



Behavioral and Neurochemical Effects of Repeated Exposure to Low Doses of Bacterial Lipopolysaccharide 'LPS' in Wistar Rats Reversibility by Imipramine and Pentoxifylline

Thesis

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ABSTRACT

Background: Multiple evidences suggest that acute immune challenge by bacterial lipopolysaccharide (LPS) causes short-term depression-like behavior. The present study sought to examine the hypothesis that repeated challenge by low doses of LPS followed by exposure to chronic mild stress (CMS) might induce behavioral, biochemical, neurochemical changes that are comparable to those induced by CMS in a trial to develop a new animal model. **Methods:** Male Wistar rats were divided into these groups; Group I control (saline i.p.), Group II exposed to repeated LPS (50 µg/kg i.p.) over 2 weeks then examined, Group III exposed LPS over 2 week and left 4 weeks, Group IV exposed to CMS protocol for 4 weeks, Group V exposed to LPS over 2 weeks then 4 weeks CMS. The last 3 groups were examined at the end of 6th week. The sixth group was exposed to LPS over 2 weeks in concomitant with 4 weeks CMS then examined. Another 2 groups were exposed to LPS-then-CMS and treated with either tricyclic antidepressant (imipramine) or anti-TNF- α (pentoxifylline). Rats were examined for behavioral, biochemical, neurochemical and gene expression changes. **Results:** Animals exposed to LPS-then-CMS elaborated depressive-like symptoms compared to other schemes. LPS-then-CMS model showed significant increase in both serum corticosterone and TNF- α level compared to saline

group as well as groups for CMS model alone and LPS injections alone. Hippocampal kynurenine/tryptophan molar ratio and TNF- α gene expression showed significant increase in the LPS-then-CMS model compared to saline, LPS or CMS groups. Chronic treatment with imipramine or pentoxifylline could reverse behavioral, biochemical, neurochemical and gene expression changes induced by LPS-then-CMS protocol. **Conclusion:** This study gives a clue to the neurobiological processes underlying at least subtypes of depressive disorders. It highlights the possible interaction between stress and immune-inflammatory pathways in the pathogenesis of depression and suggests an animal model that addresses these pathways.

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LIST OF CONTENTS

	Page
Abstract.....	i
List of Tables	iv
List of Figures.....	vii
List of Abbreviations.....	x
Introduction & Aim of the work	1
Review of Literature	6
Materials and Methods	29
Results	73
Discussion.....	122
Summary & Conclusion.....	146
References.....	157
Arabic summary	

LIST OF TABLES

Table no.	Title	Page no.
1	Modified CMS protocol.....	39
2	Kynurenine & tryptophan calibration curve concentrations points.....	55
3	Within-day and between-day retention time means of kynurenine (KYN) and tryptophan (TRP)	57
4	Within-day precision for kynurenine (KYN) and tryptophan (TRP) concentrations, precision is expressed as coefficient of variation.....	58
5	Between-day precision for kynurenine (KYN) and tryptophan (TRP) concentrations, precision is expressed as coefficient of variation.	59
6	Effects of exposure of Wistar rats to single intraperitoneal (<i>i.p.</i>) injection of lipopolysaccharide (LPS) in a dose of 250 µg/kg on the immobility time in the forced swim test (FST) and active social interaction time in the social interaction test (SIT)	76
7	Effects of exposure of Wistar rats to repeated (<i>i.p.</i>) injections of different lipopolysaccharide (LPS) doses (LPS 25 µg/kg, LPS 50 µg/kg and LPS 100 µg/kg) on the immobility time in the forced swim test (FST) and active social interaction time in the Social interaction test (SIT).....	79
8	Effects of exposure of Wistar rats to repeated <i>i.p.</i> injections of LPS and CMS protocol either alone or in combination on Immobility time in the forced swim test (FST) and active social interaction time in the social interaction test (SIT)	82
9	Effects of exposure of Wistar rats to repeated <i>i.p.</i> injections of LPS and CMS protocol either alone or in combination on the open field test (OFT) parameters (number of crossed squares, frequency of rearing and of grooming)	85

Table no.	Title	Page no.
10	Effect of exposure of Wistar rats to repeated <i>i.p.</i> injections of LPS and CMS protocol either alone or in combination on body weight gain.....	89
11	Effects of exposure of Wistar rats to repeated <i>i.p.</i> injections of LPS and CMS protocol either alone or in combination on serum level of corticosterone and TNF- α	92
12	Effects of exposure of Wistar rats to repeated <i>i.p.</i> injections of LPS and CMS protocol either alone or in combination on tryptophan molar concentration, kynurenine molar concentration and kynurenine/tryptophan molar ratio (KYN/TRP) in hippocampus brain homogenates	95
13	Effects of exposure of Wistar rats to repeated <i>i.p.</i> injections of LPS and CMS protocol either alone or in combination on TNF- α gene expression by (RT-PCR) in hippocampus brain homogenates.....	99
14	Effects of imipramine (20 mg/Kg/day for 4 weeks) and pentoxiphylline (100 mg/Kg/day for 6 weeks) on immobility time in FST, on time of active social interaction in SIT in Wistar rats exposed to LPS-then-CMS model	102
15	Effects of imipramine (20 mg/Kg/day for 4 weeks) and pentoxiphylline (100 mg/Kg/day for 6 weeks) on the on the open field test (OFT) parameters (number of crossed squares, frequency of rearing and of grooming) in Wistar rats exposed to LPS-then-CMS model.....	105
16	Effect of imipramine (20 mg/Kg/day for 4 weeks) and pentoxiphylline (100 mg/Kg/day for 6 weeks) on the body weight gain in Wistar rats exposed to LPS-then-CMS model.....	108
17	Effects of imipramine (20 mg/Kg/day for 4 weeks) and pentoxiphylline (100 mg/Kg/day for 6 weeks) on serum level of corticosterone and TNF- α in Wistar rats exposed to LPS-then-CMS model.....	111

Table no.	Title	Page no.
18	Effects of imipramine (20 mg/Kg/day for 4 weeks) and pentoxiphylline (100 mg/Kg/day for 6 weeks) on tryptophan molar concentration, kynurenine molar concentration and kynurenine/tryptophan molar ratio (KYN/TRP) in hippocampus brain homogenates of Wistar rats exposed to LPS-then-CMS model.....	114
19	Effects of imipramine (20 mg/Kg/day for 4 weeks) and pentoxiphylline (100 mg/Kg/day for 6 weeks) on TNF- α gene expression by (RT-PCR) in hippocampus brain homogenates of Wistar rats exposed to LPS-then-CMS model.....	118

LIST OF FIGURES

Fig. no.	Title	Page no.
1	Genetic and environmental impacts on tryptophan metabolism.....	10
2	Overview of the tryptophan catabolite (TRYCAT) pathway.....	15
3	The tryptophan catabolites (TRYCATs) pathway and indoleamine 2,3-dioxygenase (IDO) and their interconnections with peripheral and central immune, inflammatory pathways	24
4	Flow Chart for the Study Design	32
5	HPLC-UV determination of kynurenine and tryptophan in a hippocampus homogenate.....	56
6	Calibration curves of kynurenine (KYN) and tryptophan (TRP).	61
7	Effects of exposure of Wistar rats to single intraperitoneal (<i>i.p.</i>) injection of LPS in a dose of 250 µg/kg.....	77
8	Effect of exposure of Wistar rats to repeated <i>i.p.</i> injections of different doses of LPS (LPS 25 µg/kg, LPS 50 µg/kg and LPS 100 µg/kg).....	80
9	Effects of exposure of Wistar rats to repeated <i>i.p.</i> injections of LPS and CMS protocol either alone or in combination, immobility time in the forced swim test (FST) and active social interaction time in social interaction test (SIT).....	83
10	Effects of exposure of Wistar rats to repeated <i>i.p.</i> injections of LPS and CMS protocol either alone or in combination on the open field test (OFT) parameters	86

Fig. no.	Title	Page no.
11	Effects of exposure of Wistar rats to repeated <i>i.p.</i> injections of LPS and CMS protocol either alone or in combination on the sucrose consumption percent change.	87
12	Effects of exposure of Wistar rats to repeated <i>i.p.</i> injections of LPS and CMS protocol either alone or in combination on body weight gain.....	90
13	Effect of exposure of Wistar rats to repeated <i>i.p.</i> injections of LPS and CMS protocol either alone or in combination on serum level of corticosterone and TNF- α	93
14	Effects of exposure of Wistar rats to repeated <i>i.p.</i> injections of LPS and CMS protocol either alone or in combination on tryptophan molar concentration, kynurenine molar concentration and kynurenine/tryptophan molar ratio	96
15	Ethidium bromide-stained agarose gel electrophoresis showing the amplified RT-PCR products of TNF- α and β -actin as an internal standard, from hippocampus brain homogenates of Wistar rats	98
16	Effects of exposure of Wistar rats to repeated <i>i.p.</i> injections of LPS and CMS protocol either alone or in combination on TNF- α gene expression by (RT-PCR) in hippocampus brain homogenates.....	100
17	Effects of imipramine (20 mg/Kg/day for 4 weeks) and pentoxiphylline (100 mg/Kg/day for 6 weeks) on immobility time in the forced swim test (FST) and active social interaction time in social interaction test (SIT).....	103
18	Effects of imipramine (20 mg/Kg/day for 4 weeks) and pentoxiphylline (100 mg/Kg/day for 6 weeks) on the open field test (OFT) parameters	106
19	Effects of imipramine (20 mg/Kg/day for 4 weeks) and pentoxiphylline (100 mg/Kg/day for 6 weeks) on the sucrose consumption percent change.	107

Fig. no.	Title	Page no.
20	Effect of imipramine (20 mg/Kg/day for 4 weeks) and pentoxiphylline (100 mg/Kg/day for 6 weeks) on body weight gain in Wistar rats exposed to LPS then CMS	109
21	Effects of imipramine (20 mg/Kg/day for 4 weeks) and pentoxiphylline (100 mg/Kg/day for 6 weeks) on serum level of corticosterone and TNF- α	112
22	Effects of imipramine (20 mg/Kg/day for 4 weeks) and pentoxiphylline (100 mg/Kg/day for 6 weeks) on tryptophan molar concentration, kynurenine molar concentration and kynurenine/tryptophan molar ratio	115
23	Ethidium bromide-stained agarose gel electrophoresis showing the amplified RT-PCR products of TNF- α (122bp) and β -actin (289bp) as an internal standard, from hippocampus brain homogenates of Wistar rats	117
24	Effects of imipramine (20 mg/Kg/day for 4 weeks) and pentoxiphylline (100 mg/Kg/day for 6 weeks) on TNF- α gene expression by (RT-PCR) in hippocampus brain homogenates	119

LIST OF ABBREVIATIONS

3-OHKYN	3-hydroxykynurenine
5-HT	serotonin
BDNF	Brain derived neurotrophic factor
CMS	Chronic mild stress
CS	Corticosteroids
ELISA	Enzyme Linked Immunosorbant Assay
FB	Foreign body
FD	Food deprivation
FST	Forced swim test
FWD	Food deprivation
HPA-axis	Hypothalamic-pituitary-adrenal axis
HPLC-UV	High Performance Liquid Chromatography- Ultraviolet
<i>i.p.</i>	intraperitoneal
IDO	Indoleamine 2, 3 dioxygenase
IFN- γ	Interferon-gamma
IFN-α	Interferon-alpha
IL-1	Interleukin-1
IL-10	Interleukin-10
IL-13	Interleukin-13
IL-1β	Interleukin-1 β
IL-2	Interleukin-2
IL-4	Interleukin -4
IL-6	Interleukin-6
IMD	Intestinal mucosal dysfunction
IMP	Imipramine
IS	Internal standard
KYN	Kynurenine
KYNA	Kynurenic acid
LPS	lipopolysaccharide
MAOIs	Monoamino -oxidase inhibitors
MDD	Major depressive disorder

NMDA	N-methyl-D-aspartate
NO	Nitric oxide
OFT	Open field test
PTX	Pentoxifylline
QUIN	Quinolinic acid
RT-PCR	Reverse Transcriptase-Polymerase Chain Reaction
SIT	Social interaction test
SPT	Sucrose preference test
SSRI	Selective serotonin reuptake inhibitor
SSRIs	Selective serotonin reuptake inhibitors
TCA	Tricyclic antidepressant
TCAA	Trichloroacetic acid
TDO	Tryptophan 2, 3-dioxygenase
TNF-R1	TNF- α receptor type 1
TNF-R2	TNF- α receptor type 2
TNF-α	Tumor necrosis factor alpha
TRP	Tryptophan
TRYCATs	Tryptophan catabolites
WD	Water Deprivation
WHO	World Health Organization