VITAMIN - A

HISTORY

- Therapeutically used about 3,600 years ago
- Hippocrates (about 500 B.C.) treated ‘night blindness’ – whole ox - liver dipped in honey
- Pioneer workers who studied nutritional role & functions: McCOLLUM, DAVIS SIMMONDS & HOPKINS
- Carotenoids was discovered by STUNBOCK in 1919
- Chemical structure of β-carotene & Vitamin A were described in 1930 & 1931 respectively
- Structure was described by Paul Karrer & synthesis was achieved by Kuhn & Morris (1937)
**OCCURRENCE**

- Carotenoids: family members related to $\beta$-carotene, chiefly the plant sources
- Retinoids: family members related to Vitamin A, chiefly animal sources; also includes synthetic forms
NOMENCLATURE

✓ PROVITAMIN A : β-Carotene
✓ VITAMIN A₁ : Retinol (Vitamin A alcohol)
✓ VITAMIN A₂ : 3 – Dehydro-retinol
✓ VITAMIN A ALDEHYDE : Retinal
✓ VITAMIN A ACID : Retinoic acid
✓ VITAMIN A ESTER : Retinyl ester
✓ NEO VITAMIN A : Stereoisomer of Vitamin A₁, has 70 – 80% of biological activity of Vitamin A₁
CHEMISTRY

- Vitamin A is composed of ‘β - IONONE RING’ (CYCLOHEXENYL) to which ‘POLY ISOPRENOID SIDE CHAIN’ is attached
- Polyisoprenoid chain – all trans configuration, contains 4 double bonds, has 2 methyl groups with terminal carbon having ‘R’ group
- ‘R’ Group – alcohol/aldehyde/acid
- β - I onone ring – contains 1 double bond with 3 methyl groups
Retinol

Retinal

Retinoic acid (all trans)

11-cis-retinal (formed by photoisomerization of all trans-retinal)
CHEMISTRY

• Retinol : - CH$_2$OH
  - found in animal tissues as ‘Retinyl esters’ with long chain fatty acids

• Retinal : - CHO
  - oxidation of retinol by ‘retinal reductase’ requiring NAD/NADP
  - Retinol & Retinal are inter-convertible
CHEMISTRY

• Retinoic acid : - COOH
  - oxidation of retinal
  - Retinoic acid cannot form retinal or retinol

• β - Carotene : Hydrolysed by β - carotene dioxygenase in presence of oxygen & bile salts to 2 molecules of retinal
**SOURCES**

- **Animal**: Fish Liver oil, Butter, Milk, Cheese, Egg Yolk
- **Plant**: All Yellow – Orange – Red – Dark Green fruits & vegetables like Tomatoes, Carrots, Spinach, Papayas, Mangoes, Corn, Sweet Potatoes
RECOMMENDED DIETARY ALLOWANCE (RDA)

- Unit of activity is expressed as ‘RETINAL EQUIVALENT’ (R.E.) / ‘INTERNATIONAL UNIT’ (I.U.)

- 1 Retinal Equivalent = 1 µg of Retinol OR 6 µg of β-carotene

- 1 I.U. = 0.3 µg of Retinol OR 0.34 µg of Retinyl acetate OR 0.6 µg of β-carotene

- Infants & Children: 400 to 600 µg/day
- Adults (Men & Women): 600 to 800 µg/day
- Pregnancy & Lactation: 1000 to 1200 µg/day
Dietary β - carotene is oxidatively cleaved into 2 molecules of retinal
- Few β - carotenes are absorbed directly into the intestinal cells
Dietary Retinyl esters are also acted upon by hydrolases to yield Retinal & free fatty acid
- Bile salts plays an important role in this process
The absorbed β - carotene & Retinal are converted to Retinol in the intestinal mucosal cells
ABSORPTION ...

- Finally, in the mucosal cells all of the Retinol are re-esterified with free fatty acids to form ‘Retinyl esters’
- Re-esterified Retinyl esters are carried by chylomicrons
- Via the thoracic duct they are carried into the circulation and then to the liver, where it is taken up & stored
- Greatest concentration: Liver; appreciable amounts are also seen in kidneys, adrenals, lungs & retina
- 95% of Vitamin A is stored in liver as ‘Retinyl palmitate’
- Vitamin A in plasma is 20 to 60 μg% & β-carotene is 100 to 300 μg%
**MECHANISM OF ACTION**

- Retinyl esters is hydrolysed to Retinol and is transported to the target tissues.
- It is attached to ‘Plasma Retinol Binding Protein’ (PRBP), an $\alpha_1$-globulin which in turn is bound to pre-albumin.
- Retinol – PRBP complex attaches itself to the specific receptors on the cell surface, releasing retinol, which enters into the cells.
- In the target tissues retinol combines with ‘Cellular Retinol Binding Protein’ (CRBP) present in the cytosol.
MECHANISM OF ACTION...

- Retinol-CRBP attaches to the receptors present on the nucleus
- As it enters the nucleus, it is converted to Retinoic acid
- Retinoic acid binds to the inactive nuclear receptor & converts it into active receptor complex
- This activated complex causes gene activation, synthesis of m-RNA and specific proteins → cell differentiation
- Mechanism of action: analogous to steroid hormone action
(1) VISUAL CYCLE

- Only function of Vitamin A clearly understood to its molecular details
- Overall mechanism through which the Vitamin A functions – ‘Wald’s Visual Cycle’ OR ‘Rhodopsin Cycle’

- George Wald, Nobel Prize
FUNCTIONS (Contd)

- Vitamin A is a component of ‘VISUAL PIGMENTS’ of Rods & Cones
- ‘Rhodopsin’ – Visual pigment of rod cells in retina
  - Conjugated protein
  - ‘11-Cis-retinal’ bound to Apoprotein ‘Opsin’
  - Aldehyde group of retinal linked to ε-amino group of lysine in opsin
  - Mol Wt : 40,000
VISUAL CYCLE

- Rhodopsin, when exposed to light → a series of photochemical isomerisations
- Results in bleaching of visual pigment & release of All-trans-retinal & Opsin
- Process triggers nerve impulse → transmitted by optic nerve to the ‘Visual Centre’ of brain
- Regeneration of rhodopsin requires isomerisation of All-trans-retinal to 11-Cis-retinal
- It combines spontaneously with Opsin in the dark to form ‘Rhodopsin’
VISUAL CYCLE (Contd)

- When light strikes on retina – a number of biochemical changes occurs → membrane hyperpolarization → generation of nerve impulse
- Hyperpolarisation is brought about by a visual cascade involving cGMP
- When a photon is absorbed by rhodopsin, metarhodopsin II is produced → activation of protein ‘TRANSDUCIN’, involving GTP
- Activated transducin further activates enzyme ‘cGMP phosphodiesterase’ → degrades 3’5’-GMP to 5’-GMP
- Rapid ↓ in cGMP closes Na+ channels in the membranes of rods → hyperpolarisation; an excitatory response transmitted as nerve impulse to brain
Cones are specialised in bright & colour vision.

Colour vision is governed by 3 colour sensitive pigments:
- Porphyropsin (Red)
- Iodopsin (Green)
- Cyanopsin (Blue)

All these are retinal-opsin complexes.

When bright light strikes the retina → one or more of these pigments are bleached, depending on the colour of light → pigment(s) dissociating into All-trans-retinal & Opsin.

Nerve impulse generated by visual cascade causes perception of a specific colour in brain.
FUNCTIONS (Contd)

(2) MAINTENANCE OF EPITHELIAL CELLS

- Normal growth & differentiation
- Involvement in:
  - Metabolism of intracellular structures
  - Glycoprotein synthesis
  - Metabolism of mucopolysaccharides
  - Prevention of keratin synthesis
FUNCTIONS (Contd)

(3) REPRODUCTION
- Both Retinol & Retinal are essential for reproduction
- Plays an important role in ‘Steroid hormone’ formation
  - Supports spermatogenesis in males
  - Prevents foetal miscarriages in females

(4) GROWTH
- Plays a role in growth & development process
  - Sulfation of heteropolysaccharides in the matrix of bone & cartilage
(5) SYNTHETIC FUNCTIONS
- Vitamin A is involved in synthesis of various compounds:
  - Transferrin, the iron transfer protein
  - Cholesterol
  - Glucocorticoids

(6) IMMUNE FUNCTIONS
- Vitamin A plays an important role in the maintenance of immune system
Deficiency Manifestations

- Vitamin A deficiency may result from:
  - Dietary insufficiency of Vitamin A / Precursors
  - Interference with absorption from intestines
    eg: diarrhoea, malabsorption syndrome, bile salt deficiency
  - Defect in the transport due to protein malnutrition – ‘Kwashiorkar’
  - Defect in the storage due to diseases of liver
    - ‘Cirrhosis’
Deficiency Manifestations...

- Tissues chiefly affected – ‘Epithelial’
- principally which are not normally keratinised

- Includes epithelium of respiratory tract, gastrointestinal tract, genitourinary tract, eye & paraocular glands, salivary glands, accessory glands of tongue & buccal cavity and pancreas

- Fundamental change: Metaplasia of normal non-keratinised living cells into keratinising type of epithelium
Ocular Manifestations

(1) NYCTALOPIA (NIGHT BLINDNESS)
- First symptom, often neglected
- Diminished visual acuity in ‘dim light’

(2) XEROPHTHALMIA (DRYNESS OF CORNEA & CONJUNCTIVA)
- Conjunctiva loses normal transparency and becomes dry, thick, wrinkled & smoky
- Cornea becomes glazy & lusterless
(3) BITOT’S SPOTS

- Greyish-white triangular spots/plaques
- Seen on the medial canthus of the eye
- Firmly adherent to conjunctiva

✓ “ALL THE ABOVE OCULAR CHANGES ARE COMPLETELY REVERSIBLE WHEN VITAMIN A IS SUPPLEMENTED”
BITOT’S SPOT

- Bilateral
- Grayish white silvery
- Triangular
- Adherent lateral conjunctiva
Our clinical departments

1. General Medicine
2. Chest & TB
3. Psychiatry
4. General Surgery
5. Ophthalmology
6. Endoscopy
7. Obstetrics & Gynec.
8. Dermatology
9. Dentistry
10. Pediatrics
11. Plastic Surgery
12. Anesthesia
13. Orthopedics
14. Maxillofacial Surgery
15. Pediatric Surgery
16. ENT
17. Nephrology
18. Endocrinology
19. Neurosurgery
20. Physiotherapy
21. Speech Therapy
22. Audiometry
Ocular Manifestations (Contd)

(4) KERATOMALACIA (CORNEAL SOFTENING)

- Persistence of xerophthalmia progresses to softening of cornea
- Occurs due to degradation of corneal epithelium
- Further it results in bacterial infection → ‘Corneal Ulceration’
- Healing of corneal ulcers leads to formation of opacities → ‘PARTIAL BLINDNESS’
- Further, ‘TOTAL BLINDNESS’ occurs due to the perforation of cornea & prolapse of the iris
‘PHRYNODERMA’ (TOAD SKIN)

Follicular hyperkeratosis – hyperkeratinisation of epithelium lining the follicles

Skin becomes rough with papular eruptions

Keratinising metaplasia of epithelium of respiratory, gastrointestinal & genitourinary tracts → ↓ mucous secretion & infections of these systems
**Other Manifestations**

- Growth retardation – esp failure of skeletal growth
- ↓ immunopotency

**Assessment of Vitamin A Deficiency**

- Dark Adaptation Time - ↑ due to ↑ visual threshold
- ↓ Retinol Binding Protein (RBP) in plasma
- ↓ Vitamin A levels in serum
Hypervitaminosis A

- Excessive intake for prolonged periods
- Consumption of > 7.5 mg of retinol/day
- Commonly seen in:
  - Children supplemented by Vitamin A
  - Eskimos, who consume polar bear liver
Hypervitaminosis A

- **Signs & Symptoms includes:**
  - Skin – dry, pruritic with coarse sparse hairs
  - Liver – enlarged and can become cirrhotic
  - Bones – painful due to enlargement
  - Nervous system – headache, irritability & vomiting due to increased intracranial pressure
  - Pregnancy – congenital malformations in the developing foetus

- **Treatment** – Symptomatic & avoiding Vitamin A rich foods
Thank You