



PEROXISOMES AND THEIR RECEPTORS IN DERMATOLOGY

Essay

Submitted for partial fulfillment of Master Degree in
Dermatology, Venereology and Andrology

By

Ghada Mohamed Elkatory

M.B.,B.Ch.

Faculty of Medicine – Ain Shams University

Supervised by

PROF. DR. HANAN MOHAMED EL KAHKY

Professor of Dermatology, Venereology and Andrology
Faculty of Medicine - Ain Shams University

DR. HEBA MAHMOUD EL-SAYED DIAB

Lecturer of Dermatology, Venereology and Andrology
Faculty of Medicine - Ain Shams University

Faculty of Medicine
Ain Shams University
2011



تأثير البيرو وجزيرومز ومستقبلاتها في الجلد

□□□□ □

تمهيداً للحصول علي درجة الماجستير في
الأمراض الجلدية والتناسلية

□□ □□□□□□

طبيبة/ غادة محمد القطوري

بكالوريوس الطب و□□□□□□ – جامعة عين شمس

تحت إشراف

أ.د/ حنان محمد الكحكي

□□□□ □ الأمراض الجلدية والتناسلية
كلية الطب- جامعة عين شمس

د./ هبة محمود السيد دياب

□□□ □ الأمراض الجلدية والتناسلية
كلية الطب- جامعة عين شمس

كلية الطب

جامعة عين شمس □

٢٠١١

SUMMARY

Peroxisomes are intra cellular, spherical, small, membrane-enclosed organelles, that are 0.2 - 1.7 μ m and bound by a single membrane. They contain enzymes involved in a variety of metabolic reactions including several aspects of energy metabolism.

The main function of peroxisomes is the breakdown of the very long chain fatty acid through beta oxidation. They play an important role in the cell metabolism of lipids, hormones and regulation of cell proliferation and differentiation which in turn modulate inflammatory responses. Peroxisomal receptors are nuclear hormone receptors that present as three isotypes PPAR α , PPAR β/δ , PPAR γ . On their activation or inhibition by either natural or synthetic agonist and antagonist they exert their action in inflammatory skin disorders; ie acne vulgaris since activators of PPARs in particular of the δ subset might have beneficial effects on acne vulgaris by inhibiting the release of lipids in the context of sebocyte apoptosis, In atopic dermatitis PPARs might exert a beneficial role through the combination of it's properties in immune responses and epidermal differentiation and regulation of epidermal protein and lipid production. In contact dermatitis the anti-inflammatory properties of PPAR α agonists, coupled with

Acknowledgment

I wish to express my deep gratitude and appreciation to Professor Dr. Hanan Mohamed El Kahky professor of Dermatology, Venereology and Andrology, Faculty of medicine, Ain Shams University, who gave me the honor of working under her meticulous supervision.

I am sincerely grateful to Dr. Heba Mahmoud El-Sayed Diab Assistant professor of Dermatology, Venereology and Andrology, Faculty of medicine, Ain Shams University, for her kind help and constructive suggestions to achieve this work.

I would like to thank all members of the department of Dermatology and Venereology, Ain Shams University for their support and cooperation.

Finally, I am truly grateful to my family for helping and supporting me all through the period of the research.

Ghada Mohamed Elkatory

CONTENTS

	Page
List of Abbreviations	iii
List of Figures	v
List of Tables	vi
Introduction & Aim of the essay	1
Chapter 1: Peroxisomes	4
• Definition	4
• Evolution	7
• Structure and ultrastructure	9
• Genes	11
• Peroxisomal biogenesis	11
• Functions	14
• Cellular functions and physiology	15
• Peroxisome Proliferator-activated Receptors.....	17
• Tissue distribution of PPARs	18
• Peroxisomal disorders	26
• Peroxisome biogenesis disorders	26
• Zellweger spectrum	27
• Rhizomelic chondrodysplasia punctata	28
• Disorder due to single-enzyme deficiencies with intact peroxisomal structure	29

Chapter 2: PPARs in dermatology	30
• PPARs and their relevance in human skin physiology ..	30
• PPARs Expression in Skin.....	30
• Effect on epidermal differentiation, epidermal proliferation and cell death	30
• Role in permeability barrier function.....	33
• Role in lipid metabolism in the epidermis	38
• Stratum corneum formation	39
• Role in skin homeostasis	41
• Role in wound healing.....	42
• Relevance of peroxisome proliferator- activated receptor targeting in skin disorders	44
• Role of PPAR activation in inflammatory skin disorder ..	45
• Psoriasis.....	45
• Acne Vulgaris	46
• Contact dermatitis	48
• Atopic dermatitis	51
• Role of PPAR in skin cancer.....	53
• Actinic keratosis and Squamous cell carcinoma	54
• Malignant melanoma.....	55
Summary	57
References	59
Arabic summary	-

LIST OF ABBREVIATIONS

ABCA12	ATP-binding cassette, sub-family A (ABC1), member 12
AD	Atopic dermatitis
AK	Actinic keratosis
AMP	Adenosine monophosphate
BADGE	Bisphenol A diglycidyl
BCFA	Branched chain fatty acids
CD4+ T cells	T helper cells
CD8+	Cytotoxic T cell
CNS	Central nervous system
CSF	Cerebro spinal fluid
DC	Dendritic cells
DHAP-AT	Dihydroxyacetone-phosphate acyl-transferase
DNA	DeoxyriboNucleic Acid
ER	Endoplasmic reticulum
FAAR	Fatty acid activated receptor
FABP	Fatty acid binding protein
GMP	Guanosine monophosphate
HMG-coA	3-hydroxy-3-methylglutaryl-coenzyme A
HODE	Hydroxy octadecadienoic acid
IgE	Immunoglobulin E
IRD	Infantile refsum's disease
LDL	Low density lipoproteins
LT	Leukotriene
NALD	Neonatal adrenoleukodystrophy
NR1C1	Nuclear receptor subfamily 1 Group C member 1
NR1C2	Nuclear receptor subfamily 1 Group C member 2
NR1C3	Nuclear receptor subfamily 1 Group C member 3
NUC 1	Nuclease abnormal -1
PBDs	Peroxisomes biogenesis disorders
PEX	Peroxin genes
PG	Prostaglandin
PPARs	Peroxisome proliferator activated receptors
PPREs	Peroxisome proliferator responsive elements
PTS	Peroxisomal targeting signal
RCDP1	Rhizomelic chondro dysplasia punctata type 1

RNA	Ribonucleic acid
RXR	9 cis retinoic acid receptor
SC	Stratum corneum
SCC	Squamous cell carcinoma
SULT2B1b	Cholesterol sulfotransferase type 2B isoform 1b
T3	<u>Triiodothyronine</u>
TCF3	Transcription factor 3
TH	T helper cells
TNF	Tumor necrosis factor
TPA	<u>Tissue plasminogen activator</u>
TZDs	Thiazolidinediones
UVB	Ultra violet band
VLCFA	Very long chain fatty acid
ZS	Zellweger spectrum
ZSD	Zellweger syndrome spectrum

LIST OF FIGURES

Fig. no.		Page no.
1	Diagrammatic representation of the animal cell organelles	5
2	Fluorescence digital light microscope Image of an African water mongoose skin fibroblast cell.....	6
3	Diagrammatic representation of the basic structure of peroxisome.	10
4	Diagrammatic representation of the anatomy of the peroxisome	10
5	Diagrammatic representation of the formation of new peroxisome by division	13
6	Diagrammatic representation of the role of peroxisome in metabolic processes inside the cell.....	16
7	Diagrammatic representation of PPAR α , β/δ , γ protein	19
8	Diagrammatic representation of the formation of the permeability barrier.	36

LIST OF TABLES

Table no.		Page no.
1	Peroxisome Proliferator-activated Receptor (PPAR) Subtypes and Corresponding Ligands.....	25
2	Effects of PPARs activation on the epidermis	32

INTRODUCTION

Peroxisomes are intra cellular small, membrane-enclosed organelles that contain enzymes involved in a variety of metabolic reactions including several aspects of energy metabolism. (*Sertznig et al., 2008*)

Peroxisomes play an important role in regulating cellular proliferation and differentiation as well as metabolism of lipids, hormones , modulation of inflammatory responses, they also affect cellular membranes and adipocyte formation thus play an important role in aging , they contain oxidative enzymes such as catalase, D-amino acid oxidase and uric acid oxidase . Their membrane mainly consists of phosphatidylcholine and phosphatidylethanolamine and largely resembles that of the endoplasmic reticulum (ER). (*Sato et al., 2010*)

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor superfamily and are expressed in a variety of tissues including skin and cells of the immune system. (*Friedmann et al., 2008*)

These receptors include 4 types: PPAR α , PPAR β/δ and PPAR γ , they are fatty acid activated transcription factors that are best known as transcriptional regulators of lipid and glucose metabolism, evidence has also accumulated for their importance

in skin homeostasis. The three PPAR isotypes are expressed in human skin. (*Michalik and Wahli 2007*).

Peroxisomes proliferators activated receptors and corresponding ligands have been shown in skin and other organs to regulate important cellular functions including cell proliferation and differentiation as well as inflammatory responses. These new functions identify PPARs and corresponding ligands as potential targets for the treatment of various skin diseases, other disorders and in skin repair after an injury. (*Sertznig et al., 2008*).

AIM OF THE ESSAY

The aim of this essay is to discuss the physiology of Peroxisome proliferator activated receptors and their relation to dermatology in health and disease effusing on their possible role as targets for novel therapies.

PEROXISOMES

Definition:

Peroxisomes are intracellular organelles with important roles defined in many metabolic processes (fig. 1 and 2). They derive their name from their ability to produce H_2O_2 through a group of oxidizing enzymes which use molecular oxygen to transform their substrates releasing H_2O_2 and OH which is toxic through its oxidative stress resulting in stimulation of phospholipase enzyme releasing phosphatidic acid and diacylglycerol that affect adenyl cyclase and protein kinase c respectively causing modulation of a wide array of target proteins including plasma membrane receptors, contractile proteins and regulatory enzymes affecting cellular oxidation, respiration, lipid synthesis, metabolism and transport, sex steroid metabolism, regulation of adipose cell numbers, microsomal oxidation and ketogenesis, insulin sensitivity as well as metabolism of a wide range of xenobiotics which is a chemical found in an organism but not normally produced or expected to be present in it. *(Wanders and Waterham 2006)*

It can also cover substances which are present in much higher concentrations than are usual. Specifically drugs such as antibiotics are xenobiotics in humans because the human body

does not produce them itself nor are they part of a normal diet. (Vatsyayan *et al.*,2005)

Catalase, the enzyme which breaks down hydrogen peroxide is the necessary identifying marker of the peroxisomes and by definition a peroxisome must contain it. (Gabaldón 2010)

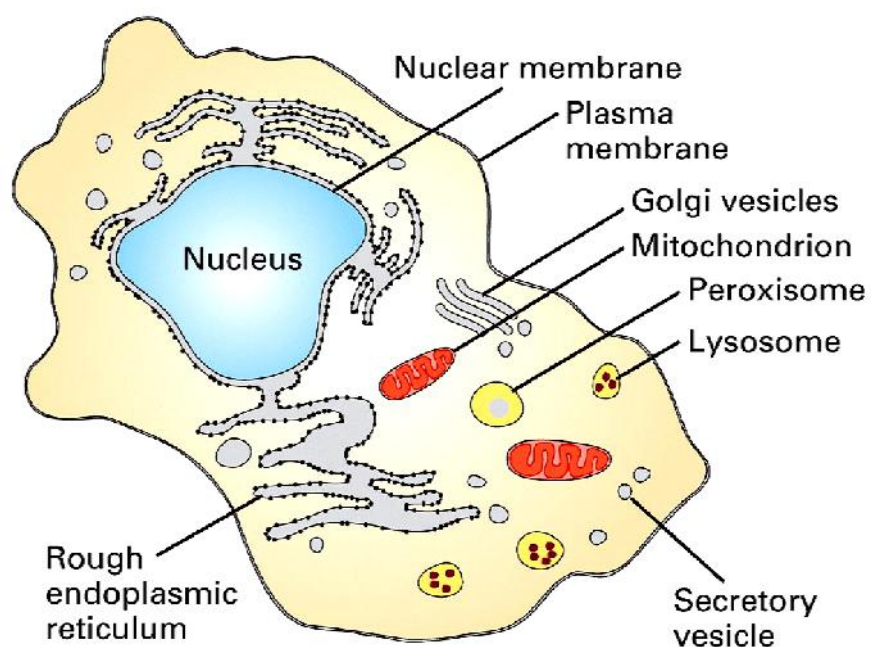


Fig. (1): Diagrammatic representation of the animal cell organelles
(<http://slideshare.com>)