Potential utility of angiotensin two receptor blocker in a rat model of ulcerative colitis

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Faculty of Pharmacy
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بسم الله الرحمن الرحيم

﴿وَعَلَّمَكَ مَا لَمْ تَكُنْ تَعْلَمُ وَكَانَ فَضْلُ اللَّهِ عَلَيْكَ عَظِيمًا﴾

صدق الله العظيم

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Title of Thesis

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Pre- requisite Postgraduate Courses

Besides the work presented in the thesis, the candidate has attended pre-requisite postgraduate courses including the following topics:

General Courses:

- Instrumental Analysis
- Physical Chemistry
- Computer skills
- Statistics

Special Courses:

- Pharmacology
- Clinical Pharmacology and Therapeutics
- Neuropharmacology
- Molecular Pharmacology
- Selected topics in pharmacology and Toxicology

The candidate has successfully passed the examination in these courses with general grade ***Very Good***.

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Marwa Mohamed Nagib

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List of Abbreviations

ACE	Angiotensin converting enzyme
ADHP	10-Acetyl-3,7-dihydroxyphenoxazine
Ang II	Angiotensin II
ARB	Angiotensin receptor blocker
5-ASA	5-Aminosalicylic acid
AT1	Angiotensin II receptor, type one
BHT	Butylated hydroxy toluene
BSA	Bovine serum albumin
CAMs	Cell adhesion molecules
CD	Crohn's disease
CD1	Cluster of differentiation 1
CMC	Carboxy methyl cellulose
CRC	Colorectal cancer
COX	Cyclo-oxygenase enzyme
DAI	Disease activity index
DMSO	Dimethyl sulfoxide
DSS	Dextran sodium sulphate
DTPA	Diethylene triamine penta acetic acid
EGF	Epidermal growth factor
ELISA	Enzyme-linked immunosorbent assay
GSH	Reduced glutathione
HRP	Horseradish peroxidase
IBD	Inflammatory bowel diseases
ICAM-1	Intracellular adhesion molecule-1
IFN-γ	Interferon gamma
IgG	Immunoglobulin G
IL	Interleukin
iNOS	Inducible nitric oxide synthase
KGF	Keratinocyte growth factor
5-LO	5-Lipo-oxygenase enzyme
MDA	Malondialdehyde
MPA	Metaphosphoric acid
MPO	Myeloperoxidase
NADPH	Nicotinamide adenine dinucleotide phosphate
NF-KB	Nuclear Factor kappa-light chain enhancer of activated B cells
NKT	Natural killer T cells
OLM-M	Olmesartan medoxomil
PBS	Phosphate buffer saline
PGE_2	Prostaglandin E_2
PG-PS	Peptidoglycan-polysaccharide
P.O.	Per os (oral)
RAAS	Renin angiotensin aldosterone system
ROS	Reactive oxygen species

SASP	Salicylazosulphapyridine
SDS	Sodium dodecyl sulfate
SH	Sulfhydryl
SP	Sulfapyridine
TBA	Thiobarbituric acid
TBARS	Thiobarbituric acid reactive substances
Th2	T helper cell type-2
TMB	Tetra methyl benzidine
TNBS	2,4,6-Trinitrobenzene sulphonic acid
TNF-α	Tumor necrosis factor-alpha
UC	Ulcerative colitis

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Anti-inflammatory and anti-oxidant activities of olmesartan medoxomil ameliorate experimental colitis in rats

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ABSTRACT

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) driven through altered immune responses with production of proinflammatory cytokines. Many therapies are used, but side effects and loss of response limit long-term effectiveness. New therapeutic strategies are thus needed for patients who don't respond to current treatments. Recently, there is suggested involvement of the proinflammatory hormone angiotensin II in inflammatory bowel disease. The aim of this study was to investigate the possible role of olmesartan medoxomil (OLM-M), an angiotensin II receptor blocker in ameliorating ulcerative colitis. Colitis was induced in male Wistar rats by administration of 5% dextran sodium sulphate (DSS) in drinking water for 5 days. OLM-M (1, 3 and 10 mg/kg) was administered orally during 21 days prior to the induction of colitis, and for 5 days after. Sulfasalazine (500 mg/kg) was used as reference drug. All animals were tested for changes in colon length, disease activity index (DAI) and microscopic damage. Colon tissue concentration/activity of tumor necrosis alpha (TNF-α), myeloperoxidase (MPO), prostaglandin E2 (PGE2), reduced glutathione (GSH) and malondialdehyde (MDA) were assessed. Results showed that the OLM-M dose-dependently ameliorated the colonic histopathological and biochemical injuries, an effect that is comparable or even better than that of the standard sulfasalazine. These results suggest that olmesartan medoxomil may be effective in the treatment of UC through its anti-inflammatory and antioxidant effects.

Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are the two major forms of chronic inflammatory bowel disease (IBD) (Blumberg and Strober, 2001). UC primarily affects the mucosal lining of the colon and rectum, whereas CD can involve any segment of the gastrointestinal tract (Podolsky, 2002). Although the etiology remains unclear, yet studies showed that a combination of genetic susceptibility factors and altered immune response driven by microbial factors in the enteric environment are involved in the pathophysiology of these chronic disorders (Korzenik and Podolsky, 2006). The activation of the intestinal immune system results in the production of pro-inflammatory cytokines, such as tumor necrosis factor (TNF-α) and interleukin-1β (IL-1β), prostaglandins and leukotrienes (Krimsky et al., 2003). IL-1β appears to be a primary stimulator of diarrhea, the main symptom of intestinal inflammation (Siegmund et al., 2001). In addition, TNF-α and IL-1β are the key immunoregulatory cytokines that amplify the inflammatory response by activating a cascade of immune cells, such as neutrophils and others (Jainu et al., 2006). Infiltration of neutrophils assessed by myeloperoxidase (MPO), result in the production of cytotoxic reactive oxygen species (ROS) that are destructive on intestinal cell macromolecules, ultimately leading to mucosal disruption and ulceration (Fiocchi, 1998).

Currently available treatments for IBD are only effective in ameliorating the disease symptoms while having many concomitant disadvantages. Antibiotics, one of the commonly used therapies, could adversely change the environmental conditions of microflora and also trigger resistance. Moreover, immunosuppressant and anti-inflammatory drugs (as corticosteroids) have many undesirable side effects (Sartor, 2004).

Angiotensin II (Ang II) is the primary effector peptide of the renin–angiotensin–aldosterone system (RAAS) through its action on both angiotensin receptors Ang II type 1 (AT1) and AT2 receptors (Padia and Carey, 2012). Activation of the AT1 receptor by Ang II is responsible for all of the known cardiovascular effects of Ang II: acute vasoconstriction, aldosterone secretion and sympathetic overactivity, while activation of the AT2 receptor results in the opposite effects (Burnier, 2001). Ang II is a proinflammatory hormone that participates in several key events of the inflammatory response: it increases vascular permeability (via release of prostaglandins and vascular endothelial cell growth factor/vascular permeability factor) (Suzuki et al., 2000) and enhances neutrophil infiltration, possibly contributing to intestinal ulceration.

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