Metamorphosis In Amphibians

Metamorphosis is the transition (change) from a larval stage to an adult stage. In many species that undergo metamorphosis, a large proportion of the animal's structure changes, and the larva and the adult are unrecognizable as being the same individual.

- Direct Developers: Animals (including humans) whose young are smaller versions of the adult (they don't undergo metamorphosis).
- Indirect Developers: Animals in which embryonic development includes a larval stage with characteristics very different from those of the adult organism, which emerges only after a period of metamorphosis.

Amphibian metamorphosis is associated with morphological changes that prepare an aquatic organism for a primarily terrestrial existence. In urodeles (salamanders/order Caudata), these changes include the degeneration of the tail fin, the destruction of the external gills, and a change in skin structure. In anurans/order Anura (frogs and toads), the metamorphic changes are more dramatic, almost every organ is modified.

The changes in amphibian metamorphosis are initiated by thyroid hormones such as thyroxine (T_4) and tri-iodothyronine (T_3) that travel through the blood to reach all the organs of the larva. When the larval organs encounter these thyroid hormones, they can respond in any of four ways: growth, death, remodeling, and re-specification.

Amphibian Metamorphosis: Morphological Changes

(1) Growth of new structures:

The hormone tri-iodothyronine induces the formation of certain adult-specific organs:

- The limbs of the adult frog emerge from specific sites on the metamorphosing tadpole.

- In the eye, both nictitating membranes and eyelids emerge. Also, the eyes move to the front of the head from their originally lateral position (eyes are on sides in tadpole larva). The frontally located eyes of the frog befit its more predatory lifestyle. Frontally placed eyes give a binocular field of vision to the frog (inputs from both eyes converge in the brain).
- Moreover, T_3 induces the proliferation and differentiation of new neurons to serve these newly formed organs. As the limbs grow out from the body axis, new neurons proliferate and differentiate in the spinal cord. These neurons send axons to the newly formed limb musculature (muscles).

(2) Cell death during metamorphosis:

The hormone T_3 also induces certain larval-specific structures to die.

- T_3 causes the degeneration of the paddle-like tail, which was important for larval (but not adult) movement.
- T_3 also causes the degeneration of gills, which were important for larval (but not adult) respiration.
- Tadpole's red blood cells are also killed. During metamorphosis, tadpole hemoglobin is changed into adult hemoglobin, which binds oxygen more slowly and releases it more rapidly. The red blood cells carrying the tadpole hemoglobin have a different shape than the adult red blood cells, and these larval red blood cells are specifically digested by macrophages in the liver and spleen.

(3) Remodeling during metamorphosis:

In frogs and toads, certain larval structures are remodeled for adult needs:

- The larval intestine, with its numerous coils for digesting plant material, is converted into a shorter intestine for a carnivorous diet.

- Much of the nervous system is remodeled as neurons grow and innervate new targets.
- Other larval neurons, such as certain motor neurons in the tadpole jaw become associated with newly formed adult muscle (they were previously associated with larval muscle). Neuronal cells associated with the tongue muscle (a newly formed muscle not present in the larva) get activated.
- The lateral line system of the tadpole (which allows the tadpole to sense water movement and helps it to hear) degenerates, and the ears undergo further differentiation. The middle ear develops, as does the tympanic membrane characteristic of frog and toad outer ears.
- The shape of the anuran skull also changes significantly. The most obvious change is that the new bone is being made. The tadpole skull is primarily cartilaginous; the adult skull is primarily made up of bone. Another outstanding change is the formation of the lower jaw.

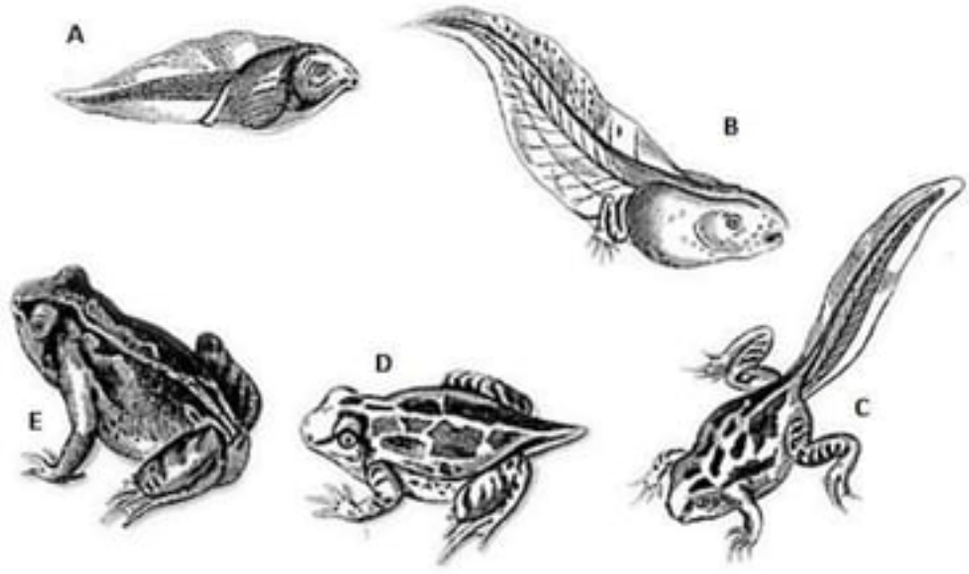

Figure: Metamorphosis. (A) Tadpole larva. (B) Hind limbs develop in larva. (C) Forelimbs also develop, gills are degenerated. (D) Once the limbs have developed, the tail degenerates. (E) Adult frog, after metamorphosis.

Amphibian Metamorphosis: Biochemical Changes

Important biochemical transformations occur during metamorphosis as T_3 induces a new set of proteins in existing cells. One of the most dramatic biochemical changes occurs in the liver. Tadpoles, like most freshwater fish, are ammonotelic (they excrete ammonia). Like most terrestrial vertebrates, many adult frogs (such as the genus *Rana*) are ureotelic (they excrete urea which requires less water than ammonia excretion). During metamorphosis, the liver begins to synthesize the enzymes necessary to create urea from carbon dioxide and ammonia, i.e. enzymes for the urea cycle are formed during metamorphosis.

Hormonal Control of Amphibian Metamorphosis

Hormonal control of amphibian metamorphosis can be explained by the threshold model, which states that the different events of metamorphosis are triggered by different concentrations of thyroid hormones.

The metamorphic changes of frog development are brought about by: (1) The secretion of the hormone thyroxine (T_4) into the blood by the thyroid gland. (2) The conversion of T_4 into the more active hormone, tri-iodothyronine (T_3) by the target tissues. (3) The degradation of T_3 in the target tissues. T_3 binds to the nuclear thyroid hormone receptors (TRs) with much higher affinity than does T_4 and causes these receptors to become transcriptional activators of gene expression.

The levels of both T_3 and TRs (thyroid hormone receptors) in the target tissues are essential for producing the metamorphic response in each tissue.

Maintenance of T_3 levels:

The concentration of T_3 in each tissue is regulated by the concentration of T_4 in the blood and by two types of deiodinases (intracellular enzymes that remove iodine atoms from T_4 and T_3).

Types of thyroid hormone receptors:

There are two types of thyroid hormone receptors in *Xenopus* (species of Frog):

1. Thyroid hormone receptor α (TR α) is widely distributed throughout all tissues and is present even before the organism has a thyroid gland.
2. Thyroid hormone receptor β (TR β) is the product of a gene that is directly activated by thyroid hormones (it is formed during metamorphosis).

Stages of metamorphosis & Thyroid concentrations:

Metamorphosis is often divided into stages based on the concentration of thyroid hormones in circulation.

1. The first stage is pre-metamorphosis; in this stage, the thyroid gland has begun to mature and is secreting low levels of T_4 (and very low levels of T_3). During the early stage of metamorphosis, the developing limbs can receive thyroid hormone and use it to start leg growth.
2. The second stage is pro-metamorphosis, in this stage, the thyroid gland is mature and it secretes more thyroid hormones.
3. The third or final stage is the metamorphic climax stage. Many major changes (such as tail resorption, gill resorption, and intestinal remodeling) happen in this stage. At the metamorphic climax, the tail begins to be resorbed. The tail undergoes absorption only after the legs are functional (otherwise, the poor amphibian would have no means of locomotion).

Ending metamorphosis (Negative feedback system):

The frog brain undergoes changes during metamorphosis, and one of the brain's functions is to downregulate metamorphosis once the metamorphic climax has been reached. Thyroid hormones eventually induce a negative feedback loop, shutting down the pituitary cells that instruct the thyroid to secrete them (the TSH secreting cells).

Response of body parts to thyroid hormones:

The type of response of a body part to thyroid hormones (proliferation, apoptosis, differentiation, migration) is determined by factors already present in the different tissues. The same stimulus causes some tissues to degenerate while stimulating others to develop and differentiate. For example, thyroid hormone instructs the limb bud muscles to grow (they die without thyroxine) while instructing the tail muscles to undergo apoptosis.