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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التاثير السلوكى والكيميائى- العصبي للتعرض المتكرر لجرعات صغيرة من الليبوبوليسكاريد المستخلص من البكتيريا فى فئران الويستر وقابليتها للا نعكاس بالإيمبرامين و البنتوكسيفيللين

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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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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.p.	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-1β
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	Pentoxyphylline
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