ADRENAL MEDULLA

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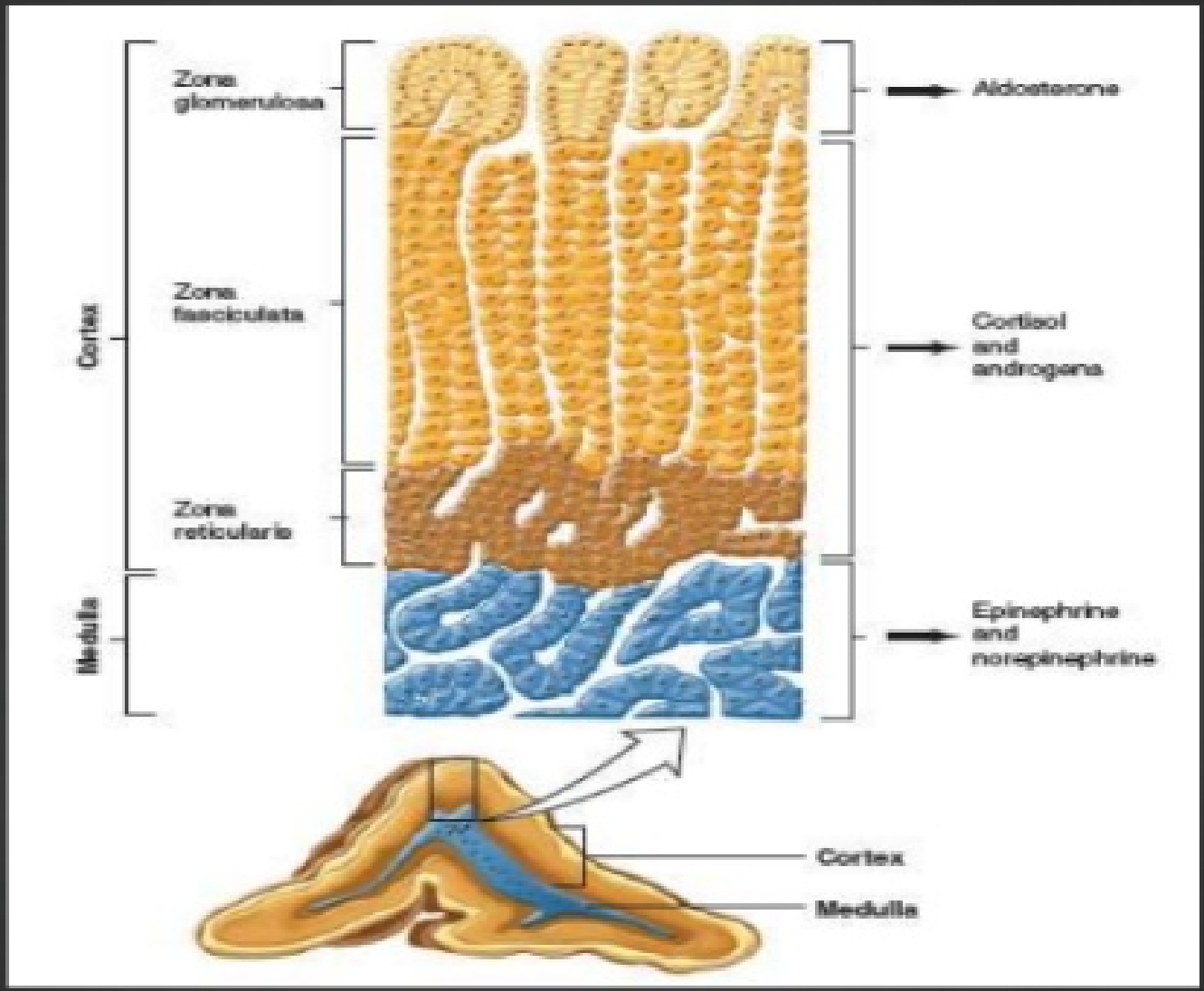
Introduction

- Medulla, the inner part of adrenal gland
- 20% of the mass of adrenal gland.
- Made up of interlacing cords of cells known as **chromaffin cells / pheochrome cells / chromophil cells**
- Contain fine granules

- Adrenal medulla is formed by two types of chromaffin cells:
  - **Adrenaline-secreting cells (90%)**
  - **Noradrenaline-secreting cells (10%)**


Zona glomerulosa
Zona fasciculata
Zona reticularis
Cortex
Medulla
Aldosterone
Cortisol and androgens
Epinephrine and norepinephrine
Cortex
Medulla

- **Hormones Of Adrenal Medulla**
  - They are the amines derived from **catechol**
  - So these hormones are called **catecholamines.**
  - Catecholamines secreted by adrenal medulla
    1. **Adrenaline or epinephrine**
    2. **Noradrenaline or norepinephrine**
    3. **Dopamine.**

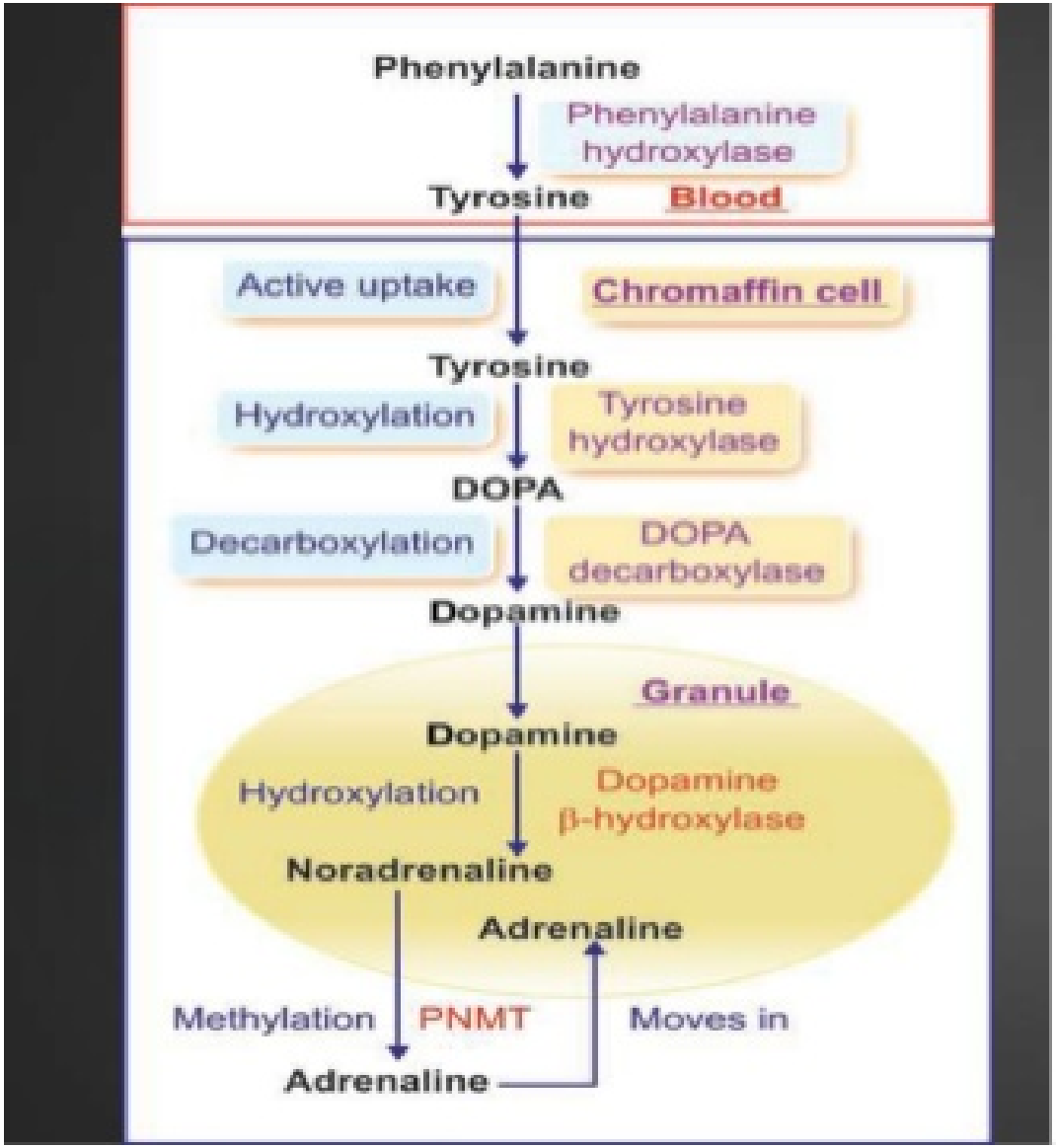
- **Plasma Level Of Catecholamines**
  - Adrenaline : 3 µg/dL
  - Noradrenaline : 30 µg/dL
  - Dopamine : 3.5 µg/dL

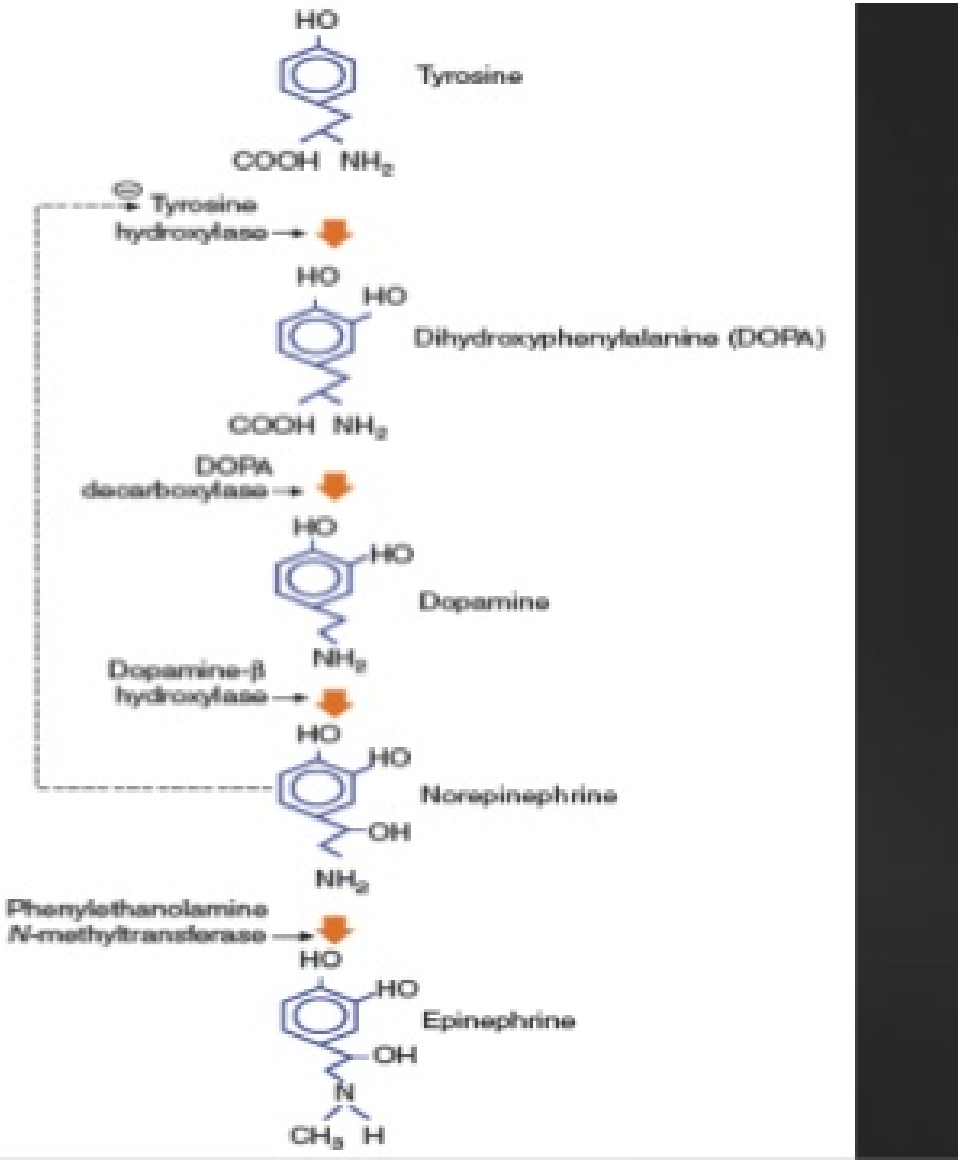
- **Half-life Of Catecholamines**
  - Half-life of catecholamines is about 2 minutes.

- **Synthesis Of Catecholamines**
  - Synthesized from the amino acid **tyrosine** in the **chromaffin cells** of adrenal medulla.
  - These hormones are formed from **phenylalanine** also.
  - But phenylalanine has to be converted into tyrosine

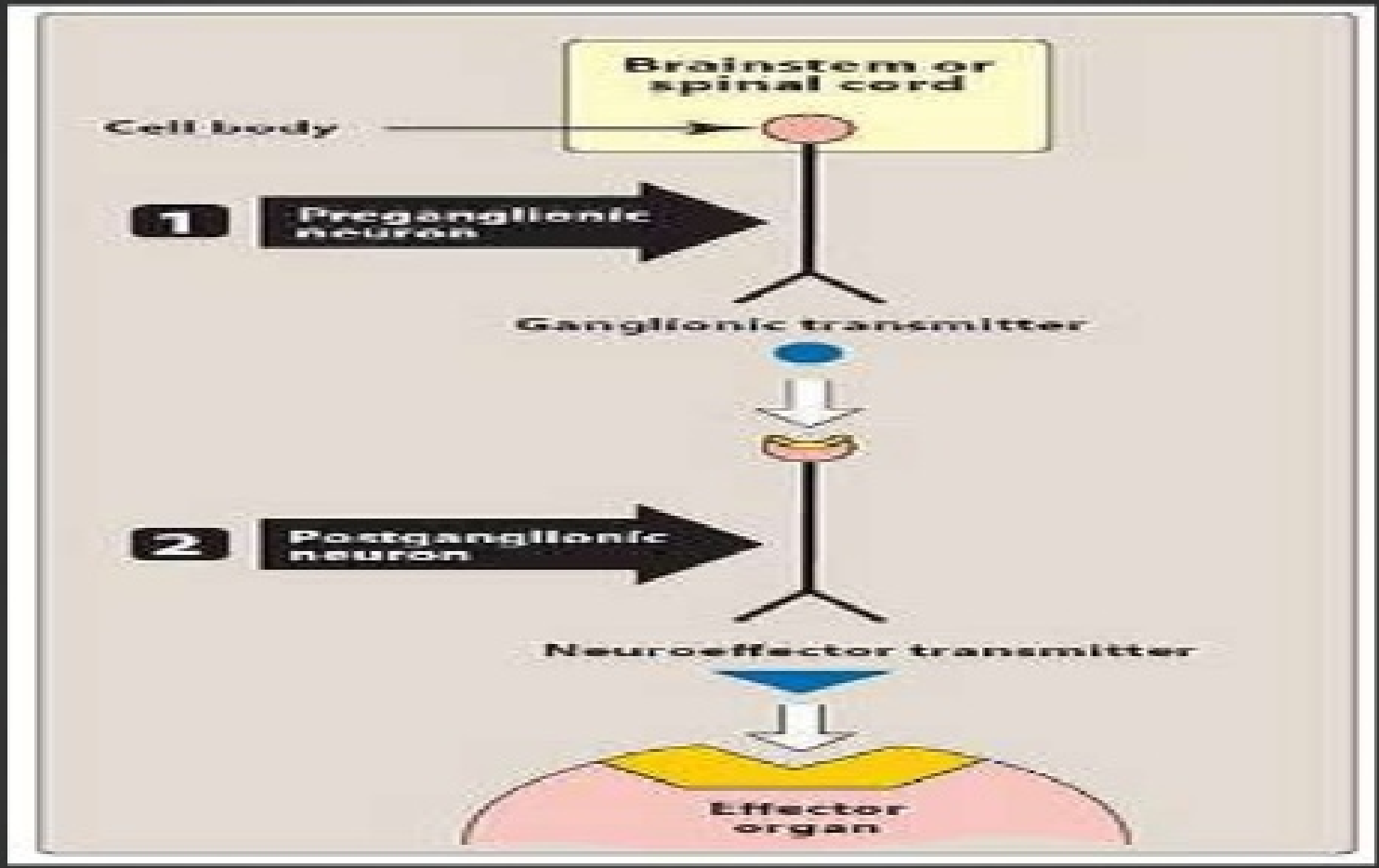
- **Stages of Synthesis of Catecholamines**
  1. Formation of tyrosine from phenylalanine in the presence of enzyme phenylalanine hydroxylase
  2. Uptake of tyrosine from blood into the chromaffin cells of adrenal medulla by active transport
  3. Conversion of tyrosine into dihydroxyphenylalanine (DOPA) by hydroxylation in the presence of tyrosine hydroxylase
  4. Decarboxylation of DOPA into dopamine by DOPA decarboxylase

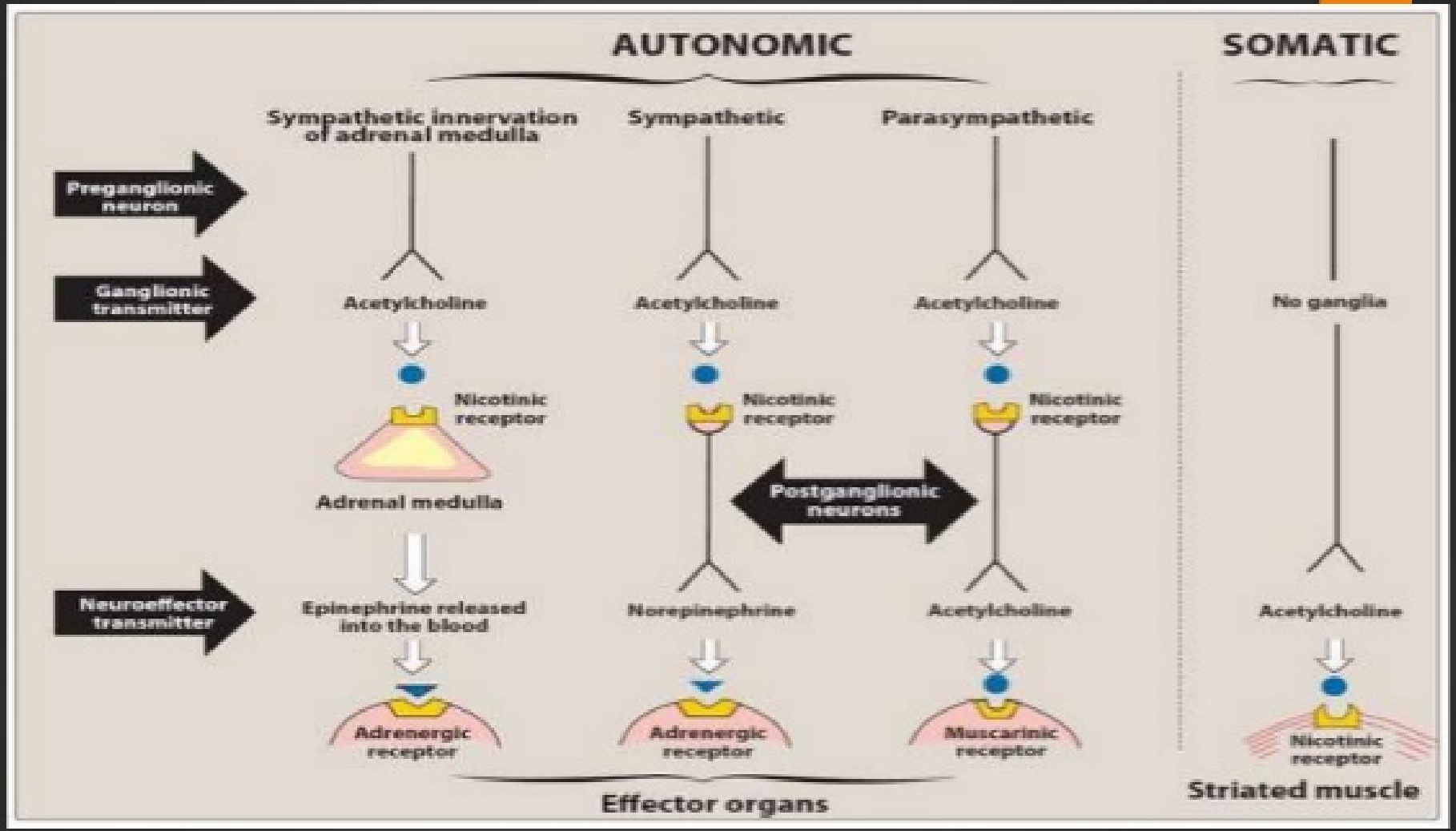
5. Entry of dopamine into granules of chromaffin cells
6. Hydroxylation of dopamine into noradrenaline by the enzyme **dopamine beta-hydroxylase**
7. Release of noradrenaline from granules into the cytoplasm
8. Methylation of noradrenaline into adrenaline by the most important enzyme called phenylethanolamine- N-methyltransferase (PNMT). PNMT is present in chromaffin cells.

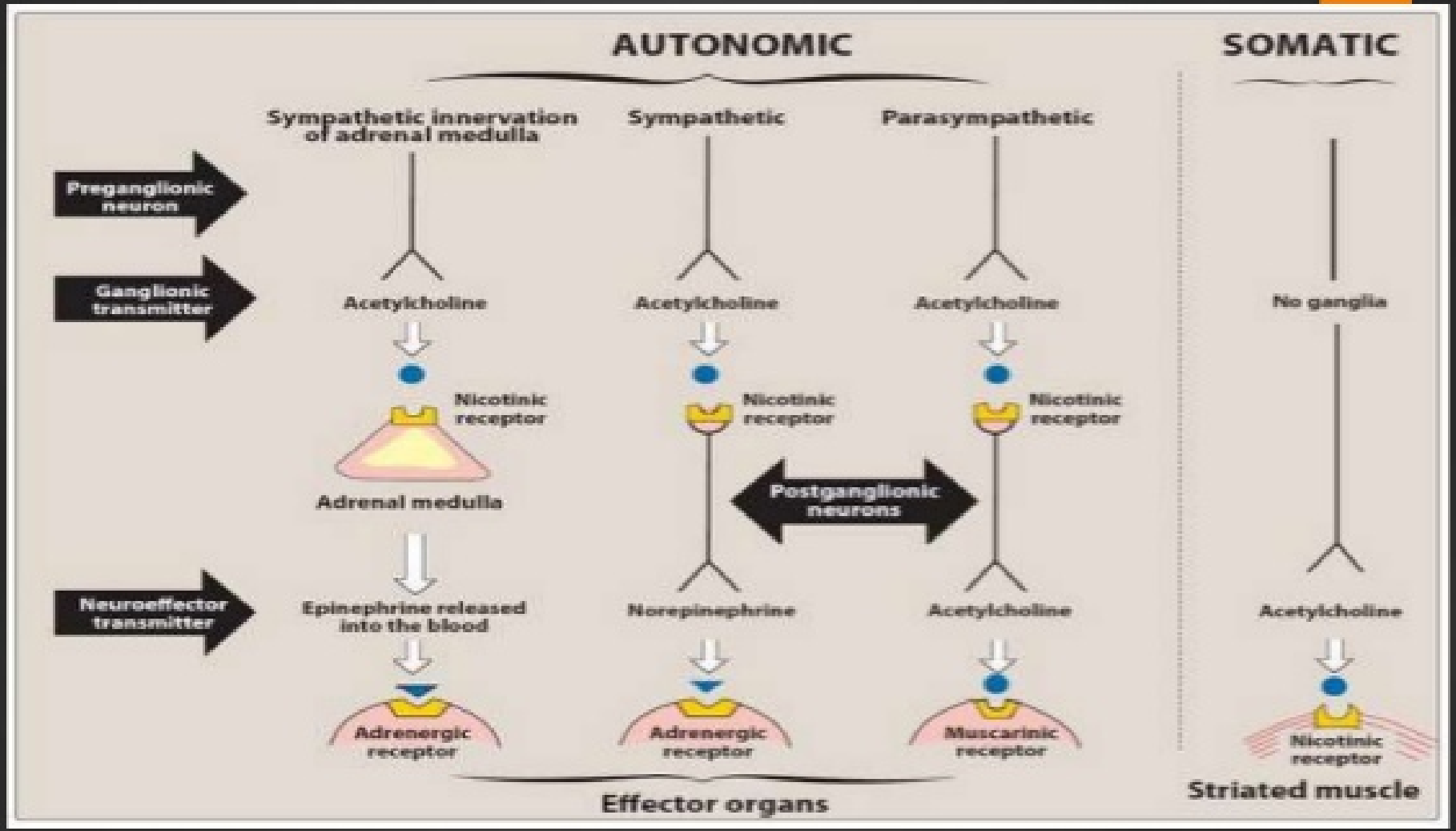

Phenylalanine
Phenylalanine hydroxylase
Tyrosine
Blood
Active uptake
Chromaffin cell
Tyrosine
Hydroxylation
Tyrosine hydroxylase
DOPA
Decarboxylation
DOPA decarboxylase
Dopamine
Granule
Dopamine
Hydroxylation
Dopamine β-hydroxylase
Noradrenaline
Adrenaline
Methylation
PNMT
Moves in
Adrenaline


Tyrosine
Tyrosine hydroxylase
Dihydroxyphenylalanine (DOPA)
DOPA decarboxylase
Dopamine
Dopamine-β hydroxylase
Norepinephrine
Phenylethanolamine N-methyltransferase
Epinephrine

- **Metabolism Of Catecholamines**
  - 85% of nor-adrenaline is taken up by the sympathetic adrenergic neurons.
  - Remaining 15% of noradrenaline and adrenaline are degraded.


Brainstem or spinal cord
Cell body
1
Preganglionic neuron
Ganglionic transmitter
2
Postganglionic neuron
Neuroeffector transmitter
Effector organ


AUTONOMIC
SOMATIC
Sympathetic innervation of adrenal medulla
Sympathetic
Parasympathetic
Preganglionic neuron
Ganglionic transmitter
Acetylcholine
Acetylcholine
Acetylcholine
No ganglia
Nicotinic receptor
Nicotinic receptor
Nicotinic receptor
Adrenal medulla
Postganglionic neurons
Neuroeffector transmitter
Epinephrine released into the blood
Norepinephrine
Acetylcholine
Acetylcholine
Adrenergic receptor
Adrenergic receptor
Muscarinic receptor
Nicotinic receptor
Effector organs
Striated muscle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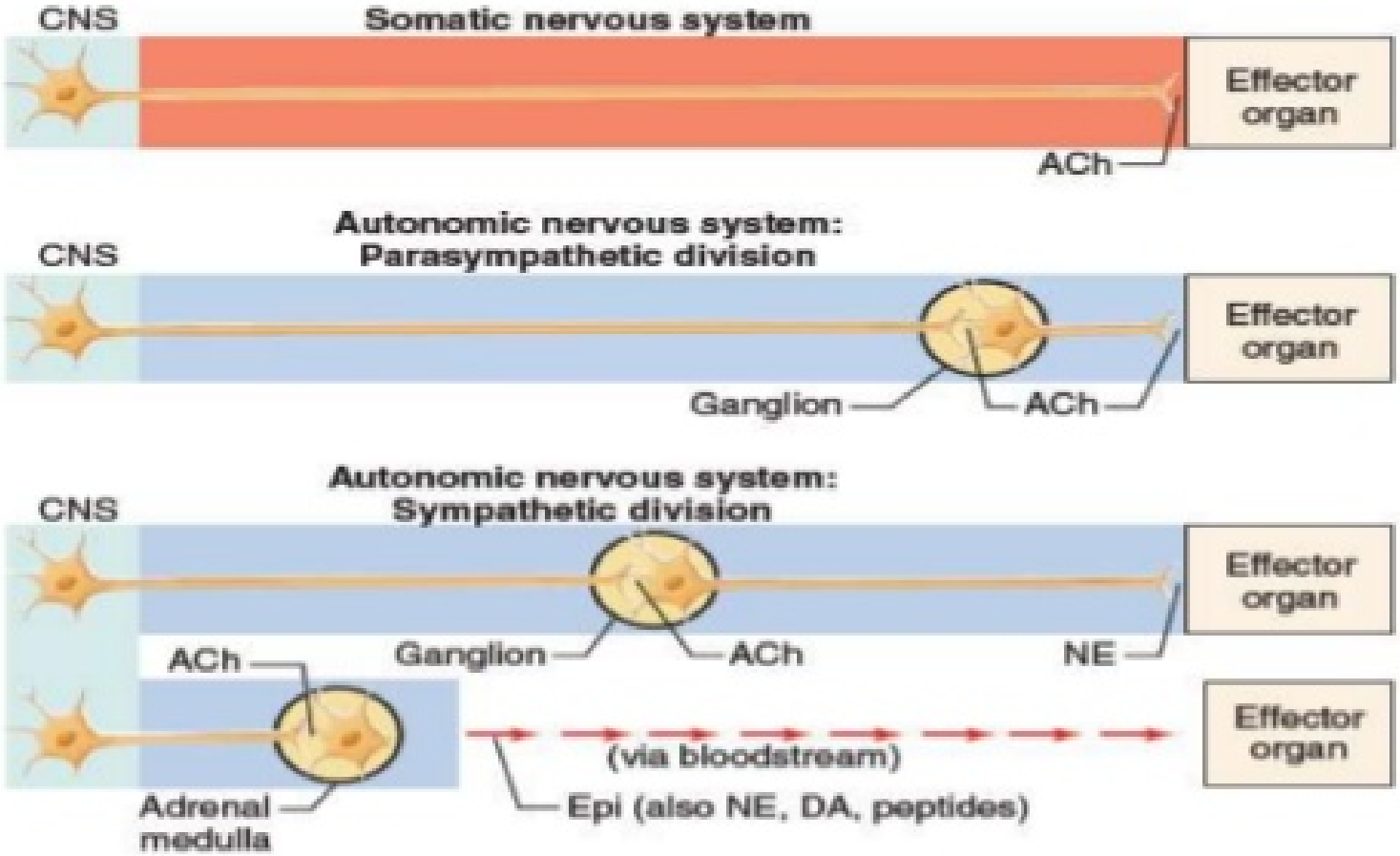
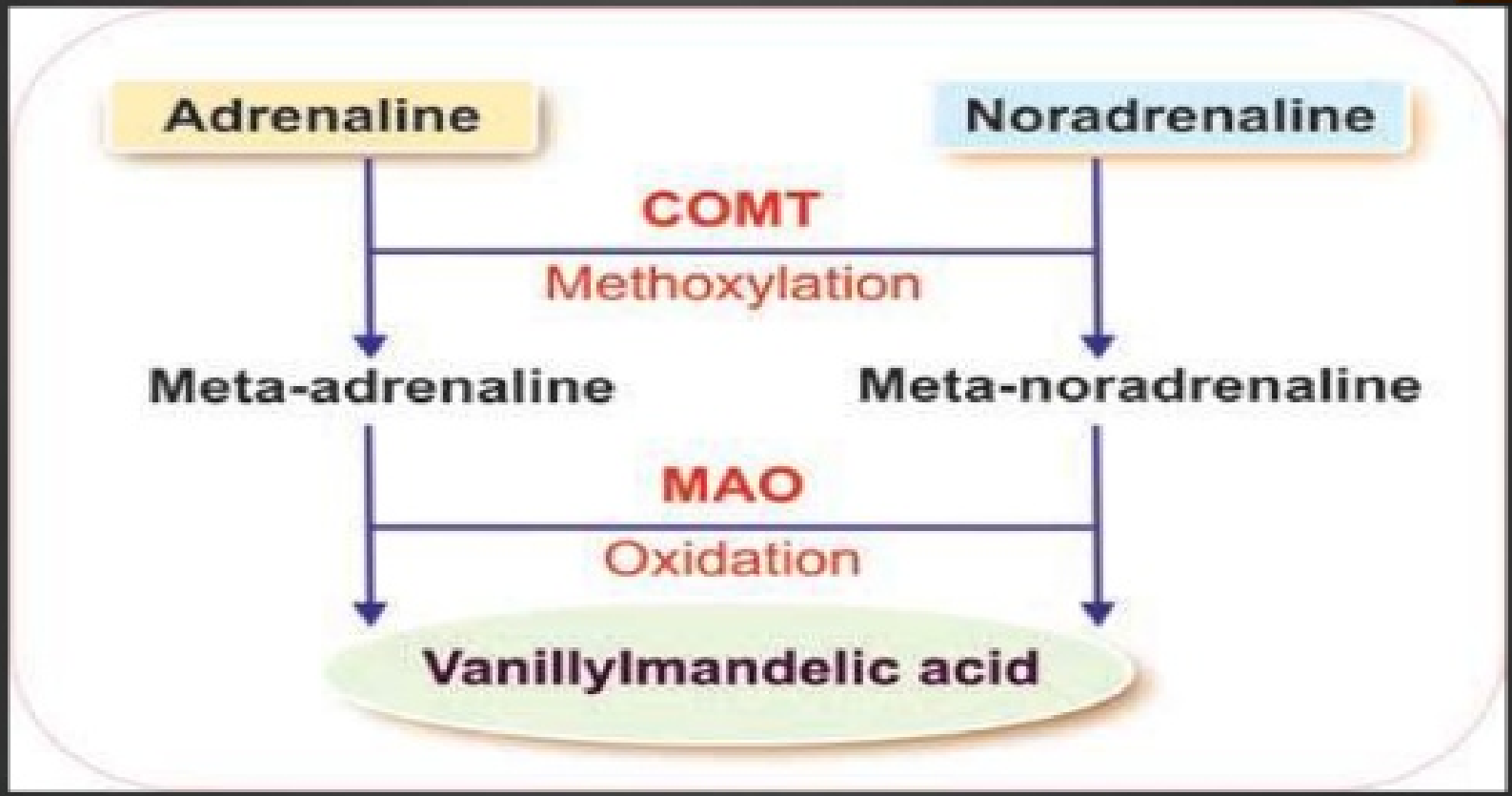

CNS
Somatic nervous system
Effector organ
ACh
Autonomic nervous system:
Parasympathetic division
CNS
Effector organ
Ganglion
ACh
Autonomic nervous system:
Sympathetic division
CNS
Effector organ
ACh
Ganglion
ACh
NE
Effector organ
(via bloodstream)
Epi (also NE, DA, peptides)
Adrenal medulla

- **Stages of Metabolism of Catecholamines**
  - Methoxylation of **adrenaline into meta-adrenaline**
  - Methoxylation of **noradrenaline into metanoradrenaline** in the presence of **catechol-O-methyltransferase (COMT).**
  - Meta-adrenaline and meta-noradrenaline are together called **metanephrines**
  - Oxidation of metanephrines into **vanillylmandelic acid (VMA)** by **monoamine oxidase (MAO)**


Adrenaline
Noradrenaline
COMT
Methoxylation
Meta-adrenaline
Meta-noradrenaline
MAO
Oxidation
Vanillylmandelic acid

- **Removal of Catecholamines**
  - Catecholamines are removed from body through urine in three forms:
    - **15%** as free adrenaline and free nor-adrenaline
    - **50%** as free or conjugated meta-adrenaline and meta-noradrenaline
    - **35%** as vanillylmandelic acid (VMA)

- **Actions Of Adrenaline And Noradrenaline**
  - Adrenaline and noradrenaline stimulate the nervous system.
  - Adrenaline has significant effects on metabolic functions
  - Both adrenaline and nor-adrenaline have significant effects on cardiovascular system

- **Mode Of Action Of Adrenaline & Noradrenaline – Adrenergic Receptors**
  - Actions of adrenaline and noradrenaline are executed by binding with receptors called adrenergic receptors, which are present in the target organs

- Adrenergic receptors are of two types:
  - **Alpha-adrenergic receptors**, which are subdivided into alpha-1 and alpha-2 receptors
  - **Beta-adrenergic receptors**, which are subdivided into beta-1 and beta-2 receptors.

- **Actions**
  - Circulating adrenaline and noradrenaline have similar effect of sympathetic stimulation.
  - Effect of adrenal hormones is prolonged 10 times more than that of sympathetic stimulation.
  - It is because of the slow inactivation, slow degradation and slow removal of these hormones.
  - Effects of adrenaline and noradrenaline on various target organs depend upon the type of receptors present in the cells of the organs.

- Adrenaline acts through both alpha and beta receptors equally.
- Nor-adrenaline acts mainly through alpha receptors and occasionally through beta receptors

1. **On Metabolism (via Alpha and Beta Receptors)**
   - Adrenaline influences the metabolic functions more than noradrenaline.
     1. **General metabolism:**
        - Adrenaline increases oxygen consumption and carbon dioxide removal.
        - It increases basal metabolic rate, so called calorigenic hormone

2. **Carbohydrate metabolism**

- Adrenaline increases the blood glucose level by increasing the glycogenolysis in liver and muscle.
- So, a large quantity of glucose enters the circulation

3. **Fat Metabolism:**
   - Adrenaline causes mobilization of free fatty acids from adipose tissues.
- Catecholamines need the presence of glucocorticoids for this action

2. **On Blood (via Beta Receptors)**
   - Adrenaline decreases blood coagulation time.
   - It increases RBC count in blood by contracting smooth muscles of splenic capsule and releasing RBCs from spleen into circulation

3. **On Heart (via Beta Receptors)**
   - Adrenaline has stronger effects on heart than noradrenaline.
   - It increases overall activity of the heart, i.e.
     1. Heart rate **(chronotropic effect)**
     2. Force of contraction **(inotropic effect)**
     3. Excitability of heart muscle **(bathmotropic effect)**
     4. Conductivity in heart muscle **(dromotropic effect)**

4. **On Blood Vessels (Via Alpha And Beta-2 Receptors)**
   - Noradrenaline has strong effects on blood vessels.
   - It causes constriction of blood vessels throughout the body via alpha receptors.
   - So it is called **'general vasoconstrictor'.**
   - Vasoconstrictor effect of noradrenaline increases total peripheral resistance.
   - Adrenaline also causes constriction of blood vessels.

- However, it causes dilatation of blood vessels in skeletal muscle, liver and heart through beta-2 receptors.
- So, the total peripheral resistance is decreased by adrenaline.
- Catecholamines need the presence of gluco corticoids, for these vascular effects

5. **On Blood Pressure (Via Alpha And Beta Receptors)**
   - Adrenaline increases **systolic blood pressure by** increasing the force of contraction of the heart and cardiac output.
   - But, it decreases **diastolic blood pressure by reducing the total peripheral resistance.**
   - Noradrenaline increases **diastolic pressure due to** general vasoconstrictor effect by increasing the total peripheral resistance.

- It also increases the **systolic blood pressure to a slight extent by its actions on heart.**
- The action of catecholamines on blood pressure needs the presence of glucocorticoids.
- Thus, hypersecretion of catecholamines leads to hypertension

6. **On Respiration (via Beta-2 Receptors)**
   - Adrenaline increases rate and force of respiration.
   - Adrenaline injection produces apnea, which is known as **adrenaline apnea.**
   - It also causes **bronchodilation.**

7. **On Skin (via Alpha and Beta-2 Receptors)**
   - Adrenaline causes contraction of **arrector pili.**
   - It also increases the secretion of sweat.

8. **On Skeletal Muscle (via Alpha and Beta-2 Receptors)**
   - Adrenaline causes severe contraction and quick fatigue of skeletal muscle.
   - It increases glycogenolysis and release of glucose from muscle into blood. It also causes **vasodilatation in skeletal muscles.**

9. **On Smooth Muscle (via Alpha and Beta Receptors)**
   - Catecholamines cause contraction of smooth muscles in the following organs:
     1. Splenic capsule
     2. Sphincters of gastrointestinal (GI) tract
     3. Arrector pili of skin
     4. Gallbladder

5. Uterus
6. Dilator pupillae of iris
7. Nictitating membrane of cat.

- Catecholamines cause relaxation of smooth muscles in the following organs:
  1. Non-sphincteric part of GI tract (esophagus, stomach and intestine)
  2. Bronchioles
  3. Urinary bladder

10. **On Central Nervous System (via Beta Receptors)**
    - Adrenaline increases the activity of brain.
    - Adrenaline secretion increases during **'fight or flight reactions' after** exposure to stress.
    - It enhances the cortical arousal and other facilitatory functions of central nervous system.

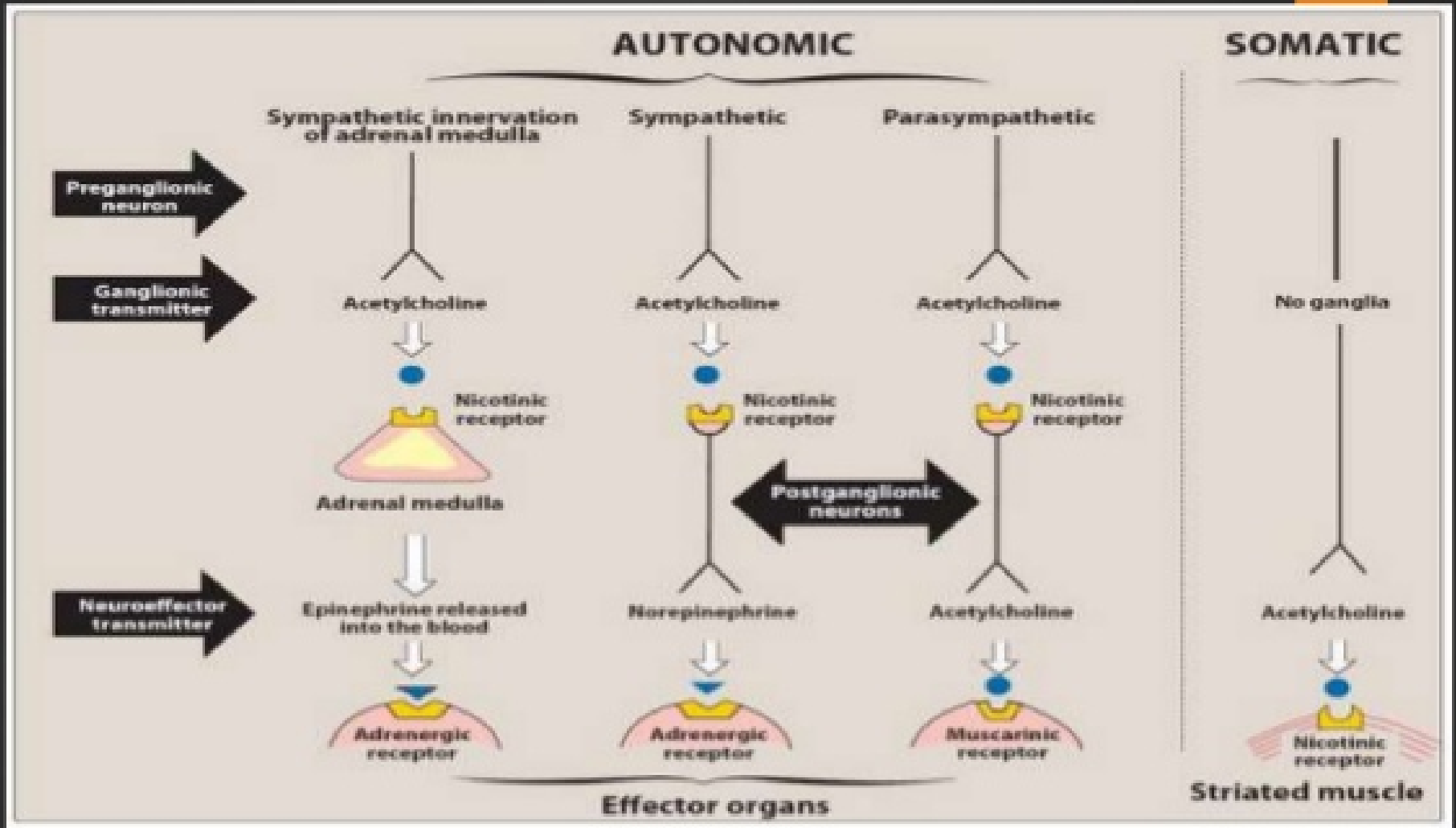
11. **Other Effects of Catecholamines**
    1. **On salivary glands (via alpha and beta-2 receptors):**
        - Cause vasoconstriction in salivary gland, leading to mild increase in salivary secretion
    2. **On sweat glands (via beta-2 receptors):**
        - Increase the secretion of apocrine sweat glands
    3. **On lacrimal glands (via alpha receptors):**
        - Increase the secretion of tears

4. **On ACTH secretion (via alpha receptors)**
   - Adrenaline increases ACTH secretion
5. **On nerve fibers (via alpha receptors)**
   - Adrenaline decreases the latency of action potential in the nerve fibers, i.e. electrical activity is accelerated
6. **On renin secretion (via beta receptors)**
   - Increase the rennin secretion from juxtaglomerular apparatus of the kidney

Adrenergic Receptors and Function

Alpha Receptor	Beta Receptor
Vasoconstriction	Vasodilation (β_2)
Iris dilation	Cardioacceleration (β_1)
Intestinal relaxation	Increased myocardial strength (β_1)
Intestinal sphincter contraction	Intestinal relaxation (β_2)
	Uterus relaxation (β_2)
Pilomotor contraction	Bronchodilation (β_2)
Bladder sphincter contraction	Calorigenesis (β_2)
	Glycogenolysis (β_2)
	Lipolysis (β_1)
	Bladder wall relaxation (β_2)

- **Regulation Of Secretion Of Adrenaline And Noradrenaline**
  - Adrenaline and noradrenaline are secreted from adrenal medulla in small quantities even during rest.
  - During stress conditions, due to **sympatho-adrenal discharge**, a large quantity of catecholamines is secreted.
  - These hormones prepare the body for fight or flight reactions.
  - Catecholamine secretion increases during exposure to cold and hypoglycemia also.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- **Dopamine**
  - Secreted by adrenal medulla.
  - Also secreted by dopaminergic neurons in some areas of brain, particularly basal ganglia.
  - In brain, this hormone acts as a neurotransmitter.

- Injected dopamine produces the following effects:
  1. Vasoconstriction by releasing norepinephrine
  2. Vasodilatation in mesentery
  3. Increase in heart rate via beta receptors
  4. Increase in systolic blood pressure but does not affect diastolic blood pressure.