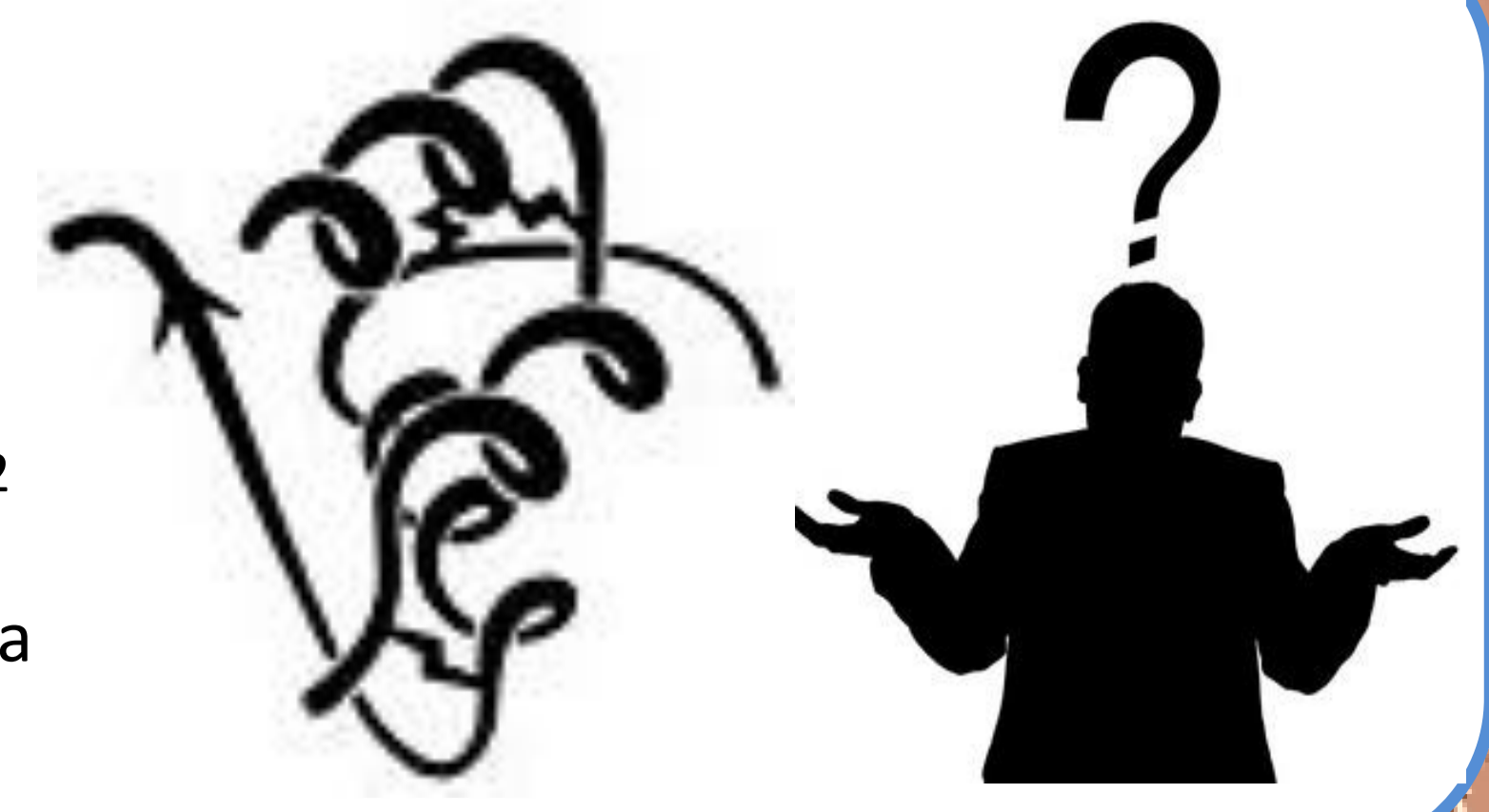


# MAKING SENSE OF INSULIN

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## Introduction & Objectives

Physicians routinely prescribe insulin without being aware of its biological role beyond the control of glycemia.

We set out to elucidate the complex role of insulin, from its inception in the earliest pluricellular animals.

## Material & Methods

Review of the scientific literature with emphasis on the insulin phylogeny; personal reflections.

## Results (I)

In mammals, the binding of insulin to its receptor elicits a cascade of events resulting in translocation of GLUT4 glucose transporters to the cell membrane, allowing glucose uptake by striated muscle and adipose tissues.

The earliest known Metazoa with differentiated tissues including a nervous system (Cnidaria: jellyfish, etc.) have a signaling system with insulin-like peptides (ILP) and receptors. Nucleotide sequences have been highly preserved ever since, including the intron-exon sequences, proving a common ancestry about 550-600 million years old.

Among animals, only Porifera (sea sponges, etc.), which have no nervous system and have apparently derived from protozoan ancestors independently of the rest of the Metazoa, are devoid of insulin-like peptides and receptors.

However, of all animals only the Chordata (vertebrates) have insulin-dependent glucose transporters (GLUT4). Therefore invertebrates have insulin-like peptides but their functions are not glucose uptake or glycemic control.

## Results (II)

The fact that glucose uptake is insulin-independent in most of our tissues, except fat and striated muscle (the only tissues with GLUT4 insulin-dependent glucose transporters) and that in invertebrates glucose uptake is independent of insulin in all tissues raises an interesting series of questions:

Why did striated muscle and adipose tissue in vertebrates need to have GLUT4 and therefore insulin dependency?

What do invertebrates use insulin for, and how did the new insulin functions develop in vertebrates?

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

## Results (III)

The glyco-centric roles of insulin appear in Chordata; the GLUT4 transporter is present in the earliest fish but not in animals earlier than Agnatha (lampreys) which were developed about 420 million years ago.

However, in all known invertebrates (with the exception of Porifera), insulin-like peptides and their receptors play a paramount role activating functions such as growth, development, tissue differentiation, reproductive maturation and fertility, and generally regulating the distribution of energy resources.

A well-studied case is the nematode *Caenorhabditis elegans*, in which 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 ILP is released by an interneuron and binds an insulin receptor homologue. Under low food or high population density, both neurons are inhibited. Insulin-like activity phosphorylates DAF-16 and removes it from the nuclei, enabling metabolism, growth and reproduction, and shortening the lifespan. The absence of insulin-like activity keeps the unphosphorylated DAF-16 in the nuclei repressing gene transcription for reproductive growth and metabolism, and triggering expression of the dauer program (long-lasting dormant state).

In *Drosophila melanogaster* (fruit fly) 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 growth and reproduction but increases lifespan.

## Results (IV)

In the evolution of Chordates, insulin-like growth factors (IGFs) are developed from ILPs (and also their receptors). 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 Agnatha (lampreys) and GLUT4 are present in early fish.

In Chordata, IGFs assume part of the ancestral ILP roles (growth, differentiation...), but insulin is not limited to a glucose uptake regulatory role. Although neurons have GLUT 3 transporters and are not insulin-dependent for glucose uptake, insulin receptors are highly expressed in the brain. Insulin/IGF signaling is implied in brain growth and differentiation, and in building circuitry essential for metabolic adaptation. In the adult brain, insulin, IGF-1 and IGF-2 have different roles, but ultimately their actions regulate energy homeostasis.

In invertebrates, neurons produce insulin-like peptides in order to control energy allocation. In our brain, insulin controls the transition between the anabolic and catabolic energy allocation states.

## Conclusions

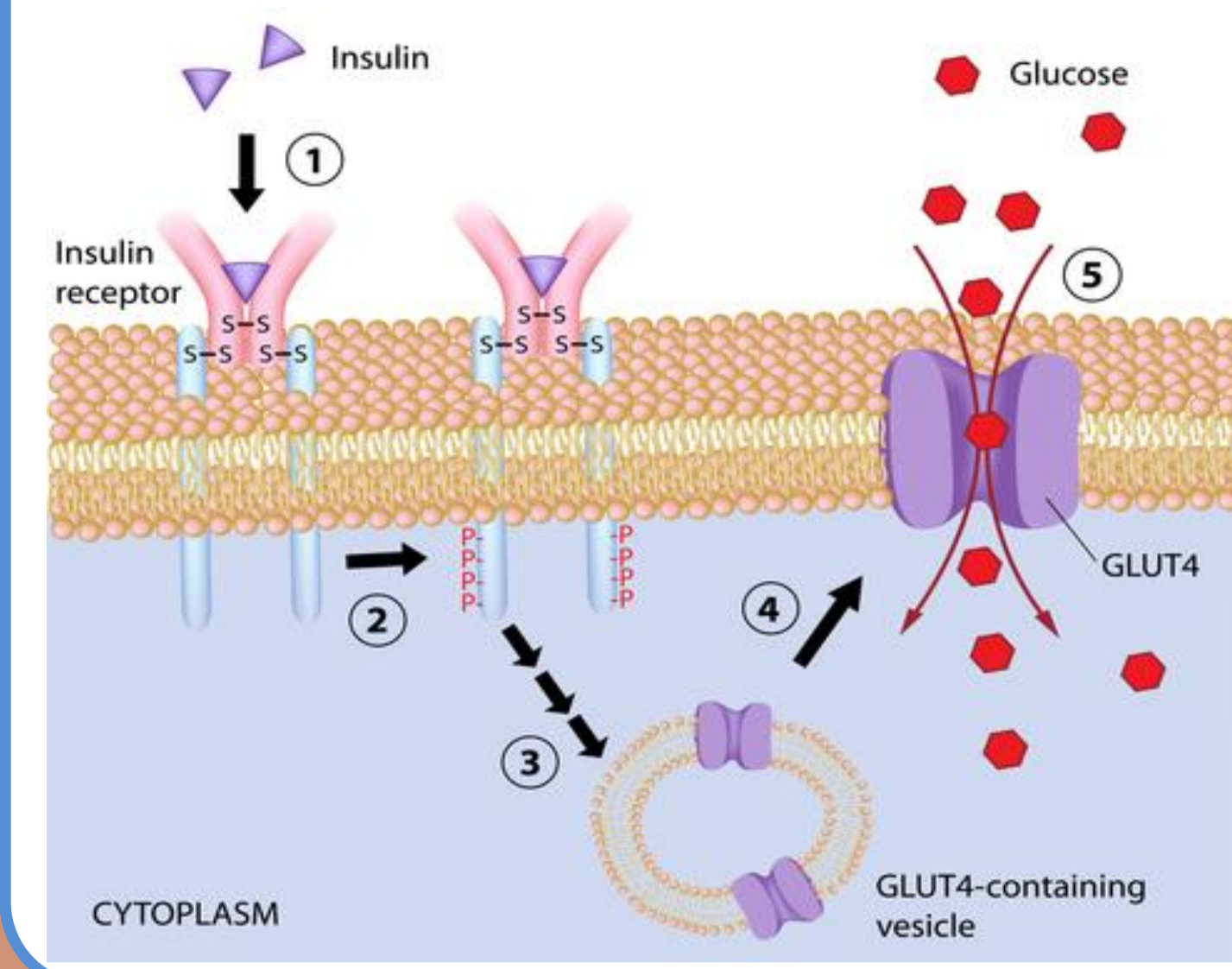
**Insulin and its receptor are lock and key. But having a lock and key in a door only makes sense if sometimes we need to close it. Our gluco-centric concept of insulin needs rethinking.**

**We need the insulin signaling system, not to allow glucose uptake in muscle and fat (in the postprandial state), but to be able to close it (in the fasting state), presumably in order to save glucose for non-dependent tissues (since striated muscle and specially fat have a very large capacity for energy storage).**

**Therefore, 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 at least one hundred million years, and is highly preserved along the evolutionary tree.**

**In chordates part of this functionality has been transferred to the IGF signaling system, but insulin keeps a regulatory role of the developmental and reproductive functions in the central nervous system.**

## Effect of Insulin on Glucose Uptake



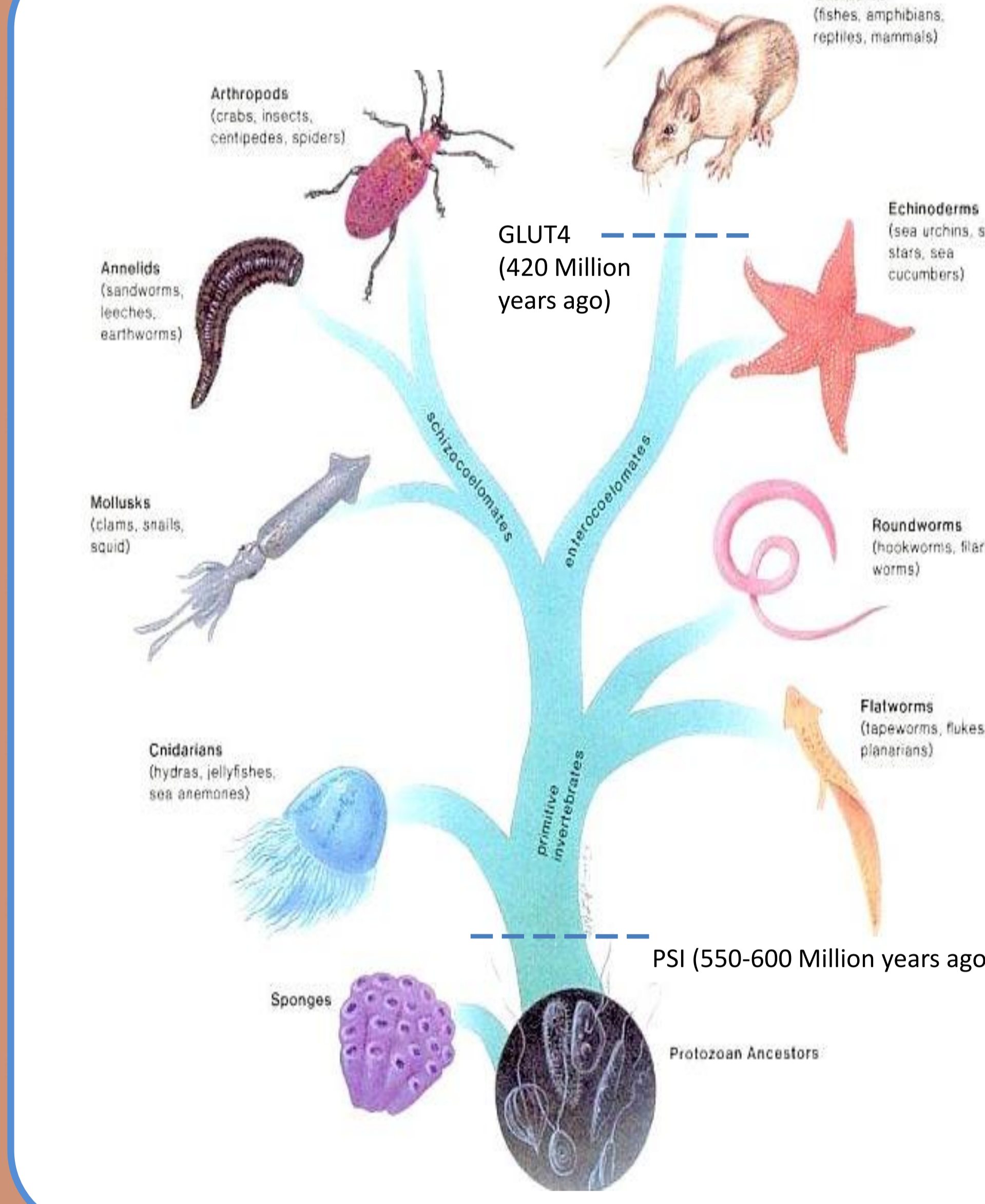
The geographic cone snail can send whole schools of fish into hypoglycaemic shock by releasing insulin into the water



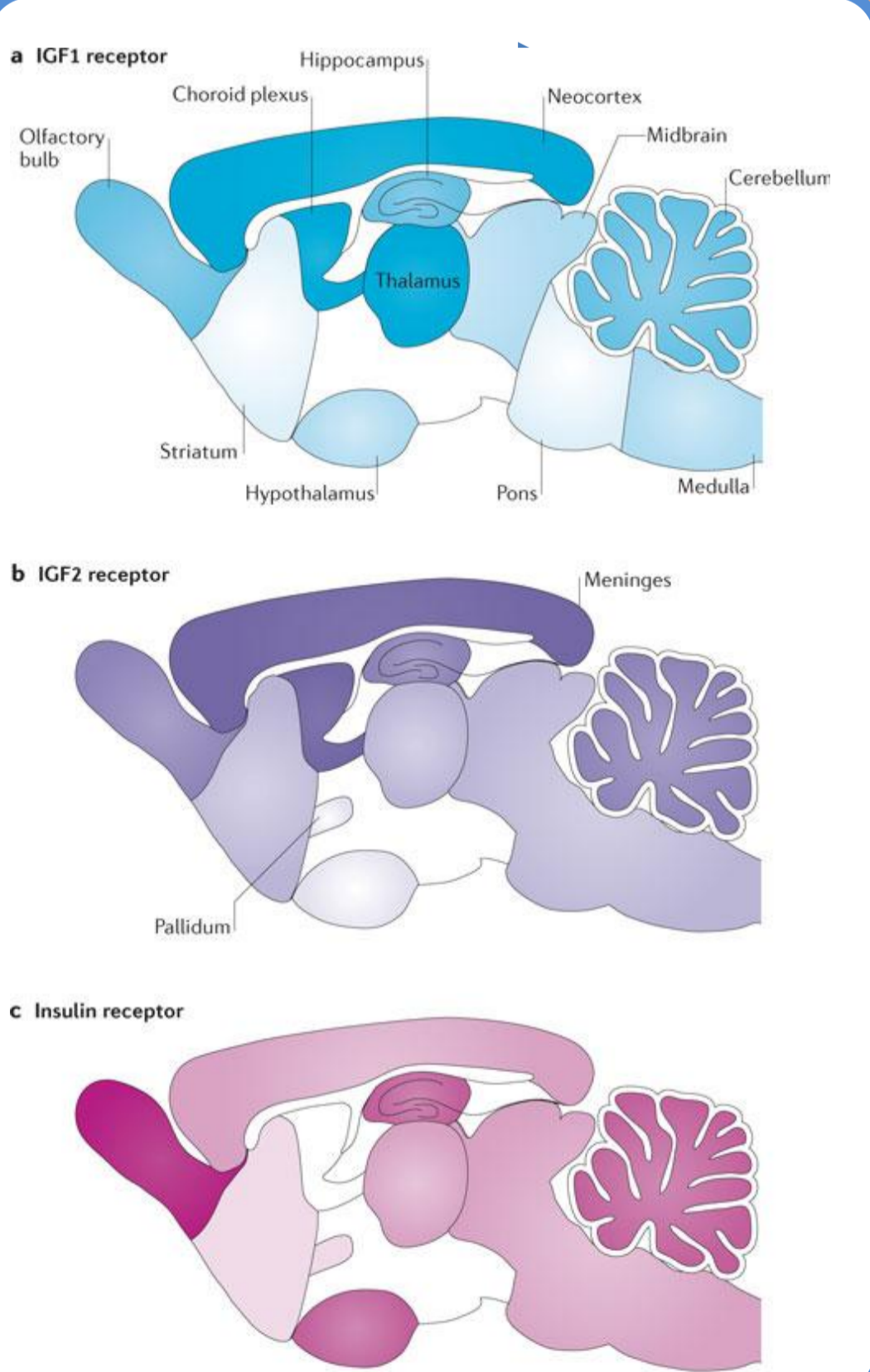
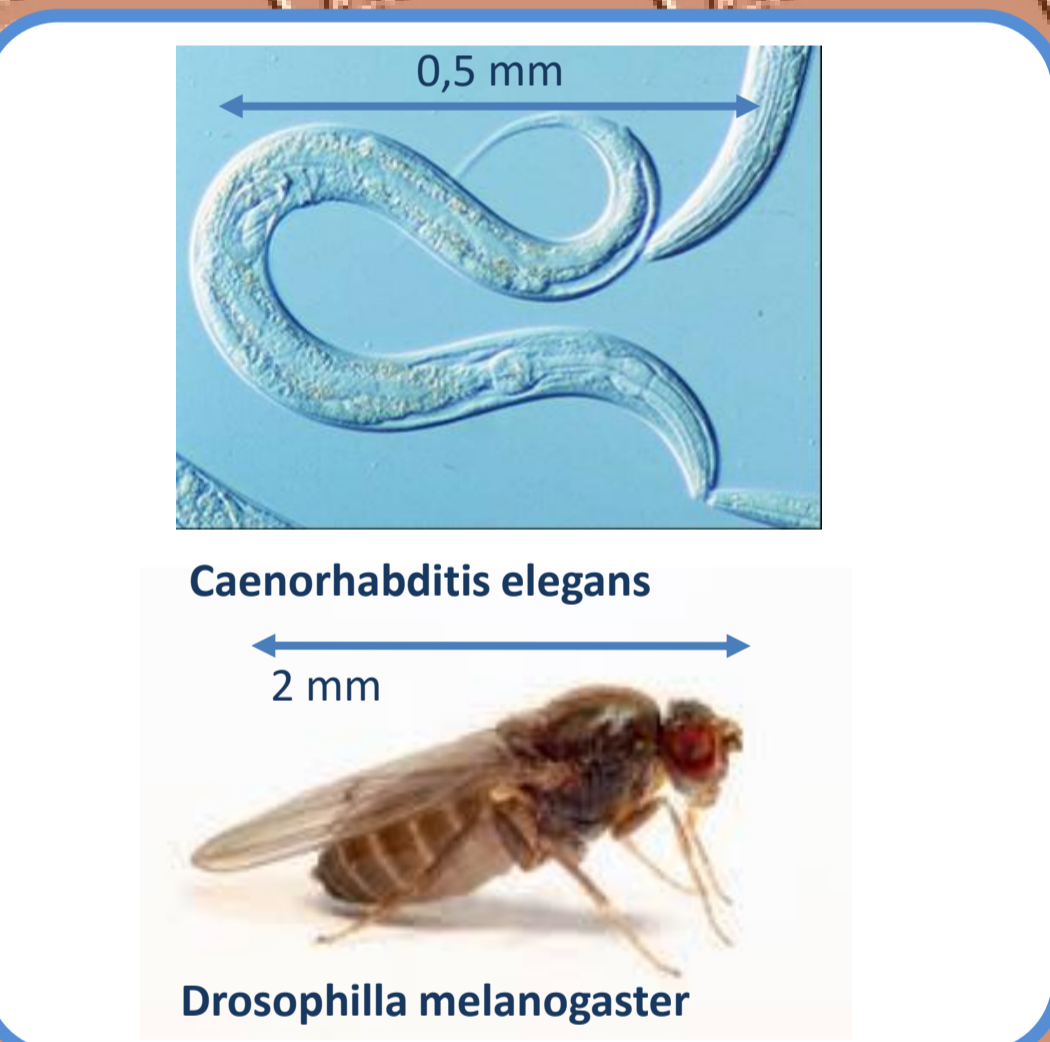
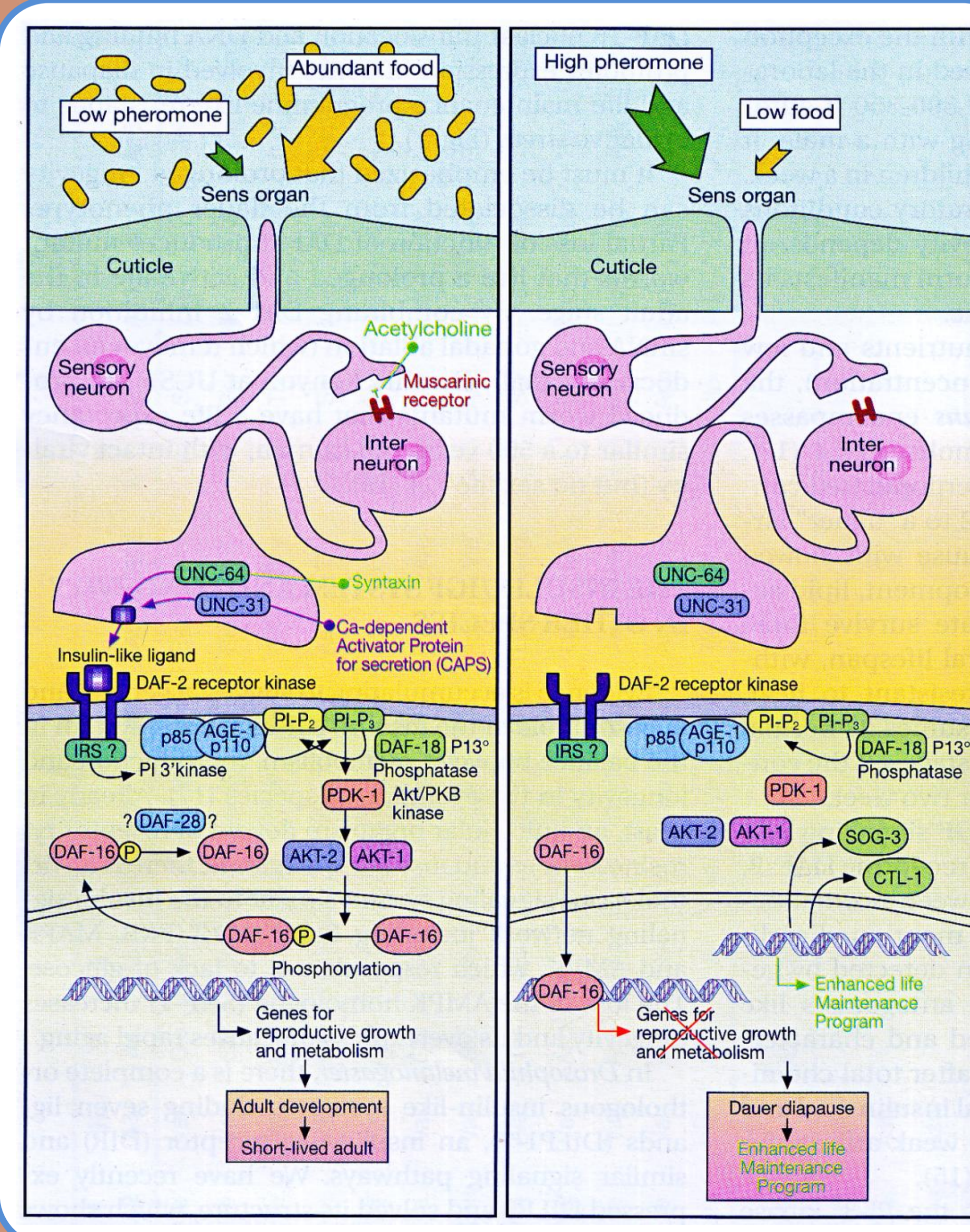
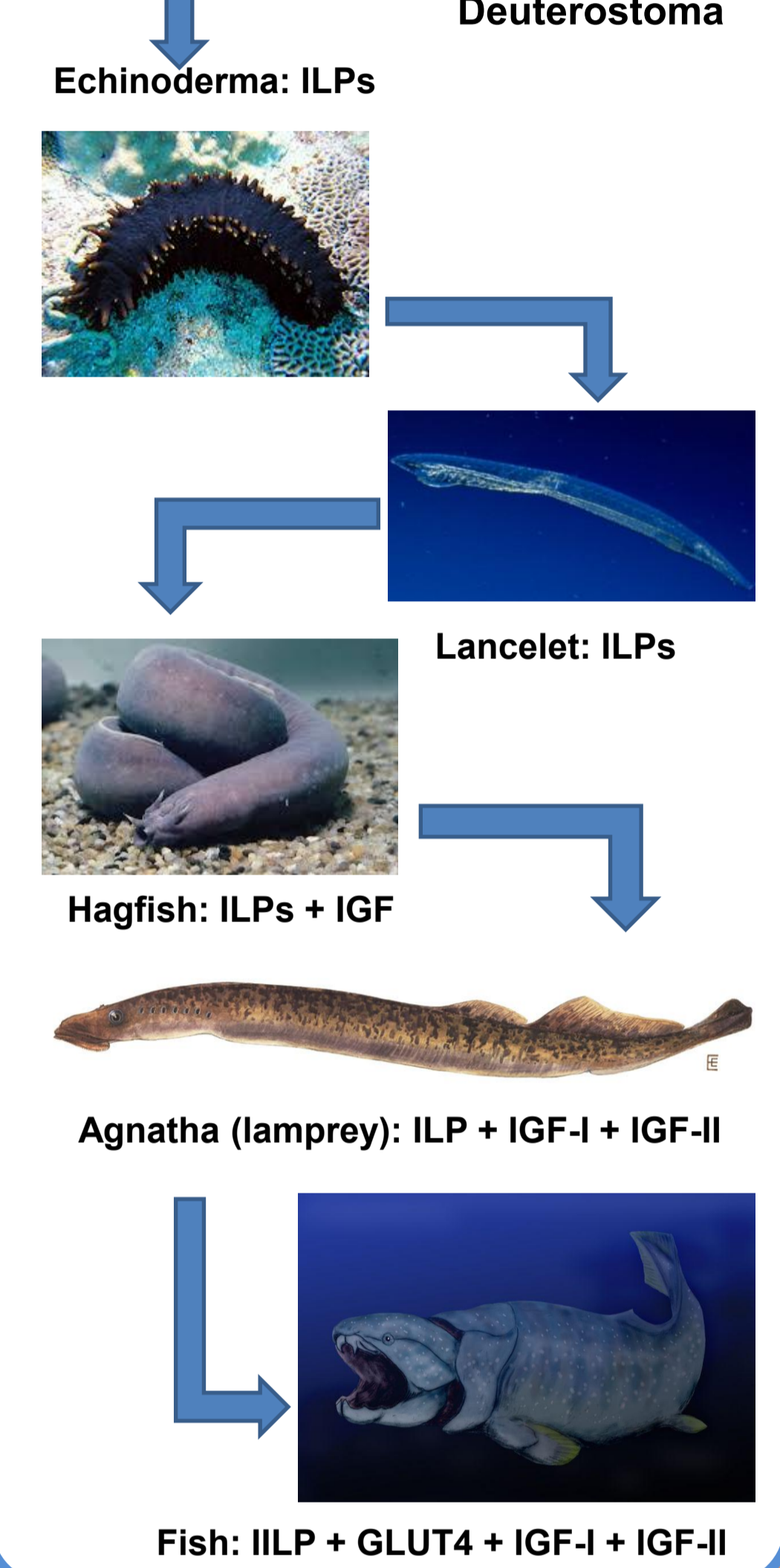
Deadly sea snail uses weaponised insulin to make its prey sluggish

Specialized insulin is used for chemical warfare by fish-hunting cone snails. *PNAS* | February 10, 2015 | vol. 112 | no. 6 | 1743-1748

## Evolutionary tree of the Metazoa (Pluricellular animals)



## Ancestral Deuterostoma



## Bibliography

- Fernández AM, Torres-Alemán I. The many faces of insulin-like peptide signalling in the brain. *Nature Reviews Neuroscience* 13: 225-39, 2012.
- Conlon JM. Evolution of the insulin molecule: insights into structure-activity and phylogenetic relationships. *Peptides* 22:1183-93, 2001.
- Plum L, Belgardt BF, Brüning JC. Central insulin action in energy and glucose homeostasis. *J Clin Invest* 116:1761-6, 2006.
- LeRoith D, Kavan VM, Koval AP. Phylogeny of the insulin-like growth factors and receptors: a molecular approach. *Mol Reprod Dev* 35:332-6, 1993.
- Chan SJ, Steiner DF. Insulin Through the Ages: Phylogeny of a Growth Promoting and Metabolic Regulatory Hormone. *Amer Zool* 40:213-22, 2000.
- Planas JV, Méndez E, Baños N, Capilla E, Castillo J. Fish Insulin, IGF-I and IGF-II Receptors: A Phylogenetic Approach. *Amer Zool* 40:223-33, 2000.
- Altintas O, Park S, Lee SV. The role of insulin/IGF-1 signaling in the longevity of *C. elegans* and *D. melanogaster*. *BMB Rep.* 2015 Dec 24. pii: 3438.