EXPERIMENTAL STUDY OF THE POTENTIAL ANTI-INFLAMMATORY ROLE OF REBAMIPIDE IN SOME EXPERIMENTAL ANIMAL MODELS

thesis

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بسم الله الرحمن الرحيم

"يُؤْتِي الْحِكْمَةَ مَنْ يَشَاءُ وَمَنْ يُؤْتَ الْحِكْمَةَ فَقَدْ أُوتِيَ خَيْراً كَثِيراً وَمَا يَذَّكَّرُ إِلاَّ أُولُو الْأَلْبَابِ"

صدق الله العظيم

سوره البقره: الايه ٢٦٩

Dedication

To my parents and my husband

who gave me continous guidance

and support

Acknowledgement

Before all I would like to express my deep thanks to **Allah** *without his great blessings, I would never accomplish this work.*

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Abstract

Background: Inflammation contributes to the pathophysiology of many chronic diseases. Chronic inflammatory diseases, such as asthma, rheumatoid arthritis and inflammatory bowel disease. TNFα plays a pivotal role in pathogenesis of them. Although Corticosteroids ,Immunosuppressive agents, and Biological agents such as TNFα inhibitors, they alleviate the symptoms but do not cure the disease and have some limitations owing to their severe side effects. Consequently, looking for new agents that are equally or more effective and cause fewer side effects are needed. One of these drugs is rebamipide . Recent pharmacological studies have demonstrated that rebamipide has many pleiotropic pharmacological effects including Anti-Inflammatory, free radical scavenging and immunomodulatory are the most important effects.

Aim of the work: we intended to illucidate, compare and evaluate possible anti-inflammatory and immunomodulatory role of rebamipide in some experimental animal models of colitis, asthma and arthritis

Methods and experimental designs

Acetic acid 4% induced ulcerative colitis, OVA sensitized guinea pig model of bronchial asthma and acute non immunological formaldehyde1% induced arthritis

Results and Conclusion

In the present study we verified the well established protective therapeutic effect of rebamipide in amelioration of AA induced ulcerative colitis in rats, which could be explained by its potent anti-inflammatory , antioxidant and cytoprotective effects .The significant attenuation of pathological changes associating the OVA sensitized guinea pig model of bronchial asthma could be attributed anti-inflammtory and immunomodulatory role .

Its insignificant role in ameliorating pathlogical changes associating formaldehyde induced arthritis could explain that its immunomodulator role is more obvious in ulcerative colitis and asthma models in which cell medited immunity was illicited or the choosen dose of the rebamipide in this study could not illicit anti-inflammatory and immunomodulatory

Key words

Inflammation,ulcerative colitis , Asthma, Arthritis, Rebamipide, Dexamethazone, TNFα, MPO, IgE,Acetic acid, Ovaalbumin , Formaldhyde

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List of abbreviations

5-ASA	5-amino salycilic acid
5HT	Sertonin
AA	Acetic acid
ADAMT	Adesintegrin and metalloprotease with thrombospondintype 1 motif
AHR	Airway hyperresponsiveness
ANOVA	Analysis of variance
APC	Antigen presenting cell
AZA	Azathioprine
C^0	Degree centigrade
CAM	Cellular adhesion molecule
CARD	Caspase recruitment domain
CD	Cluster of differentiation
COX	Cyclooxygease enzyme
CTL	Cytotoxic Tlymphocytes
CW/BW	Colonic weight to body weight ratio
CXCR	Chemokine receptor
DAI	Disease activity index
DEX	Dexamethazone
DMARD	Disease modifying anti rheumatic drugs
DSS	Dextran sulphate sodium
ERK	Extracellular signal regulated kinase
EPR	electron paramagnetic resonance
FADD	Fas –associated death domain
GINA	Global initiative for asthma
GM-CSF	Granulocyte macrophage colony stimulating factor
H& E	Haematoxyllin and Eosin staining
HCQ	Hydroxychloroquine
HIFα	Hypoxia inducible factorα
HO-1	Hemoxygenase -1
IBD	Inflammatory bowel disease
ICS	Inhaled corticosteroids
IFN	Interferron
IgE	Immunoglobulin E
Ik_B	Inhibitor of NF-kB
IKK	Inhibitor for $kappa_B$ kinase

IL	Interlukin
JAM	Juxta adhesion molecules
JUK	C-jun-N-terminal kinase
LABA	Long acting beta2 agonist
LEF	Leflunomide
LOX	Lipooxygenase enzyme
LT	Leukotrien
MADCAM	Mucosal addressin cellular adhesion molecule
MAPK	Mitogen activated protein kinase
MCP	Monocyte chemoattractant protein
M-CSf	Macrophage colony stimulating factor
MEKK1	MAP/ERK kinase kinase1
MHC	Major histocomptibility
MKK7	MAP kinase kinase7
MPO	Myeloperoxidase enzyme
mM	Milli mole
MTX	Methotrexate
NF-K_B	Nuclear factor kappa
NK	Natural killer cell
NSAID	Nonsteroidal inflammatory drugs
OVA	Ovaalbumin
PAF	Platlet activating factor
PG	Prostaglandin
PKC	Protein kinase c
PLA2	Phospholipase A2
PMNs	Polymorphnuclear cell
PPAR	peroxisome proliferator-activated receptor
PSGL	P selectin glycoprotein ligand
RANKL	Receptor activator of nuclear factor kappa
Reb	Rebamipide
RIP	Receptor interacting protein
SABA	Short acting beta agonist
SOD	Superoxide dismutase
SPZ	Sulphazalasine
TAK1	TGF-$_B$ transforming growth factor beta activated kinase
Th	T helper
TIMP	Tissue inhibitors of metalloprotienases
TNBS	Trinitrobenzene sulphonic acid
TNF	Tumer necrosis factor
TRADD	TNF receptor associated death domain
$TRAF_2$	TNF activated factor 2

TXA	Thromboxane

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INTRODUCTION

Inflammation is considered the cornerstone of pathology in that the changes observed are indicative of injury and disease. it is recognised that inflammation is far more complex than might first appear and is a major response of the immune system to tissue damage and infection, These processes involve the major cells of the immune system, including neutrophils, basophils, mast cells, T-cells, B-cells, etc. These events are controlled by a host of extracellular mediators and regulators, including cytokines, growth factors, eicosanoids (prostaglandins, leukotrines, etc), complement and peptides. Inflammation is now considered as the full circle of events, from initiation of a response, through the development of the cardinal signs of inflammation to healing and restoration of normal appearance and function of the tissue or organ. However, in certain conditions there appears to be no resolution and a chronic state of inflammation develops that may last the life of the individual. Such conditions include the inflammatory disorders rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, retinitis, multiple sclerosis, psoriasis and atherosclerosis. (**Neville et al., 2004).**

It was postulated that any discussion of inflammation must involve consideration of the molecular level, and should also include the full range of cell types involved in the acute and chronic injury response. Thus, the positive or negative outcome of the process is influenced by the simultaneous responses and interactions of these cell types **(Scott et al., 2004).**

The concept that some cytokines function primarily to induce inflammation is based on the genes coding for the synthesis of small