The effect of Ibuprofen and Celecoxib on Fluoxetine's antidepressant activity: Role of tumor necrosis factor alpha and p11 protein

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LIST OF ABBREVIATIONS

5-HT: Serotonin

5HTR1B: Serotonin-1B receptors

5HTR4: Serotonin 4 receptors

AA: Arachidonic acid

ACTH: Adrenocorticotropic hormone

ANOVA: One way analysis of variance

BBB: Blood brain barrier

BCG: Bacillus Calmette-Guerin

BDNF: Brain-derived neurotrophic factor

CA1: Cornus ammonis 1

CA3: Cornus ammonis 3

CFU: Colony forming unit

CMS: Chronic mild stress

CNS: Central nervous system

COMED: Combining Medications to Enhance Depression outcomes

COX: Cyclo-oxygenase

CRF: Corticotropin releasing factor

ECT: Electroconvulsive therapy

ELISA: Enzyme-linked Immunosorbent Assay

FADD: Fas-associated death domain protein

FGF: Fibroblast growth factor

FST: Forced swim test

GFP: Green fluorescent protein

h: Hour

H_2O_2: Hydrogen peroxide

HPA axis: Hypothalamic-Pituitary-Adrenal axis

Hx&E: Haematoxylin and eosin

i.p.: Intraperitoneally

IDO: Indoleamine-2,3-dioxygenase

IL: Interleukin

INF-α: Interferon alpha

INF-γ: Interferon gamma

IRS: Inflammatory response system

KYN: Kynurenine

LPS: Lipopolysaccharide

MAOI: Monoamine oxidase inhibitors

MDD: Major depressive disorder

min: Minute

NCAM: Neural cell adhesion molecule

NO: Nitric oxide

NSAIDs: Non-steroidal anti-inflammatory drugs

O&NS: Oxidative and nitrosative stress

PBS: Phosphate buffer saline

PGE_2: Prostaglandin E_2

PGs: Prostaglandins

QUIN: Quinolinic acid

S.D.: Standard deviation

S.E.M.: Standard error of mean

SNRI: Serotonin and norepinephrine reuptake inhibitor

solTNF: Soluble TNF

SSRI: Selective serotonin reuptake inhibitor

STAR*D: Sequenced Treatment Alternatives to Relieve Depression

TACE: TNF alpha converting enzyme

TCA: Tricyclic antidepressant

Th-1: T-helper cell 1

TMB: Tetra-methyl-benzidine

tmTNF: Transmembrane protein TNF

TNFR1: TNF receptor 1

TNFR2: TNF receptor 2

TNF-α: Tumor necrosis factor alpha

TRADD: TNFR1-associated death domain protein

TRAF-2: TNFR-associated factor 2

TRP: Tryptophan

TRYCATs: Tryptophan catabolites

TST: Tail suspension test

ABSTRACT

Abstract

Background: Mounting evidence indicates that inflammation play a role in the pathophysiology of major depressive disorders. NSAIDs have been proposed to be of clinical use in the treatment of depression. However, a limited body of clinical research has been conducted with mixed results.

Objectives: The aim of this study was to explore the effect of ibuprofen and celecoxib on fluoxetine's antidepressant activity in a chronic inflammation-induced model of depression in mice using BCG vaccine.

Methods: Swiss albino mice were randomly divided into 8 groups; control, fluoxetine (20mg/kg/day), fluoxetine/ibuprofen (100mg/kg/day) or celecoxib (20mg/kg/day)- treated groups, BCG-inoculated group, BCG fluoxetine/ibuprofen or celecoxib-treated groups. All drugs were given by intraperitoneal injection. The behavioral tests done at the end of the study included locomotor assessment, FST, TST, followed by measurement of TNF-α, p11 protein levels and immune-histochemical staining of 5HT1B receptors in prefrontal cortex and hippocampus.

Results: BCG-inoculation induced a depressive-like behavior manifested by a significant increase in immobility time in both the FST and TST with no locomotor impairment, increase in TNF-α level, decrease in p11 protein level with decreased staining of 5HT1B receptors in prefrontal cortex and hippocampus. Fluoxetine treatment reversed the depressive-like state, however co-administration of either ibuprofen or celecoxib along with fluoxetine resulted in abolishing the previously manifested antidepressant activity of fluoxetine in both behavioral tests, along with decreasing p11 protein level and staining of 5HT1B receptors in both prefrontal cortex and hippocampus.

Conclusion: The administration of either ibuprofen or celecoxib along with fluoxetine attenuated the antidepressant activity of fluoxetine in the behavioral despair tests, p11 protein and staining of 5HT1B receptors in the BCG-model of depression.

Key words: depression; BCG; fluoxetine; ibuprofen; celecoxib; p11; TNF-α; 5HTR1B; FST; TST. **Abbreviations:** NSAIDs: non-steroidal anti-inflammatory drugs; FST: forced swim test; TST: tail suspension test.