CUTANEOUS BLEACHING MODALITIES

ESSAY

SUBMITTED IN PARTIAL FULFILMENT OF

THE MASTER DEGREE IN

DERMATOLOGY AND VENEREOLOGY

BY

SALAH ELDIN BADAWI ESSA

M.B.,B.CH.

616.55
S.B

UNDER SUPERVISION OF

PROF. DR. MOUSTAFA MOKHTAR KAMEL

PROF. OF DERMATOLOGY AND VENEREOLOGY

PROF. DR. ADEL AHMED HALIM IMAM

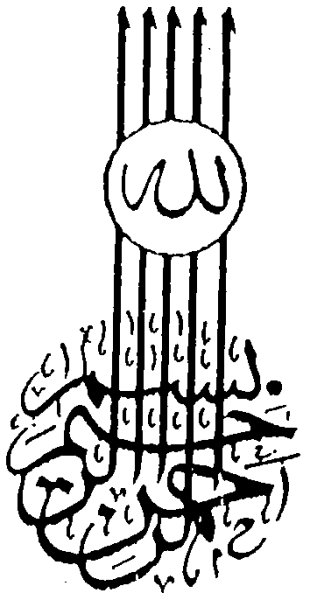
ASST. PROF. OF DERMATOLOGY AND VENEREOLOGY

FACULTY OF MEDICINE

AIN SHAMS UNIVERSITY

1994

Central Library - Ain Shams University

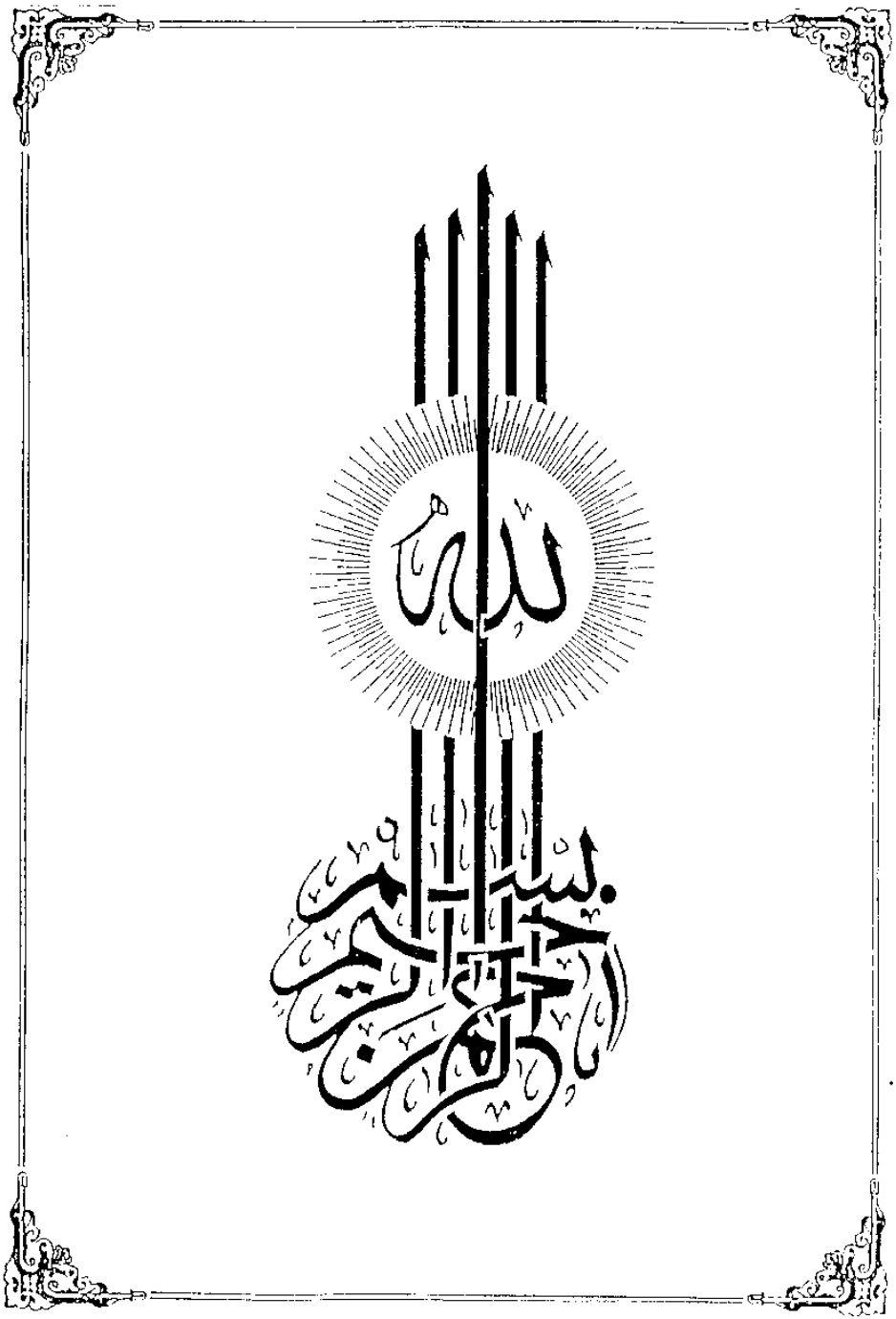


سبحانك لا علم لنا إلا ما علمتنا إنك أنت
العليم الحكيم

صدق الله العظيم

سورة البقرة آية ٣٢

Central Library - Ain Shams University



Central Library - Ain Shams University

ACKNOWLEDGEMENT

First and foremost, I fell always indebted to God, the most kind and the most merciful. I wish to express my sincere thanks and deepest gratitude to professor Dr. Moustafa Mokhtar Kamel, Professor of dermatology and venereology for his interest, encouragement and valuable advice.

I am greatly indebted to professor Dr. Adel Ahmed Imam assistant professor of dermatology and venereology for his valuable and sincere guidance throughout this essay.

Also my thanks and appreciation to every one who gave advice or help throughout this essay.

Central Library - Ain Shams University

Contents

Central Library - Ain Shams University

I Introduction and biology of melanogenesis

Central Library - Ain Shams University

Introduction and biology of melanin formation (Melanogenesis)

Normal skin colour is dependent on hemoglobin (in both oxygenated and reduced state), carotenoids and melanin pigment. Melanin is the major colour determined factor. Racial differences in skin colour are related to the number, size, shape, distribution, and degradation of melanin laden organelles (melanosomes) which are produced by the melanocytes [1].

Melanin is synthesized in mammalian skin in the melanocytes. These cells contain the enzyme tyrosinase which is responsible for the conversion of tyrosine to 3,4 dihydroxy phenylanine (DOPA) and dopa quinone, and the conversion of 5-6 dihydroxy indole to indole 1-5 quinone [2, 3] . This latter monomer is then oxidized and polymerized to form melanin which is attached to the protein matrix of the melanosome by various linkages [4, 5].

Much knowledge about the subcellular localization of melanin biosynthesis has been gained using techniques such as ultracentrifugal separation of cell particles (melanosomes, mitochondria, smooth surface membranes, rough surface membranes and ribosomes) [4]. Density gradient centrifugation and electron microscopic monitoring of the separated cell fractions have been also used to provide information regarding subcellular sites of melanogenesis within the melanocyte. It is generally accepted that tyrosinase is synthesized on the ribosomes, transferred via the rough endoplasmic reticulum to the Golgi apparatus where it is assembled into units each of which is surrounded by a smooth surface membrane to form a vesicle, these vesicles are named "melanosomes" [6].

Central Library - Ain Shams University

The melanin polymer is then gradually deposited within this vesicle on an inner membranous structure [4,5].

It has been demonstrated that tyrosinase activity can be demonstrated in melanosomes smooth surface membranes, rough surface membranes and ribosomes [5]. Various stages (premelanosomes) between the smallest vesicle containing tyrosinase and the fully developed melanosome have been described [7]. Incorporation study of dopa - c^{14} into various cell particles isolated from mouse melanoma were carried out by Seiji et al., [4], in order to clarify the site of melanin formation in the melanocytes. They proved that dopa c^{14} incorporation occurs only in melanosomes. It is therefore suggested that melanosomes are the specific site of melanin formation in the melanocyte, and that the presence of tyrosinase activity is not necessarily related to the formation of melanin [4,8,5].

In 1963 Seiji et al [6] proposed that three terms "premelanosome", melanosome and melanin granules to refer to the melanin forming organelles in different stages of development, melanization and electron density. As originally proposed these terms are defined as follows:

Premelanosome, a distinctive particulate protein matrix upon which melanin is usually deposited with consequent formation of the melanosome, a premelanosome after the onset, but prior to the completion, of melanin synthesis which characteristically possesses an active tyrosinase system. Melanin granule, a melanin containing organelle in which melanization is complete and no tyrosinase can be detected. These terms have been used widely, although certain difficulties arise in their application. For example, it has not yet been determined whether the degree of

Central Library - Ain Shams University

melanization is the only factor that determines the electron density of the melanin containing organelle. Further more, it is difficult to determine precisely the onset of melanin synthesis and therefore to distinguish clearly between premelanosomes and melanosomes [5]. Accordingly, Fitzpatrick et al., [9] proposed that the term melanosome be used to designate the fully pigmented melanin containing organelle only. They suggested that the term premelanosomes would then be applied to all stages in the genesis of melanosomes that preceeded the fully developed state. At the direction of investigator, and within the restriction of his definition, the premelanosomal stage might be subdivided into early, intermediate, and late phases. The term melanin granule could be appropriately retained to include all melanin - containing particulates that can be observed with light microscopy. The additional terms (premelanosome and melanosome) for pigmented organelles would provide the amplification required by the electron microscopist and biochemist.

Toda et al., [7] suggested the application of the term melanosome to all stages of the development of the organelle, and they classified the development into four stages.

The current classification of melanosomes into stages should permit a clearer definition of the structural and functional events occurring during the development of melanosomes. This view is later supported by Jimbow et al., [10], who stated that four stages of melanosomal ontogeny are recognized.

The present view of the development of melanosomes is therefore, that tyrosinase is synthesized in ribosomes and transferred via the endo-

Central Library - Ain Shams University

plasmic reticulum (rough- surface membrane) to the Golgi area, where it accumulates in vesicles that are derived from the Golgi area [7,5].

These vesicles are the first of the four stages in melanosome formation. during stage II, the inner membranous structure of the melanosome is fully developed, although there is no evidence of melanin deposition. Melanin deposition gradually occurs and accumulates on the inner membranes, and this is called stage III. Finally, the melanin deposition transforms the melanosome into a uniformly dense particle without discernible internal structure; this is stage IV.

Ultrastructural studies have shown that the fully melanized melanosomes are not as amorphous as previously considered. It is suggested that they contain certain spherical structures 400 A° in diameter which are electron lucent and have been called vesico-globular bodies [11]. Fitzpatricket al., [12] and Toda et al., [8] reported that melanosomes in their development from stage I to stage IV gradually move from the Golgi area through the cytoplasm of the melanocyte in the dendritic processes. However, even in the dendritic processes stage II melanosomes may be seen.

Melanin Transfer:-

The actual method of transfer of melanosomes from melanocytes to epidermal keratinocytes had not been clearly explained.

Charless and Ingram [13] suggested that the dendrite of melanocyte and the epidermal cell fused and that external pressures caused a breakdown of the thin separating membranes and forced the melanosomes from one cell to the other.

Central Library - Ain Shams University

Drochmans [14] indicated that phagocytosis is probably involved in the transfer of melanosomes. He noted that the melanocyte is an active cell in the exchange and that it forced its dendrite into the receiving cell.

Swift [15] on the other hand, hypothesized that melanosomes are secreted first to the extra cellular space through small pores or openings in the tip of the dendritic process before reaching other cells.

In a study by the electron microscope, Mottaz and Zelickson [16] came to the conclusion that melanosomes are transferred from melanocytes by means of phagocytic activity of the cortical cells or the keratinocytes. Pseudopodia - like cytoplasmic projections of keratinocytes or cortical cells wrappe around the tip of the dendrites. These projections continue to enlarge until they completely envelope the tip of the dendrite which is then apparently pinched off. At first the melanosomes in the pinched - off dendrite are separated from the cytoplasm of the keratinocyte by the plasma membranes of the dendrite and that of the keratinocyte. After the breakdown of these two plasma membranes, the melanosomes are dispersed through the cytoplasm of the keratinocyte.

Melanocytes distribution :-

Melanocytes distribution are found to vary according to the age or sex. Although the number of melanocytes in relation to the basal cells varies with the body region and increases with the repeated exposures to ultra violet light, one cell in ten in the basal layer is a melanocyte [17]. Melanocytes occur more frequently in adults compared to children and fetuses but the incidence probably decreases with increasing age [17, 18].

Central Library - Ain Shams University

Cochran [17] added that there is no significant difference in distribution when comparing male and female skin in adults and children.

There is considerable variation in the density of melanocytes from individual to individual and from area to area within the same individual as regards the distribution of melanocytes [19].

Staricco and Pinkus [20] came to the conclusion that the concentration of melanocytes varies in different areas, being highest in exposed areas such as the face and neck It is also higher in the genital region.

The activity and distribution of melanocytes vary according to the race. It is found also that the racial factor controls the distribution of melanosomes within the keratinocytes. [19].

Investigations of Szabo et al., [19] revealed that epidermal melanocytes of very pale caucasoids contain practically no melanosomes. These melanocytes are weakly. DOPA-Positive in "split" epidermal preparations. There are very few, if any, stage II and IV melanosomes located in the dendrites. The keratinocytes are practically pigmentless. In caucasoids who are somewhat more heavily pigmented, stage I,II and III melanosomes are present in the melanocytes, but stage IV melanosomes are not found within the dendrites. In the surrounding keratinocytes, however, there are often groups of stage IV melanosomes. There are numerous stage II, III and IV melanosomes in the melanocytes in Mongoloids, whereas there are mainly stage IV melanosomes at this site in Negroids.

After ultraviolet irradiation, numerous stage IV melanosomes appear in the melanocytes of Caucasoids, and stage II and III melanosomes appear in the melanocytes of Negroids [21].

Central Library - Ain Shams University

In the non exposed skin of Caucasoids, especially those with light skin, the melanosomes are found almost exclusively in the basal cell layer and to a slight degree in the adjacent layer of keratinocytes. In Negroids, however, even though melanosomes are principally seen in the basal cell layer, moderate quantities of melanosomes are found throughout the epidermis, including the stratum corneum [22].

In addition, Negroid skin contains larger and more highly dendritic melanocytes than Caucasoid skin [20].

In addition to the described racial differences in the morphology of melanocytes, there are also racial differences in the arrangement of melanosomes within the keratinocytes. In all Caucasoids and Mongoloids, melanosomes are usually arranged in groups in the keratinocytes. Each melanosome group is surrounded by a membrane (melanosome complexes). There may be two or more melanosomes forming, a single group, and only a small proportion of melanosomes are seen to be singly dispersed. The melanosomes present within these melanosome complexes often show signs of degeneration [19, 22].

Unlike the melanosomes in caucasoids and Mongoloids the great majority of melanosomes in Negroids are dispersed within the keratinocytes and rather few melanosome complexes are found [22,23]. Melanosome dispersal contributes to the darker colour and superior sunlight protection of negro skin [22].

The investigations of Hori et al., [24] showed that there is considerable acid phosphatase activity in the melanosome complexes within the kerati-

Central Library - Ain Shams University

nocytes of caucasoids and Mongoloids. They came to the conclusion that these membrane bound melanosome complexes represent "phagolysosomes" in which the melanosomes are being degraded.

Olson et al., [22] supported this view and added that, in addition to melanosome complexes, individual melanosomes, both in melanocytes and keratinocytes, also exhibit lysosomal properties of phagocytosis and hydrolytic enzyme activity. Thus melanosomes are removed more rapidly in caucasoids than in Negroids.

Degradation by lysosomal enzyme explains the limitation of melanin principally to the basal layer.

Flaxman et al., [25] reported that the difference in skin color between caucosoids and Negroids can be summarized as follows: in Negroid skin. there is a greater production of melanosomes per melanocyte; the individual melanosome shows a higher degree of melanization, and they are larger in size. As a consequence of their larger size, there is a higher degree of dispersion in the keratinocytes and a slower rate of degradation.

Central Library - Ain Shams University

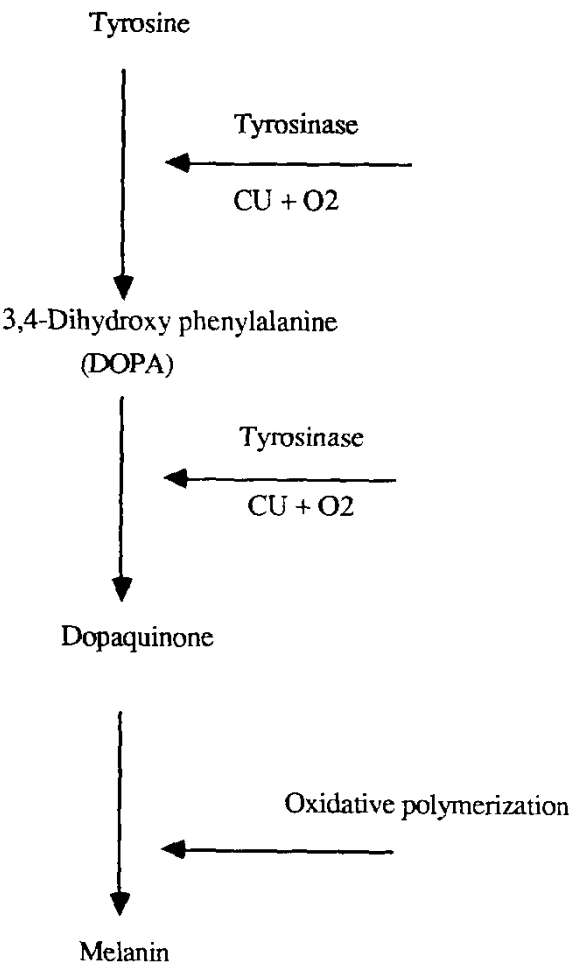


Fig (1)

Steps of Melanin Formation [26]

Central Library - Ain Shams University