

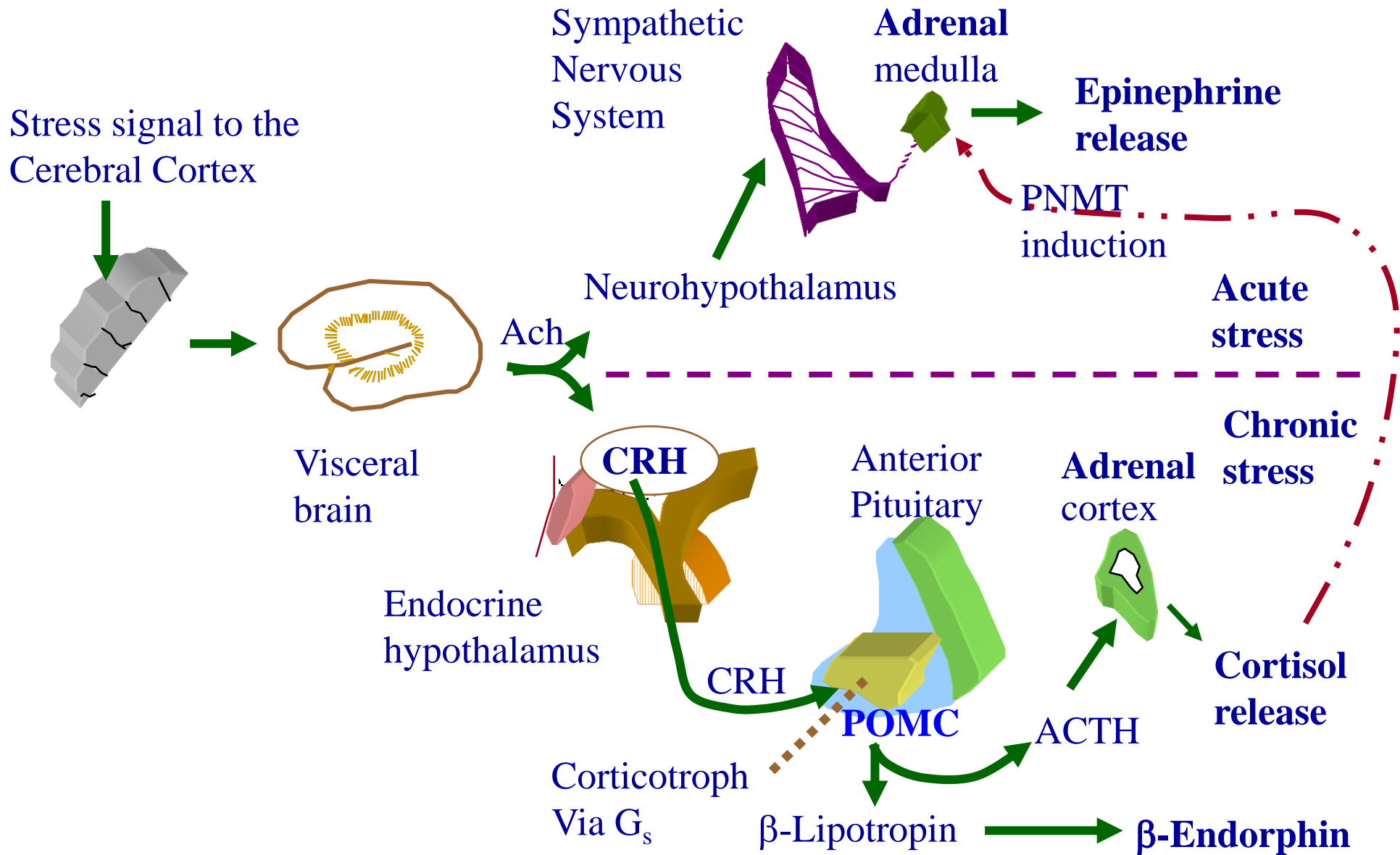
Chapter 5

Opiomelanocortins

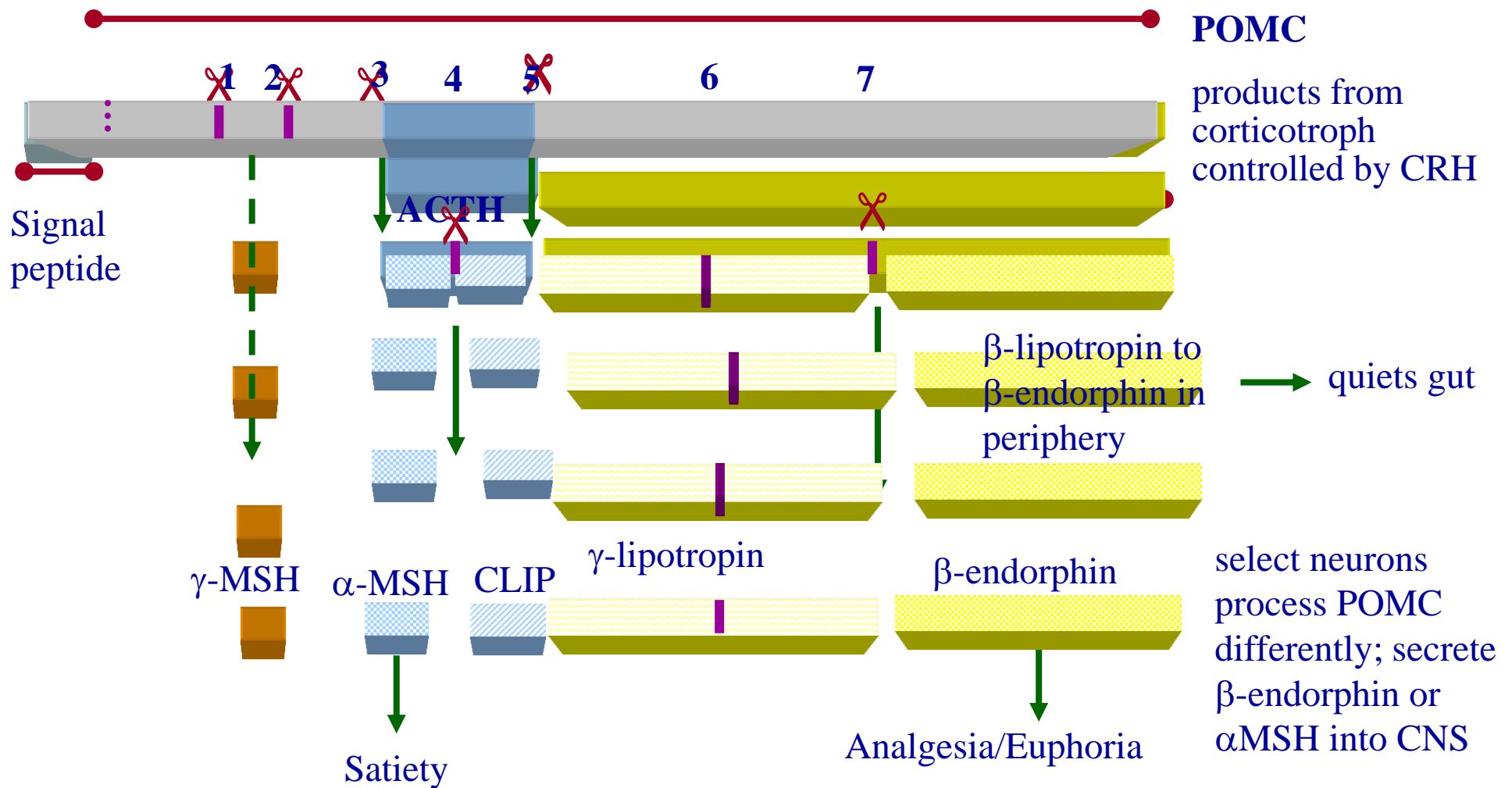
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1. Proopiomelanocortin (POMC): A Multifunctional Precursor

- ACTH (corticotropin)
 - Synthesized in pars distalis
 - Precursor = POMC (proopiomelanocortin)
 - 241 aa's
 - Holds ACTH, β -LPH, β -MSH
 - β -MSH not physiological active
 - w/ β -LPH: β -endorphin, met-enkephalin (neurohormones)
 - Proprotein convertase 3 catalyzes POMC \rightarrow ACTH + β -LPH
 - Cleaved \rightarrow α -MSH in pars distalis
 - Similar sequence
 - ACTH melanotropic activity
 - Circadian adrenocortical rhythm

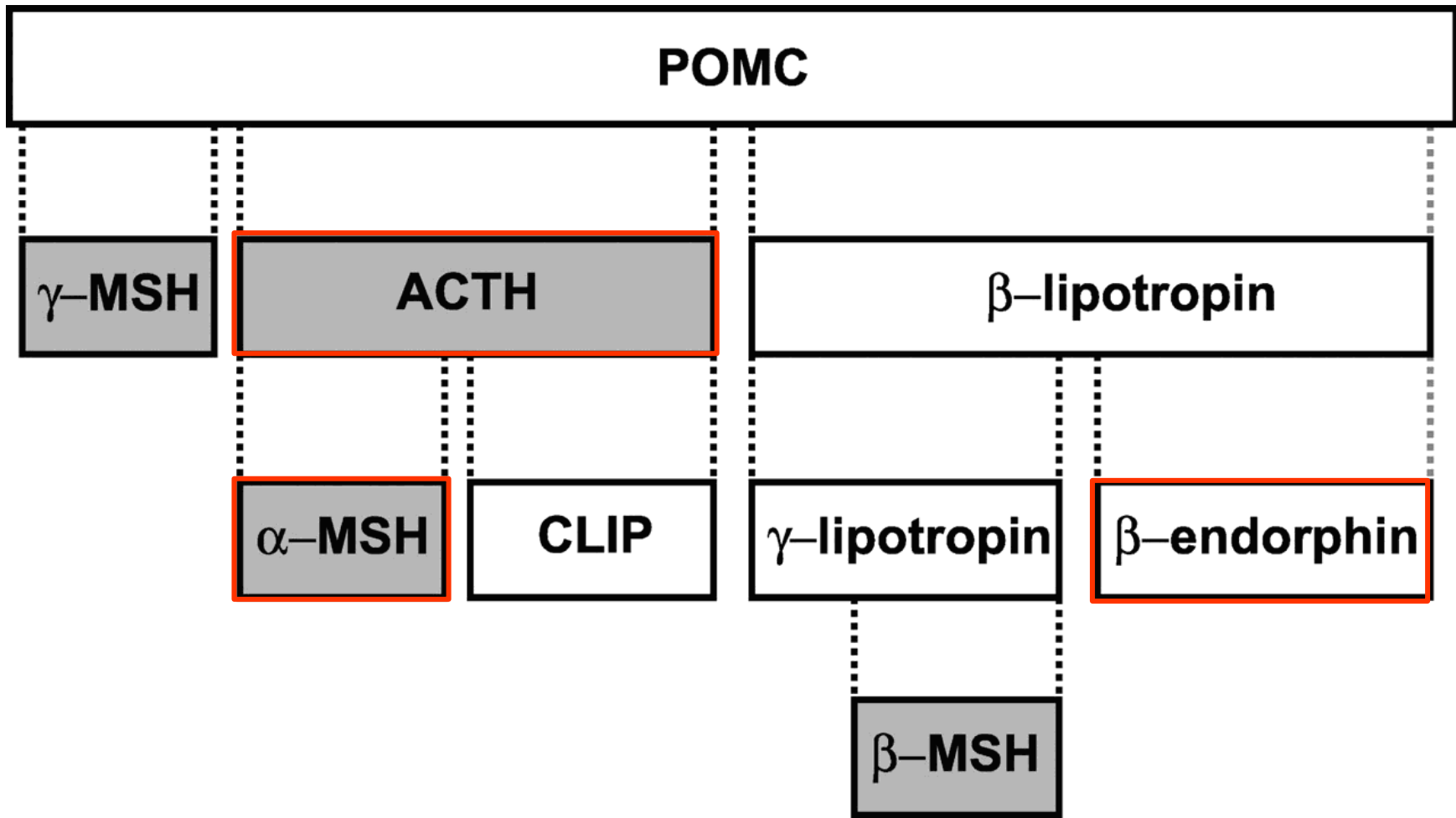


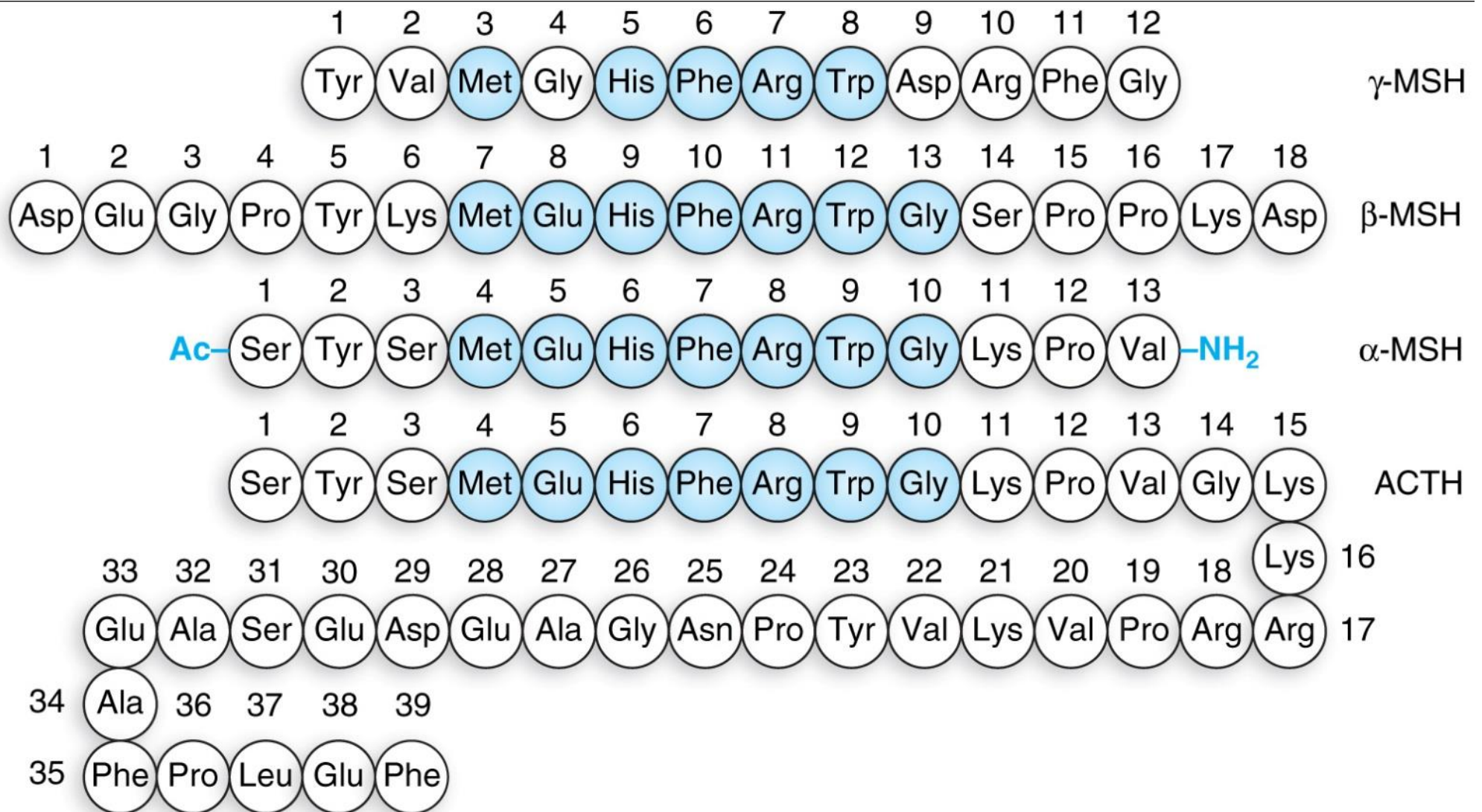
Neuroendocrine pathways in emotional stress leading to adrenal activation



CLIP: corticotropin-like intermediary peptide

Proopiomelanocortin (POMC) is a polypeptide product encoded by a single gene. The dark vertical bars represent proteolytic cleavage sites for specific enzymes. These sites consist of pairs of basic amino acids (Arg, Lys) just as occurs in the processing of glucagon and vasopressin.





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Fig. 8-1: Amino acid sequences of bovine γ -, β -, and α -MSH compared to ACTH.

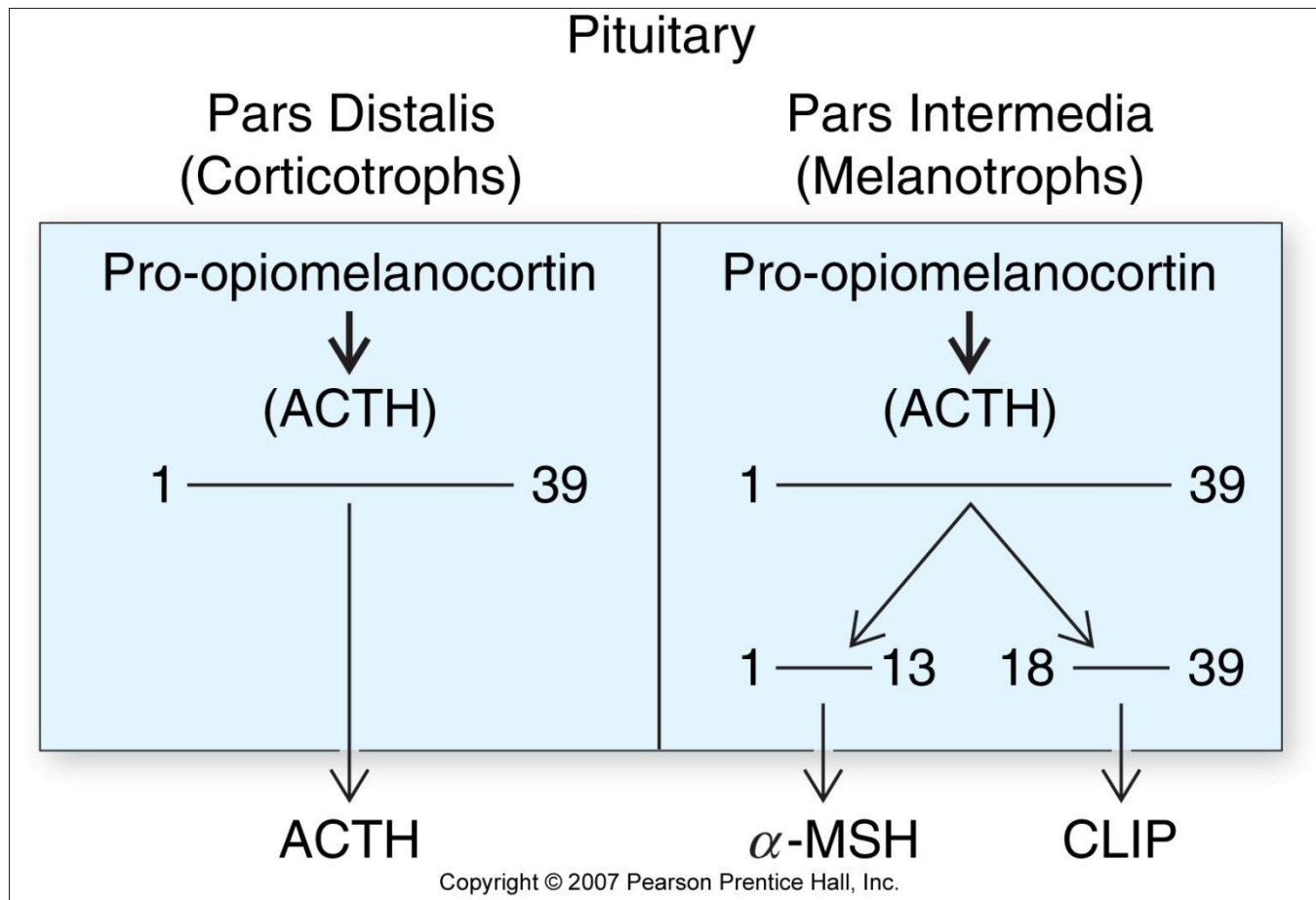
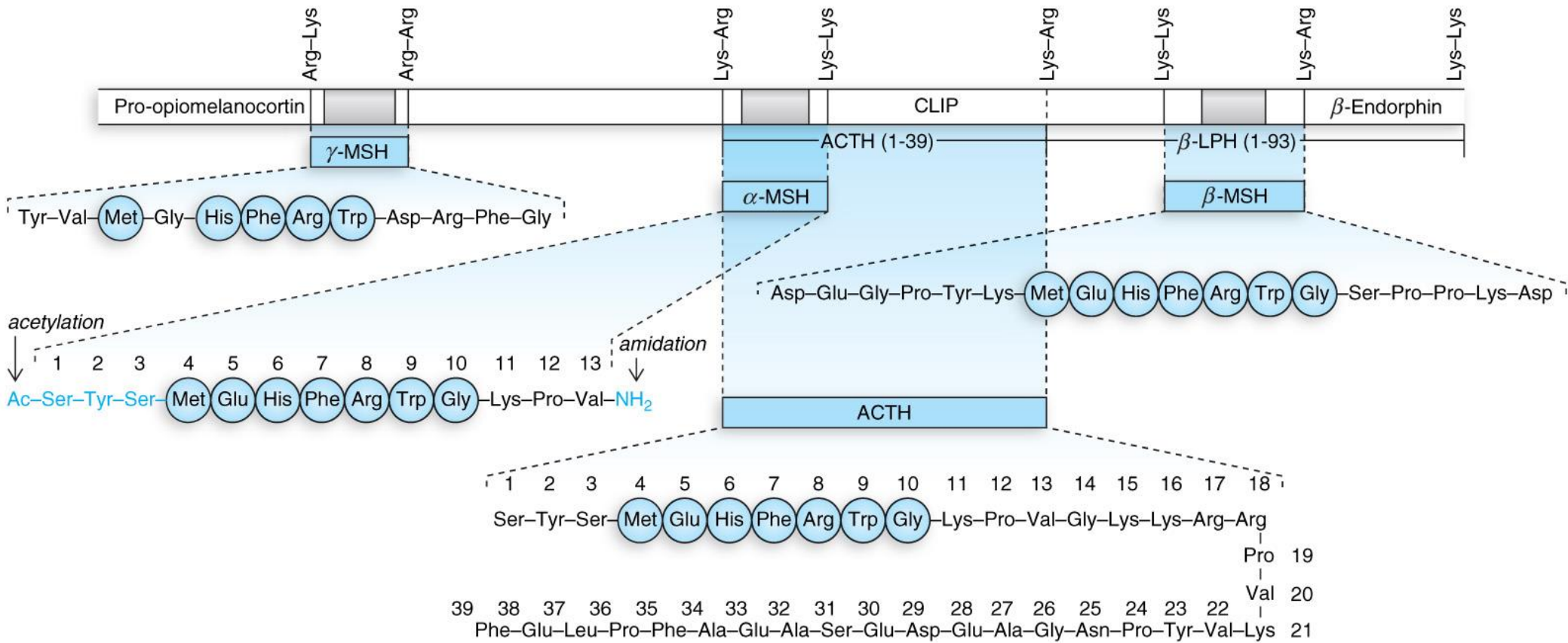


Fig. 8-2: Prohormone theory of ACTH and α -MSH biosynthesis. It is unclear whether in the pars intermedia ACTH is first enzymatically released from POMC to yield α -MSH and corticotropin-like-intermediate lobe peptide (CLIP), or whether the latter two peptides are liberated directly from POMC.



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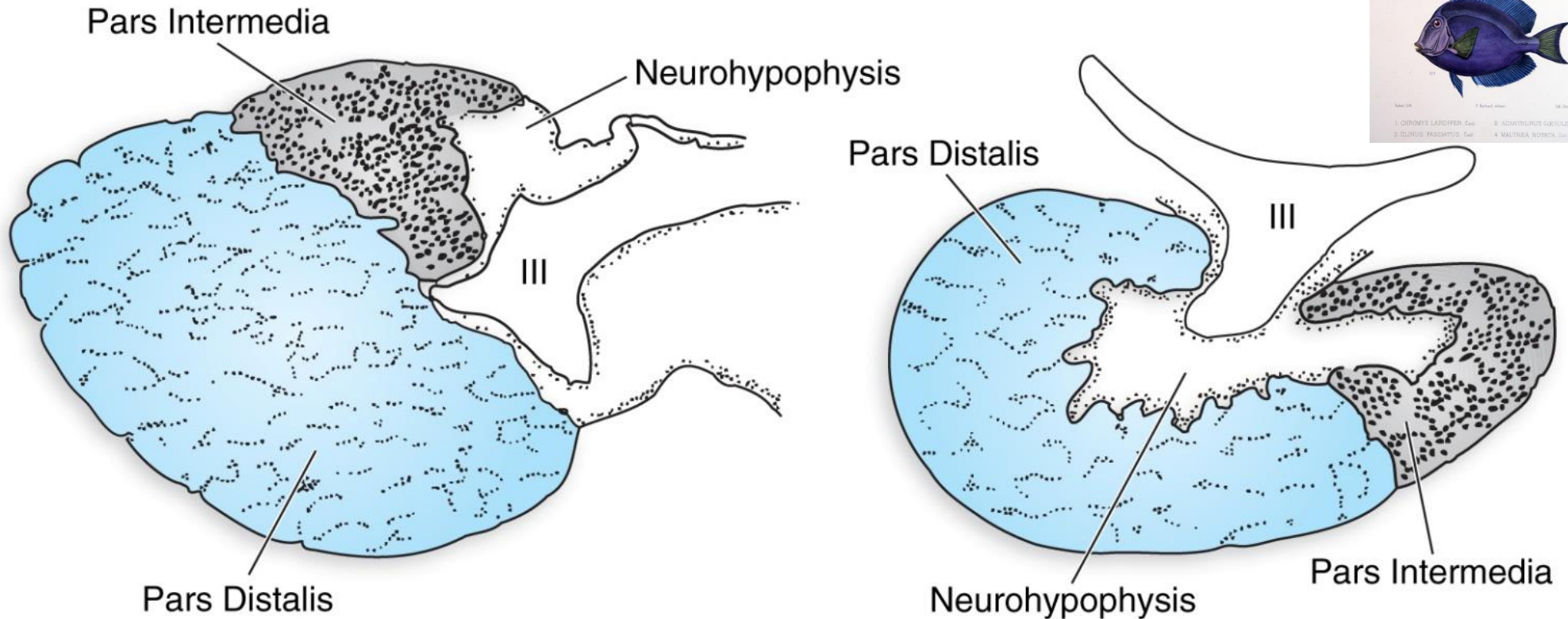
Fig. 8-3: Schematic representation of the known, biologically active peptides derived from proopiomelanocortin, which is found in the vertebrate pituitary (corticotrophs and melanotrophs) and hypothalamus.

2. The Pars Intermedia: A Source of Melanotropins



Amphibian

Teleost



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Fig. 8-4: Sagittal sections of an amphibian (salamander, 불도마뱀) pituitary gland (left) and a teleost (경골어류) pituitary gland (right). The three lobular components of the glands are indicated: neurohypophysis, pars intermedia, and pars distalis. The third ventricle (III) is also indicated.

3. Control of MSH Secretion

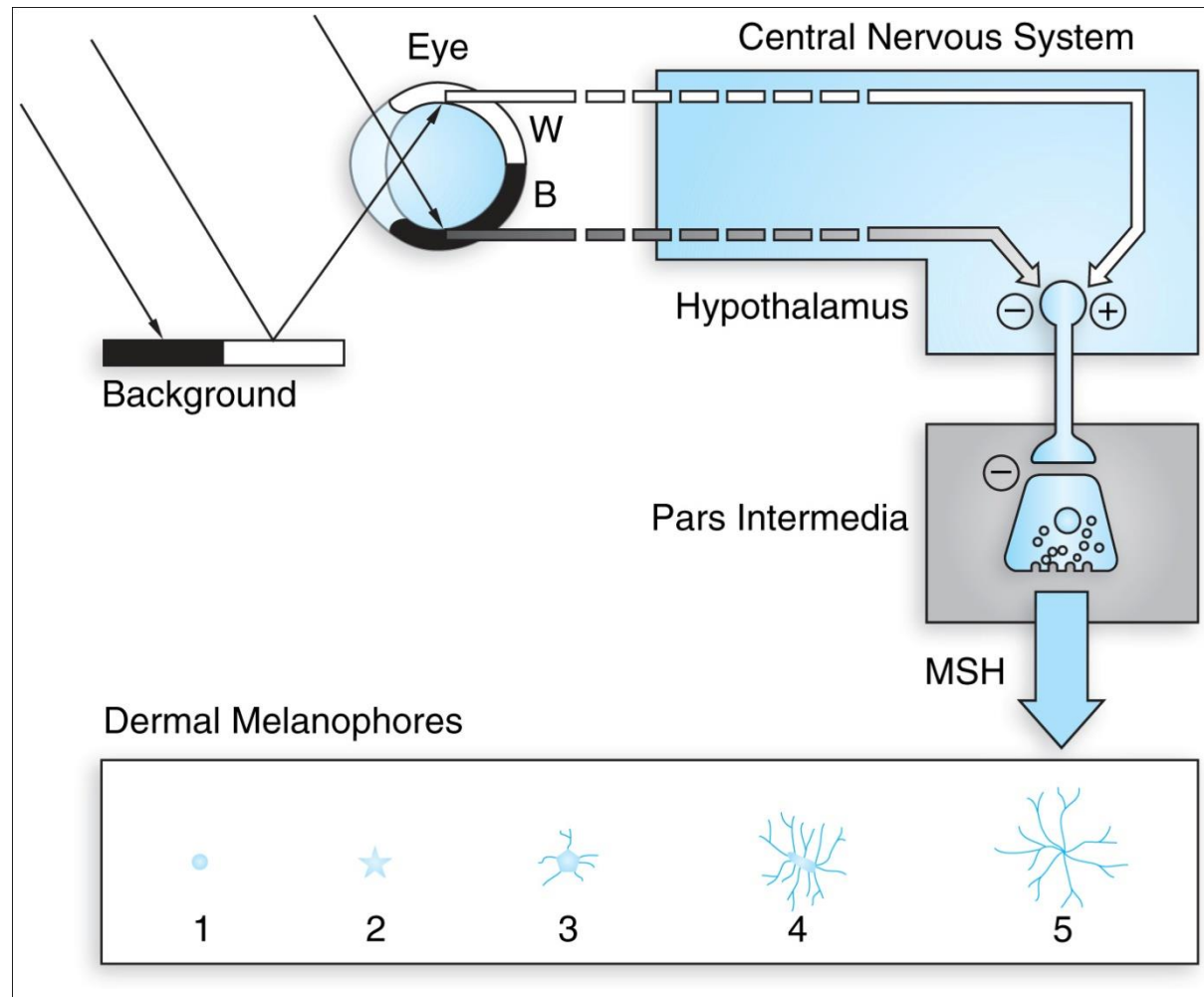
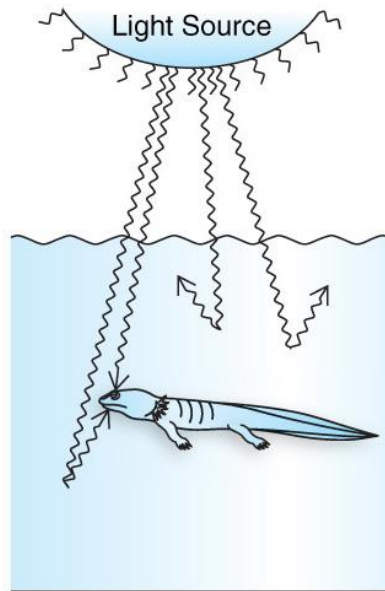
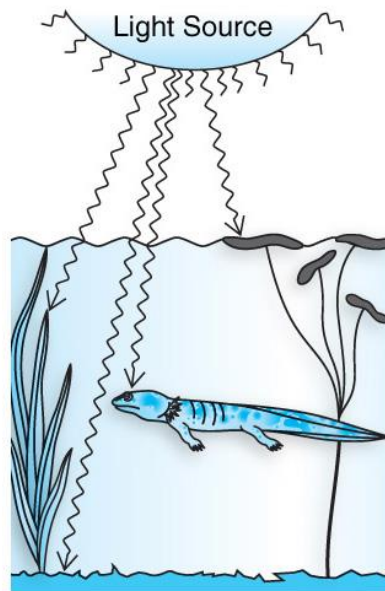


Fig. 8-6: The neuroendocrine reflex regulating pigment dispersion in **dermal melanophores** of amphibians during the process of background adaptation.



High Albedo Environment



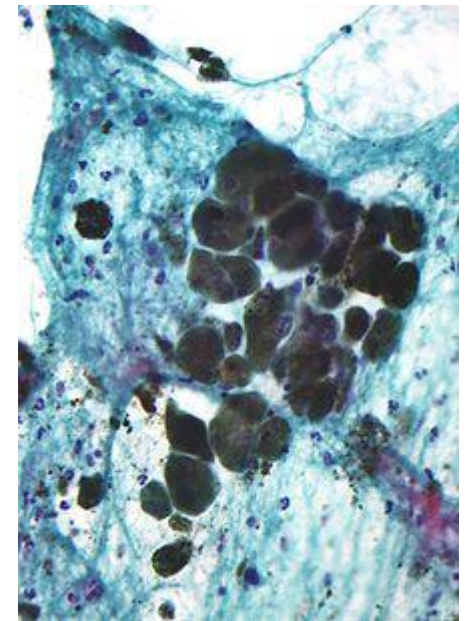
Low Albedo Environment

Fig. 8-7: Model for the visual control of MSH secretion and the regulation of integumental coloration.

4. Physiological Roles of MSH

1) MSH regulates melanin pigmentation of the skin

- Melanocytes
- Melanin
- Premelansome → melanosome
- Brown and black melanins = referred to as *eumelanins*
- Red or lighter-colored melanins = known as *pheomelanins*
- Functional unit = “epidermal melanin unit”
- Melanocortins and tanning of the skin in humans



Melanin pigment (dark granular material - center of image) in a pigmented melanoma. Pap stain.

Melanocortins and tanning of the skin in humans

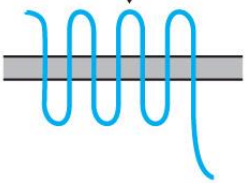
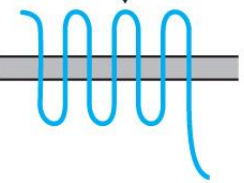
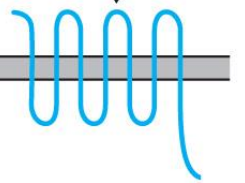
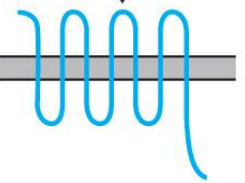
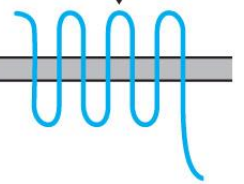
- **Sun tanning** or simply **tanning** is the process whereby skin color is darkened or tanned.
- The process is most often a result of exposure to **ultraviolet (UV) radiation** from the sun or from artificial sources, such as a tanning bed, but can also be a result of windburn or reflected light.
- Many people deliberately tan their skin by exposure to the sun, called **sun bathing**, or by the use of artificial tanning methods.
- Some people use chemical products which can produce a tanning result without exposure to ultraviolet radiation.
- Moderate exposure to the sun has a beneficial impact, including the **production of vitamin D** by the body; **but excessive exposure to ultraviolet rays has detrimental health effects, including possible sunburn and even skin cancer.**
- To avoid sunburn, most people apply suitable sunscreen to skin exposed to the sun, but others use oils to accelerate the tanning process.



- Some people tan or sunburn more easily than others. This may be the result of different skin types and natural skin color, and these may be as a result of genetics. In general, a paler skin color is more quickly burnt than a darker one.
- The term "tanning" has a cultural origin, arising from the color tan. Its origin lays in **the Western culture of Europe** when it became fashionable for young white ladies to seek a less pale complexion.

2) Melanocortin receptors regulate animal pigmentation

TABLE 8.1 Melanocortin Ligands, Receptors, Responses

Ligand	MSH	ACTH	MC*	MC*	MC*
Receptor					
Receptor Subtype	MC1	MC2	MC3	MC4	MC5
Expression	Skin Melanocytes	Adrenal Cortex	Brain	Brain	Exocrine Glands
Response	¹ Melano-genesis	² Steroido-genesis	³ Cardio-vascular?	⁴ Weight Homeostasis	⁵ Secretion

*Melanocortin (MC): Natural Ligand Unknown.

¹Tyrosinase activation and melanin production.

²Cortisol production in the zone fasciculata.

³Variable effects on blood pressure; by modifying sympathetic outflow?

⁴Melanocortins induce satiety (reduce food intake); energy homeostasis.

⁵Lacrimal gland secretion; sebum production/pheromone production.

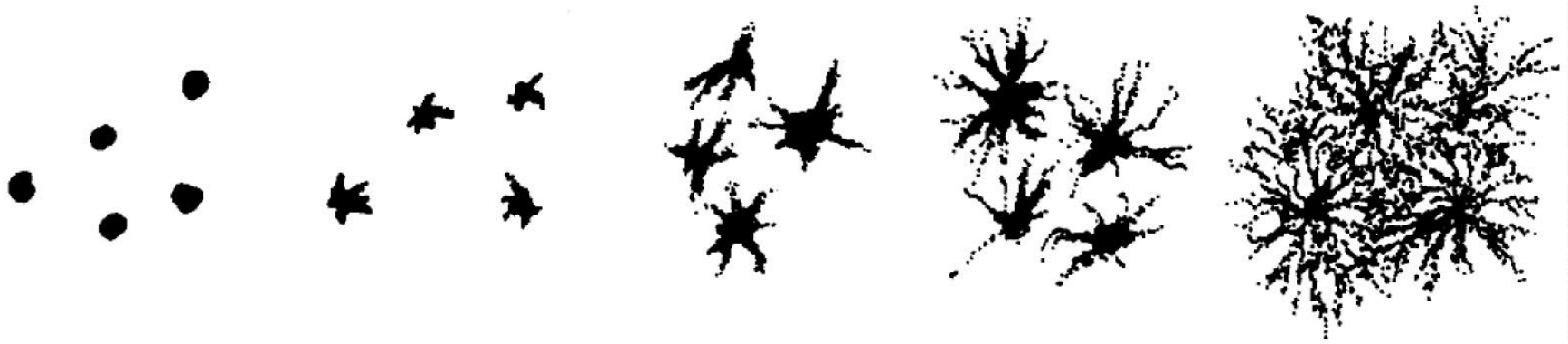
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TABLE 8.1 Melanocortin ligands, receptors, responses

3) MSH directs color changes in nonmammalian vertebrates

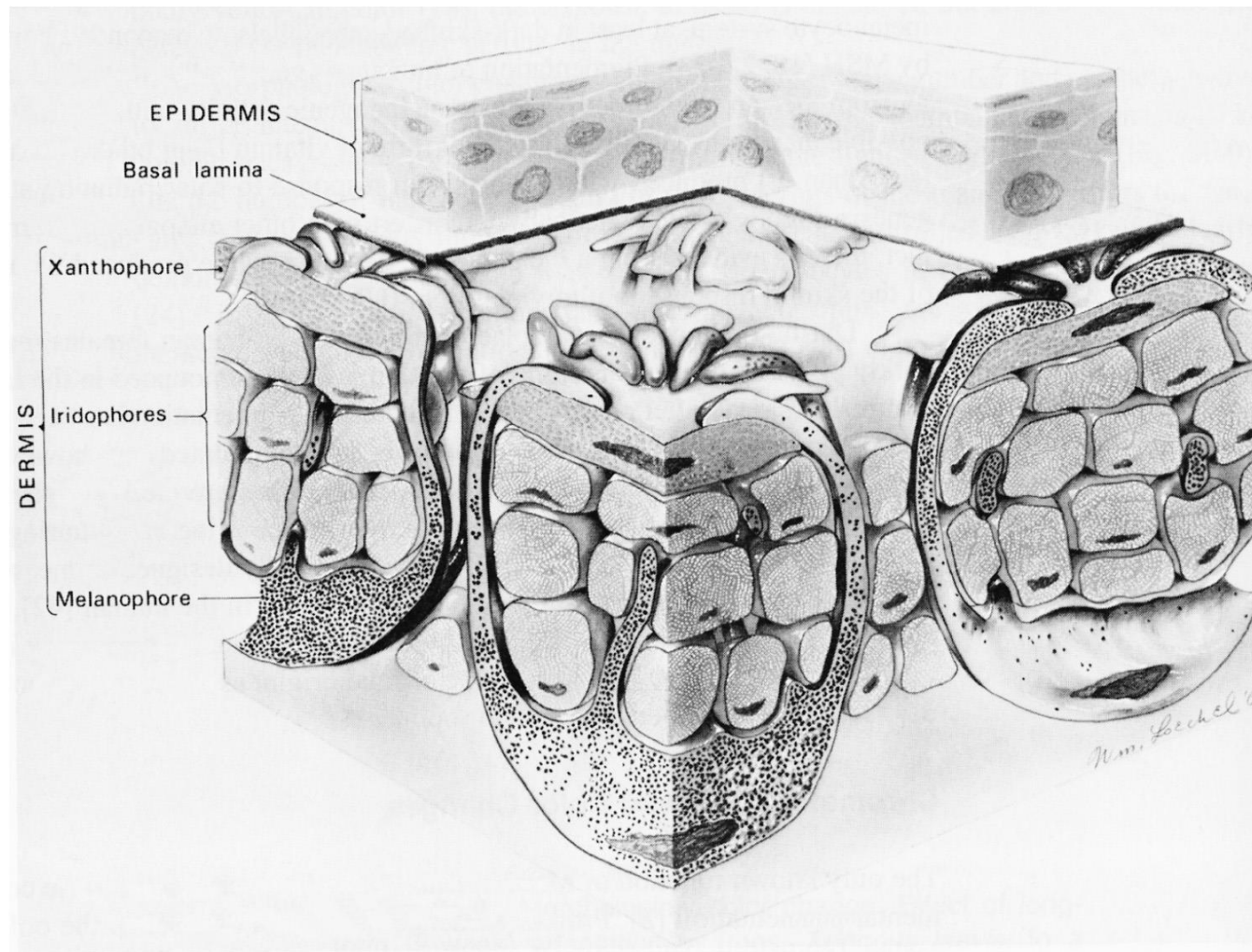
- Fishes, amphibians, reptiles → rapidly adapt to the color of the background over which they reside.

→ rapid physiological color changes



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Fig. 8-12: **A melanophore index** is used to evaluate melanosome movements, centrifugal (dispersion) or centripetal (perinuclear aggregation), in response to MSH or other stimuli.



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Fig. 8-13: **Dermal chromatophore unit** of the lizard *Anolis carolinensis*.

5. Other Roles of Melanocortins

1) Sexual function:

- Melanocortins injected into the third ventricle of the brain of rats cause an erectile response.
- A superpotent analog of α -MSH, Ac-Nle-c[Asp-His-Dphe-Arg-Trp-Lys]-NH₂ → s.c. injection in men → causes erections

2) Satiety and energy homeostasis: Melanocortins acting within the brain are also implicated in energy homeostasis since agonists of MC4R reduce food intake and targeted mutation of the MC4R causes obesity.

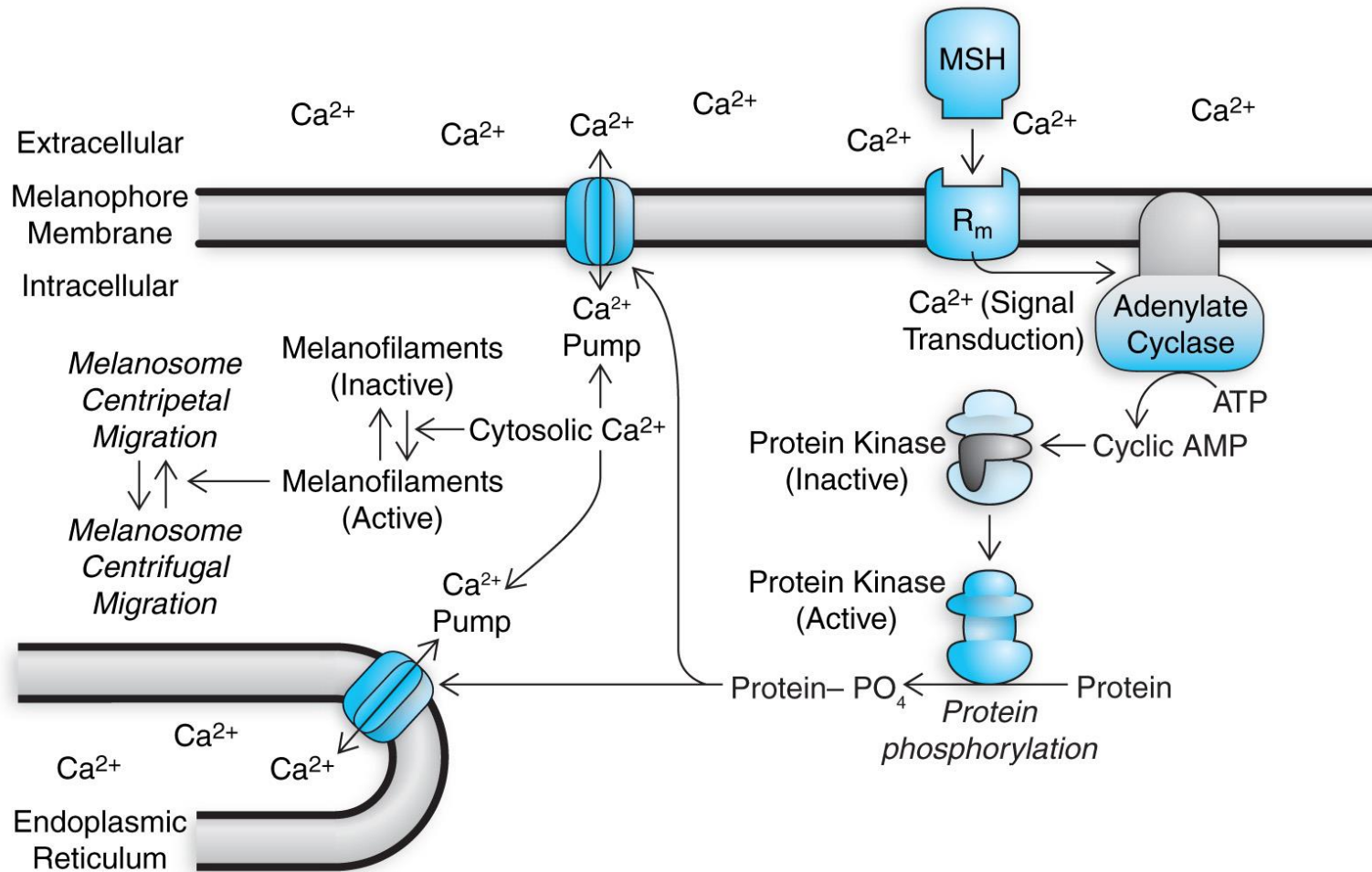
3) Thermoregulation: Adaptive chromatic response is regulated by MSH and that darker skin is able to absorb more radiant energy

4) Melanocortins and behavior: affect CNS activity in laboratory animals and humans

5) Neuroplasticity: Melanotropic peptides have been shown to alter neurotransmitter synthesis, the electrophysiological parameters of neurotransmission, excitability in the spinal cord and peripheral nerves, and to affect a number of behavioral responses.

6. Mechanism of MSH Action

1) Melanosome movements



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Fig. 8-14: Hypothetical model for a role of MSH and Ca^{2+} ions in the control of melanosome (melanin granules) movements within melanophores.

2) Melanogenesis

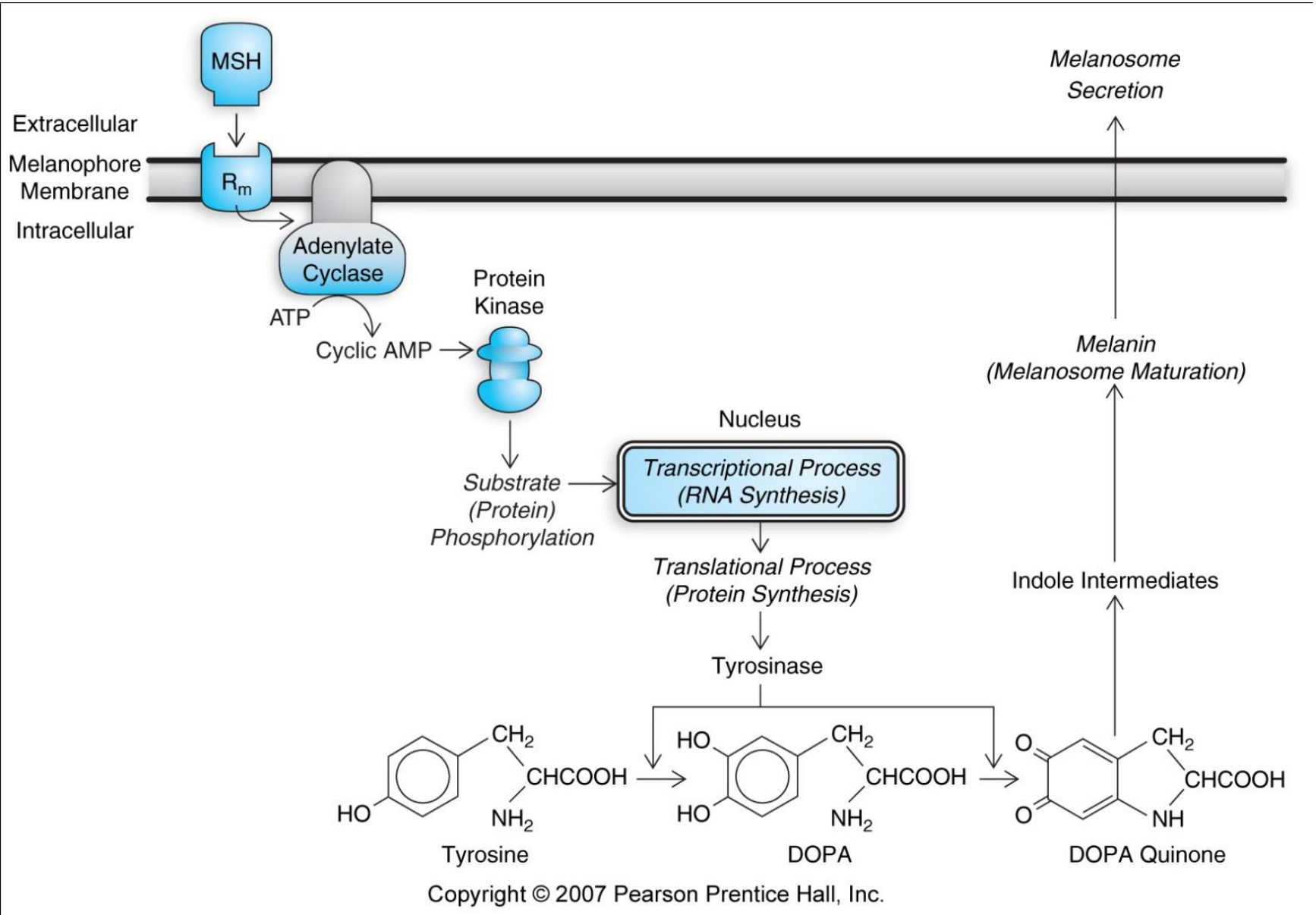


Fig. 8-15: Model for MSH activation of melanocyte tyrosinase and melanin synthesis. The substrate for cAMP-dependent protein kinase is unknown. The end result of tyrosinase activation, melanosome formation and release into surrounding keratinocytes, is enhanced skin pigmentation (or follicular melanogenesis in some animals).

7. Melanin-Concentrating Hormone

- 1) **Melanin-concentrating hormone (MCH)** is a cyclic 19-amino acid orexinogenic hypothalamic peptide originally isolated from the pituitary gland of teleost fish (경골어류) where it controls skin pigmentation.
- In mammals it is involved in the regulation of feeding behavior, mood and energy balance.
 - MCH expressing neurons are located within the lateral hypothalamus and zona incerta.
 - Despite this restricted distribution MCH neurons project widely throughout the brain.
 - MCH knockout mice are hypophagic (eat less) and are lean. When administered centrally it increases food intake and weight gain.

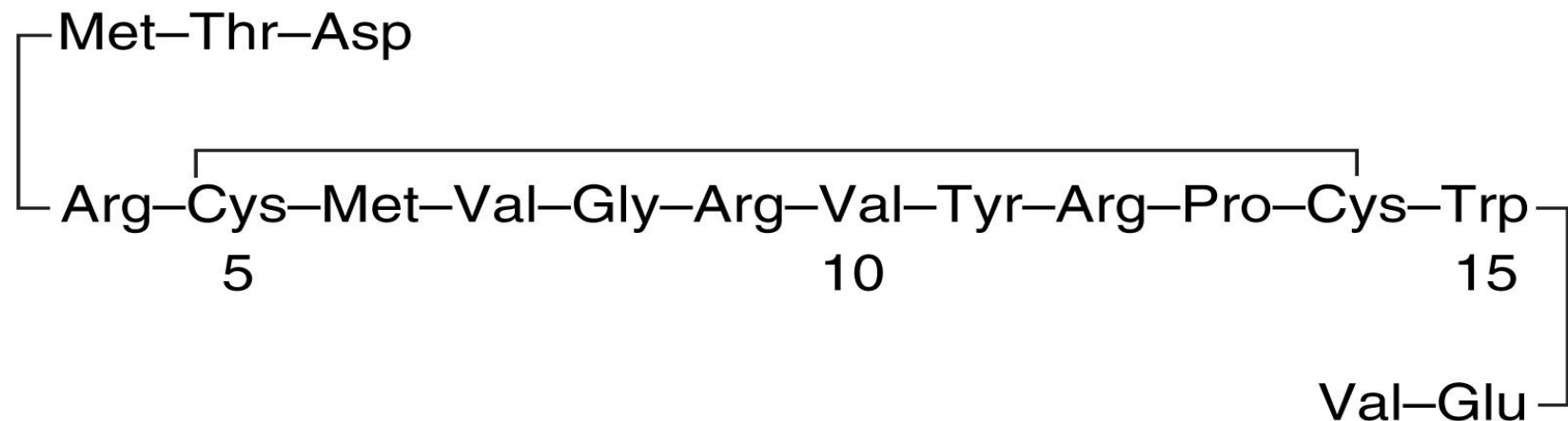


Fig. 8-16: Primary structure of melanin-concentrating hormone (MCH).²⁰

- 2) **MCH and color change:** Salmon MCH is effective at concentrations as low as 1 nmol, or less, in causing melanosome concentration within teleost melanophores.
- 3) **MCH and energy homeostasis:** MCH injected into discrete hypothalamic nuclei known to express MCH receptors elicited a rapid and significant increase in feeding in satiated rats.

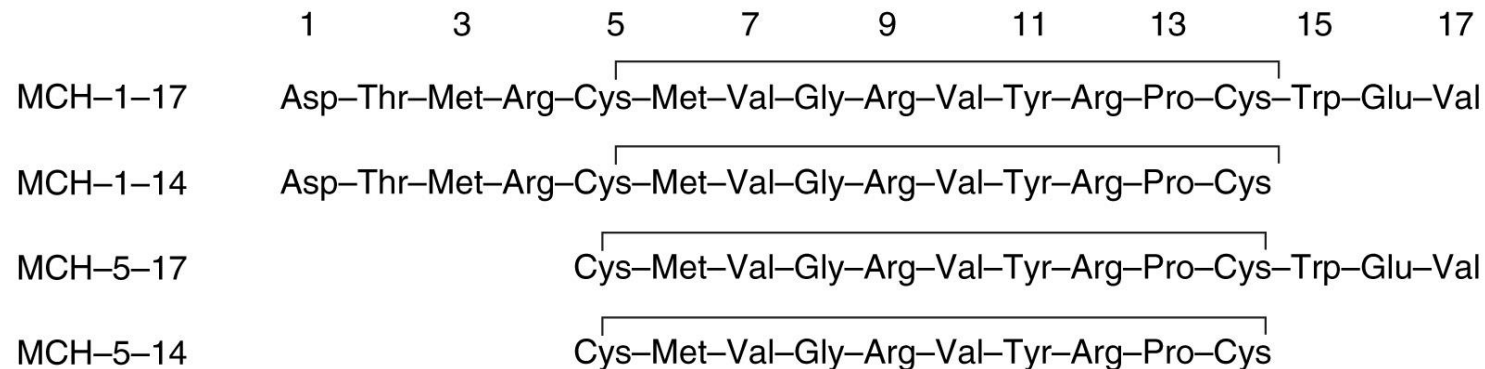
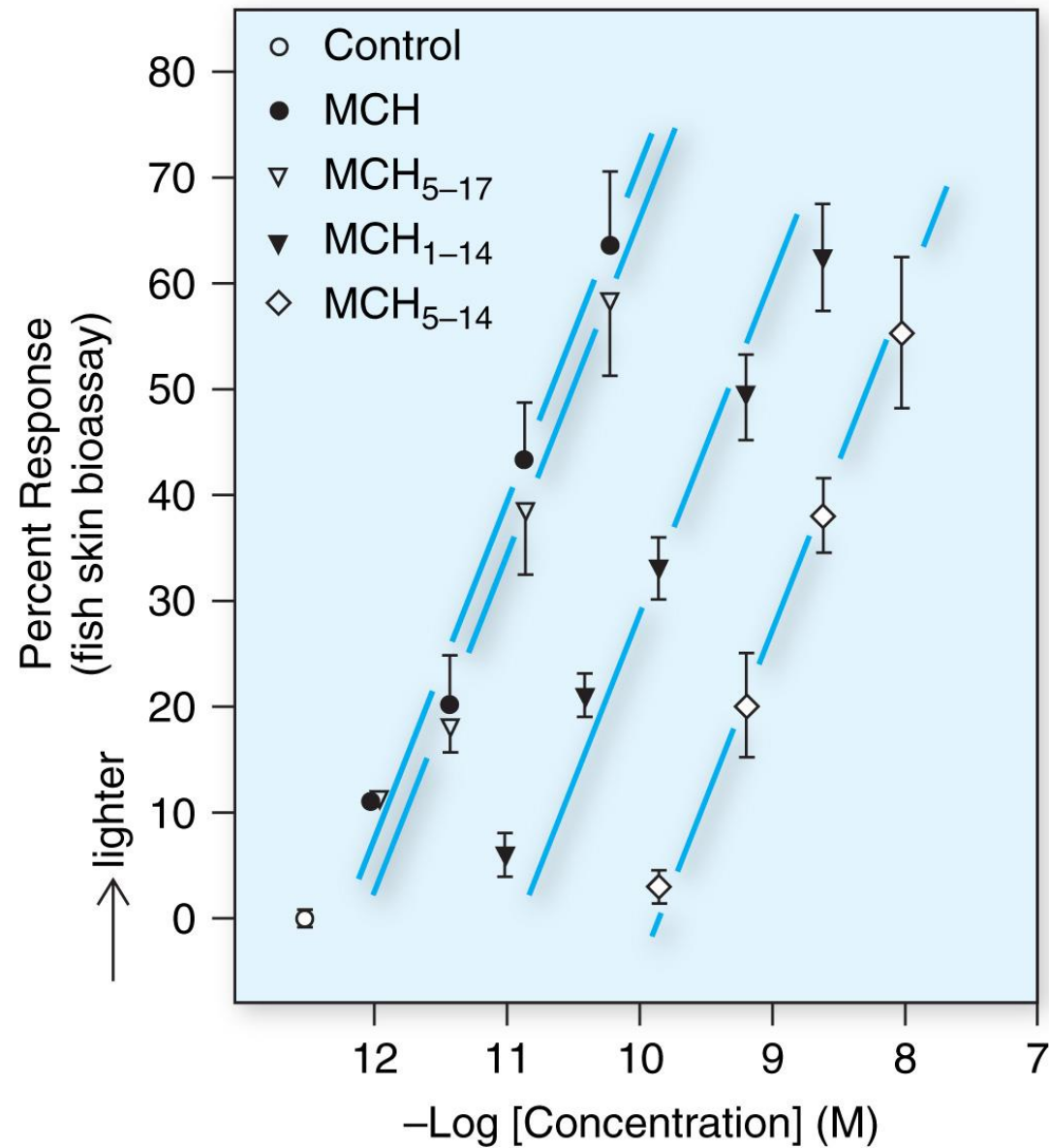


Fig. 8-17. Primary structures of MCH and related fragment analogs.

Fig. 8-18: In vitro bioassay of MCH and related analogs using skins of the fish *Synbranchus marmoratus* (an eel, 뱀장어).



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- 4) **Pathophysiologies involving melanotropic hormones** can accompany other endocrinopathies.
- **Hyperpigmentation**, a cardinal symptom of Addison's disease, develops because excessive circulating levels of ACTH or other melanotropic sequences are stimulatory to melanogenesis within epidermal melanocytes.
 - In **Cushing's syndrome** (of pituitary origin), where excessive amounts of ACTH are secreted, hyperpigmentation is often noted and may be due, again, to elevated circulating levels of POMC-derived melanotropic peptides.
 - **Vitiligo (백반증)**: a malady of the skin where melanocytes in certain areas are absent or fail to become pigmentogenic.

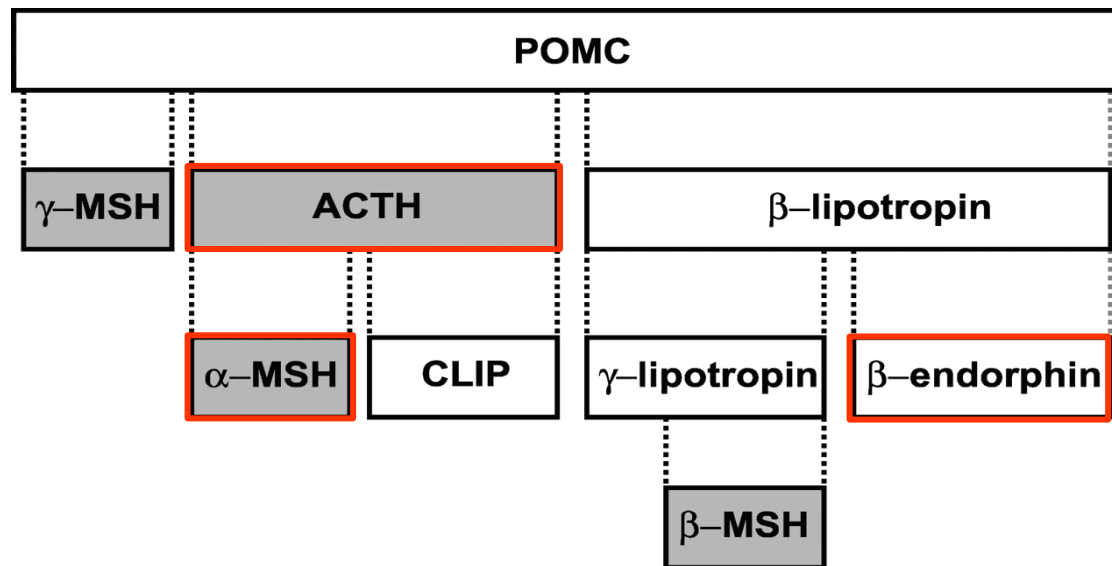


5) **Biomedical applications of melanocortins** are in development.

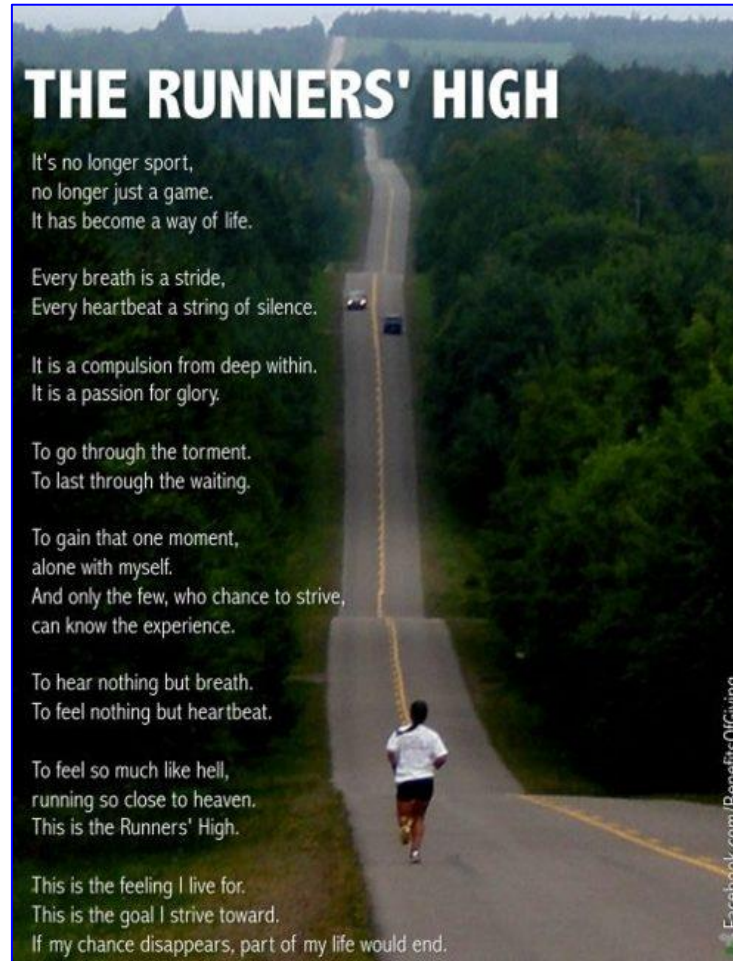
- A number of unique **α -MSH analogs** have been synthesized that are superpotent, prolonged acting, and resistant to inactivation by proteolytic enzymes.
- **α -MSH peptide analogs**: can be conjugated to radioisotopes or fluorescent ligands for the cellular- (receptor-) specific delivery to melanoma (cancer)
- **Melanotropins** can also be conjugated to **anticancer drugs**.
- **Melanotropin analog**, therefore, might be utilized for the **localization and chemotherapy of melanoma**.
- **MSH-related analogs** may prove useful as a “**tanning hormone**” for increasing the pigmentation of light-skinned individuals or possibly even for treating people with certain hypopigmentary disorders:

8. The Endorphins

- In 1965, C.H. Li discovered a peptide in the pituitary of cattle and named it β -lipotropin.
- Lipotropic peptide, β -LPH:
- **Endorphins**: a class of substances isolated from the brain and pituitary gland that exhibit **opiate-like activity**.
- β -Endorphin, as well as the **enkephalins** and other endorphins, are possible candidates for the body's own anti-pain (analgesic) hormones.

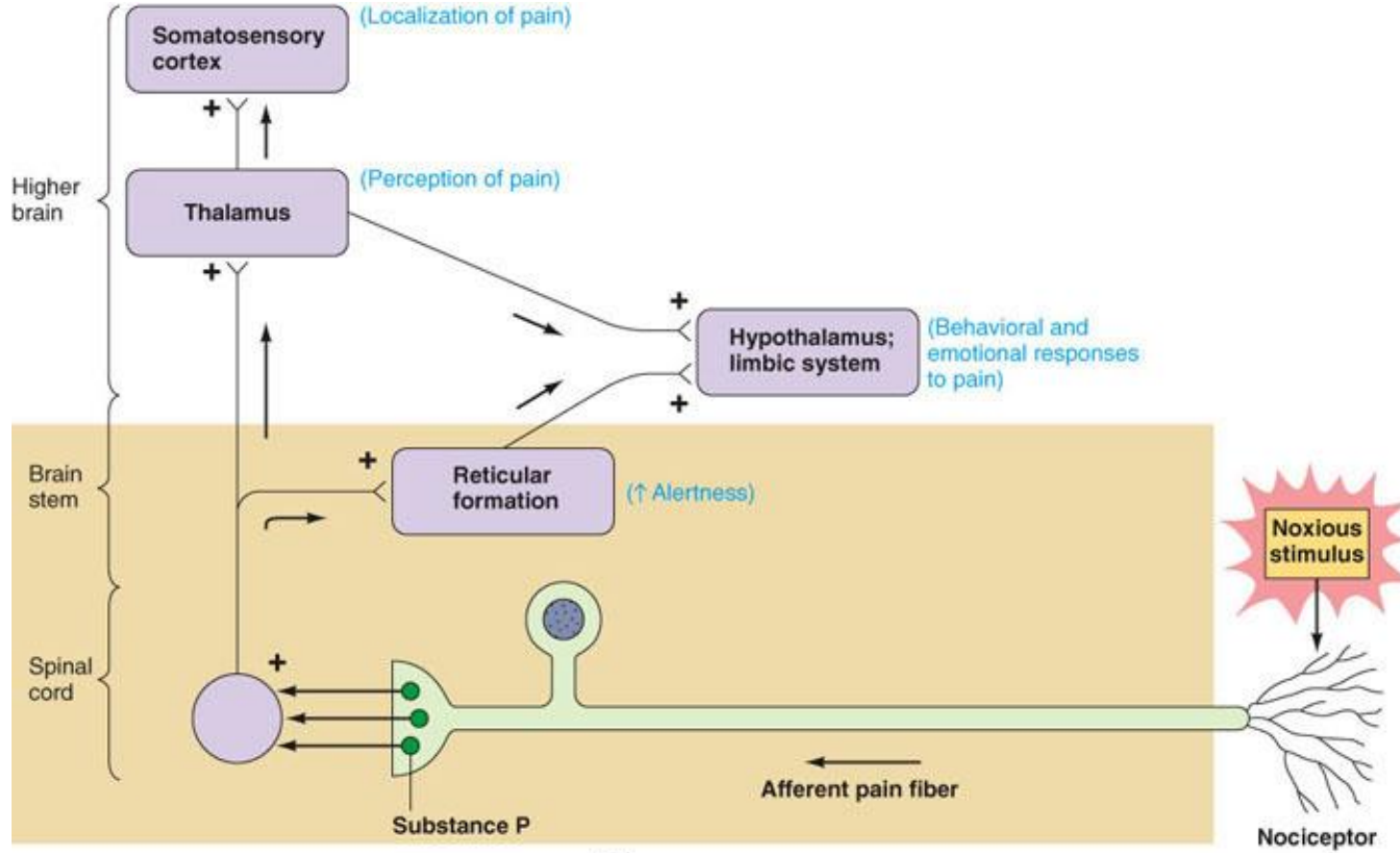


β-Endorphin: Runner's High

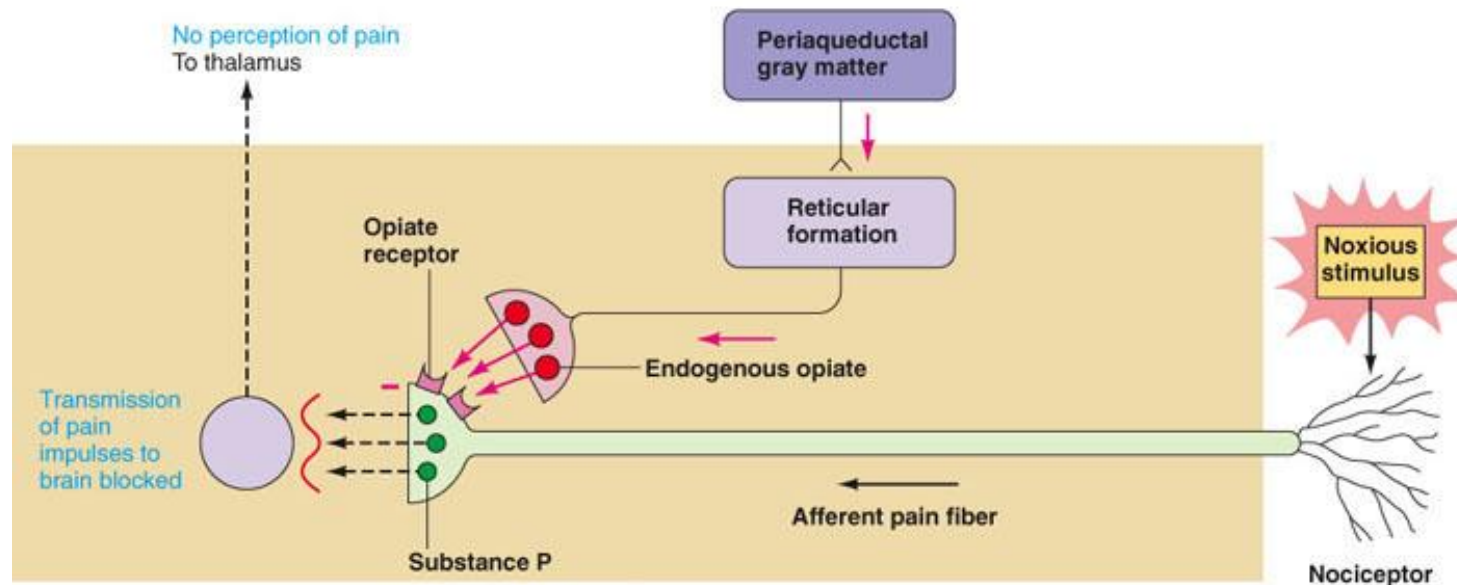


Pain

- Two best known **pain neurotransmitters**
 - **Substance P**
 - Activates ascending pathways that transmit nociceptive signals to higher levels for further processing
 - **Glutamate**
 - Major excitatory neurotransmitter
- Brain has built in **analgesic system**
 - Suppresses transmission in pain pathways as they enter spinal cord
 - Depends on presence of opiate receptors
 - Endogenous opiates – **endorphins**, **enkephalins**, **dynorphin**



(a)



(b)

- 1) The Physiological roles of **opioid peptides** are remarkably diverse
- Analgesic function
 - Endorphins as possible adrenomedullary hormones
 - Control of pituitary hormone secretion
 - Role in reproductive physiology