An inflammation induced by lipopolysaccharide causes the death of neuronal cultures and produces *in-vivo* brain dysfunction: The preventive effect of dexamethasone

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NEUROFIT PRECLINICAL RESEARCH

Introduction

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

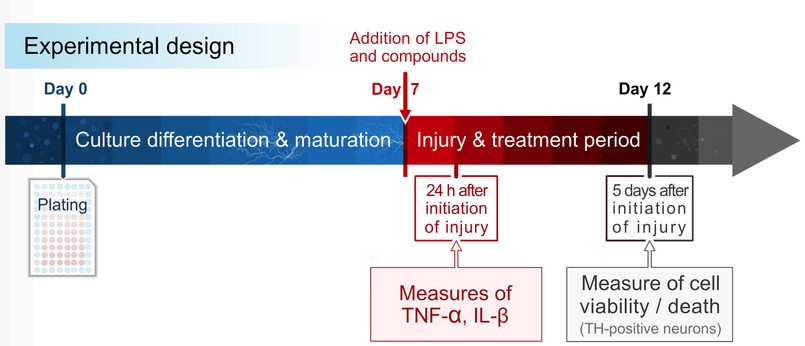
Objective

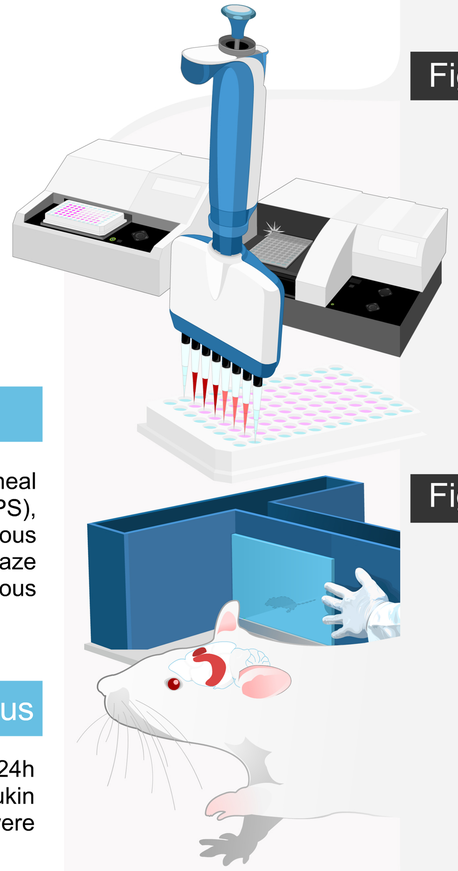
In the present study, the effect of the immunosuppressive drug, dexamethasone, was evaluated to characterize the inflammatory cytokines and neuronal damage following LPS stimulated cocultures of glia-neuron.
The same approach was carried out *in-vivo* to ascertain the role of inflammation in LPS-induced cognitive deficiency in mice.

Material and Methods

Cellular model of brain inflammation

Glia neuron culture from the mesencephalic brain of rat embryos (day 15 of gestation).





Animal testing and measure of cognitive function

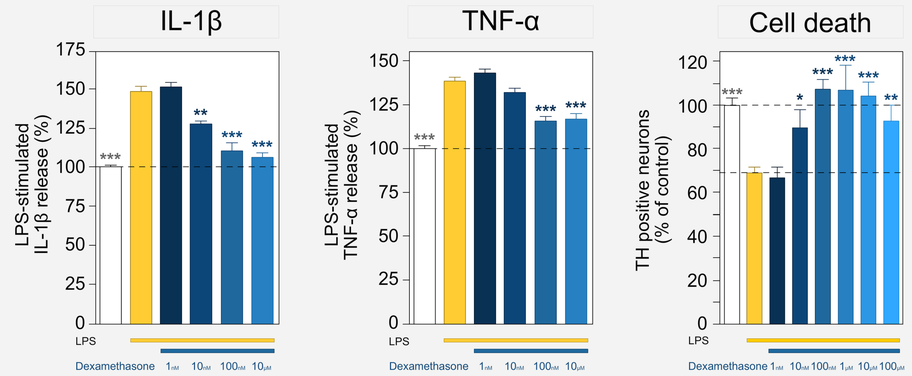
Male CD-1 mice were used for the study and received a single intraperitoneal injection of 0.25 mg/kg of LPS. At different timepoints (7, 14 and 21 days post-LPS), they were assessed for their spontaneous alternation in the T-maze. Spontaneous alternation is the innate tendency of rodents to alternate 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 tumor necrosis factor α (TNF-α) and interleukin 1β (IL-1β) in the hippocampus samples were assessed. TNF-α and IL-1β were measured by their respective ELISA kits.

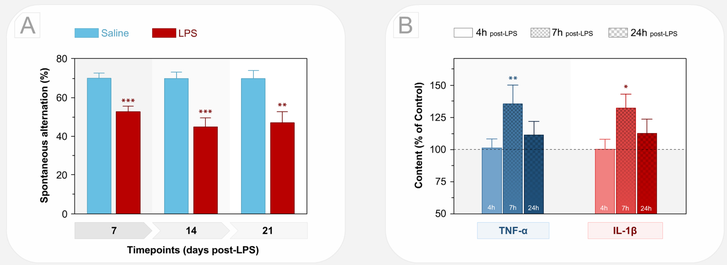
Results

Figure 1: LPS produced a dexamethasone sensitive increase in IL-1β and TNFα and neuronal death.



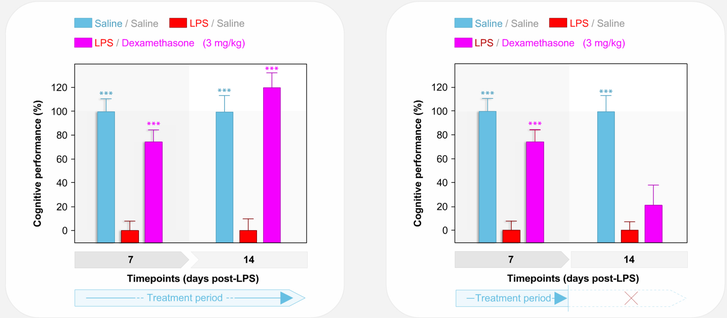
- **Dexamethasone** markedly reduced the release of IL-1β, TNF-α.
- **Dexamethasone** fully prevented LPS-induced neuronal death.

Figure 2: LPS challenged mice demonstrated a sustained cognitive deficit and a transient increase in brain pro-inflammatory mediators (as assessed by a reduced spontaneous alternation in the T-maze).



- Mice challenged with LPS showed cognitive deficit (A) as assessed by a reduced spontaneous alternation in the T-maze.
- LPS mice showed a transient increase in the pro-inflammatory mediators (B) in the hippocampus (100% refers to the control level)

Figure 3: LPS-induced cognitive deficit is reversed by subchronic anti-inflammatory treatment but it relapses upon withdrawal of the treatment.



Key points

These data draw a parallel between **inflammation-associated neuronal death** in microglia / astrocyte / neuron co-cultures and **inflammation-mediated brain dysfunction** *in-vivo*.