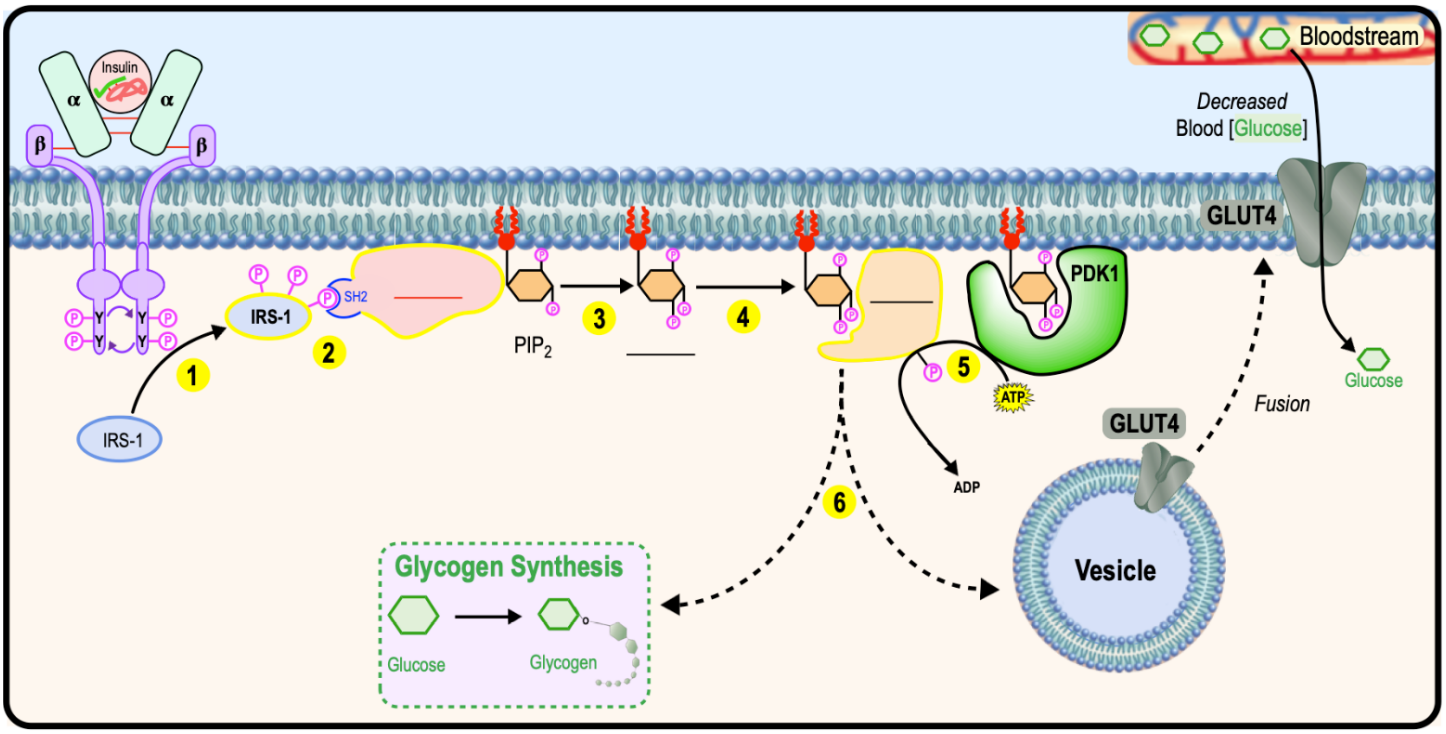
□ Insulin signals ↓ blood [glucose] via the following pathway: PI3K → PIP_3 → PDK1 → PKB.

Insulin Signaling Decreases Blood [Glucose]

●_____ steps in insulin's RTK signaling cascade to decrease blood glucose levels:

1. After a high-glucose meal, *insulin* is released & binds its receptor, which *phosphorylates & activates* _____.
2. Active IRS-1 binds SH2 domain of ***P**hospho**i**nositide **3** **K**inase* (_____) to *activate* it.
3. ***P**hosphatidyl**i**nositol 4,5-bis**p**hosphate* (PIP___) —*PI3K*→ ***P**hosphatidyl**i**nositol 3,4,5-tris**p**hosphate* (PIP___).
4. PIP_3 *binds* **P**rotein **K**inase **B** (_____ or Akt).
5. **P**IP_3-**D**ependent **K**inase **1** (_____) *phosphorylates* & *activates* PKB.
6. Active PKB phosphorylates targets controlling _____ *expression* & _____ *synthesis*.

□ Both events help _____ blood [glucose].



EXAMPLE: If you delete the PKB gene from insulin-responsive cells, what would you likely observe in insulin's presence?

a) PI3K is not activated.

b) PDK1 is not activated.

c) GLUT4 is not expressed & is retained in intracellular vesicles.

d) Phosphatidylinositol is cleaved by phospholipase C.

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Insulin Signaling Activates Glycogen Synthesis

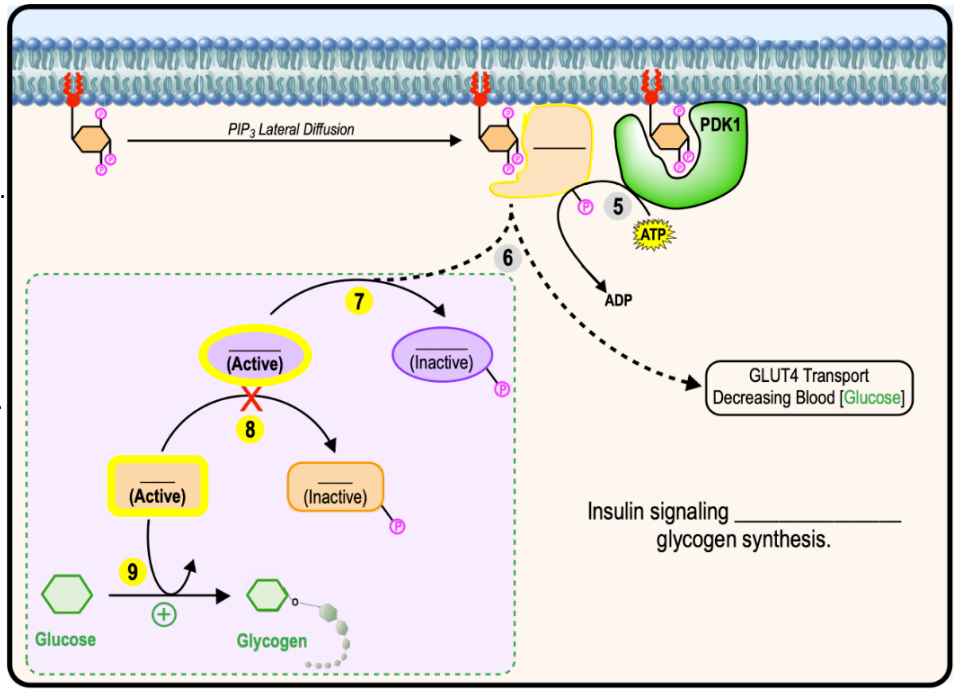
- ***G**lycogen **S**ynthase* (GS): enzyme that synthesizes _____ (converting glucose into glycogen).
  - □ Usually ***G**lycogen **S**ynthase **K**inase **3*** (_____) *phosphorylates* & _____ GS.
  - □ HOWEVER, active PKB *phosphorylates* & _____ GSK3 (which allows *activation* of GS).

EXAMPLE: Insulin Activates Glycogen Synthesis.

7 PKB phosphorylates & inhibits _____.

8 Inactive GSK3 can no longer inhibit GS.

9 Active GS synthesizes _____.



PRACTICE: Place the following insulin signaling transduction events in order of occurrence (event 9 is provided).

a) Full activation of PKB/Akt _____.

b) Activated PI3K converts PIP_2 to PIP_3 _____.

c) GLUT4 expressed in the cell membrane ___9___.

d) Ligand/insulin binding to the insulin receptor _____.

e) GSK3 is phosphorylated & inactivated _____.

f) Activated PDK1 phosphorylates & activates of PKB/Akt _____.

g) IRS-1 is phosphorylated & activated by the insulin receptor _____.

h) Autophosphorylation of the insulin receptor _____.

i) PI3K is activated upon its SH2 domain binding phosphorylated IRS-1 _____.

j) Glycogen synthase converts glucose to glycogen _____.

k) PIP_3 molecules laterally diffuse to bind PKB/Akt & PDK1 _____.

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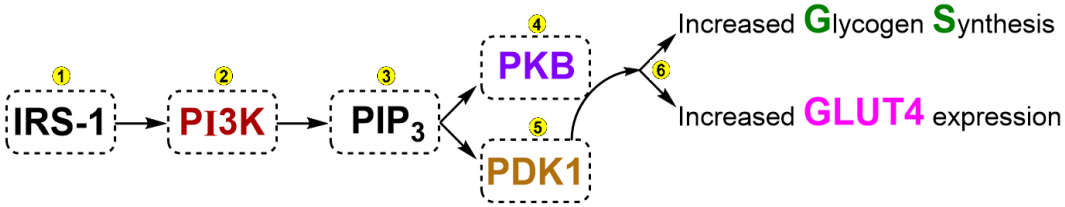
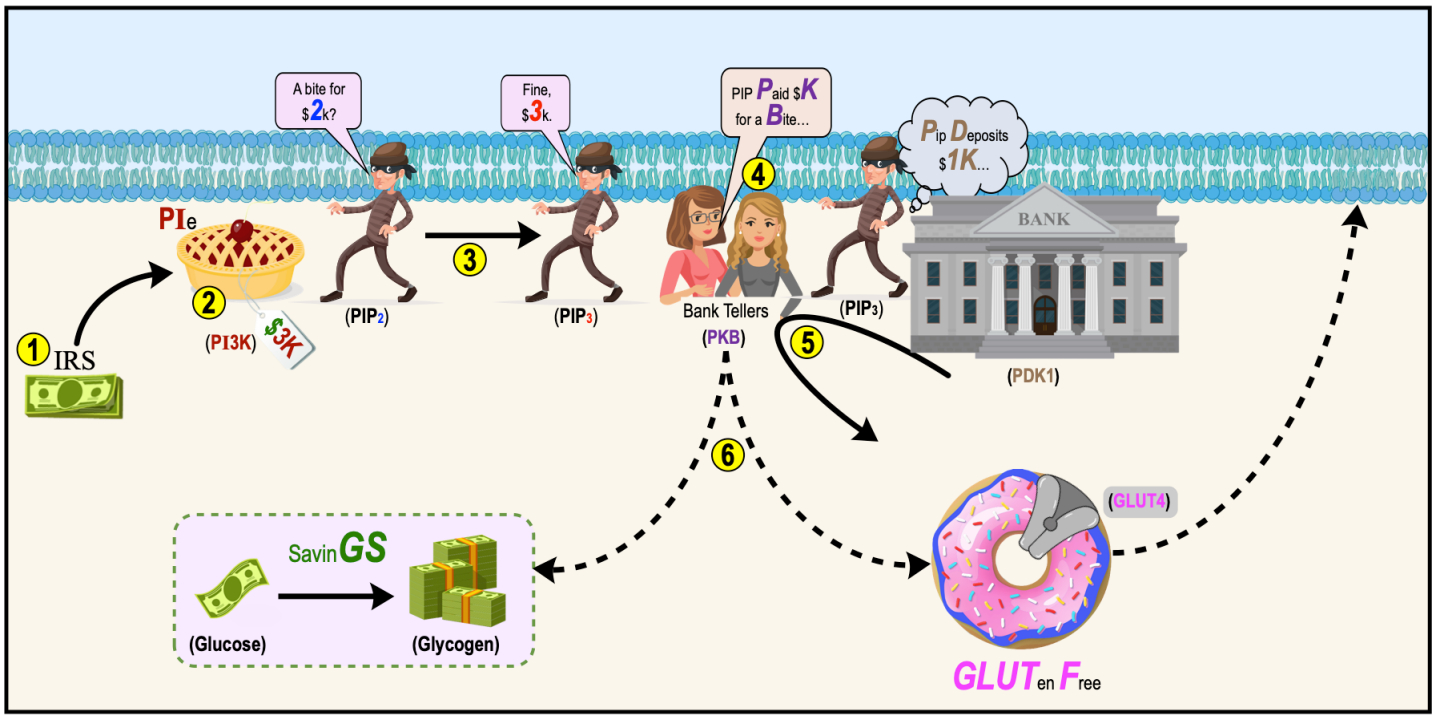
How to Remember Insulin RTK Signaling on Glucose Metabolism?



1. **IRS** gives a tax refund (**IRS-1**).
2. Cell buys a ***PI***e & puts a fake $***3K*** label on it (***PI3K***) to prank PIP (*activation* of ***PI3K***).
3. ***PIP*** first offers $***2***k for a *bite*, but then agrees to pay $***3***k (***PIP2*** *conversion* to ***PIP3***).
4. Bank tellers are shocked when they hear PIP **P**aid thousands ($***K***) for a ***B***ite (***PKB***).
5. ***P***IP ***D***eposits ***1K*** (***PDK1***) at the bank but bank tellers (***PKB***) handle the transaction (***PDK1*** *activates* ***PKB***).
6. Bank tellers *increase* PIP's savin***GS*** (***G***lycogen ***S***ynthesis) & *express* order ***GLUT***en ***F***ree (***GLUT4***) donut.



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EXAMPLE: Place the following insulin signal transduction events in order of occurrence (1-8).

a) Activation of PI3K _____.
b) Activation of the insulin receptor _____.
c) Activation of PDK1 _____.
d) GLUT4 transporter expressed in the membrane _____.
e) Conversion of PIP_2 to PIP_3 _____.
f) Binding of insulin to the receptor _____.
g) Full activation of PKB _____.
h) Phosphorylation of IRS-1 _____.

PRACTICE: All of the following are true of the reaction catalyzed by PI3K EXCEPT:

a) Phosphatidylinositol bisphosphate is a substrate of PI3K.
b) Inositol triphosphate is a substrate of PI3K.
c) ATP is a substrate of PI3K.
d) Phosphatidylinositol triphosphate is a product of PI3K.
e) ADP is a product of PI3K.

PRACTICE: Which of the following results would you predict to occur if a mutation changes a Tyr residue of the Insulin Receptor to Ala?

a) Inability to take up glucose from the bloodstream.
b) Constant uptake of glucose from the bloodstream.
c) Upregulated glycogen synthesis and GLUT4 transport to the membrane.
d) B and C.

PRACTICE: IRS-1 is an essential adaptor protein in the insulin signaling pathway. If IRS-1 was under expressed in muscle cells, what effect would you expect to see on glycogen synthesis?

a) Protein kinase B would remain inactive, resulting in increased glycogen synthesis.
b) Protein kinase B would be overstimulated, resulting in increased glycogen synthesis.
c) Protein kinase B would remain inactive, resulting in decreased glycogen synthesis.
d) Protein kinase B would be overstimulated, resulting in decreased glycogen synthesis.