Cognitive impairment induced by systemic inflammation in mice

Emile Andriambeloson, Bertrand Huyard, Etienne Poiraud, Fabien Lauga, Cindy Neveu and Stephanie Wagner

NEUROFIT SAS, 850 boulevard Sébastien brant - Bioparc 1
Parc d'Innovation, 67400 Illkirch-Graffenstaden, FRANCE www.neurofit.com

NEUROFIT
PRECLINICAL RESEARCH

Introduction

Cognitive impairment and dementia are disabling conditions that are increasingly common in ageing population. Evidence available suggests association between chronic low-grade systemic inflammation and cognitive decline in the aged and vulnerable brains. An increased brain level of pro-inflammatory cytokines appears as a significant driver of cognitive impairment.

Objective

The present study was conducted to characterize the potential cognitive impairment in mice following induction of low-grade systemic inflammation through an administration of a single non-septic dose of lipopolysaccharide (LPS). Notably, the time course of cognitive decline and the potential symptomatic effect cognitive enhancers and anti-inflammatory drugs were investigated.

Material and Methods

Animal testing and measure of cognitive function

Male CD-1 mice were used for the study and received a single intraperitoneal injection of 0.25 mg/kg of LPS. At different timepoints (7, 14 and 21 days post-LPS), they were assessed for their spontaneous alternation in the T-maze. Spontaneous alternation is the innate tendency of rodents to alternate free choices in a T-maze over a series of successive runs. This sequential procedure is sensitive to various pharmacological manipulations affecting the cognitive processes.

Measure of pro-inflammatory mediators in the hippocampus

The hippocampus was harvested from naïve and LPS-treated mice at 4, 7 and 24h post-LPS injection. The amount of nitric oxide (NO), tumor necrosis factor α (TNF-α) and interleukin 1β (IL-1β) in the hippocampus samples was assessed. NO content was measured by Griess reaction. TNF-α and IL-1β were measured by their respective ELISA kits.

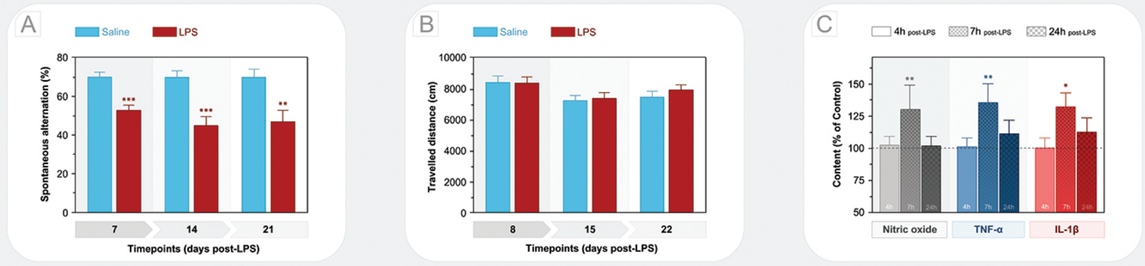
Drug treatments

Immediately after the LPS injection, different treatments aiming at preventing the development of cognitive deficit were undertaken. Cognitive enhancer drugs (donepezil and memantine) and anti-inflammatory drugs (dexamethasone and ibuprofen) were used. Treatment was conducted subchronically once daily until the timepoint at which the cognitive performance was evaluated in the T-maze. In some set of experiments, the cognitive performance of mice was reassessed 1 week after the cessation of subchronic treatment.

The **T-maze** apparatus is made of gray Plexiglas with **a main stem** (55 cm long × 10 cm wide × 20 cm high) and **two arms** (30 cm long × 10 cm wide × 20 cm high) positioned at 90 degree angle relative to the main stem. A **start box** (15 cm long × 10 cm wide) is separated from the main stem by a guillotine door. Horizontal doors are also provided to close specific arms during the force choice alternation task.

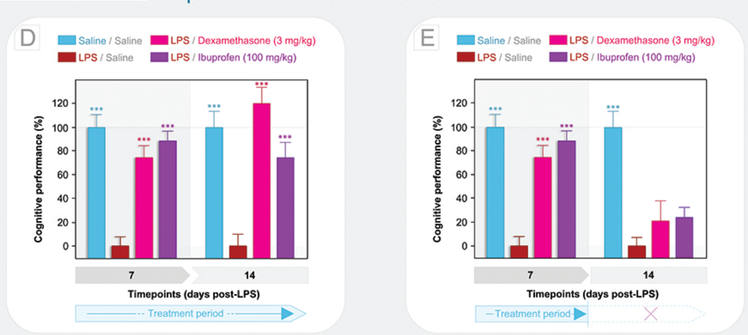
Results

Figure 1 : LPS challenged mice demonstrate sustained cognitive deficit and transient increase in brain pro-inflammatory mediators whilst showing virtually normal general behavior



Mice challenged with LPS showed cognitive deficit (A) as assessed by a reduced spontaneous alternation in the T-maze. Their general behavior as assessed by the travelled distance in the open-field test (B) remained comparable to that of naïve mice. LPS mice showed a transient increase in the pro-inflammatory mediators (C) in the hippocampus (100% refers to the control level).

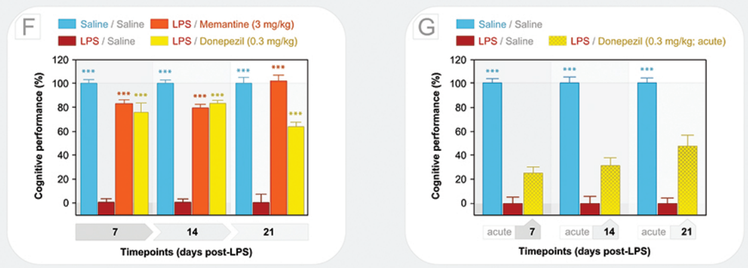
Figure 2 : LPS-induced cognitive deficit is reversed by subchronic anti-inflammatory treatment but it relapses upon withdrawal of the treatment



Subchronic treatment for 7 or 14 (D) consecutive days with anti-inflammatory drugs (dexamethasone or ibuprofen) fully suppressed LPS-induced cognitive deficit.

However, the deficit relapsed on day 14 upon withdrawal of anti-inflammatory treatment on day 7 (E) which suggests the presence of persistent inflammatory process several days after the injection of LPS.

Figure 3 : LPS-induced cognitive deficit is reversed by subchronic treatment with cognitive enhancers



Subchronic treatment (F) with cognitive enhancer drugs (donepezil or memantine) markedly reversed the cognitive deficit. Acute treatment with donepezil (G) appeared insufficient to significantly restore the cognitive function which may suggest an insufficient drug exposure.

Key points

- Non-septic dose of LPS induces an inflammatory-driven cognitive deficit in mice.
- The model favorably responds to anti-inflammatory drugs but promptly relapses upon withdrawal of the treatment.
- The model favorably responds to cognitive enhancing drugs.