Lipopolysaccharide aggravates the restraint stress-induced behavioral deficits and hippocampal damage: Effect of Fisetin treatment

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Introduction
Neuropsychiatric disorders like depression, anxiety, and dementia in humans often coexist together in certain medical conditions such as cancer, cardiovascular diseases, neurodegenerative disease which decreased the quality of life in patients and increase rate of mortality.

Numerous reports provided insights for implications of chronic restraint stress and lipopolysaccharide (LPS) results in hippocampal neuronal damage and various neurobehavioral anomalies in rodents [1, 2].

In this present study, we have tried to establish a model where 28 days chronic restraint stress mediated neurobehavioral and neurochemical changes got aggravated by a single dose of LPS triggering various neuroinflammatory cascade resulting hippocampus neuronal damage.

We further investigated the effect of Fisetin (3, 7, 3’, 4’-tetrahydroxyflavone) flavonol in preventing the restraint stress (RS) exposure and lipopolysaccharide (LPS) treatment induce neurobehavioral deficits and hippocampal damage.

Methods
All experiments were performed in accordance with the CPCSEA, Government of India guidelines. Adult male Swiss albino mice (25–30 g) were divided into following experimental groups:
Group 1: No stress/no LPS normal control
Group 2: Restraint stress exposure for 6 h per day for 28 days (RS).
Group 3: LPS injected (0.83 mg/kg, i.p.) on the 28th day (LPS control).
Group 4: Restraint stress (6 h per day) and LPS injected (0.83 mg/kg, i.p.) on the 28th day (RS + LPS).
Group 5: Restraint stress (6 h per day) and Fisetin (15 mg/kg, p.o.) treatment from 15th to 28th day.
Group 6: Fisetin (15 mg/kg, p.o.) treatment from 15th to 28th day and LPS injected (0.83 mg/kg, i.p.) on the 28th day.
Group 7: Restraint stress (6 h per day for 28 days) and LPS injected (0.83 mg/kg, i.p.) on the 28th day; and Fisetin (15 mg/kg, p.o.) treatment for last 14 days.

Hypothesis
Fisetin (3, 7, 3’, 4’-tetrahydroxyflavone) flavonol in preventing the restraint stress (RS) exposure and lipopolysaccharide (LPS) treatment induce neurobehavioral deficits and hippocampal damage.

Illustration of the study plan
Restraint Stress (6 h per day) → LPS (0.83 mg/kg, i.p.) → Test for Depressive-like behavior → Forced Swim Test → Tail Suspension Test → Reverse transcriptase PCR (RT-PCR) expression → Biochemical estimations → Hippocampal section → Biochemical estimations → Biochemical estimations → Biochemical estimations

Results
1. Effect of Fisetin on Restraint stress and LPS induced learning and memory function impairment

2. Effect of Fisetin on Restraint stress and LPS induced anxiety-like behavior in mice

3. Effect of Fisetin on Restraint stress and LPS induce depressive-like behavior in mice

4. Effect of Fisetin treatment on Restraint stress and LPS modulated hippocampal gene expression levels

Conclusions
The combined paradigm of restraint stress and lipopolysaccharide represented behavioral deficits and hippocampal damage. Fisetin treatment significantly ameliorates the altered neurobehavioral and neurochemical alterations via inhibition of oxido-restractive stress and neuroinflammation through restoring of dysregulated inflammatory mediators gene expression level.

References

Disclosure: No potential conflict of interest.

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Presentations at the Conferences (National and International)
1. Jangra A presented under the theme "Pharmaceutical research" in International R&D conference on Overcoming the Bottlenecks in Drug Discovery and Development which was held in Gurgaon, Haryana, India from 29-31 March 2014 organized by "The Royal Society of Chemistry (RSC), Dalichi Sankyo India Pharma Private Limited (DSI) and Ranbaxy Laboratories Limited (RLL)". Entitled: Determination of biochemical-behavioral cross talk and ameliorative effect of Naringin in doxorubicin-induced neurotoxicity in rats.

2. A oral presentation and poster presentation was in "The 38th Annual Japanese Neurosciences Meeting, Port Island, Kobe, Japan" in which I was assigned as co-author. Work entitled "1,5-Isoquinolinolphtalein Ameliorates Chemically-Induced Deficits in Rats Fed High Fat Diet via Inhibition of Poly (ADP-Ribose) Polymers-1 Activation" Ashok Jangra, SR Chandrashker, Mohit Kwarthra, Babul Kumar Bezbaurah, Mangala Lahkar


5. Poster presentation entitled as "PPAR-y agonist Pioglitazone exerts its neuroprotective effect in Reserpine induced Parkinson- depression triads by evaluating the endoplasmic reticulum stress markers and mitochondrial cytochrome levels in rat brain" Sahabuddin Ahmed, Niyamand Bofshette, Mohit Kwarthra, Awassuddin Ahmed, Yogita Sharma. (Abstract accepted) in the 14th Meeting of the Asia-Pacific Society for Neurochemistry (APSN) 2016 held from 27th – 30th August 2016 at Kuala Lumpur, Malaysia. The abstract was published in the supplementary issue of journal "Frontiers of Cellular Neurobiology"

6. An Oral Presentation entitled as "Prenyl alcohol ameliorated restraint stress-induced neurochemical deficits in mice: prevention of neuroinflammation cascade in the hippocampus" will be given on the 49th Annual conference of Indian Pharmaceutical Society (IPSCON) 2016 on 20th-23rd Oct 2016 to be held at PIMMER, Chandigarh, India.