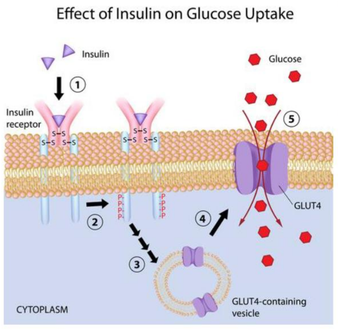
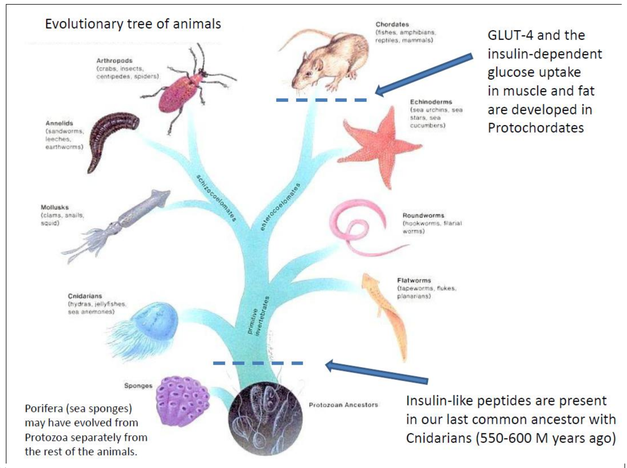
Making Sense of Insulin

Presenting Author: Francisco Javier Martínez Martín, M.D.
Endocrinology Dpt, Clin. San Roque, Las Palmas de Gran Canaria, Spain

¿What do we need insulin for?



- The binding of insulin to its receptor triggers a complex cascade of events.
- Surely the main effect is translocation of GLUT4 glucose transporters to the plasma membrane.
- This action is required for glucose uptake in striated muscle and adipose cells.



Evolutionary Background

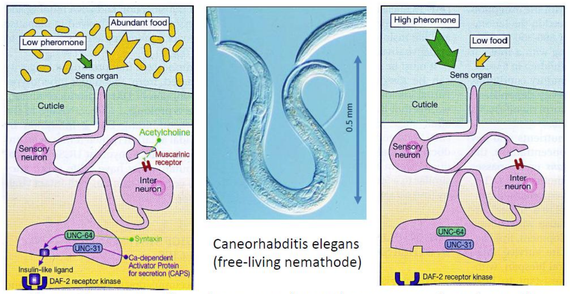
- All Metazoa with differentiated tissues including a nervous system have a signaling system with insulin-like peptides and receptors.
- Their nucleotide sequence has been highly preserved, including the intron-exon sequences, proving a common ancestry.
- However, of all animals only the Chordata have insulin-dependent glucose transporters (GLUT4)

The big question…

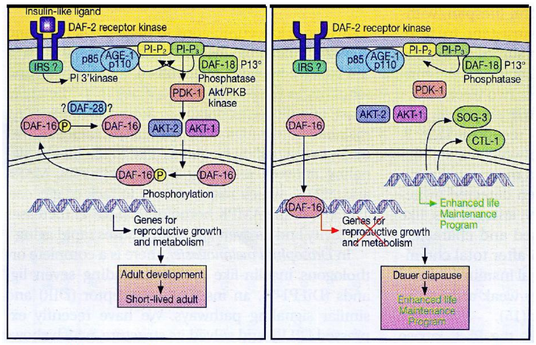
- Why did striated muscle and adipose tissue in chordates need to have GLUT4 and therefore insulin dependency for glucose uptake?
- What do non-chordates do with it?
- How did the chordate insulin functions develop?
- How does it apply to us?

- In a word, **what is the sense of having insulin?**

The case of Caneorhabditis elegans

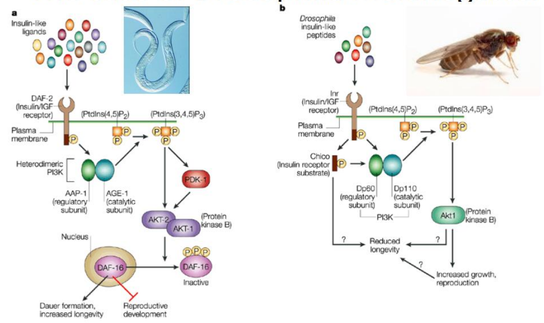


- About 60 sensory colinergic neurons detect the presence of nutrients. Also, the population density is detected by pheromone concentration.
- In conditions of abundant food and low competition, an insulin-like peptide is released by an interneuron and binds DAF-2 (insulin receptor homologue).
- Under low food or high population density, both neurons are inhibited .



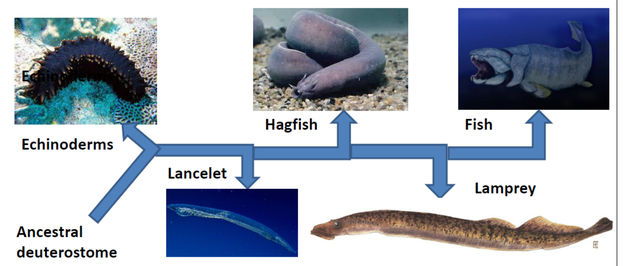
- Insulin-like activity phosphorilates DAF-16 and removes it from the nuclei, enabling metabolism, growth and reproductive processes and shortening the life span.
- The absence of insulin-like activity keeps the unphosphorilated DAF-16 in the nuclei repressing the transcription of the genes for reproductive growth and metabolism, and triggering expression of the dauer diapause program (long lasting dormant state).

The case of Drosophila melanogaster



- In Drosophila nutrient availability triggers the secretion of insulin-like peptides that activate a very similar cascade and also result in activation of metabolism, reproductive development and shortened lifespan.
- Blockade of the receptor stunts growht and reproduction but increases lifespan by 85%.

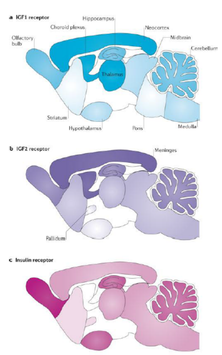
Protochordates, GLUT4 and IGF



- Amphioxus (lancelets) have only one insulin-like-peptide but Myxine (hagfish) already have distinct insulin and IGF peptides.
- Distinct IGF-1 and IGF-2 peptides appear in early fish.
- The GLUT4 phylogeny is incomplete. Fish, reptiles and mammals have it, and it possibly appeared with Agnatha (lampreys).

Insulin-like peptides in the mammalian brain

- Mammalian neurons have GLUT3, and do not need insulin for glucose uptake.
- However insulin and IGF receptors are highly expressed in the mammalian brain.
- They are implied in brain growth and differentiation, and in building circuitry essential for metabolic adaptation.
- In the adult brain each, insulin, IGF-1 and IGF-2 have different roles but , but ultimately their actions regulate energy homeostasis.
- Neurons produce insulin-like peptides in order to control energy allocation in invertebrates. In the mammalian brain, insulin and IGFs have similar roles.
- Loss of insulin signaling in the brain may be related to neurodegenerative diseases.

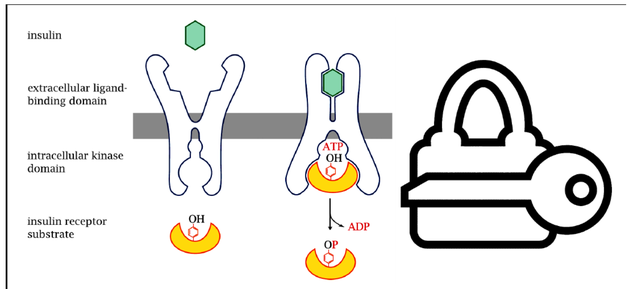


Conclusions (I)

- In most tissues (excepting striated muscle and fat) glucose uptake is not insulin-dependent.
- In non-chordate animals, not even muscle and fat are insulin-dependent for glucose uptake.
- We need the insulin signaling system, not to allow glucose uptake in muscle and fat (in the postprandial state), but in order to be able to close it (in the fasting state), saving glucose for non-dependent tissues.

Conclusions (II)

- **The insulin signaling system is the main switch between the anabolic and the catabolic state, regulating the allocation of energy resources.**
- This function is present in almost all Metazoa, predates allowing glucose uptake in muscle and fat by about 10^8 years and is quite well preserved along the evolutionary tree.
- In chordates part of this functionality has been transferred to the IGF signaling system, but insulin maintains a regulatory role of the developmental and reproductive functions in the central nervous system



- The insulin receptor and insulin are lock and key.
- But having a lock and key in a door only makes sense if sometimes we need to close it.

- Our glucocentric concept of insulin needs rethinking

Thanks for your attention. Any questions?