Stress & Catecholamines - Overview

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PBL MBBS YEAR II SEMINAR

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What is stress?

- Stress can due to:
  - Physical and Psychological reaction to excessive stimulus ;
  - Psychological disorder caused by constant mental strain or emotion
  - Environmental factors like:
    - Injury, Trauma, Temperature (very high or very low), Loud noises, etc,
  - Disease conditions like:
    - Renal Failure, Burns, Infections, etc,

What are some of the consequences of stress?

- Hormonal and Neuronal changes;
- Metabolic changes leading to:
  - Insulin Resistance,
  - Weight loss,
  - Diabetes, etc.

What metabolic changes can occur in response to stress?

- Some hormonal changes include
  - Increase blood levels of some Insulin Counter-Regulatory Hormones:
    - Cortisol,
    - Glucagon,
    - Catecholamines and
    - Growth hormone
  - Some individual may develop Insulin Resistant
    - Insulin Resistant may cause elevation of Basal Metabolic Rate, due to increase Glucose and Free Fatty Acid level in blood

- Constant stress may cause increase in Catabolism of Muscle Protein, leading to Negative Nitrogen Balance, which is partly responsible for weight loss in individuals under stress;
  - One explanation for the negative nitrogen balance is increased production of specific mediators;
  - Examples include Monocyte and Lymphocyte proteins:
    - Endogenous Pyrogens (that is, they cause fever)
    - Interleukin-1,
    - Interleukin-6,
    - Tumor Necrosis Factor (TNF)

What are the actions of the mediators?

- **Interleukin-1**:
  - Activates catabolism of Skeletal Muscle Protein
- **Interleukin-6**:
  - Stimulates synthesis of Acute Phase Reactants in the liver
    - (Acute Phase Reactants are proteins produced during injury or infection to either serve or active the defense mechanism of the body)
  - Examples are: Fibrinogen, Complement Proteins, Some Clotting Factors, Alpha-macroglobulin
- **Tumor Necrosis Factor (TNF)**:
  - Suppress synthesis of Triacylglycerides (Fat) in adipose tissue,
  - Stimulate Lipolysis (breakdown of fat),
  - Inhibits Lipoprotein Lipase and therefore prevents the uptake of circulating fat

How can environmental factors be related to stress?

- Most environmental signals are filtered by Reticular formation in Brain and “Alarm” and other signals are transmitted from CNS to Limbic System (e.g., Hippocampus)
- Limbic System then transmits the signal to the Hypothalamus
- Hypothalamus generates 2 types of signals:
  - **Neuronal signal** via Neuronal System and
  - **Chemical (Hormonal) signal** via Hormonal system

Neuronal Signals

- Generated via Peripheral Nervous System
  - Neuronal signals act via Cholinergic Neurons located in Adrenal medulla in Adrenal Gland;
  - Cholinergic Neurons cause secretion into general circulation of:
    - Epinephrine,
    - Enkephalins , and
    - Norepinephrine

Chemical (Hormonal) signals

- Generated via Anterior Pituitary by production of
  - Adrenocorticotropic Hormone (ACTH),
  - Beta-Lipotropin (beta-LTH),
  - Beta-endorphin

- ACTH acts on Adrenal Cortex in Adrenal Gland and causes release of Cortisol, which is the major stress adaptation hormone;
- ACTH also causes release of Aldosterone and Dehydroepiandrosterone (DHEA) ;

- Beta-endorphin acts on receptors in CNS to produce Analgesia;
- Ultimate effects of ACTH and Beta-endorphin are:
  - To limit deleterious effects of stress by providing immediate sources for the energy required to counter the stress ;
- If stress continues for a prolonged period of time Pathological changes can occur in the system

Briefly outline the hormonal stress pathway

- Environmental stress event is detected by the CNS
- Signals are sent to Limbic system (Hyppocampal structure) which, in turn, signals Hypothalamus to release Corticotrophin Releasing Hormone (CRH)

- CRH acts on Anterior Pituitary to produce the polypeptide called Pro-Opio-Melano-Cortin (POMC)
- POMC is split into ACTH, Beta-LTH, and Beta-endorphin;

- Beta-endorphin acts on CNS to promote Analgesia,
  - It lowers the level of cellular c-AMP in certain cells via a Beta-endorphin receptor coupled to an Inhibitory G-protein transducer and Adenylate cyclase;

- Beta-endorphin binds to receptors on Sommatotrophs and Lactotrophs of the Anterior Pituitary causing secondary release of Growth Hormone and Prolactin
  - They play some role in stress response by virtue of the Hyperglycemic actions of these hormones in liver cells

- ACTH acts on Adrenal Cortex to release Cortisol, which then circulates in blood bound to Transcortin or Corticosteroid binding globulin (CBG)

- Cortisol (Glucocorticoid) acts on appropriate tissues to produce systemic effects that constitute stress adaptation, which are useful to the body because the actions of Cortisol tends to limit the deleterious effects of stress;
- If the stress continues for a long time the effects of this system can become harmful to the body

CATECHOLAMINES

- Biogenic amines derived from L-Tyrosine:
  - **Dopamine**,
  - **Noradrenaline** (**Norepinephrine**) and
  - **Adrenaline** (**Epinephrine**)
- Catecholamines do not cross the blood-brain barrier (BBB)
- Catecholamines synthesized within the BBB act mainly as Neurotransmitters whereas, those synthesize outside the BBB act as hormones

Biosynthesis of Catecholamines

- Precursor is mainly L- Tyrosine
- Rate-limiting step in the biosynthesis is the conversion of L-Tyrosine to 3,4-Dihydroxyphenylalanine (DOPA);
- Tyrosine Hydroxylase (a mixed functional Oxygenase that utilizes molecular Oxygen) requires Tetrahydrobiopterine as cofactor;
- Tyrosine Hydroxylase can also converting Phenylalanine to Tyrosine, in conditions where Phenylalanine Hydroxylase is deficient as is the case in Phenylketonurics;
- DOPA is Decarboxylated to Dopamine in a reaction catalyzed by DOPA -Decarboxylase, an enzyme that utilizes Pyridoxal Phosphate (B6-PO4) as coenzyme;
- Dopamine is the first member of the Catecholamines;

- Dopamine is Hydroxylated to Norepinephrine by Dopamine-beta-Hydroxylase (a Copper-containing mixed functional Oxygenase that utilizes molecular Oxygen);
  - Ascorbate is essential for this reaction
- Norepinephrine is methylated to Epnephrine in a reaction catalyzed by S-Adenosyl-Methionine-Phenylethanolamine-N-Methyl Transferase;
- Methyl donor is the high-energy compound S-Adenosyl-Methionine;

How does stress affect the synthesis and release of Catecholamines?

- Adrenal Medulla releases Catecholamines into the circulation,
- Catecholamines released from Adrenal Medulla are about 80% Epinephrine and 20% Norepinephrine;
- Norepinephrine biosynthesis increases after Acute stress;
- Prolonged Stress accompanied by Chronic Sympathetic nerve activity causes increase in the activity of both Tyrosine Hydroxylase and Dopamine-beta-Hydroxylase;
- Increase in activity of these enzymes in the Catecholamine pathway is a means of adapting to Physiologic Stress;
- In Adrenal Medulla, Acetylcholine acting as the neurotransmitter of the sympathetic ganglion acts on Nicotinic receptors and promotes the release of Catecholamines into the circulation;

Mode of action of Epinephrine

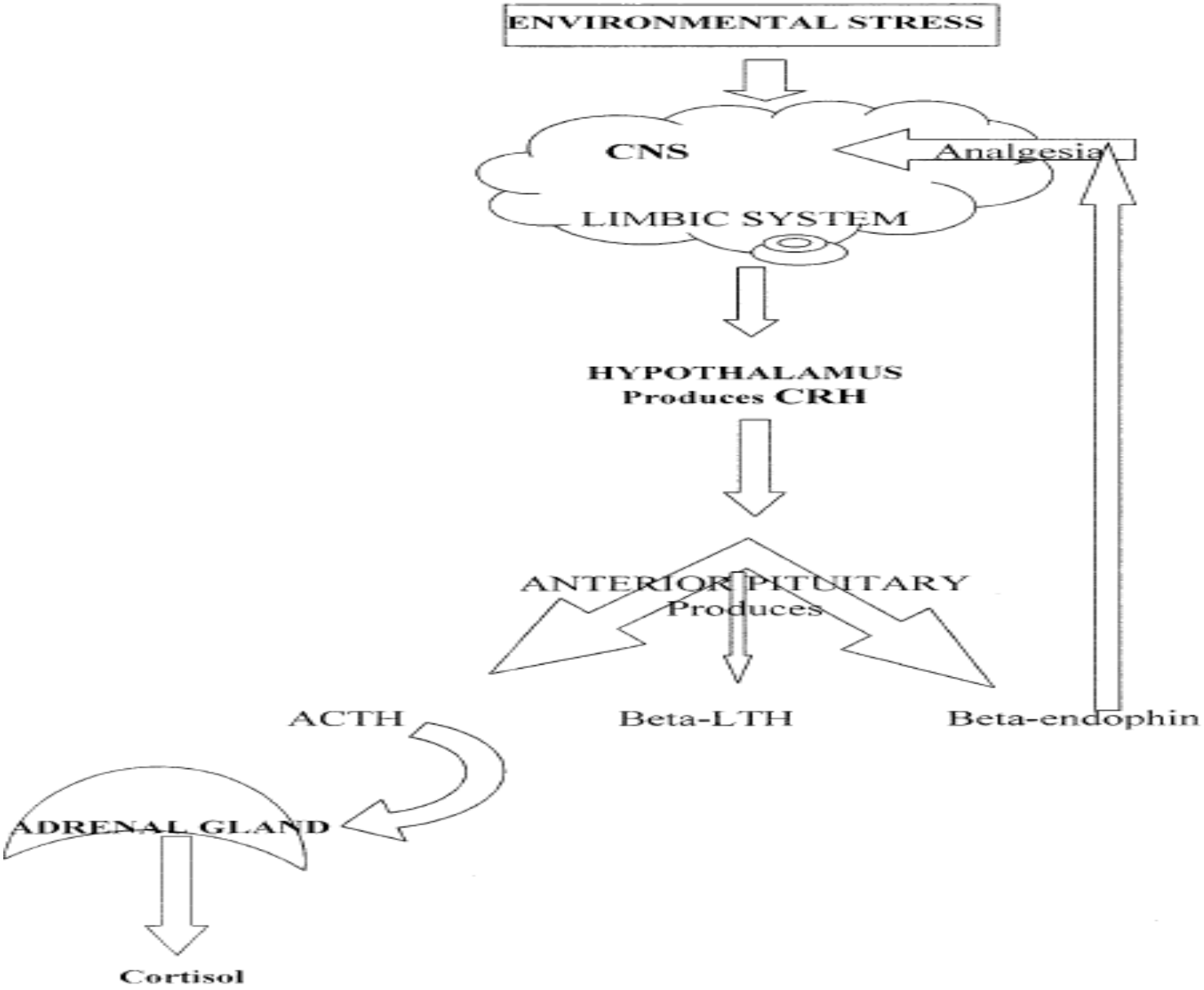
- Catecholamines act through two major classes of receptors
  - Alpha-Adrenergic and Beta-Adrenergic receptors, (Each consists of two subclasses, i.e. alpha-1, alpha-2, beta-1 and beta-2) ;
- **Epinephrine** is considered as the "Fright, Flight or Fight" hormone when produced outside the blood-brain barrier;
- **Epinephrine**:
- Interacts directly with Beta-Adrenergic receptors in Plasma membrane of liver cells to activate Adenylate cyclase, thereby causing:
  - Activation of Glycogenolysis and
  - Inhibition of Glycogenesis and Glycolysis to maximize the release of Glucose from Hepatic cells (**Fig. 2**)

- Interacts with Alpha-Adrenergic receptors to activate Phospholipase C, which then catalyzes hydrolysis of Phosphatidyl-Inositol-4, 5-Bisphosphate (PIP2) to produce 1,2-Diacylglycerol and Inositol-1, 4,5-Ttriphosphate (IP3) ;
- IP-3 acting as a Second messenger stimulates the release of Ca^{2+} ions from Endoplasmic Reticulum;
- Increase in Ca^{2+} ions ultimately results in activation of Glycogen Phosphorylase and Inhibition of Glycogen Synthase;
- Action of Epinephrine results in increased breakdown of Liver Glycogen to produce more blood Glucose for tissues that needs to meet the challenge of the stressful situation that triggered the release of Epinephrine from the Adrenal medulla (**Fig. 3**)

- Interact with Beta-Adrenergic receptors to stimulate degradation of Glycogen in Cardiac and Skeletal muscle tissues;
  - This does not lead to increase blood glucose, because Cardiac and Skeletal muscle tissues lack Glucose-6-Phosphatase
  - In addition c-AMP produced in these tissues stimulate Glycolysis
- Role of Epinephrine on Glycogen metabolism in Cardiac and Skeletal muscle is to make more Glucose-6-Phosphate available for Glycolysis in these tissues;
  - ATP generated by Glycolysis can then be used to meet the metabolic demand imposed on these muscles by the stress that triggered the release of Epinephrine (**Fig. 4**)

How are Catecholamine degraded?

- Catecholamines that diffuse into the circulation or are released, as neuro-hormones may be taken up into sympathetic nerve terminals by the Na – K pump;
- Enzymes involved in the degradation are: Monoamine Oxidase (MAO), Catechol-O-methyl Transferase (COMT) and Aldehyde Dehydrogenase (ADH)
- Depending on the location of the Catecholamine, either COMT or MAO may initiate the reaction;
- MAO initiates the degradation of intra-cellular Catecholamines,
- COMT initiates the degradation of extra-cellular Catecholamines;
- Major end product of Dopamine degradation is Homovanillic Acid (HVA)
- Major end product of Norepinephrine and Epinephrine degradation is Vanilly-Mandelic Acid (VMA), also called Methoxy-4-hydroxymandelic acid
- MAO inhibitors have been used to treat Hypertension and Depression, but serious reaction with foods or drugs that contain Sympathomimetic amines limit their usefulness



SIMPLIFIED DIAGRAM OF THE OVERVIEW OF HUMORAL STRESS PATHWAY

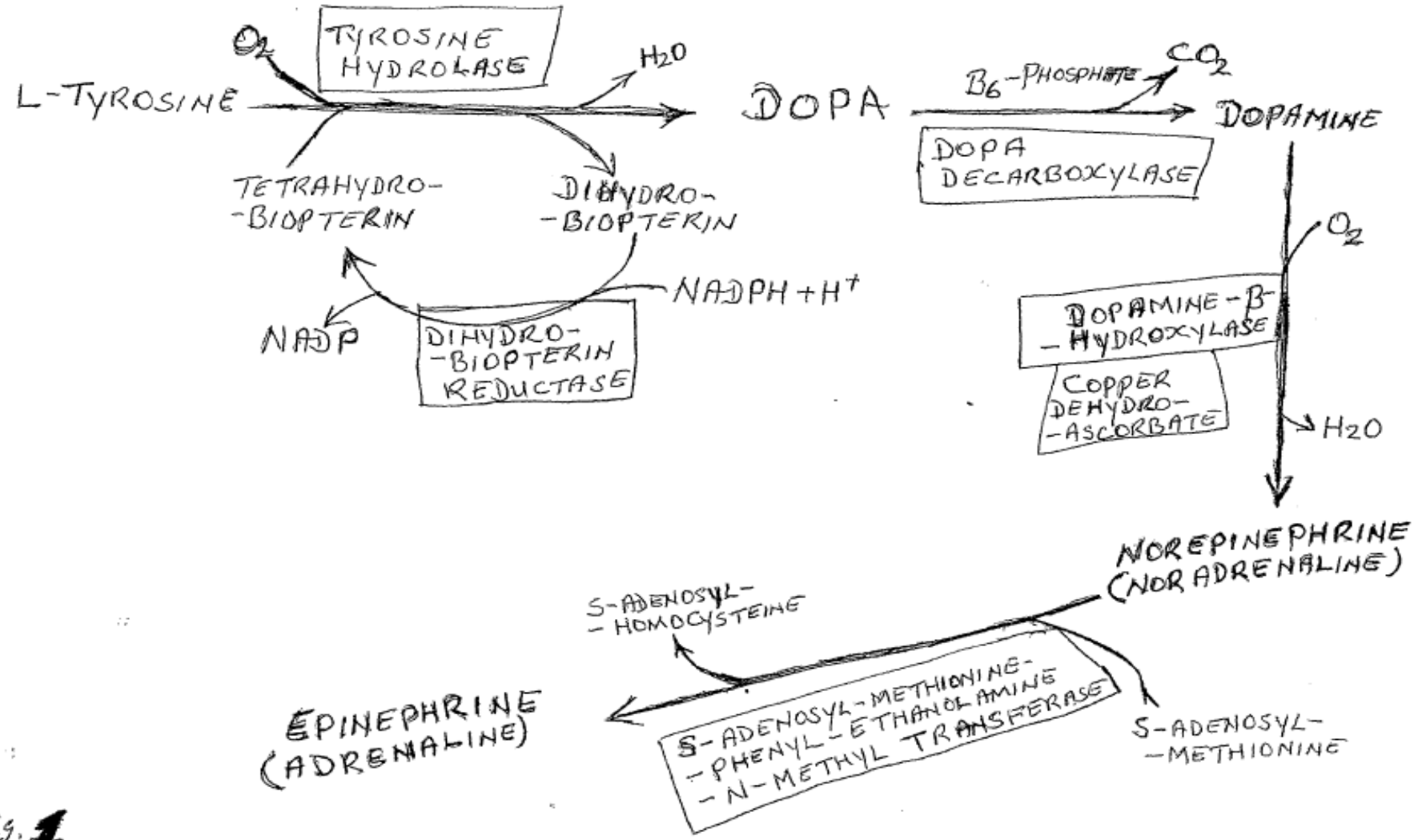


Fig. 1

BIOSYNTHESIS OF CATECHOLAMINES.

Note: DOPA = 3,4-DIHYDROXY-L-PHENYL-ALANINE

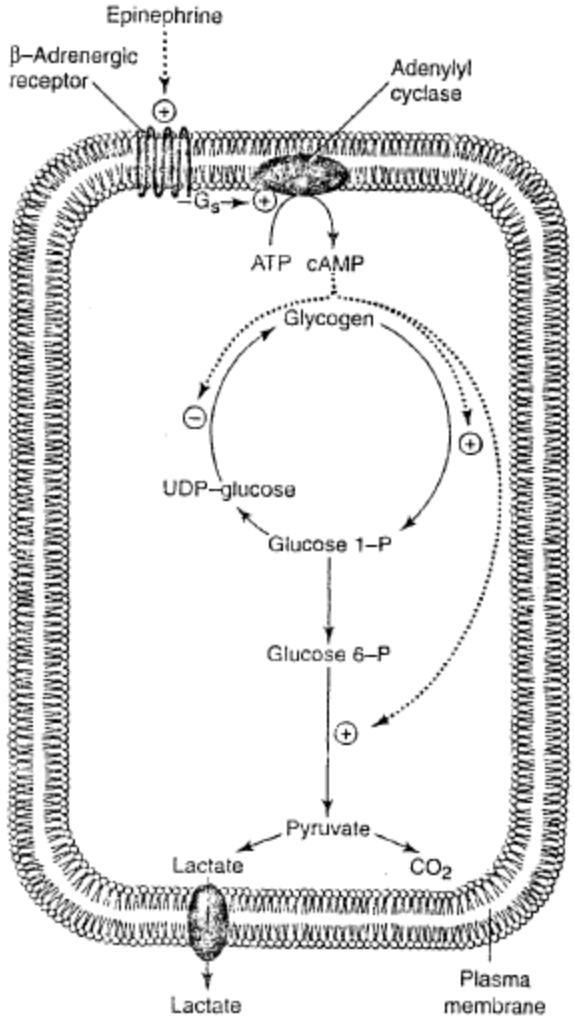
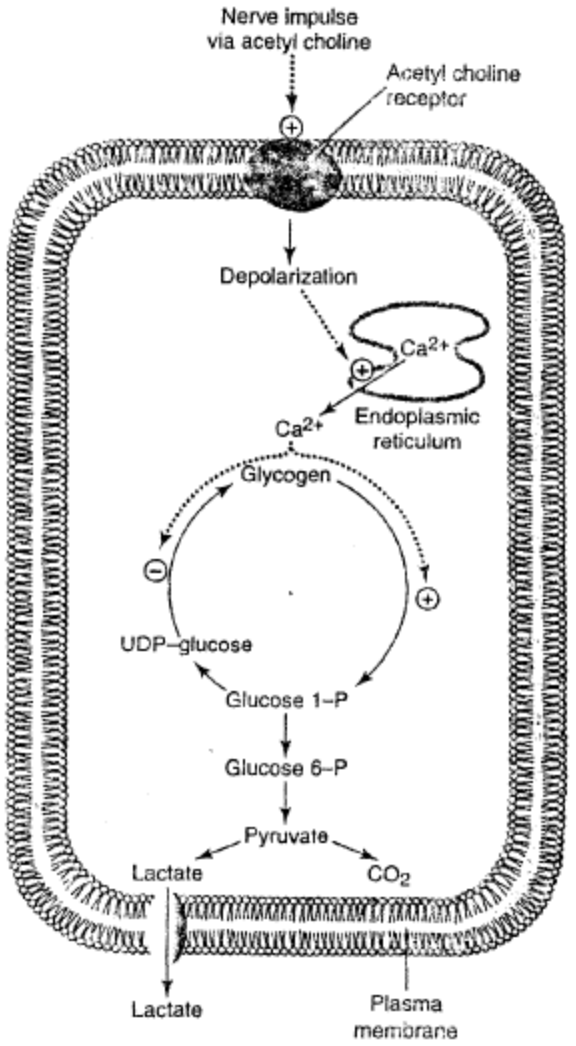


Fig. 4

Cyclic AMP mediates the stimulation of glycogenolysis in muscle by β agonists (epinephrine).

The β-adrenergic receptor is an intrinsic component of the plasma membrane that acts to stimulate adenylate cyclase via a stimulatory G-protein (G_s).



Ca^{2+} mediates the stimulation of glycogenolysis in muscle by nervous excitation.

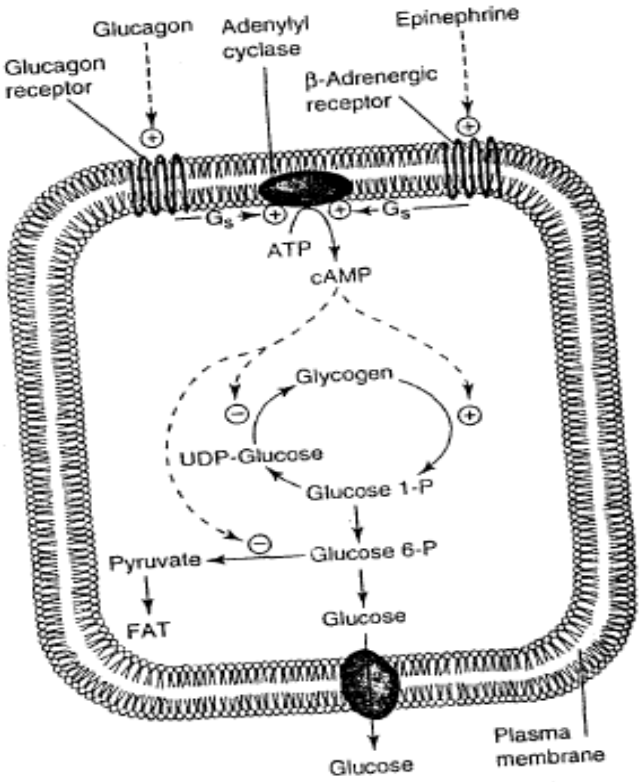


Fig. 2

Cyclic AMP mediates the stimulation of glycogenolysis in liver by glucagon and β agonists (epinephrine).

Fig 2

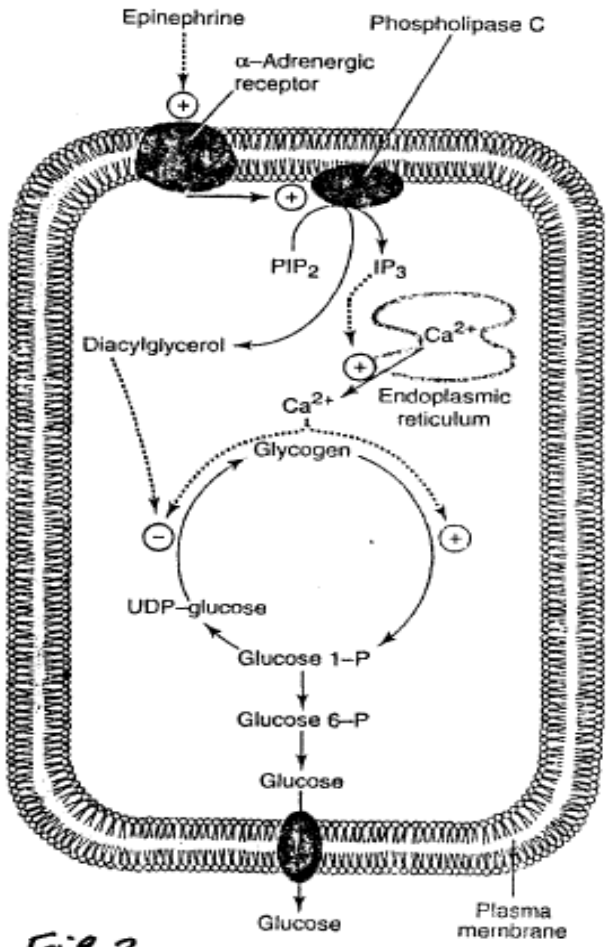


Fig. 3

Inositol trisphosphate (IP_3) and Ca^{2+} mediate the stimulation of glycogenolysis in liver by α agonists.

The α-adrenergic receptor and glucose transporter are intrinsic components of the plasma membrane. Although not indicated, phosphatidylinositol 4,5-bisphosphate (PIP_2) is also a component of the plasma membrane.

Fig 6

DEGRADATION OF DOPAMINE.