

Pharmacological Reversal of LPS-Induced Cognitive Impairments: Evidence for Inflammation-Dependent and Independent Mechanisms

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Background:

Chronic, low-grade peripheral inflammation—often driven by gut microbiota dysbiosis—has emerged as a key contributor to neuroinflammation and cognitive decline in neurodegenerative diseases like Alzheimer's and Parkinson's. Lipopolysaccharide (LPS) administration in rodents serves as a robust model for mimicking peripheral inflammation that impacts the brain, leading to microglial activation and memory impairments. Identifying effective pharmacological strategies that target different aspects of this inflammatory cascade is essential for therapeutic development.

Objective

To evaluate the therapeutic efficacy of 17 pharmacological agents—spanning anti-inflammatory, antioxidant, synaptic, metabolic, and kinase signaling mechanisms—in reversing LPS-induced cognitive deficits in mice.



Material and Methods

Animal model:

CD-1 male mice were used to model inflammation-induced cognitive impairment.

Induction of Cognitive Deficits:

A single i.p. injection of LPS (0.25 mg/kg) was administered to induce persistent, non-septic systemic inflammation leading to cognitive deficits lasting up to three weeks.

Treatment Protocol:

Mice were treated daily for 1 or 2 weeks with one of 17 candidate compounds following LPS administration.

Behavioral Assessment:

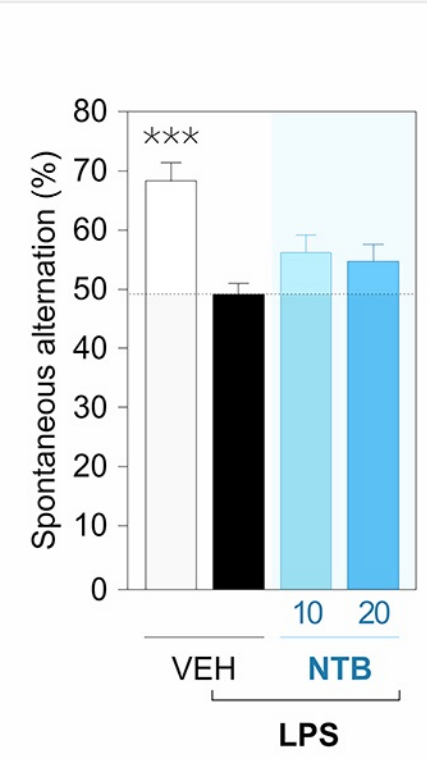
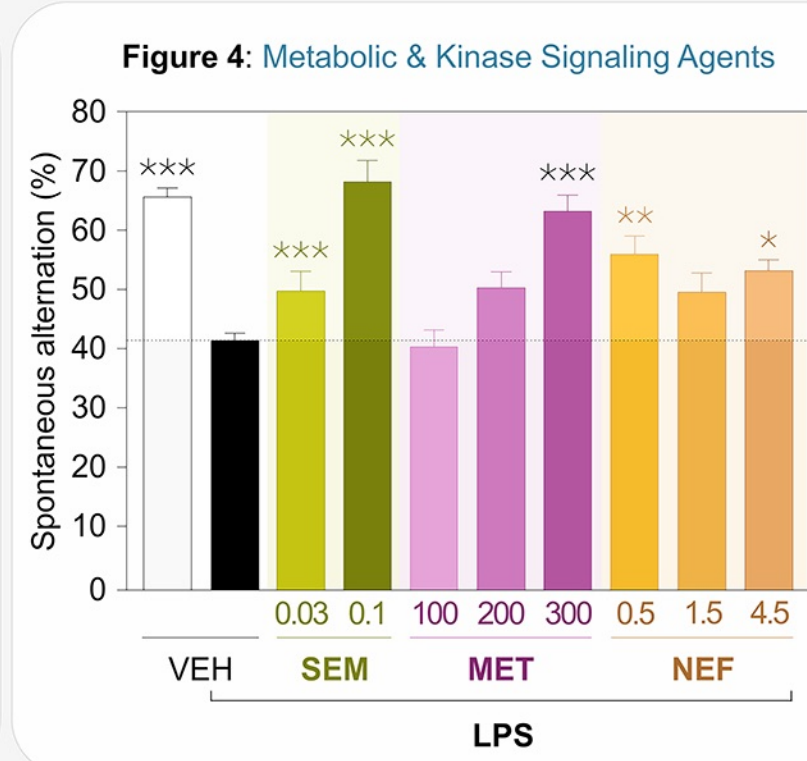
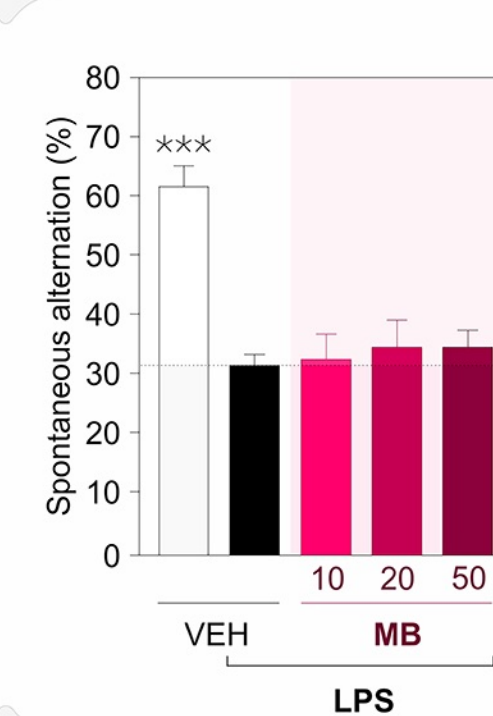
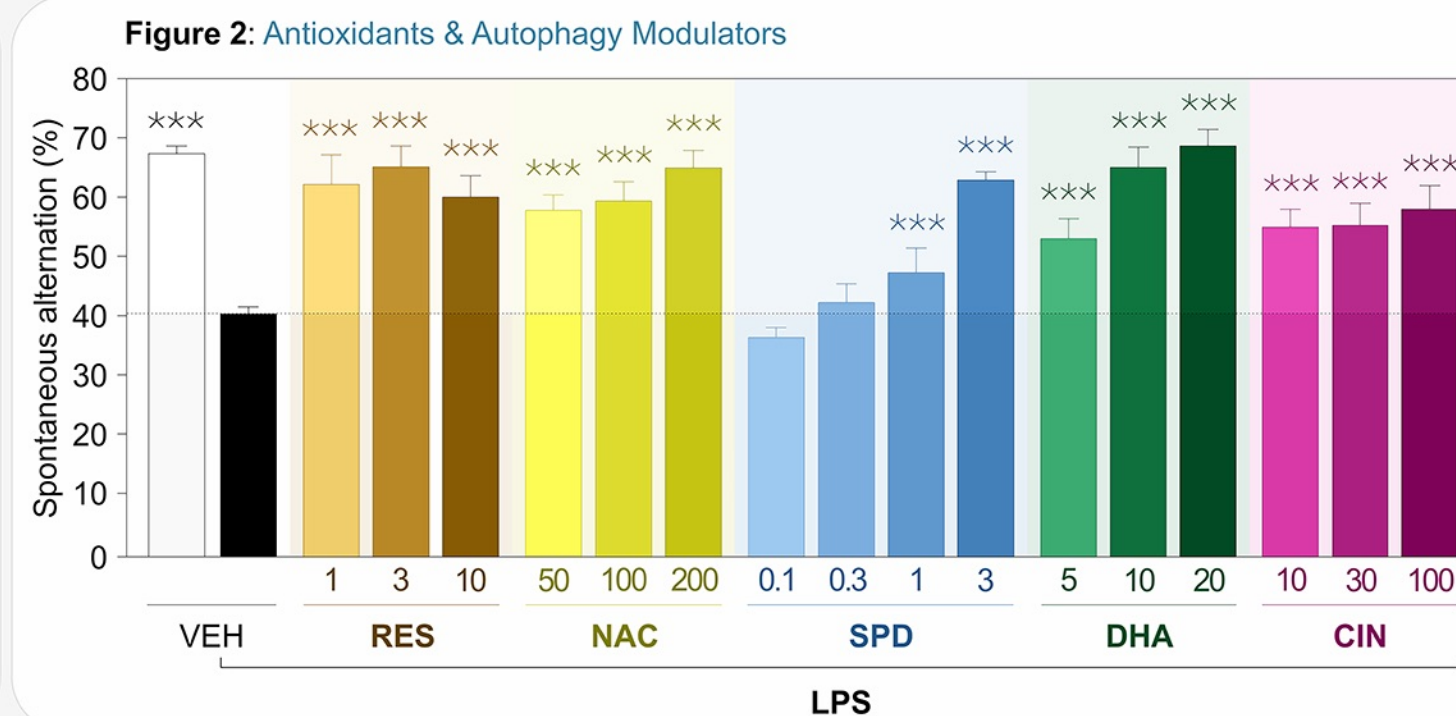
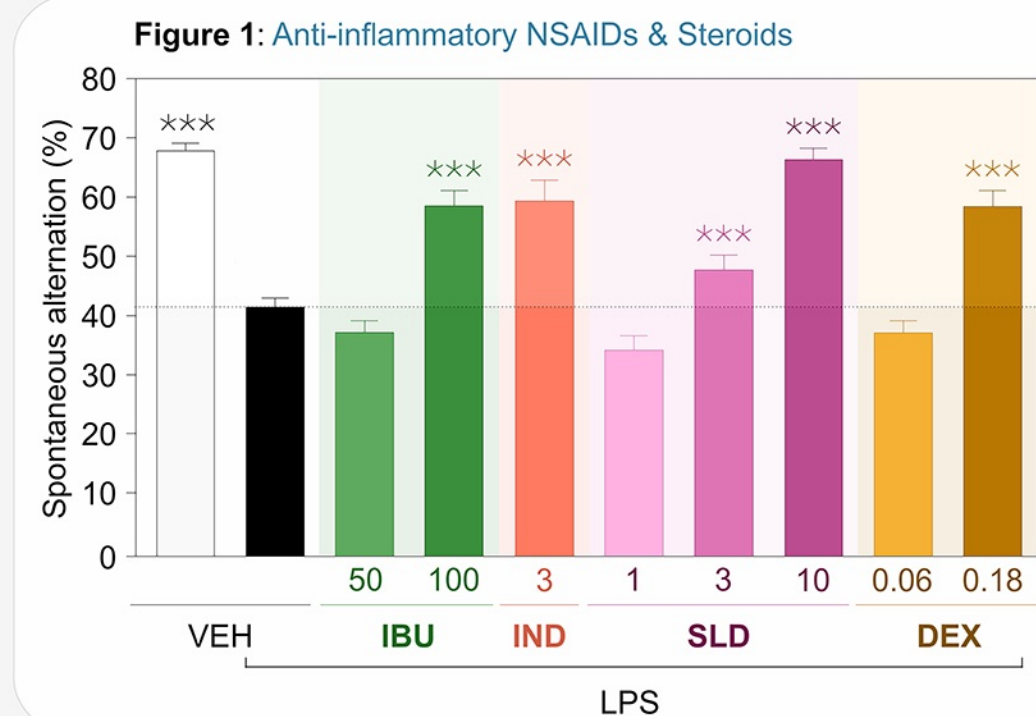
Cognitive performance was evaluated using the T-maze spontaneous alternation task after the treatment protocol.

Outcome Measure:

The percentage of spontaneous alternation was recorded as an index of cognitive performance.

Results

* indicates the level of statistical difference as compared LPS / Vehicle group



Abbreviations

- VEH : Vehicle
- IBU : Ibuprofen
- IND : Indomethacine
- SLD : Sulindac
- DEX : Dexamethasone
- RES : Resveratrol
- NAC : N-AcetylCysteine
- SPD : Spermidine
- DHA : DocosaHexaenoic Acid
- CIN : Cinnamaldehyde
- MB : Methylene blue
- MEM : Memantine
- DPZ : Donepezil
- GRN : GRN-529
- SEM : Semaglutide
- MET : Metformine
- NEF : Neflamapimod
- NTB : Nilotinib

Conclusion



This study demonstrates that reversing LPS-induced cognitive impairments is possible via multiple pharmacological mechanisms. Effective agents clustered into four categories: anti-inflammatory, antioxidant/autophagy, synaptic modulators, and metabolic/kinase signaling modulators.

The efficacy of synaptic modulators highlights a potential inflammation-independent route for cognitive recovery.

Meanwhile, the ineffectiveness of nilotinib and methylene blue underscores the importance of targeted mechanism engagement and validates the model's capacity for pharmacological discrimination.