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LEARNING OBJECTIVES

• To know the factors required for the RBC synthesis and maturation
• To know about the secretion, functions and regulation of Erythropoietin
• To identify the conditions in which recombinant erythropoietin is used
• To know other factors necessary for the development and maturation of RBC and Haemoglobin
REGULATION OF ERYTHROPOIESIS

- **General factors**
  - Hypoxia → *Erythropoietin*
  - Growth inducers
  - Vitamins

- **Maturation factors**
  - Vitamin B 12
  - Folic acid

- **Factors necessary for hemoglobin production**
  - Vitamin C → Helps in iron absorption (Fe+++ → Fe++)
  - Proteins → Amino Acids for globin synthesis
  - Iron & copper → Heme synthesis
  - calcium, bile salts, cobalt & nickel.
GENERAL FACTORS.

- Optimum levels of hormone Erythropoietin & efficient feedback mechanism controlling erythropoietin.
ERYTHROPOIETIN

A hormone which is needed for Erythrogenesis
SOURCES OF ERYTHROPOIETIN

- **Erythropoietin** – Glycoprotein with molecular wt 34000.

- **Site of formation** -
  - 90% - epithelial linings and fibroblasts of peritubular capillaries.
  - 10% - liver & cells of tissue macrophage system. (Kupffer cells),
  - Fetal liver produce more EPO than kidneys, but in adult kidney production is more

- **Breakdown**
  - In liver. Half life is 5 hours
Mainly hypoxia – is a stimulus for secretion of erythropoietin

Which causes release of Renal Erythropoietic Factor – *(hypoxic inducible factor-1)*

Which transcript *hypoxia inducible gene*-

This binds to hypoxia response element on *erythropoietin gene*

Inducing transcription of *mRNA*

form *Erythropoietin*
Erythropoietin Mechanism

**Stimulus:** Hypoxia due to decreased RBC count, decreased availability of O₂ to blood, or increased tissue demands for O₂

1. **Normal blood oxygen levels**
2. **Imbalance**
3. **Normal blood oxygen levels**
4. **Imbalance**
5. **Reduces O₂ levels in blood**
6. **Erythropoietin stimulates red bone marrow**
7. **Enhanced erythropoiesis increases RBC count**
8. **Kidney (and liver to a smaller extent) releases erythropoietin**
9. **Increases O₂-carrying ability of blood**
CIRCULATION OF ERYTHROPOIETIN

Low blood oxygen

Liver  Kidney

Release into bloodstream
Stimulation
Inhibition

Erythropoietin

Increased oxygen-carrying capacity

Bloodstream

Increased number of red cells

Red bone marrow
ERYTHROPOIETIN FUNCTIONS

- Main effect on stem cells – in bone marrow is differentiation
- Promotes every stage of RBC synthesis
- Promote Hb synthesis
- Promotes release of RBC from Bone Marrow to Peripheral Circulation.
Mechanism of action:

Erythropoietin acts on specific receptors on stem cells

↑ mitosis

Stem cell → Erythroblast → Mature erythrocyte

Erythropoietin causing speeding up of all the stages of development of proerythroblasts into mature erythrocytes
ERYTHROPOIETIN (EPO) FACTS

• Erythropoietin (EPO) is a hormone produced by the kidney in response to Hypoxia (low Oxygen)
• Erythropoietin promotes the formation of red blood cells by the bone marrow.
• The erythropoietin hormone level can be detected and measured in the blood (the EPO test).
  Normal level = 4 to 24 mu/ml
ERYTHROPOIETIN (EPO) FACTS

• Measurement of the blood erythropoietin level can be used to detect certain medical conditions.

• Erythropoietin can be synthesized and used as a treatment of some forms of anemia.

• Erythropoietin has been misused as a performance-enhancing drug by some athletes.
REGULATION OF ERYTHROPOIETIN

Stimuli for production

- Hypoxia
- Products of RBC destruction
- High altitude
- Anemia
- Chronic lung or heart diseases
- Catecholamines
- Prostaglandins
- Androgens

Inhibition

- Blood transfusion
FACTORS AFFECTING ERYTHROPOIETIN

■ Increase secretion
  ■ Hormones – Androgen, Thyroxine, GH, ACTH, Prolactin, Adrenocortical Steroids.
  ■ Haemolysates – products of RBC destruction.
  ■ Nucleotides – cAMP, NAD, NADP
  ■ Vasoconstrictor drugs – that causes renal hypoxia

■ Decrease secretion.
  ■ Adenosine antagonists – Theophylline.
  ■ Oestrogen – decreases synthesis of Globin & depressing erythropoietic response to hypoxia
Uses of erythropoietin may include treatment of anemia related to:

- **Chronic Renal Failure**
- **During medication in AIDS**
- **During chemotherapy**, anemia caused by dysfunctional bone marrow (where the blood cells are made), and
- **Anemia associated with cancer**
CHRONIC RENAL FAILURE (CRF)
- RENAL INSUFFICIENCY -

- Headaches
- ↓ Ability to Concentrate Urine
- Polyuria → Oliguria
- ↑ BUN & Serum Creatinine
- Edema
- GFR - progressively decreases from 90 to 30 ml/min
- Mild Anemia
- ↑ BP
- Weakness & Fatigue

Hypoxia → Epo → Kidney

Bone marrow → Red cells → O₂ transport
Lungs → tissues
(200 X 10⁹ RBCs/day)
SPECIAL MATURATION FACTORS.

- Vit B 12 (extrinsic factor)
- Folic acid
- Intrinsic factor of Castle.
VIT B 12 (EXTRINSIC FACTOR)

- **Vit B12** – Cyanocobalamin or extrinsic factor.
- **Daily need** – 1-2 μg.
- **Sources** – Milk, Meat, Liver of Animals
  - Also synthesized by bacterial Flora.
VIT B 12 (EXTRINSIC FACTOR)

- **ABSORPTION** – need Intrinsic Factor Of Castle, a glycoprotein secreted by parietal cells of gastric mucosa. With it form **Intrinsic Factor** - Cyanocobalamin complex

Bound to sp receptors in ileum & absorbed by **Endocytosis**.
VIT B 12 (EXTRINSIC FACTOR)

- **TRANSPORT** – in blood transported by combining with Transcobalamin-II

- **STORAGE** – In liver & Muscle

- **ROLE** – required for synthesis of DNA & maturation of cell.
FOLIC ACID

- **Folic acid** – Pteroylglutamic acid.
- **Daily requirement** – 100 μg.
- **Sources** – leafy veg, pulses, yeasts, liver.
- From breakdown of Polyglutamate to Monoglutamates.
IRON DEFICIENCY ANEMIA
THANK YOU