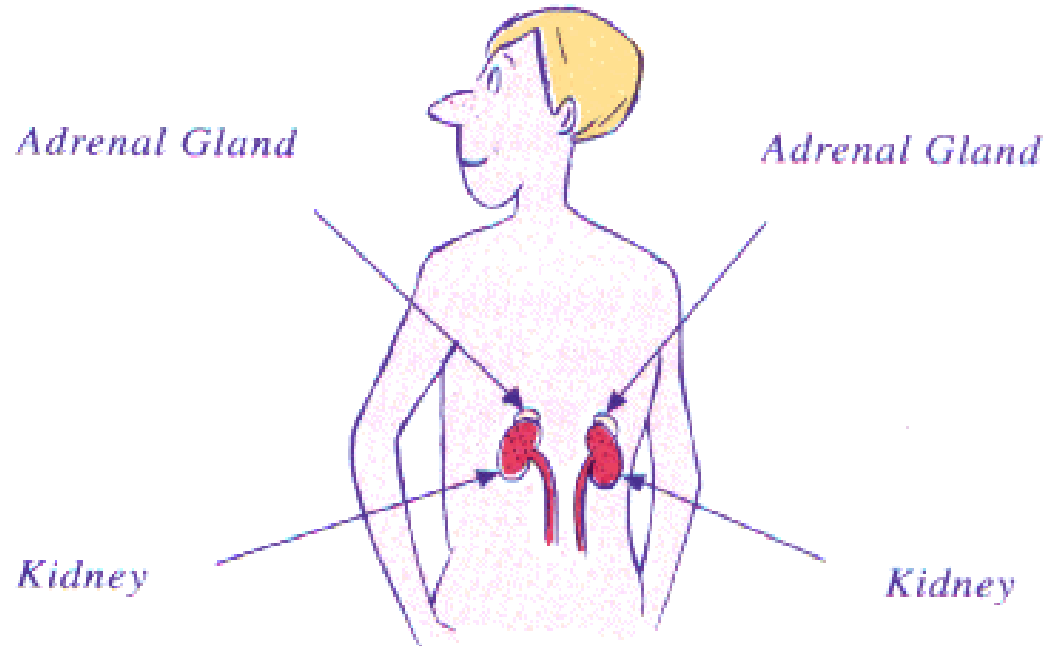


Hormones of the Adrenal Medulla

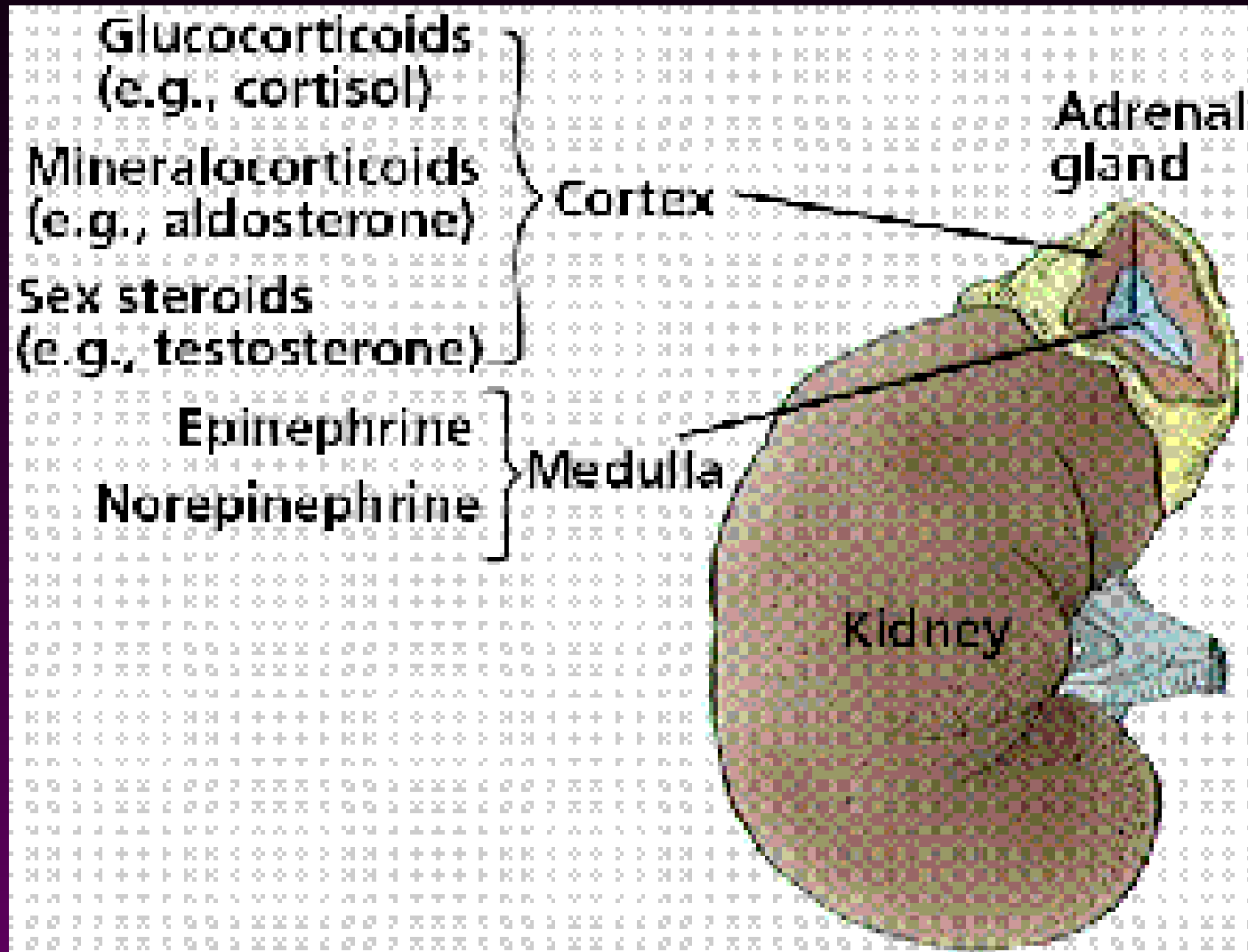


M.Sc BCH 560

2006

A.S. Wary

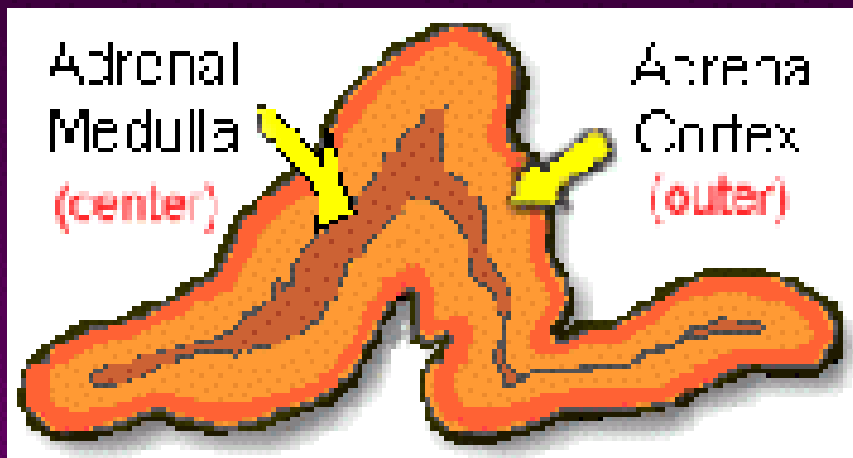
Image of Adrenal Gland



ADRENAL GLANDS

AD = UPON RENAL = KIDNEY

- One gland on top of each kidney
- Divided into 2 regions:
 - ▶ Outer region called adrenal cortex
 - ▶ Inner region called adrenal medulla

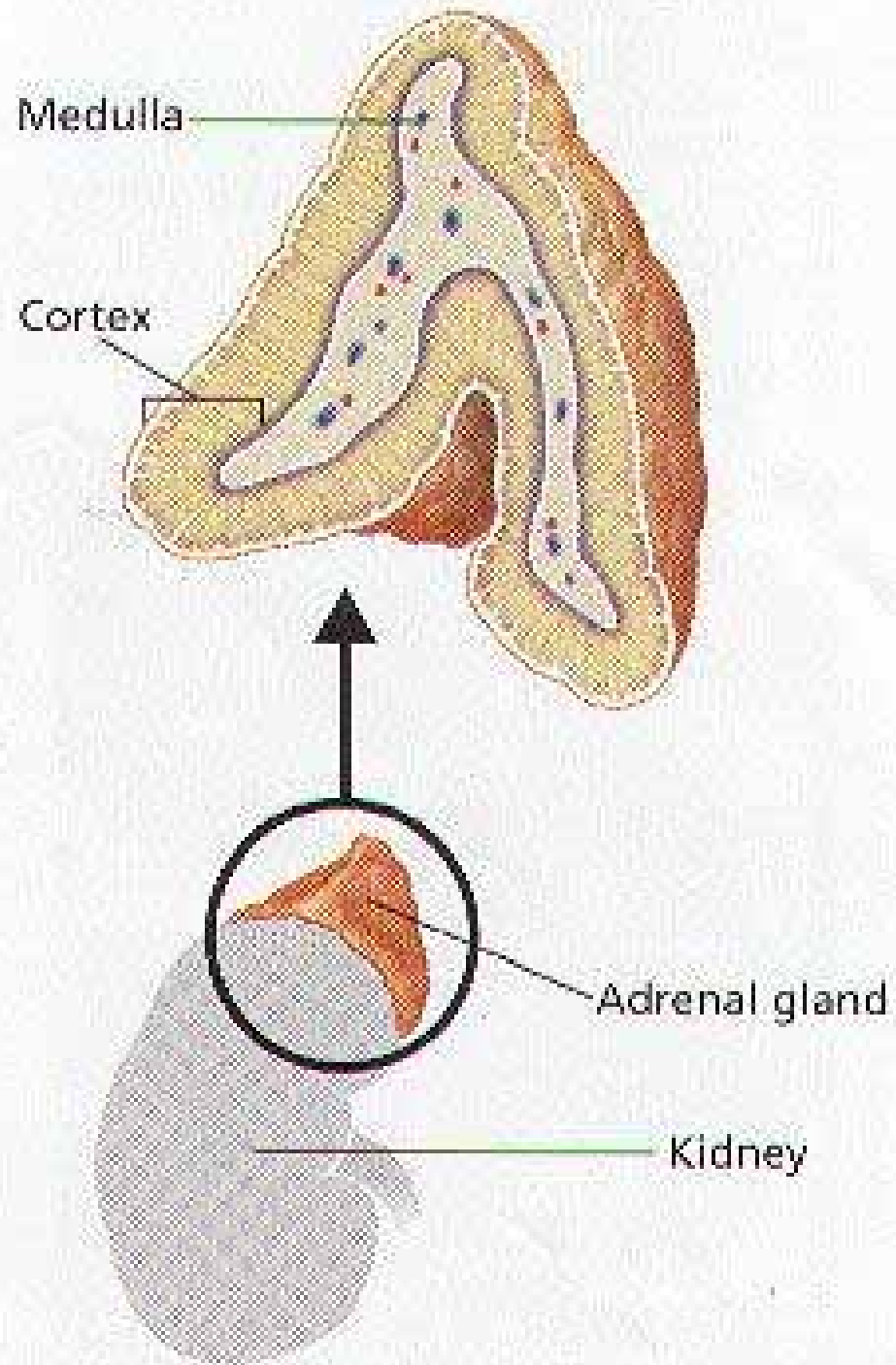


Adrenal glands

-The two adrenal glands are located immediately **anterior to the kidneys**, encased in a **connective tissue capsule** and usually partially buried in an island of fat. Like the kidneys, the adrenal glands lie **beneath the peritoneum** (i.e. they are retroperitoneal).

-The exact location relative to the kidney and the shape of the adrenal gland **vary among species**.

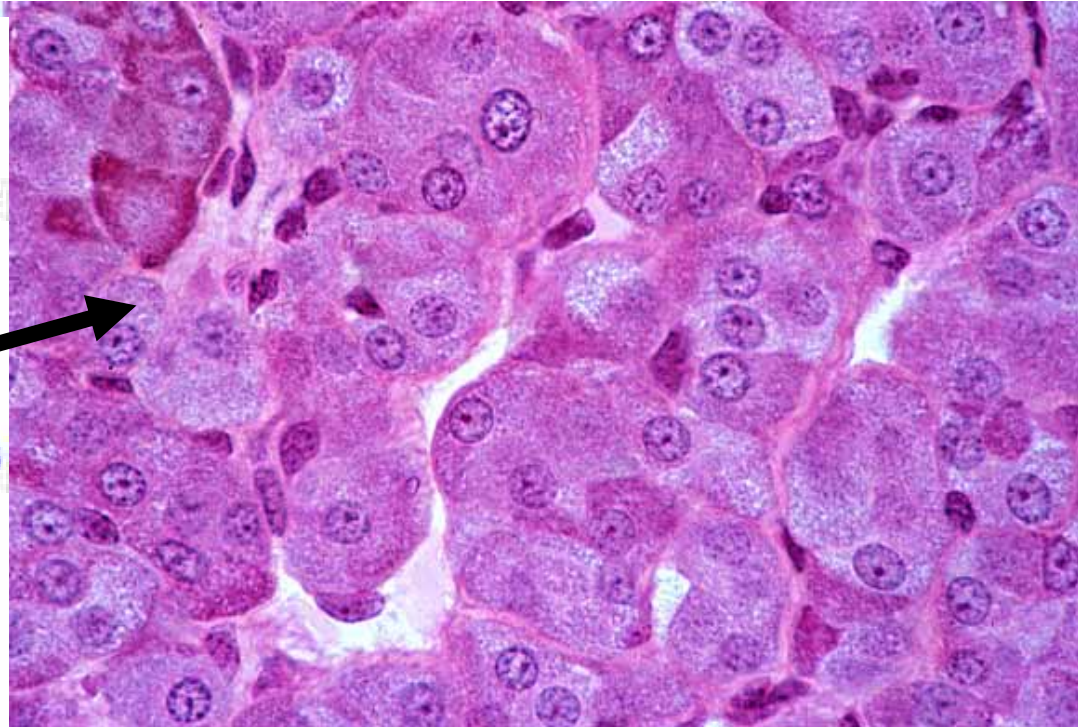
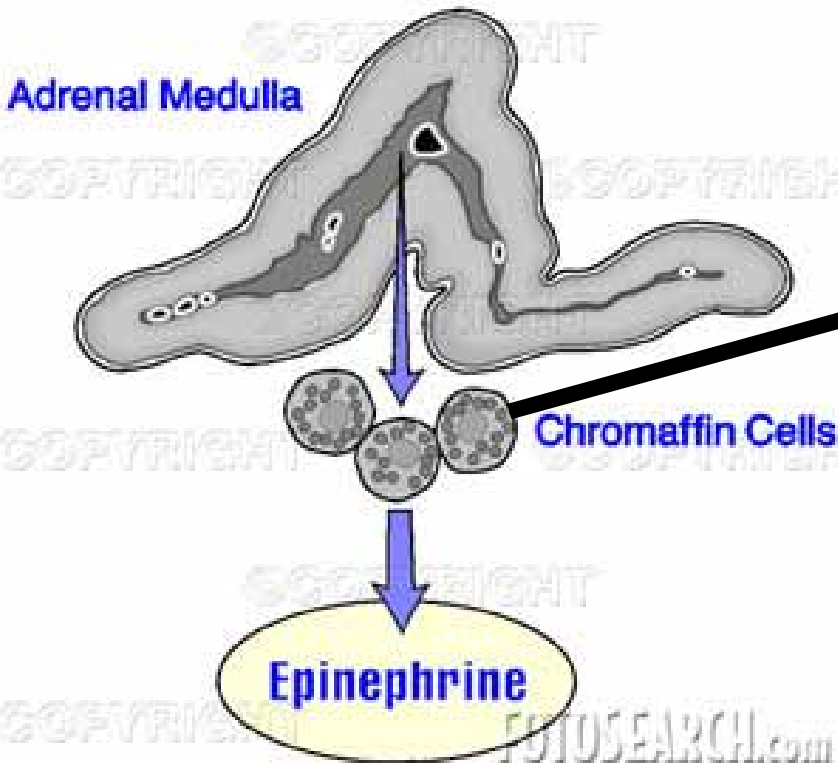
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Adrenal Medulla

- The inner **medulla**, is a source of the catecholamines epinephrine and norepinephrine.
- The **chromaffin cell** is the principle cell type.
- The medulla is richly **innervated by preganglionic sympathetic fibers** and is, in essence, an **extension of the sympathetic nervous system**.

Chromaffin cells



Catecholamines

- The naturally occurring catecholamines are
 - norepinephrine (NE, noradrenaline),
 - epinephrine (E, adrenaline),
 - and dopamine.

- Norepinephrine is the principal product synthesized in the CNS, and epinephrine is the principal catecholamine produced by the adrenal glands.

Function of adrenal medulla

- Chromaffin cells in the adrenal medulla synthesise and secrete norepinephrine and epinephrine.
- The ratio of these two catecholamines differs considerably among species: in humans, cats and chickens, roughly 80, 60 and 30% of the catecholamine output is epinephrine

Physiological actions of the catecholamines

- Diverse.
- Norepinephrine functions primarily as a neurotransmitter.
- Both norepinephrine and epinephrine influence the vascular system, whereas epinephrine affects metabolic processes such as carbohydrate metabolism.
- The biological actions of the catecholamines are initiated through their interaction with two different types of specific cell membrane receptors, the alpha-adrenergic and beta-adrenergic receptors.
- These receptors have different affinities for norepinephrine and epinephrine and cause opposing physiological effects.
- Norepinephrine primarily interacts with alpha-adrenergic receptors, whereas epinephrine interacts with both alpha- and beta-receptors.

Effect of catecholamines on different receptors

- Stimulation of alpha-adrenergic receptors results in:
 - vasoconstriction,
 - decrease in insulin secretion,
 - sweating,
 - piloerection (hair standing on end),
 - and stimulation of glycogenolysis in the liver and skeletal muscle leading to an increase in blood glucose concentration.
- Stimulation of beta-receptors leads to:
 - vasodilatation;
 - stimulation of insulin release;
 - increased cardiac contraction rate;
 - relaxation of smooth muscle in the intestinal tract;
 - bronchodilatation by relaxation of smooth muscles in bronchi;
 - stimulation of renin release, which enhances sodium resorption from the kidney;
 - and enhanced lipolysis.

Factors Regulating release

- The synthesis of epinephrine and norepinephrine is regulated by the intracellular concentrations of these hormones by negative-feedback inhibition, as stated previously.
- The catecholamines are released from the adrenal medulla in response to hypotension, hypoxia, exposure to cold, muscular exertion, pain, and emotional disturbances.

Storage and secretion

-Norepinephrine and epinephrine are stored in **electron-dense granules**, which also contain ATP and several neuropeptides.

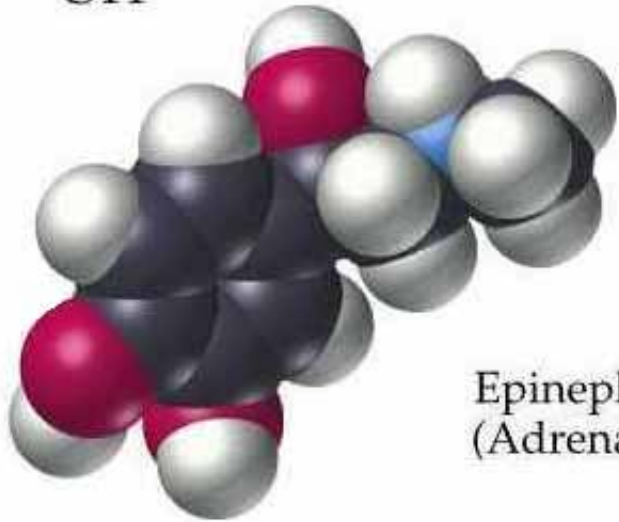
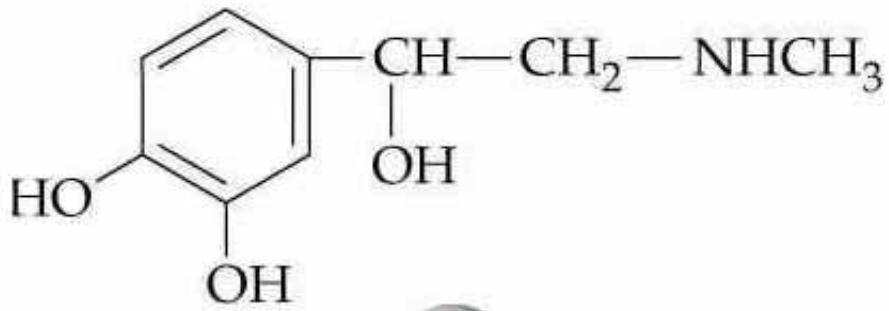
- Secretion of these hormones is stimulated by:
- acetylcholine release from preganglionic sympathetic fibre's innervating the medulla.
- Many types of "stresses" stimulate such secretion, including exercise, hypoglycaemia and trauma.

-Following secretion into blood, the catecholamines bind loosely to and are carried in the circulation by albumin and perhaps other serum proteins.

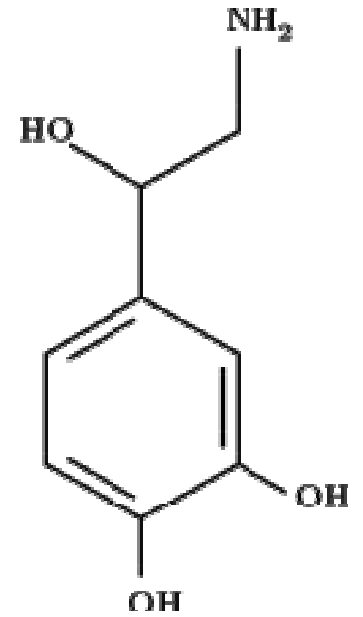
Source of circulating catecholamines

Circulating catecholamines, epinephrine and norepinephrine, originate from two sources.

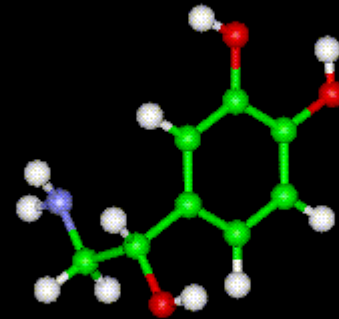
- Epinephrine is released by the adrenal medulla upon activation of preganglionic sympathetic nerves innervating this tissue.
 - This activation occurs during times of stress (e.g., exercise, heart failure, hemorrhage, emotional stress or excitement, pain).
- Norepinephrine is also released by the adrenal medulla (about 20% of its total catecholamine release is norepinephrine). The primary source of circulating norepinephrine is spillover from sympathetic nerves innervating blood vessels.
 - Normally, most of the norepinephrine released by sympathetic nerves is taken back up by the nerves (some is also taken up by extra-neuronal tissues) where it is metabolized.
 - A small amount of norepinephrine, however, diffuses into the blood and circulates throughout the body.
 - At times of high sympathetic nerve activation, the amount of norepinephrine entering the blood increases dramatically.



Epinephrine
(Adrenaline)



Norepinephrine

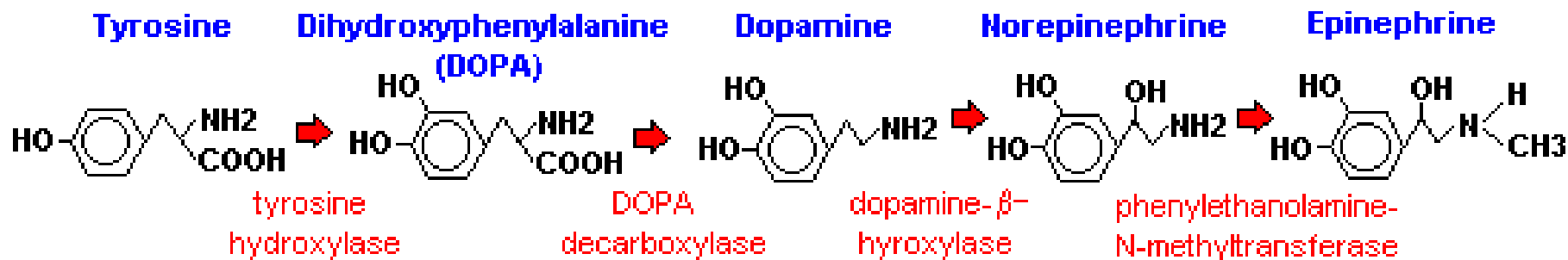


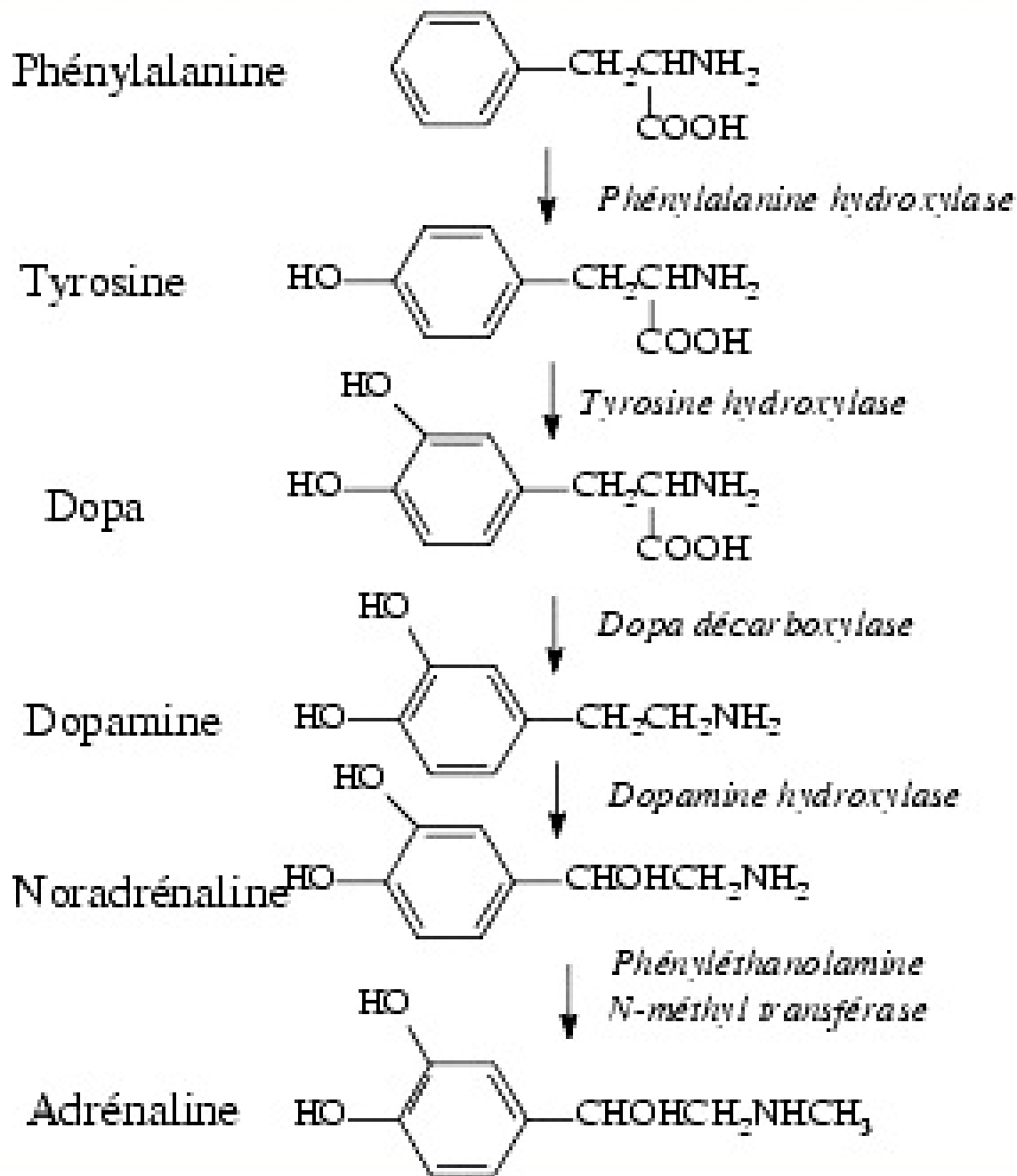
Norepinephrine *noradrenalin.*

- A substance, both a **hormone** and **neurotransmitter**,
- Secreted by the adrenal medulla and the nerve endings of the sympathetic nervous system
- **causes:**
 - vasoconstriction
 - and increases in heart rate,
 - blood pressure, and the sugar level of the blood.

Synthesis and Secretion of Catecholamines

Synthesis of catecholamines begins with the amino acid tyrosine, which is taken up by chromaffin cells in the medulla and converted to norepinephrine and epinephrine through the following steps:





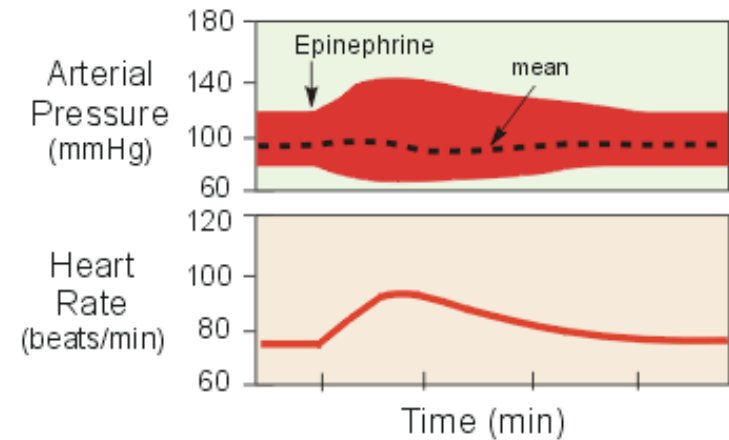
Adrenergic Receptors

Receptor	Effectively Binds	Effect of Ligand Binding
Alpha₁	Epinephrine, Norepinephrine	Increased free calcium
Alpha₂	Epinephrine, Norepinephrine	Decreased cyclic AMP
Beta₁	Epinephrine, Norepinephrine	Increased cyclic AMP
Beta₂	Epinephrine	Increased cyclic AMP

Circulating epinephrine causes:

- **Increased heart rate** and inotropy (β_1 -adrenoceptor mediated)
- **Vasoconstriction** in most systemic arteries and veins (postjunctional α_1 and α_2 adrenoceptors)
- **Vasodilation in muscle and liver** vasculatures at low concentrations (β_2 -adrenoceptor); vasoconstriction at high concentrations (α_1 -adrenoceptor mediated)
- The overall **cardiovascular response** to low-to-moderate circulating concentrations of epinephrine results in increased cardiac output and a redistribution of the cardiac output to muscular and hepatic circulations with only a small change in mean arterial pressure.
- Although cardiac output is increased, arterial pressure does not change much because the systemic vascular resistance falls due to β_2 -adrenoceptor activation.
- At high plasma concentrations, epinephrine increases arterial pressure because of binding to α -adrenoceptors on blood vessels, which offsets the β_2 -adrenoceptor mediated vasodilation.

A.S.Warsy



Pharmacologic blocking of the actions of circulating catecholamines

- As catecholamines act on the heart and blood vessels through alpha and beta adrenoceptors, the cardiovascular actions of catecholamines can be blocked by treatment with alpha-blockers and beta-blockers.
- Blocking either the alpha or beta adrenoceptor alone alters the response of the catecholamine because the other adrenoceptor will still bind to the catecholamine.
- For example, if a low dose of epinephrine is administered in the presence of alpha-adrenoceptor blockade, the unopposed b2-adrenoceptor activation will cause a large hypotensive response due to systemic vasodilation despite the cardiac stimulation that occurs due to b1-adrenoceptor activation

Dopamine

- **Naturally produced** in the body.
- In the **brain**, dopamine functions as a **neurotransmitter**, activating dopamine receptors.
- Dopamine is also a **neurohormone** released by the hypothalamus.
- Its main function as a hormone is to **inhibit the release of prolactin** from the anterior lobe of the pituitary

Dopamine as a drug

- Dopamine is used for the treatment of **Parkinson's disease**
- Dopamine can be supplied as a medication that acts on the **sympathetic nervous system**, producing effects such as increased heart rate and blood pressure.
- However, since dopamine **cannot cross the blood-brain barrier**, dopamine given as a drug does **not directly affect the central nervous system**.
- To increase the amount of dopamine in the brains of patients with diseases such as Parkinson's disease and Dopa-Responsive Dystonia, a synthetic precursor to dopamine such as **L-DOPA** can be given, since this will cross the blood-brain barrier.

Functions of dopamine in the brain

- Role in movement
- Role in cognition and frontal cortex function
- In the frontal lobes, dopamine controls the flow of information from other areas of the brain.
- Role in regulating prolactin secretion
- Role in pleasure and motivation
- Dopamine is commonly associated with the *pleasure system* of the brain, providing feelings of enjoyment and reinforcement to motivate us to do certain activities.

Dopamine and psychosis

- Disruption to the dopamine system has also been strongly linked to psychosis and schizophrenia.

Pheochromocytomas are chromaffin cell tumors

- Pheochromocytomas are chromaffin cell tumors typically arising within the adrenal medulla.
- These tumors are a rare cause of hypertension that must be excluded in a significant proportion of the 20% of the adult population of western countries who develop high blood pressure.
- In the United States alone this amounts to about 800,000 cases of newly diagnosed hypertension each year in which pheochromocytoma may represent a correctable cause of high blood pressure.
- It is not feasible or cost effective to screen for pheochromocytoma in every patient with hypertension, particularly when commonly available tests do not always detect the tumor.
- This diagnosis is most often only considered when a patient shows episodic hypertension, fails to respond to antihypertensive therapy, has a hypertensive episode during anesthesia or surgery or when there are other suggestive symptoms, such as headache, sweatiness, anxiety, palpitations or tachycardia.
- It also must be considered that some patients, particularly those with a familial predisposition to pheochromocytoma, may not show increased blood pressure or the typical symptoms of a pheochromocytoma. In these patients biochemical diagnosis of the tumor can be particularly troublesome.

- Pathways of metabolism of norepinephrine and epinephrine. Enzymes responsible for each pathway are indicated by the arrowheads. The more solid arrows indicate the more major pathways of metabolism while the dotted arrows indicate pathways of negligible importance. Compounds that are routinely measured in urine or plasma for diagnosis of pheochromocytoma are underlined. All compounds except VMA are sulfate conjugated but only pathways of sulfate conjugation for normetanephrine and metanephrine are shown. PNMT, Phenylethanolamine-N-methyltransferase; MAO, monoamine oxidase; COMT, catechol-O-methyltransferase; ADH, alcohol dehydrogenase; m-PST, monoamine preferring phenolsulfotransferase; DHPG, 3,4-dihydroxyphenylglycol; DHMA, 3,4-dihydroxymandelic acid; MHPG, 3-methoxy-4-hydroxyphenylglycol; VMA, vanillylmandelic acid.

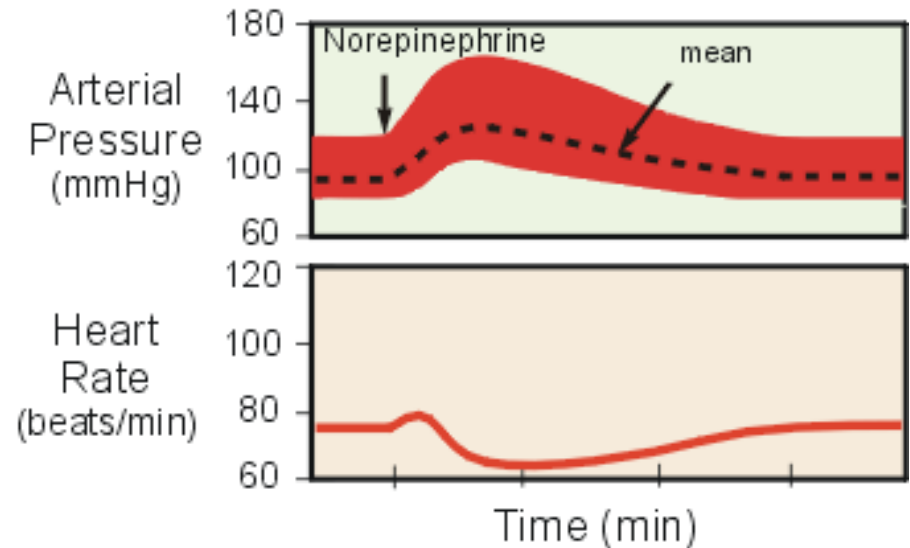
- Most of the NE released by sympathetic nerves
- (a) is removed by neuronal uptake
- (b) and a much smaller amount is removed by extraneuronal uptake
- (c) so that only a small portion escapes to enter the bloodstream
- (d). Most of the NE recaptured by sympathetic nerves is sequestered into storage vesicles by the vesicular monoamine oxidase (MAO) transporter
- (f) and a smaller proportion is metabolized intraneuronally to 3,4-dihydroxyphenylglycol (DHPG).
- However, considerably more of the NE that is sequestered into storage vesicles or metabolized intraneuronally to DHPG is derived from transmitter leaking from storage vesicles (e) than from reuptake (b).
- Very little circulating DHPG is derived from metabolism of circulating NE, whereas a significant proportion of the small amounts of circulating free NMN is formed from circulating NE.
- MHPG is mainly derived from O-methylation of DHPG before and after its entry into the bloodstream. Vanillylmandelic acid (VMA) is mainly derived from metabolism of MHPG and DHPG in the liver. COMT, Catechol-O-methyltransferase.

Vanillylmandelic acid (VMA),

- Vanillylmandelic acid (VMA), the major end-product of norepinephrine and epinephrine metabolism, is produced almost exclusively from the removal and metabolism by the liver of catecholamines and their metabolites that circulate in the bloodstream.
- VMA is a relatively insensitive marker for pheochromocytoma compared with the precursors norepinephrine, epinephrine, normetanephrine and metanephrine

Circulating norepinephrine causes:

- **Increased heart rate** (although only transiently) and increased inotropy (β 1-adrenoceptor mediated) are the direct effects of norepinephrine on the heart.
- **Vasoconstriction** occurs in most systemic arteries and veins (postjunctional α 1 and α 2 adrenoceptors)
- The overall cardiovascular response is increased **cardiac output** and **systemic vascular resistance**, which results in an elevation in arterial blood pressure.
- Heart rate, although initially stimulated by norepinephrine, decreases due to activation of baroreceptors and vagal-mediated slowing of the heart rate.



Site of synthesis of catecholamines

- **Adrenal medulla:** the main secretory products are epinephrine and norepinephrine.
- **Neurons of the sympathetic and central nervous systems (CNS):**
- and in **scattered groups of chromaffin cells** found in other regions of the abdomen and neck.
 - Norepinephrine is the principal product synthesized in the **CNS**,
 - and epinephrine is the principal catecholamine produced by the **adrenal glands**.

Physiological actions of the catecholamines.

- Diverse
- Norepinephrine functions primarily as a neurotransmitter.
- Epinephrine affects metabolic processes such as carbohydrate and lipid metabolism.
- Both norepinephrine and epinephrine influence the vascular system,

Effect of binding of catecholamines to different receptors

Receptor	Effectively Binds	Effect of Ligand Binding
Alpha1	Epinephrine, Norepinphrine	Increased free Ca
Alpha2	Epinephrine, Norepinphrine	Decreased cAMP
Beta1	Epinephrine, Norepinphrine	Increased cAMP
Beta2	Epinephrine	Increased cAMP

Adrenergic Receptors and Mechanism of Action

- The physiologic effects of epinephrine and norepinephrine are initiated by their binding to adrenergic receptors on the surface of target cells. These receptors are prototypical examples of seven-pass transmembrane proteins that are coupled to G proteins, which stimulate or inhibit intracellular signalling pathways.
- Complex physiologic responses result from adrenal medullary stimulation because there are multiple receptor types, which are differentially expressed in different tissues and cells. The alpha and beta-adrenergic receptors and their subtypes were originally defined by differential binding of various agonists and antagonists and, more recently, by analysis of molecular clones.

Physiologic Effects of Medullary Hormones

- In general, circulating epinephrine and norepinephrine released from the adrenal medulla have the **same effects on target organs** as direct **stimulation by sympathetic nerves**, although their effect is **longer lasting**.
- Additionally, circulating hormones can cause **effects in cells and tissues that are not directly innervated**.
- The physiologic consequences of medullary catecholamine release are responses, which **aid in dealing with stress**.
- These effects can be predicted to some degree by imagining what would be needed **under severe stress**.

Some major effects mediated by epinephrine and norepinephrine are:

•Increased rate and force of contraction of the heart muscle:

- This is predominantly an effect of epinephrine acting through beta-receptors.

•Constriction of blood vessels:

- Norepinephrine, in particular, causes widespread vasoconstriction, resulting in increased resistance and hence arterial blood pressure.

•Dilation of bronchioles:

- Assists in pulmonary ventilation.

•Stimulation of lipolysis in fat cells:

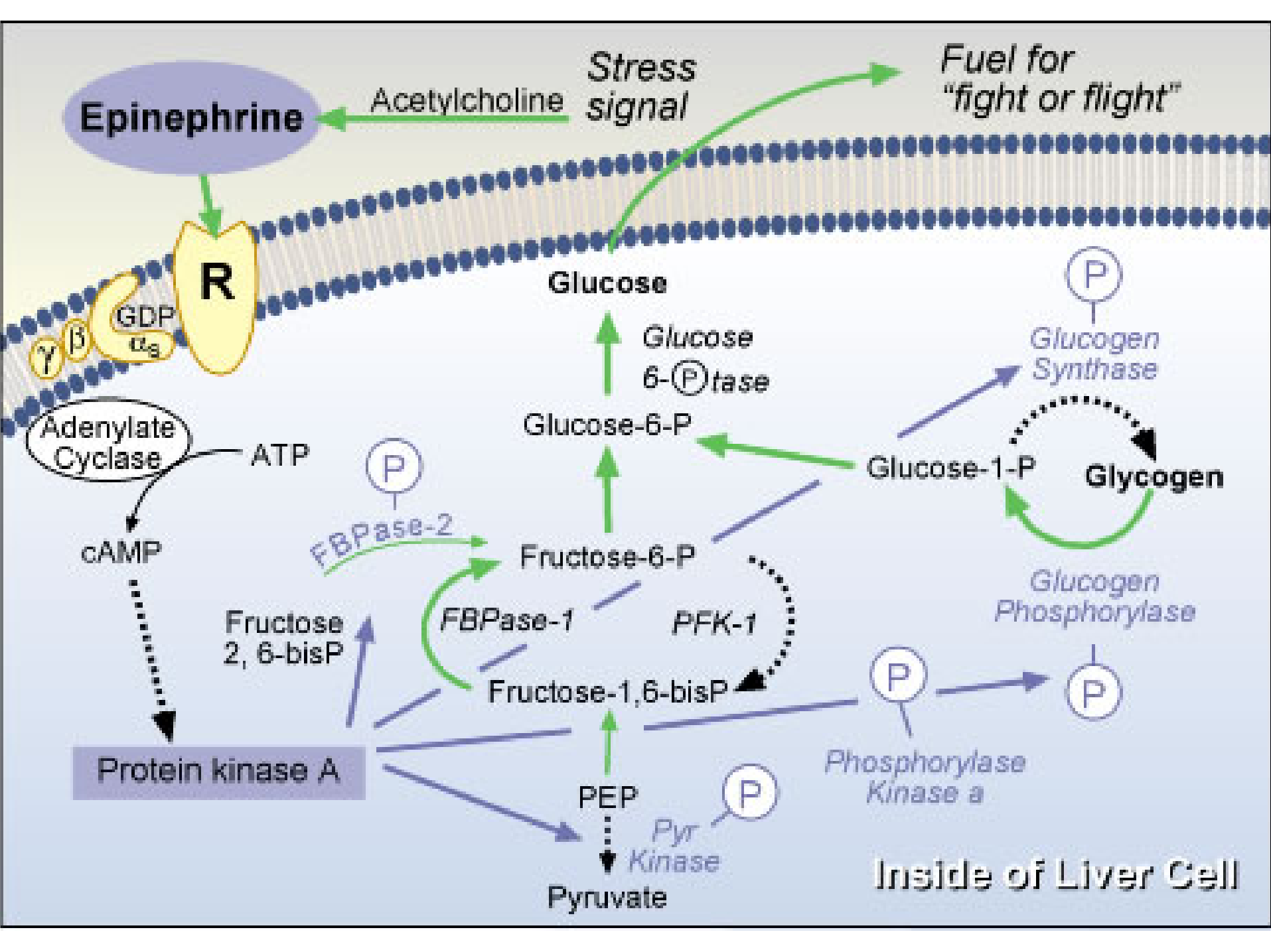
- This provides fatty acids for energy production in many tissues and aids in conservation of dwindling reserves of blood glucose.

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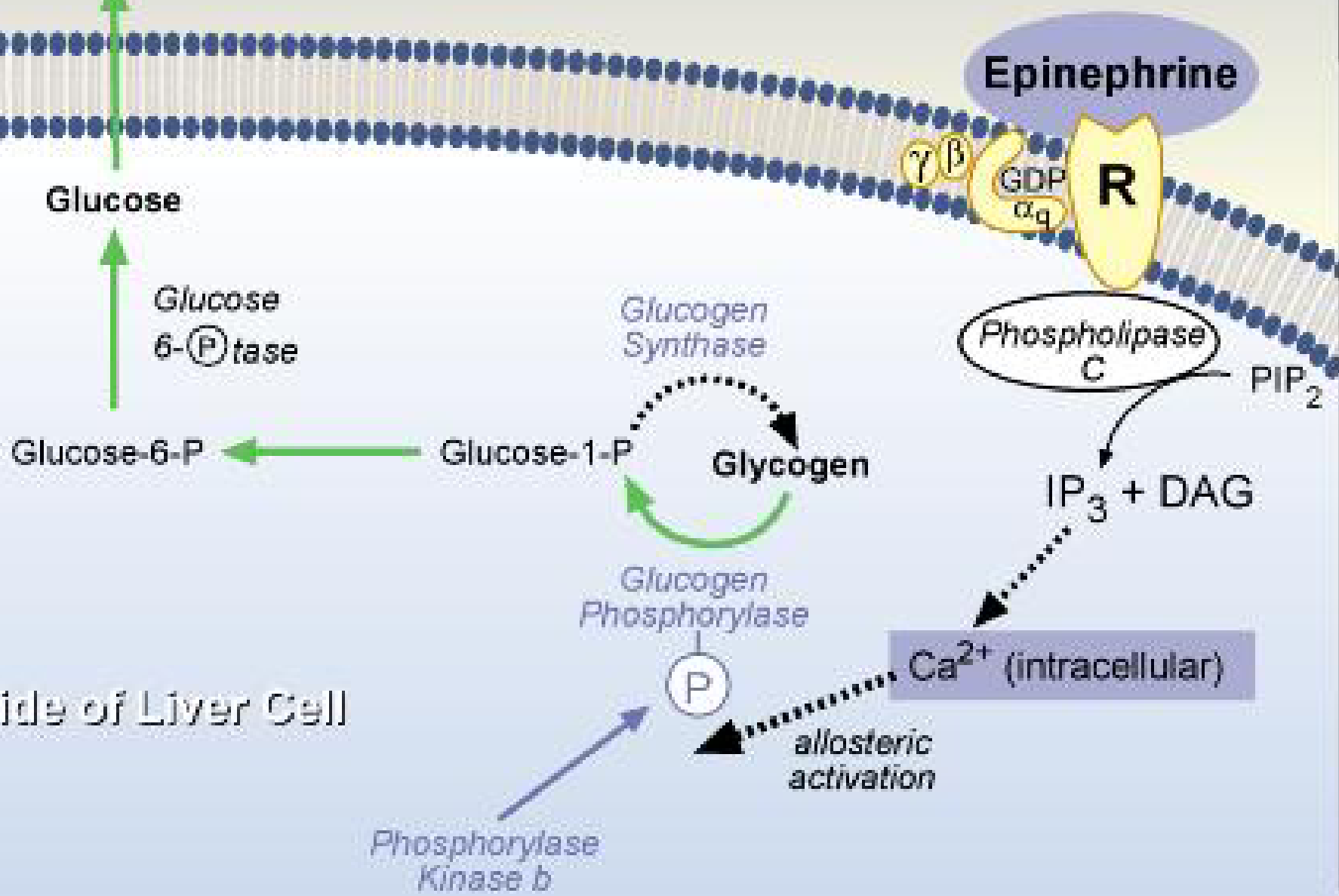
- **Increased metabolic rate:**
 - Oxygen consumption and heat production increase throughout the body in response to epinephrine. Medullary hormones also promote breakdown of glycogen in skeletal muscle to provide glucose for energy production.
- **Dilation of the pupils:**
 - Particularly important in situations where you are surrounded by velociraptors under conditions of low ambient light.
- **Inhibition of certain "non-essential" processes:**
 - An example is inhibition of gastrointestinal secretion and motor activity.

Stimuli causing release of adrenal medulla hormones

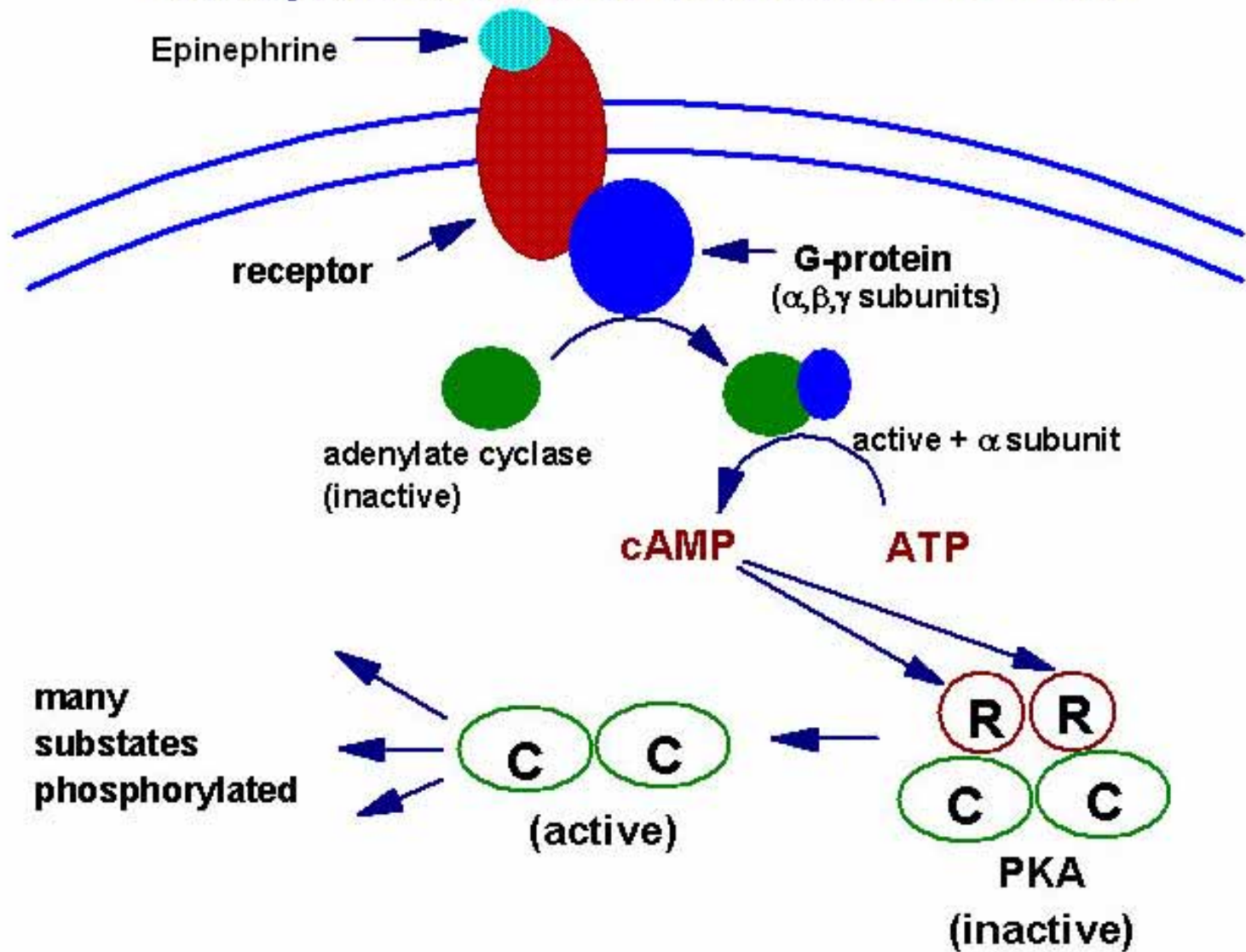
- Common stimuli for secretion of adrenomedullary hormones include:
 - exercise,
 - hypoglycaemia,
 - haemorrhage
 - and emotional distress



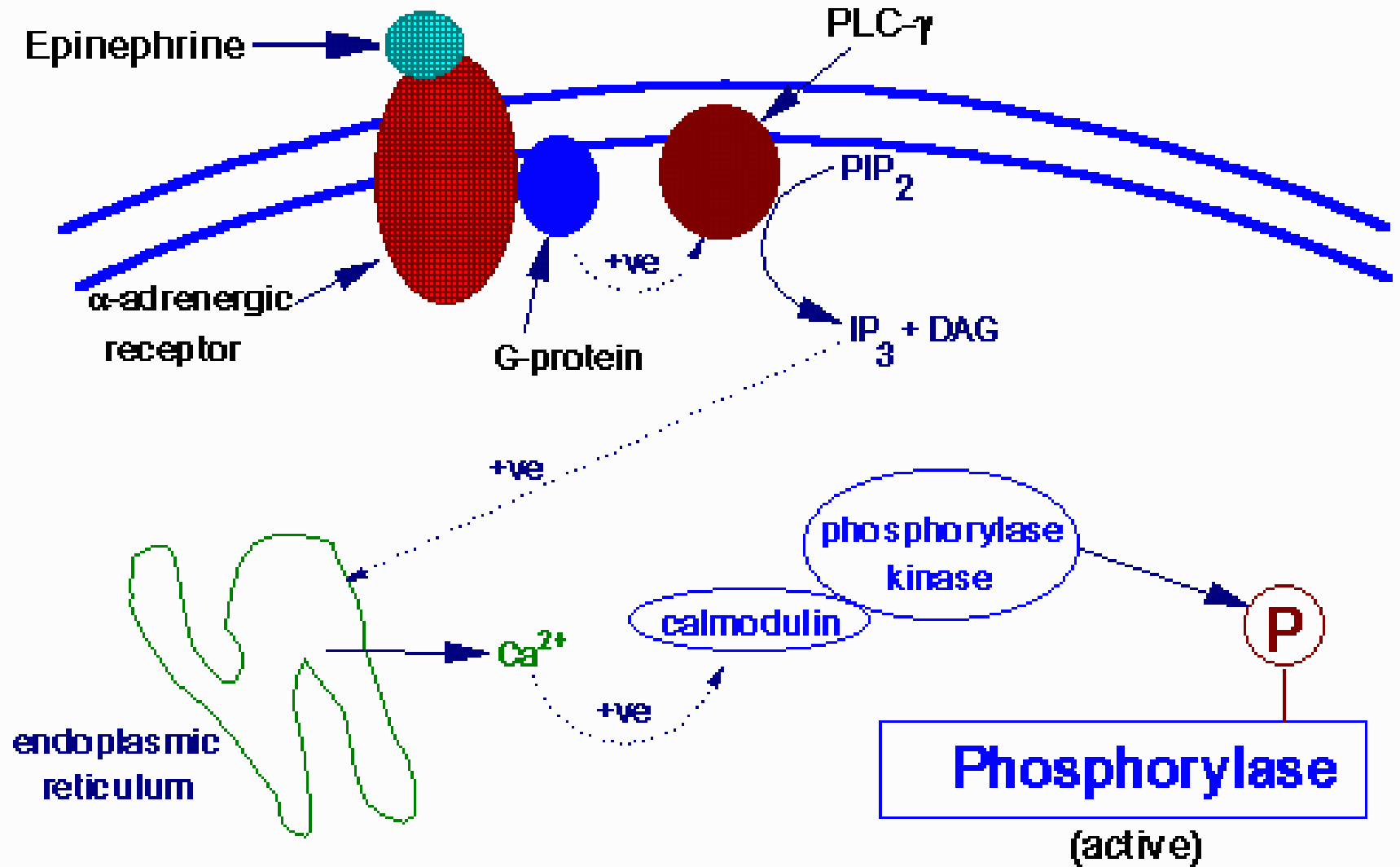
Fuel for "fight or flight"



Receptor-Mediated Activation of PKA



α -Receptor-Mediated Responses on Phosphorylase



Receptors for norepinephrine and epinephrine

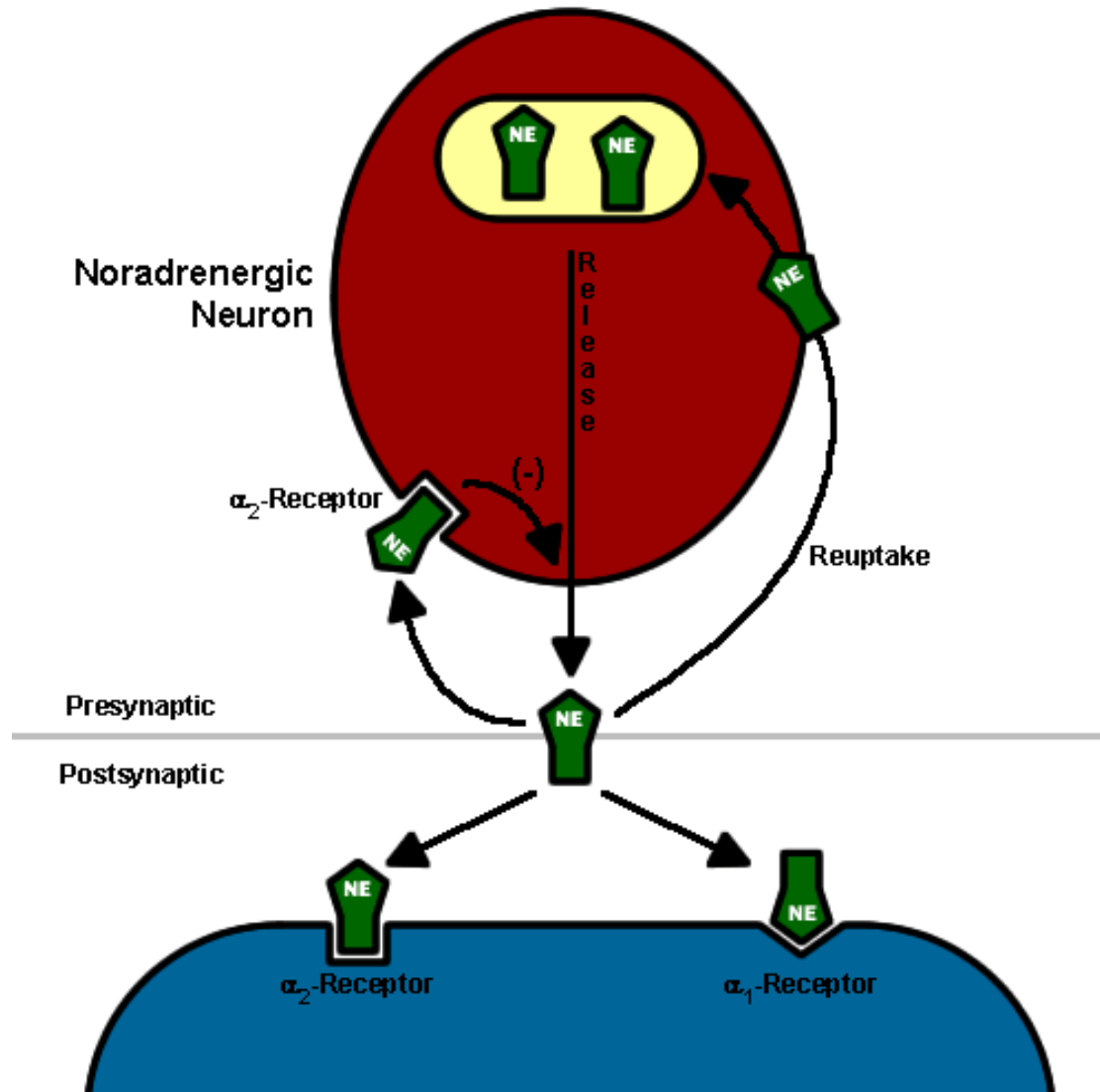
- The biological actions of the catecholamines are initiated through their interaction with two different types of specific cell membrane receptors,
 - the alpha 1, alpha 2 -adrenergic
 - and beta-adrenergic receptors.
- These receptors have different affinities for norepinephrine and epinephrine and cause opposing physiological effects.
- Norepinephrine primarily interacts with **alpha-adrenergic receptors**, whereas epinephrine interacts with both **alpha-and beta-receptors**.

α 2-Adrenergic receptors

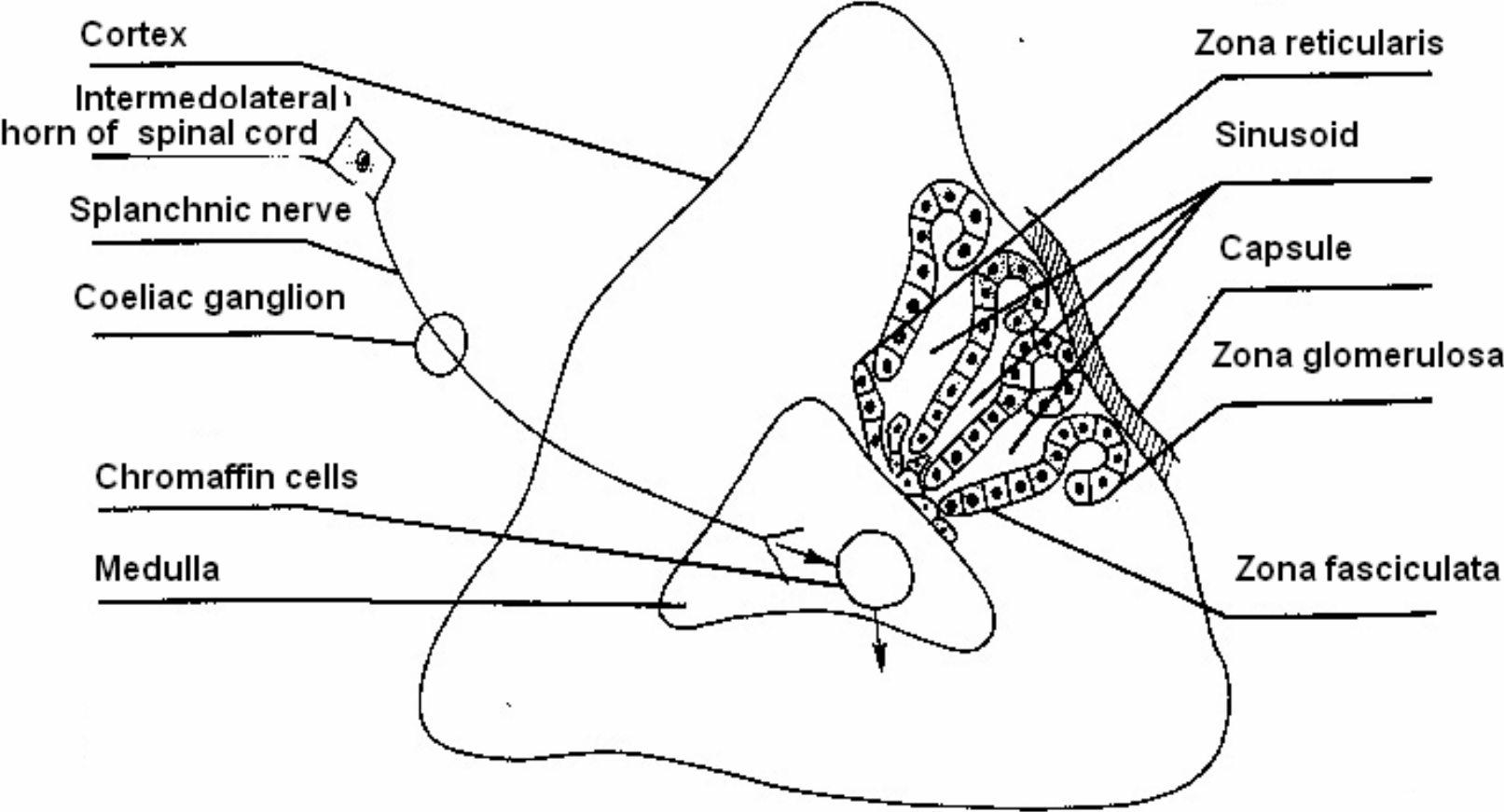
- α 2-Adrenergic receptors belong to a large superfamily of membrane proteins, known as the G-protein coupled receptors (GPCR).
- These are integral membrane proteins with seven trans-membrane helices, capable of transducing a wide variety of signals.

- The effects of the hormone epinephrine and the neurotransmitter norepinephrine are mediated by a family of proteins called adrenergic receptors.
- At least nine subtypes of adrenergic receptors have been identified to date.
- These can be grouped into three main types which are called alpha-1, alpha-2, and beta adrenergic receptors.

Alpha adrenergic receptor



The Adrenal Gland: showing zonation of adrenal cortex and the relationship between adrenal cortex and medulla



- norepinephrine (nôr'ĕpĭnĕf'rĕn), a neurotransmitter in the catecholamine family that mediates chemical communication in the sympathetic nervous system, a branch of the autonomic nervous system. Like other neurotransmitters, it is released at synaptic nerve endings to transmit the signal from a nerve cell to other cells. Norepinephrine is almost identical in structure to epinephrine, which is released into the bloodstream from the adrenal medulla under sympathetic activation. The sympathetic nervous system functions in response to short-term stress; hence norepinephrine and epinephrine increase the heart rate as well as blood pressure. Other actions of norepinephrine include increased glycogenolysis (the conversion of glycogen to glucose) in the liver, increased lipolysis (the conversion of fats to fatty acids; see fats and oils) in adipose (fat) tissue, and relaxation of bronchial smooth muscle to open up the air passages to the lungs. All of these actions represent a mobilization of the body's resources in order to meet the stressful challenge—such a response is often termed the “flight or fight” syndrome.

- Pheochromocytoma is a rare catecholamine-secreting tumor derived from chromaffin cells. Tumors that arise outside the adrenal gland are termed extra-adrenal pheochromocytomas or paragangliomas. Because of excessive catecholamine secretion, pheochromocytomas may precipitate life-threatening hypertension or cardiac arrhythmias. If the diagnosis of a pheochromocytoma is overlooked, the consequences could be disastrous, even fatal; however, if a pheochromocytoma is found, it is potentially curable.
- The term pheochromocytoma (*phios* means dusky, *chroma* means color, and *cytoma* means tumor) refers to the color the tumor cells acquire when stained with chromium salts.

Pathophysiology:

- The clinical manifestations of a pheochromocytoma result from excessive catecholamine secretion by the tumor. Catecholamines typically secreted, either intermittently or continuously, include norepinephrine and epinephrine and rarely dopamine. The biological effects of catecholamines are well known. Stimulation of alpha-adrenergic receptors results in elevated blood pressure, increased cardiac contractility, glycogenolysis, gluconeogenesis, and intestinal relaxation. Stimulation of beta-adrenergic receptors results in an increase in heart rate and contractility.
- Catecholamine secretion in pheochromocytomas is not regulated in the same manner as in healthy adrenal tissue. Unlike the healthy adrenal medulla, pheochromocytomas are not innervated, and catecholamine release is not precipitated by neural stimulation. The trigger for catecholamine release is unclear, but multiple mechanisms have been postulated, including direct pressure, medications, and changes in tumor blood flow.

- Relative catecholamine levels also differ in pheochromocytomas. Most pheochromocytomas contain norepinephrine predominantly, in comparison with the normal adrenal medulla, which is composed of roughly 85% epinephrine. Familial pheochromocytomas are an exception because they secrete large amounts of epinephrine. Thus, the clinical manifestations of a familial pheochromocytoma differ from those of a sporadic pheochromocytoma.

Frequency:

In the US: Pheochromocytomas are rare, reportedly occurring in 0.05-0.2% of hypertensive individuals. Patients may be completely asymptomatic. A retrospective study from the Mayo Clinic revealed that in 50% of cases, the diagnosis was made at autopsy (Beard, 1983). Approximately 10% of pheochromocytomas are discovered incidentally. Pheochromocytomas may occur in certain familial syndromes, including multiple endocrine neoplasia (MEN) 2A and 2B, neurofibromatosis, and von Hippel-Lindau (VHL) disease.

- **Race:** Pheochromocytomas occur in people of all races, although they are diagnosed less frequently in blacks.
- **Sex:** Pheochromocytomas occur with equal frequency in males and females.
- **Age:** Pheochromocytomas may occur in persons of any age. The peak incidence, however, is between the third and the fifth decades of life. Approximately 10% occur in children. In children, 50% of pheochromocytomas are solitary intra-adrenal, 25% are present bilaterally, and 25% are extra-adrenal.

Mortality/Morbidity:

- Although pheochromocytomas are rare, making the diagnosis is critical because the malignancy rate is 10%, they may be associated with a familial syndrome, they may precipitate life-threatening hypertension, and the patient may be cured completely with their removal.
- Cardiovascular morbidity: Many cardiac manifestations are associated with pheochromocytomas. Hypertension is the most common complication. Cardiac arrhythmias, such as atrial and ventricular fibrillation, may occur because of excessive plasma catecholamine levels. Other complications include myocarditis, signs and symptoms of myocardial infarction, dilated cardiomyopathy, and pulmonary edema, either of cardiac or noncardiac origin.
- Neurologic complications: A pheochromocytoma-induced hypertensive crisis may precipitate hypertensive encephalopathy, which is characterized by altered mental status, focal neurologic signs and symptoms, or seizures. Other neurologic complications include stroke due to cerebral infarction or an embolic event secondary to a mural thrombus from a dilated cardiomyopathy. Intracerebral hemorrhage also may occur because of uncontrolled hypertension

Symptoms

- Headache
- Diaphoresis
- Palpitations
- Tremor
- Nausea
- Weakness
- Anxiety, sense of doom
- Epigastric pain
- Flank pain
- Constipation
- Weight loss

Physical:

- The clinical signs associated with pheochromocytomas include hypertension (which may be paroxysmal in 50% of cases), postural hypotension, retinopathy, fever, pallor, tremor, café au lait spots, or neurofibromas.
- Clinical signs
 - Hypertension (paroxysmal in 50% of cases)
 - Postural hypotension: This results from volume contraction.
 - Hypertensive retinopathy
 - Weight loss
 - Pallor
 - Fever
 - Tremor
 - Neurofibromas
 - Café au lait spots: These are patches of cutaneous pigmentation, which vary from 1-10 mm and occur any place on the body. Characteristic locations include the axillae and intertriginous areas (groin). They vary from light to dark brown, hence the name café au lait.
 - Tachyarrhythmias
 - Pulmonary edema
 - Cardiomyopathy
 - Ileus
- Laboratory features
 - Hyperglycemia
 - Hypercalcemia
 - Erythrocytosis

Causes:

- Precipitants of a hypertensive crisis
 - Anesthesia induction
 - Opiates
 - Dopamine antagonists
 - Cold medications
 - Radiographic contrast media
 - Drugs that inhibit catecholamine reuptake, such as tricyclic antidepressants and cocaine
 - Childbirth

A.S.Warsy