



Neuroimmune Basis of Long-term Cognitive Impairment in Bacterial Meningitis

Tatiana Barichello, PhD

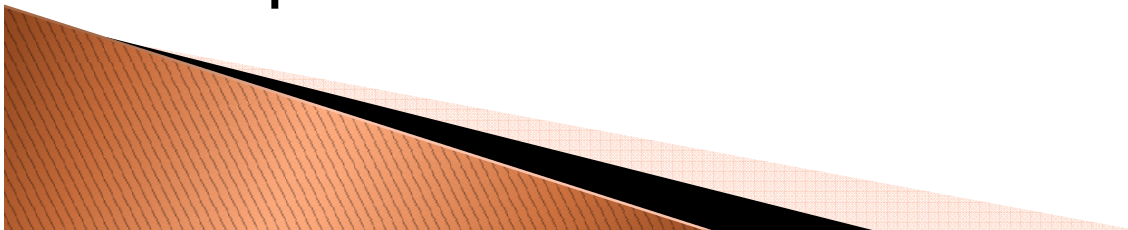
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Outline

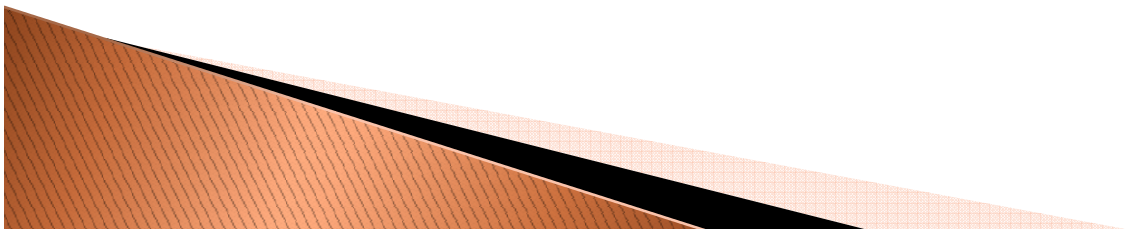
Today I'll talk about:

- ▶ Bacterial traversal of the BBB.
- ▶ Recognition receptors.
- ▶ Second messenger systems.
- ▶ Rodent model of bacterial meningitis.
- ▶ BBB integrity.
- ▶ Cytokines/chemokines.
- ▶ Cognitive impairment.
- ▶ Depressive-like behavior.

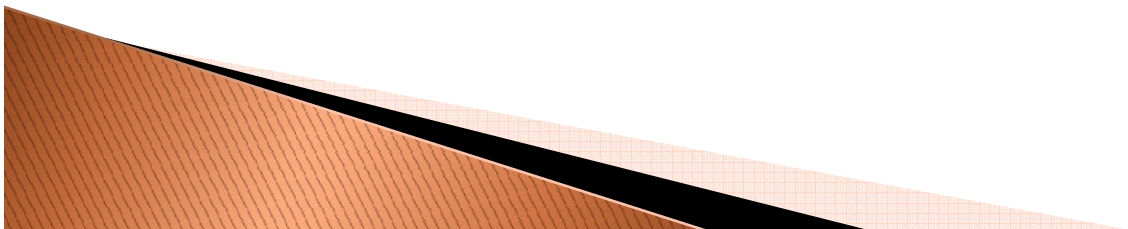


Introduction

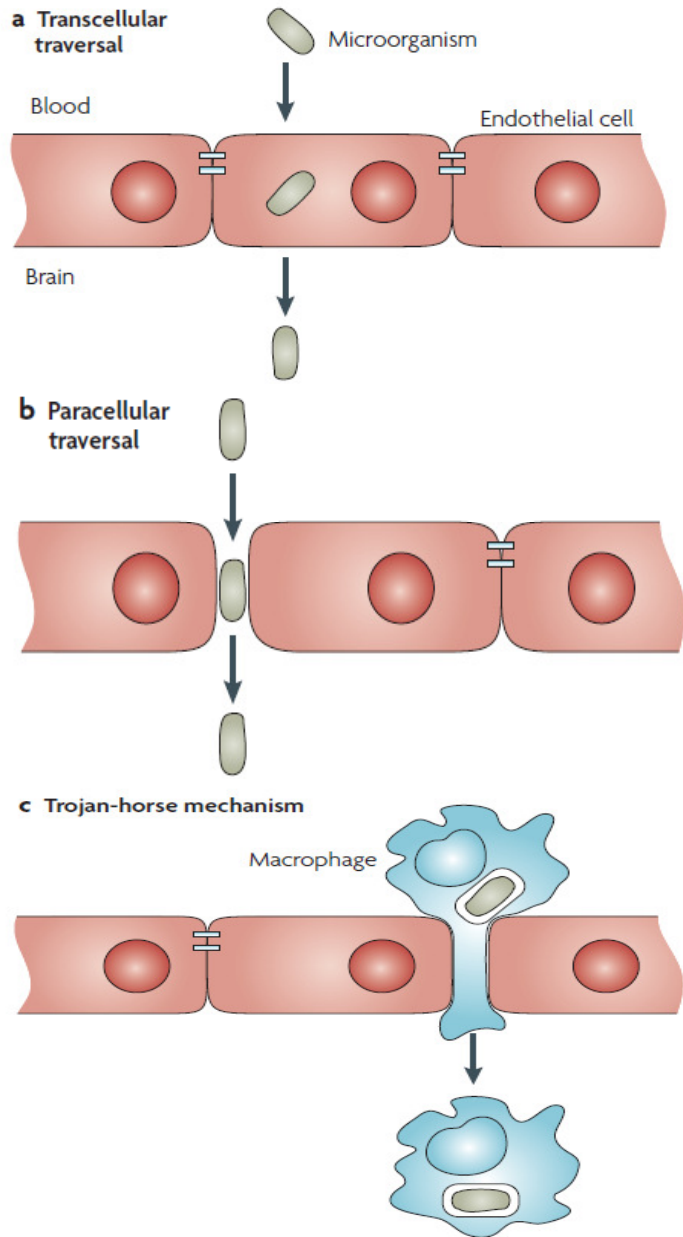
- Meningitis is characterized by acute purulent infection of the meninges affecting the pia mater, the arachnoid and subarachnoid space (van de Beek et al., N Engl J Med, 2006).
- The mortality ranges are from 16 to 37% and neurological sequelae including, hearing loss, focal neurological deficits.
- Cognitive impairment is estimated to occur in 30 to 52% of surviving patients from pneumococcal meningitis (Mook-Kanamori et al., Clin Microbiol Rev, 2011; Nau et al., Expert Rev Anti Infect Ther, 2015).



- Bacterial meningitis during early life was associated with higher depressive and anxiety symptoms, and increased risk of psychotic experiences; **risk ratio 2.22** (Avon Longitudinal Study of Parents and Children (ALSPAC), Khandaker et al., Ann Epidemiol, 2015).
- The risk of impairment from bacterial meningitis is **greater in low-income countries**.
- Africa (**25.1%**), South Asia (**21.6%**), compared with Europe (**9.4%**) (Liechti et al., Fut. Microb. 2015).



Mechanisms of Microbial Traversal of the BBB

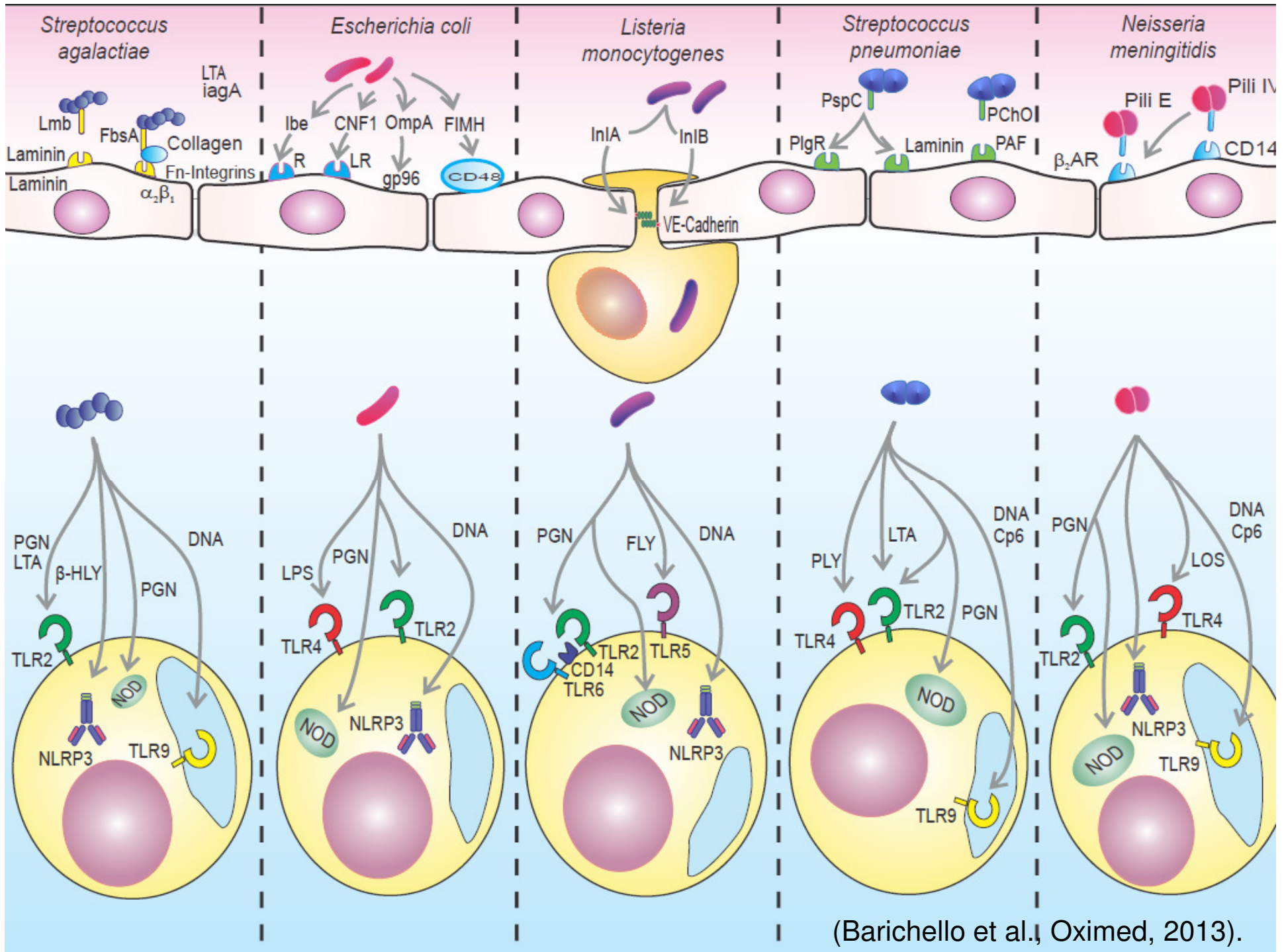


Transcellular traversal, the pathogens cross the BBB without any evidence of intercellular tight-junction disruption.

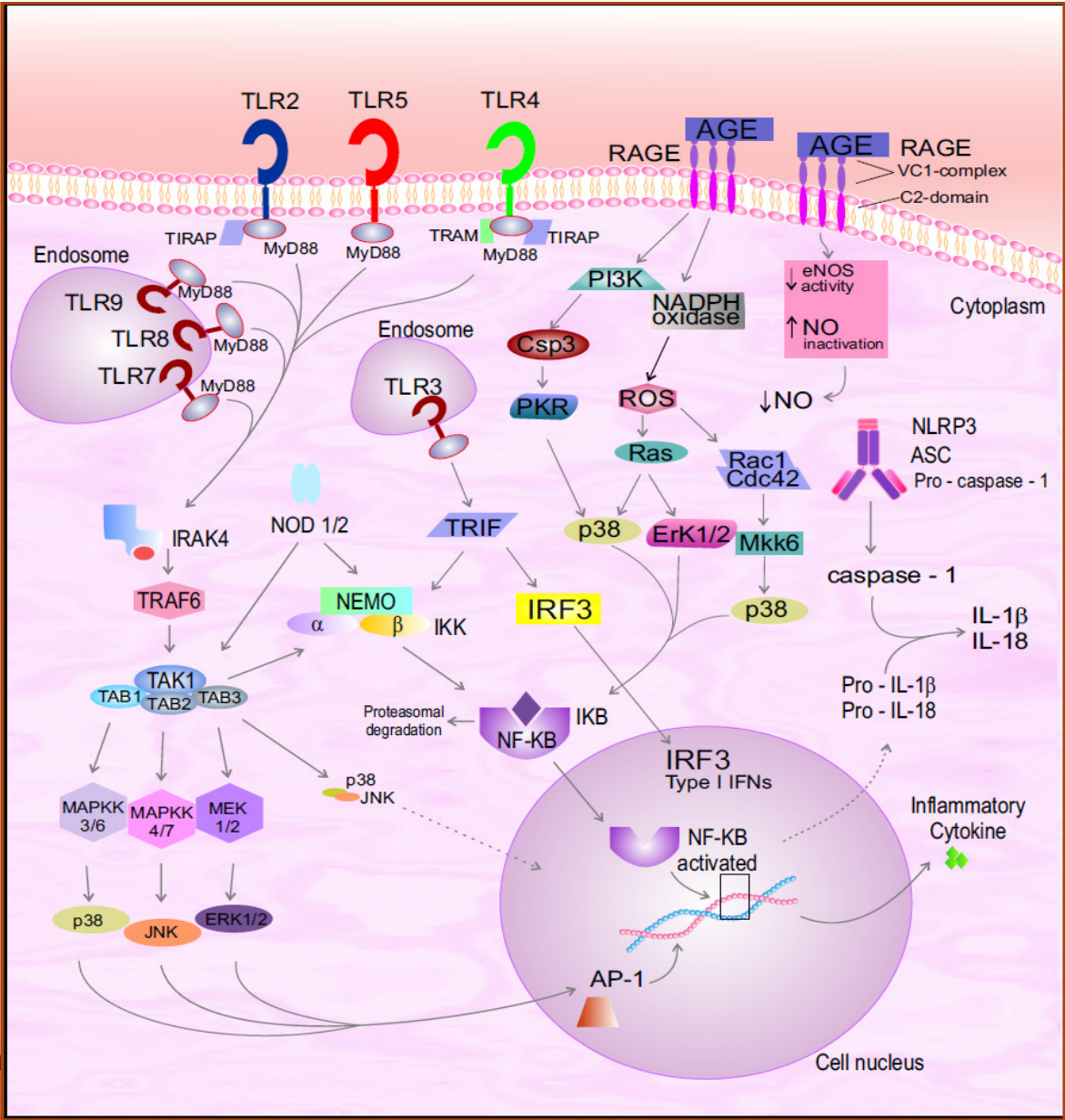
Paracellular traversal involves microbial penetration between BBB cells with and/or without evidence of tight-junction disruption.

The Trojan-horse mechanism involves microbial penetration of BBB cells using transmigration within infected phagocytes.

(Kim, Nat Rev Microbiol, 2010).

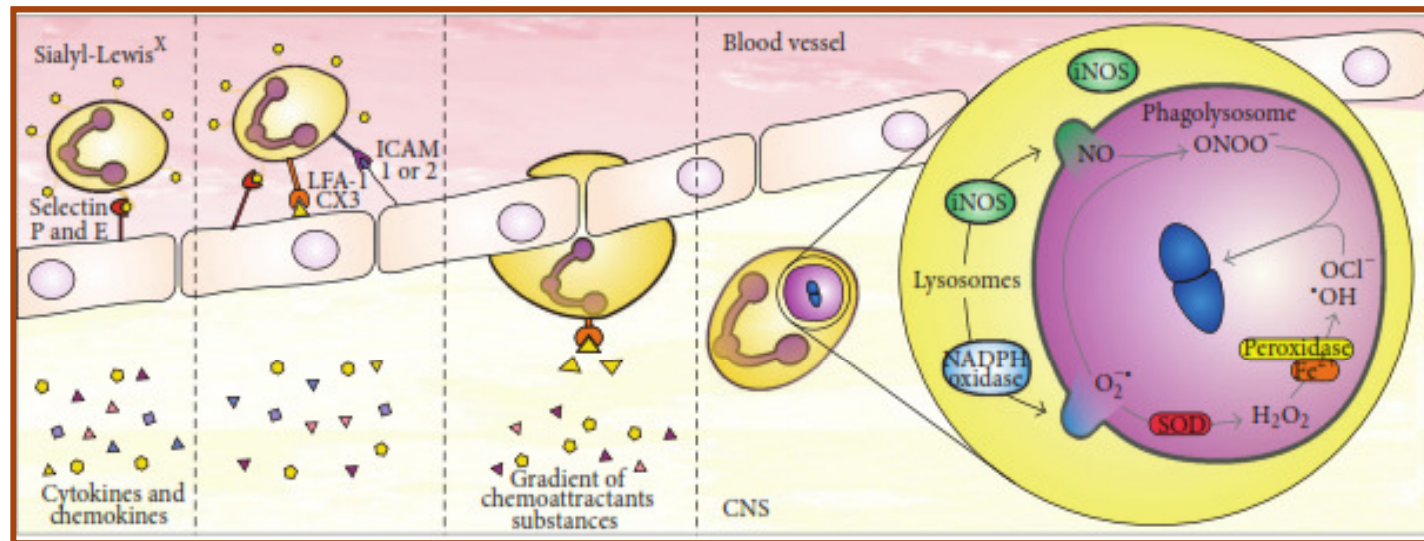


Second messenger systems



(Barichello et al., J Med Microbiol, 2013)

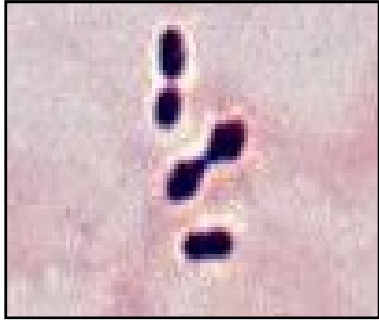
Leukocyte Migration



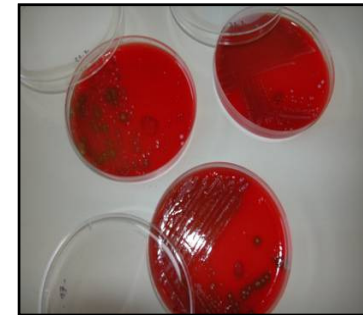
Leukocytes migrate to sites of infection. Sialyl-Lewis^X on leukocytes binds to selectins-P and -E on endothelial cells along a gradient of chemoattractants substances.

(Barichello et al., Oximed, 2013)

Meningitis Induction

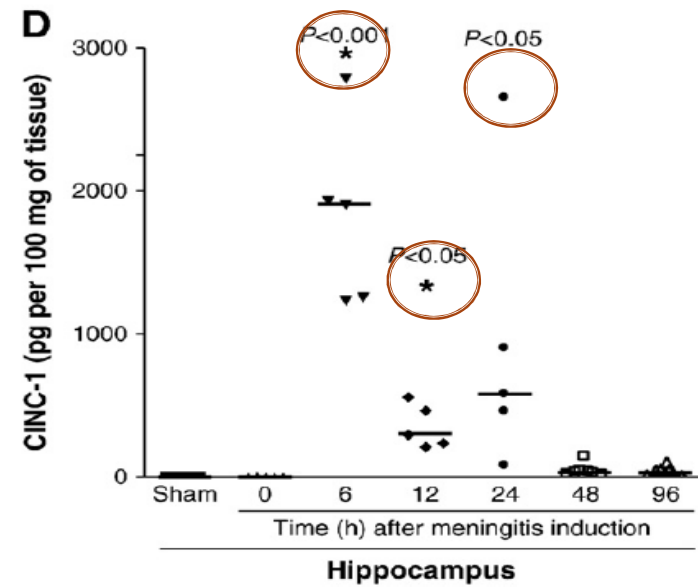
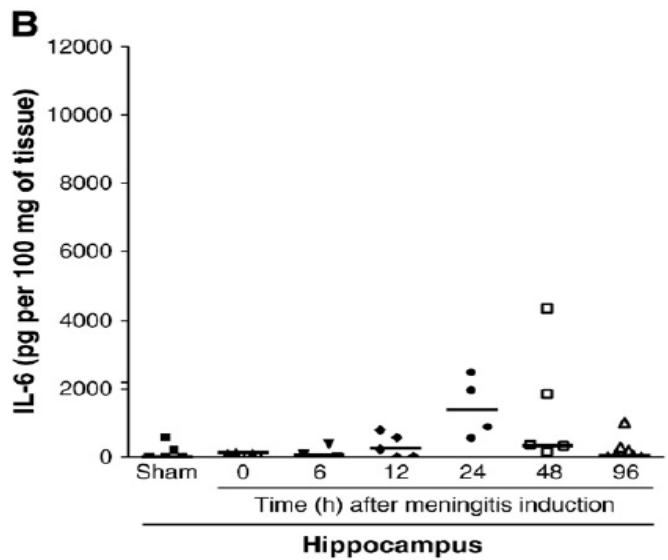
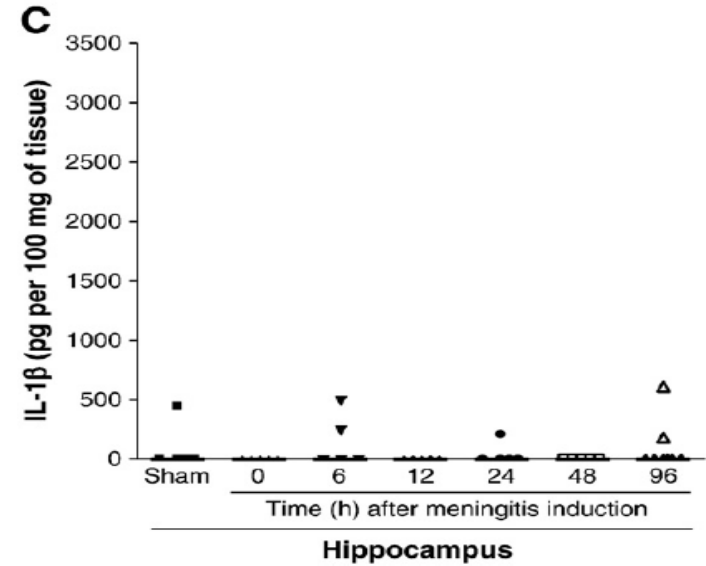
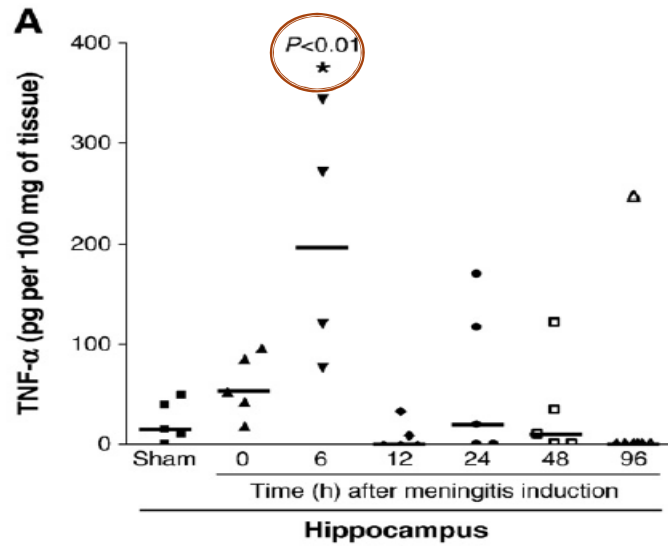


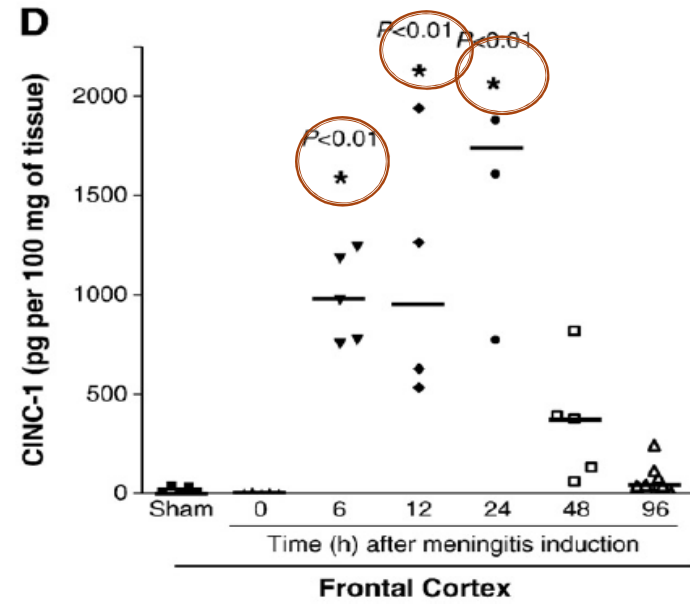
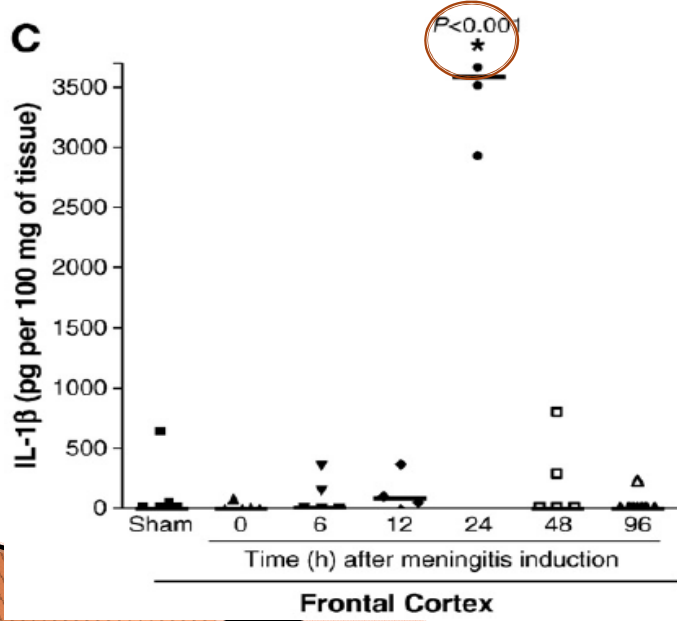
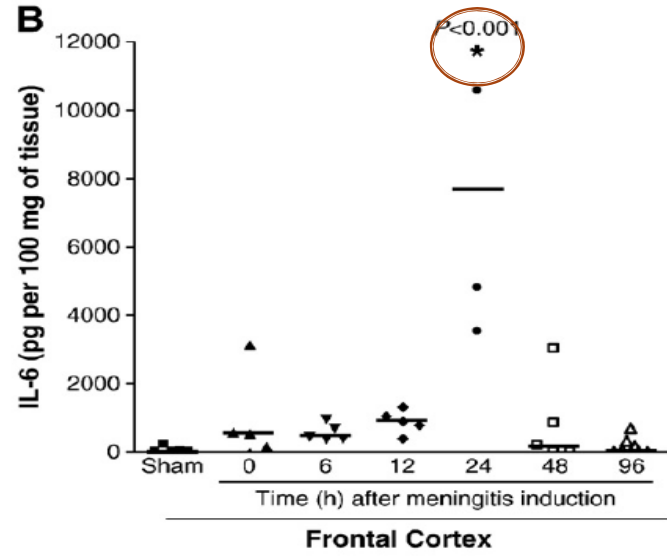
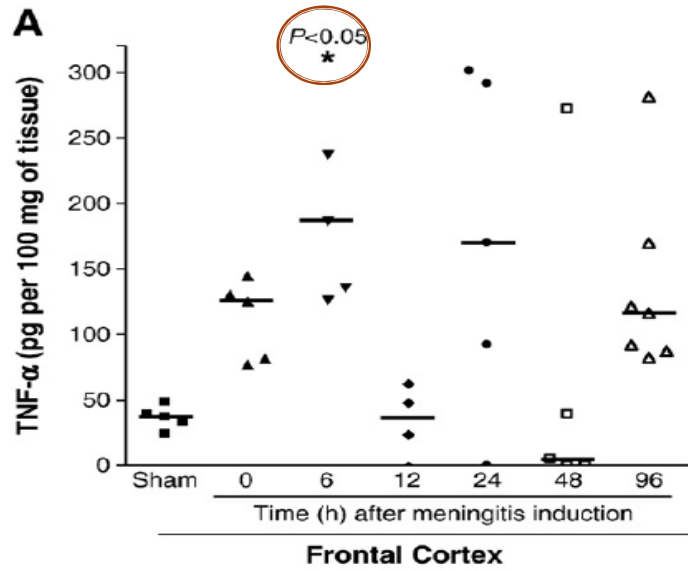
Microorganisms are cultured overnight in 10 ml of Todd Hewitt broth. The culture is centrifuged and re-suspended in sterile saline to the concentration of 5×10^9 cfu/ml.



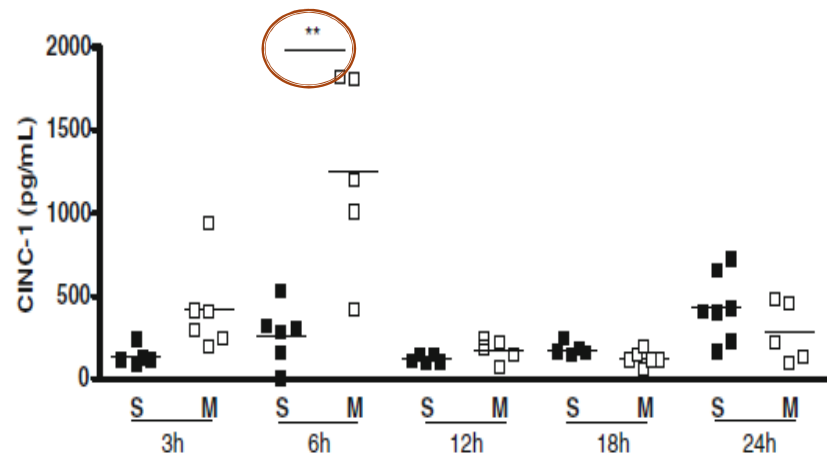
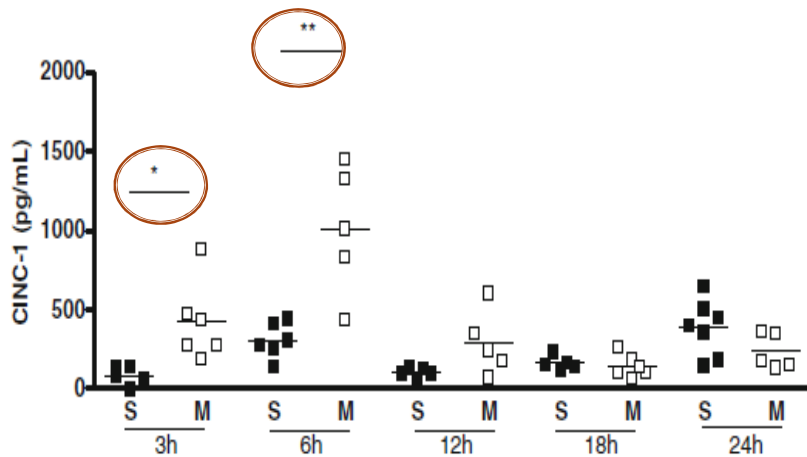
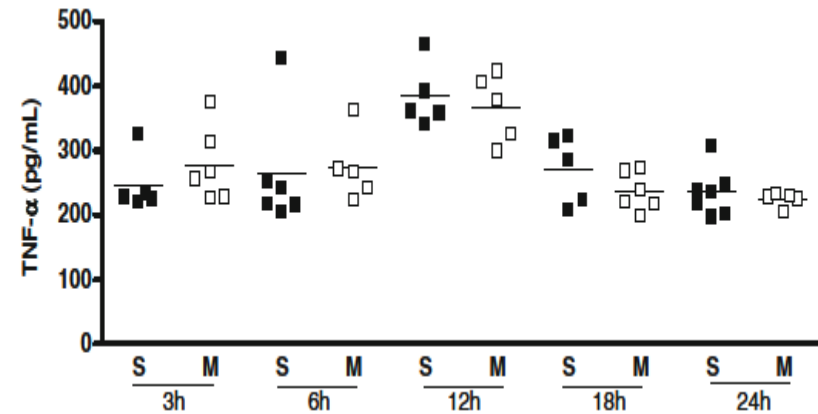
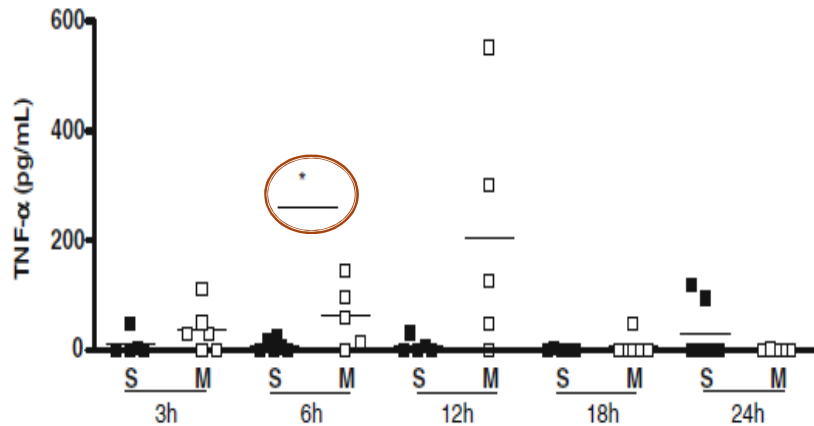
The anesthesia, consists of an intraperitoneal administration of ketamine, xylazine. Rodents receiving via cisterna magna either **10 μ l of artificial CSF** as a placebo or an equivalent volume of **bacterial suspension**.

Cytokines





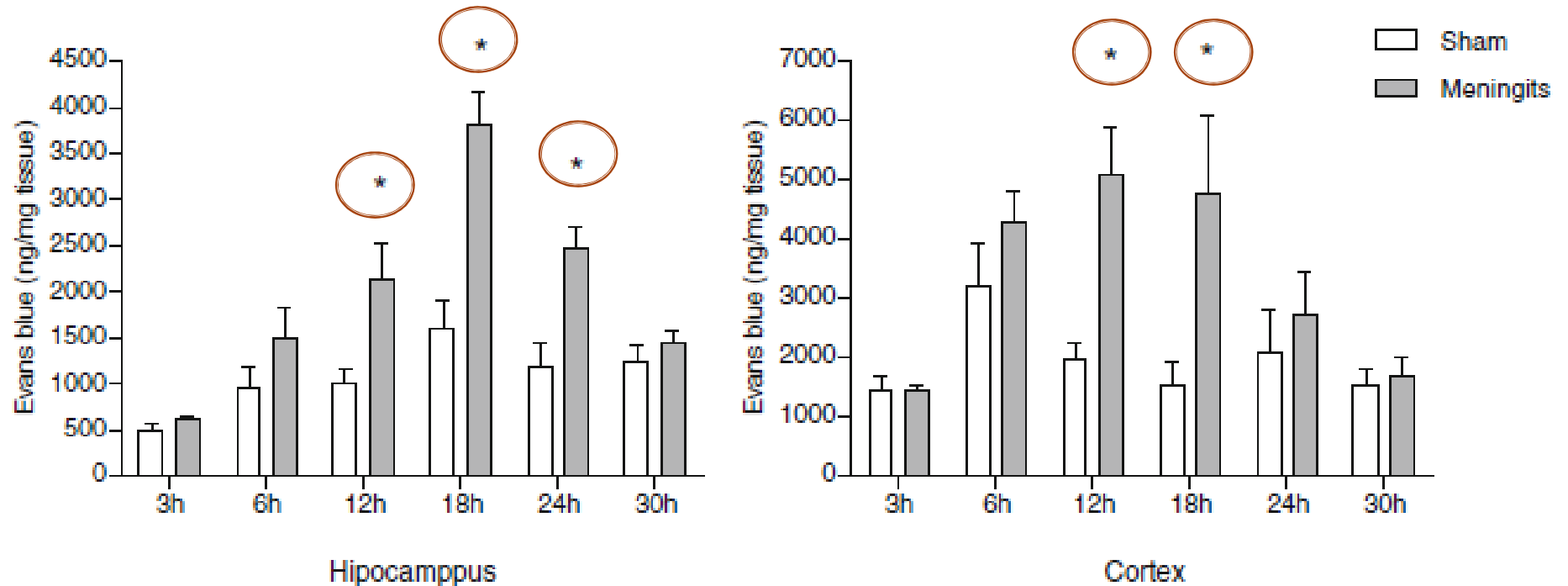
Cytokines are produced in jugular venous blood before arterial blood



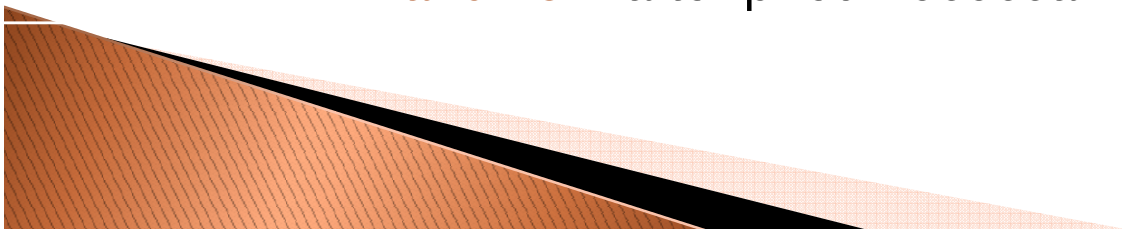
Jugular plasma: CINC-1 increased at **3** and **6h** after pneumococcal meningitis.

Arterial plasma: CINC-1 increased at **6h** after pneumococcal meningitis.

Blood Brain Barrier Integrity

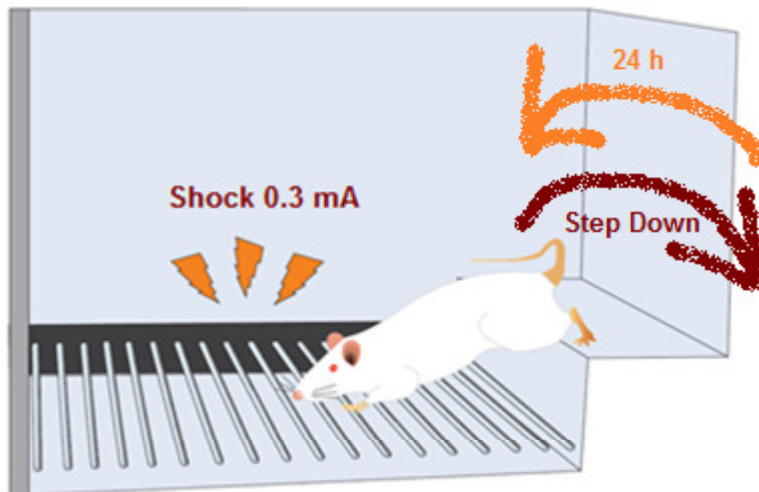


BBB breakdown between 12 and 24 h in the hippocampus and in the cortex at 12 and 18 h after pneumococcal meningitis induction.

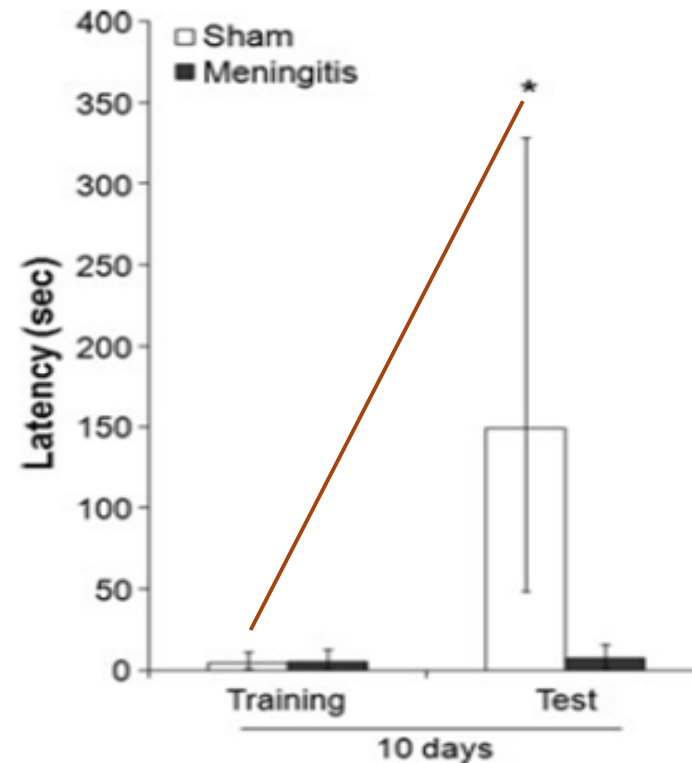


Long-term Cognitive Impairment

Step-down Inhibitory Avoidance Task

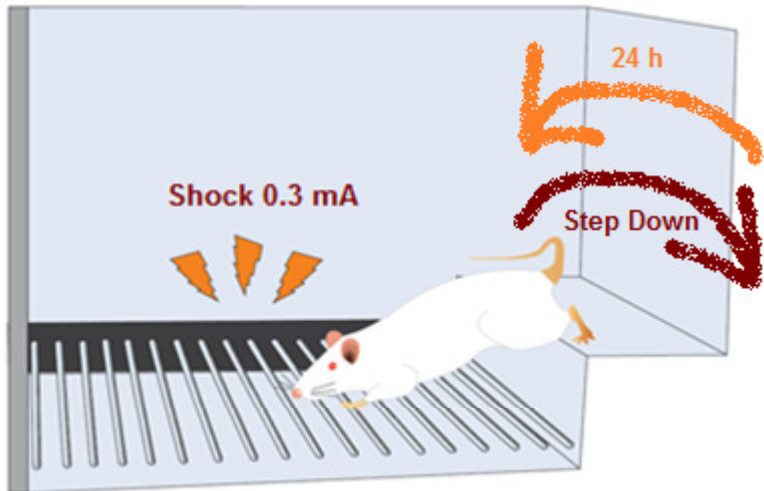


1. Training: Immediately after step down on the grid, rodents received a foot shock.
2. In test session: 24 h after training, no foot shock was given and the step-down latency was used as a measure of retention.

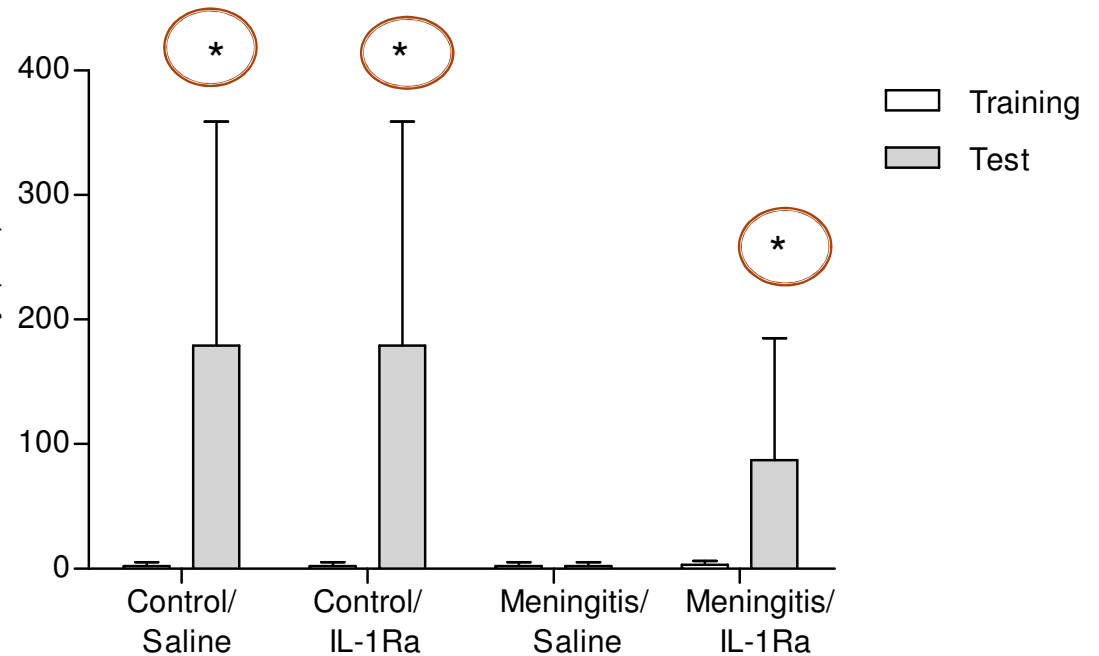


In the step-down latency, 10 days after meningitis induction, there was no significant difference between training and test in the meningitis group, suggesting **impairment of aversive memory** (Barichello et al., JNT, 2010).

IL-1Ra inhibitor: Step-down inhibitory avoidance task

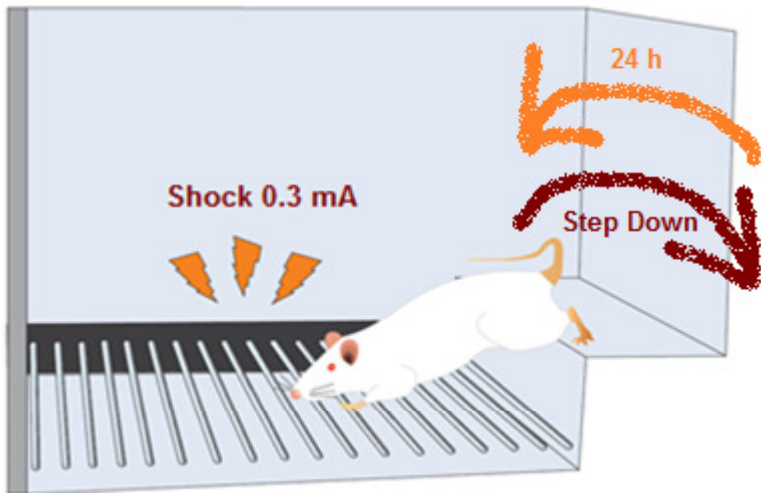


Step-down inhibitory avoidance task
1. Training: 5 min.
2. Test: 5 min/24 h after.



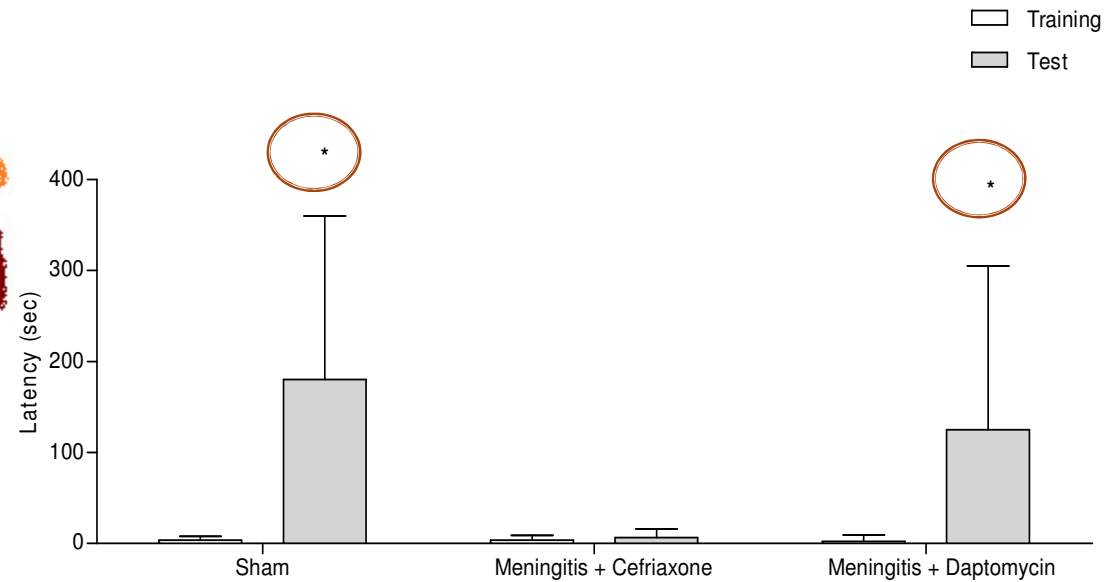
The **meningitis/IL-Ra** groups there were difference between training and test session **preserving the aversive memory** in this group.

Daptomycin: Step-down inhibitory avoidance task

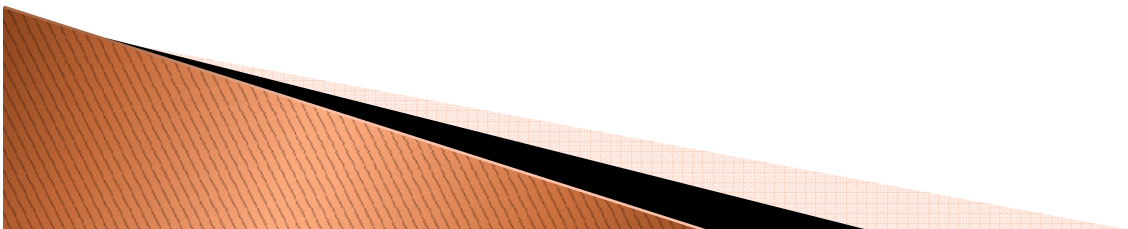


Step-down inhibitory avoidance task

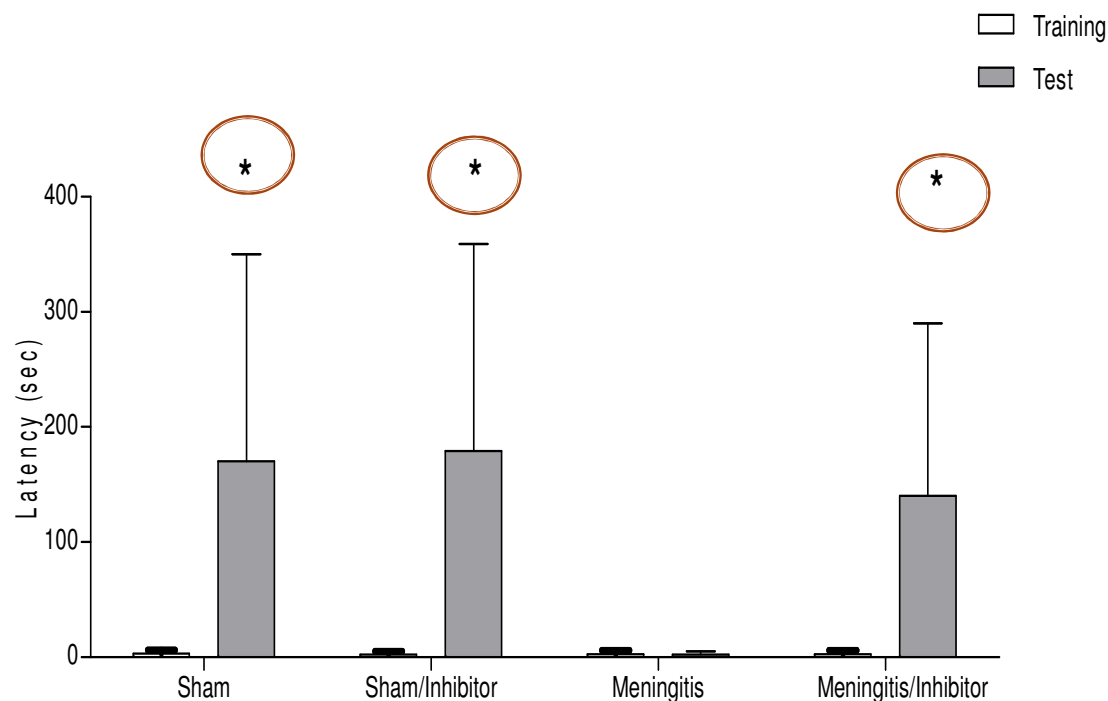
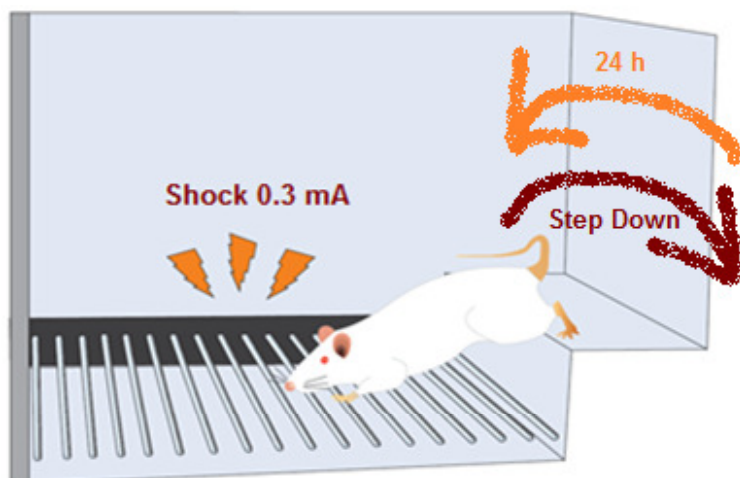
1. Training: 5 min.
2. Test: 5 min/24 h after.



Daptomycin prevented impairment of aversive memory.



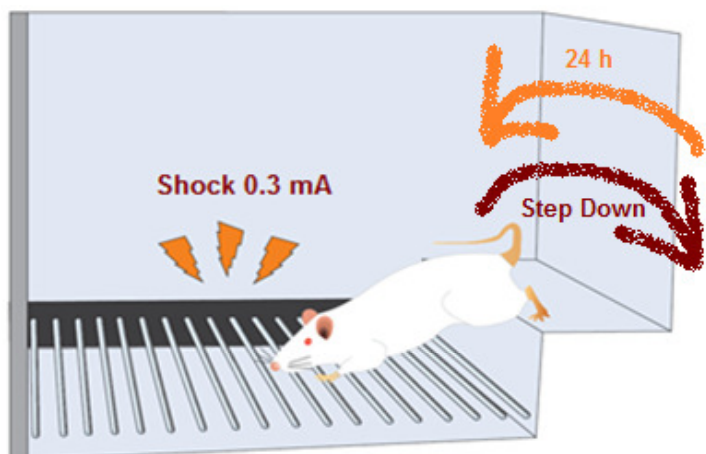
Inhibition of “IDO” prevented aversive memory



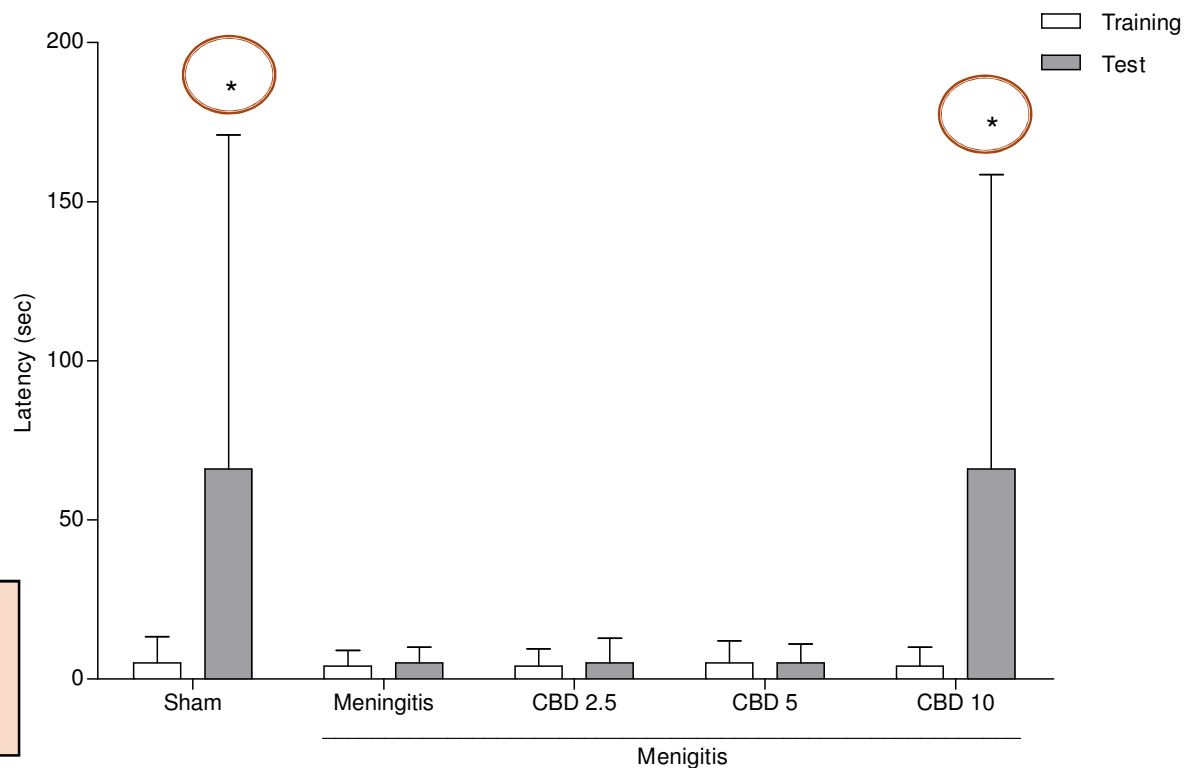
1. Training: Immediately after stepping down on the grid, rodents received a foot shock.
2. In test session: 24 h after training, no foot shock was given and the step-down latency was used as a measure of retention.

Step-down inhibitory avoidance task 10 days after the induction of meningitis.
The indoleamine 2,3-dioxygenase inhibitor prevented of aversive memory.

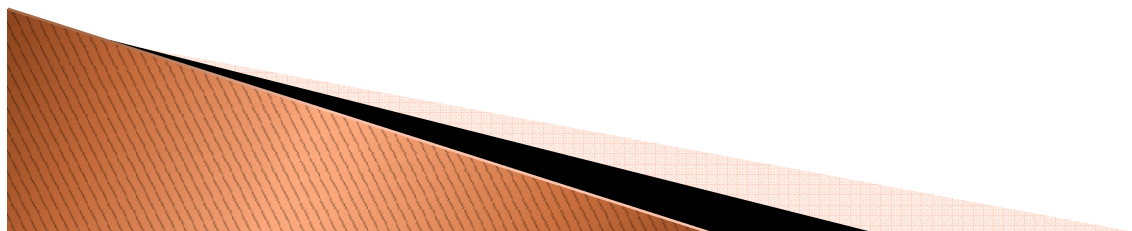
“Cannabidiol” Prevents Cognitive Impairment



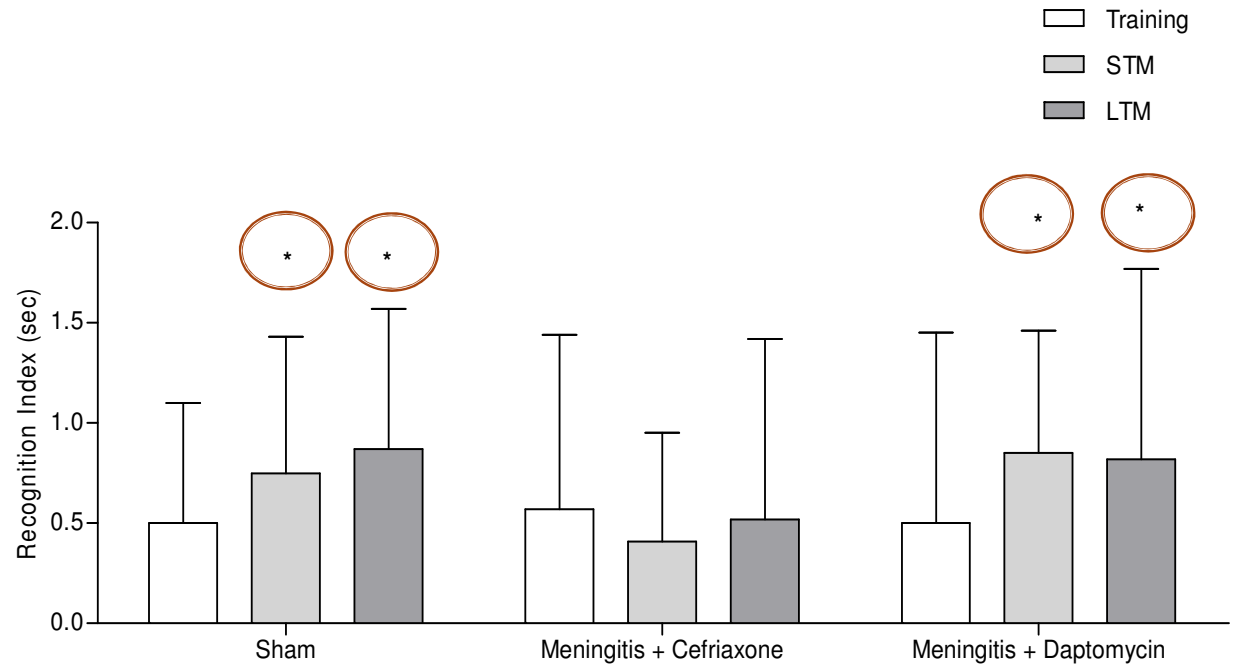
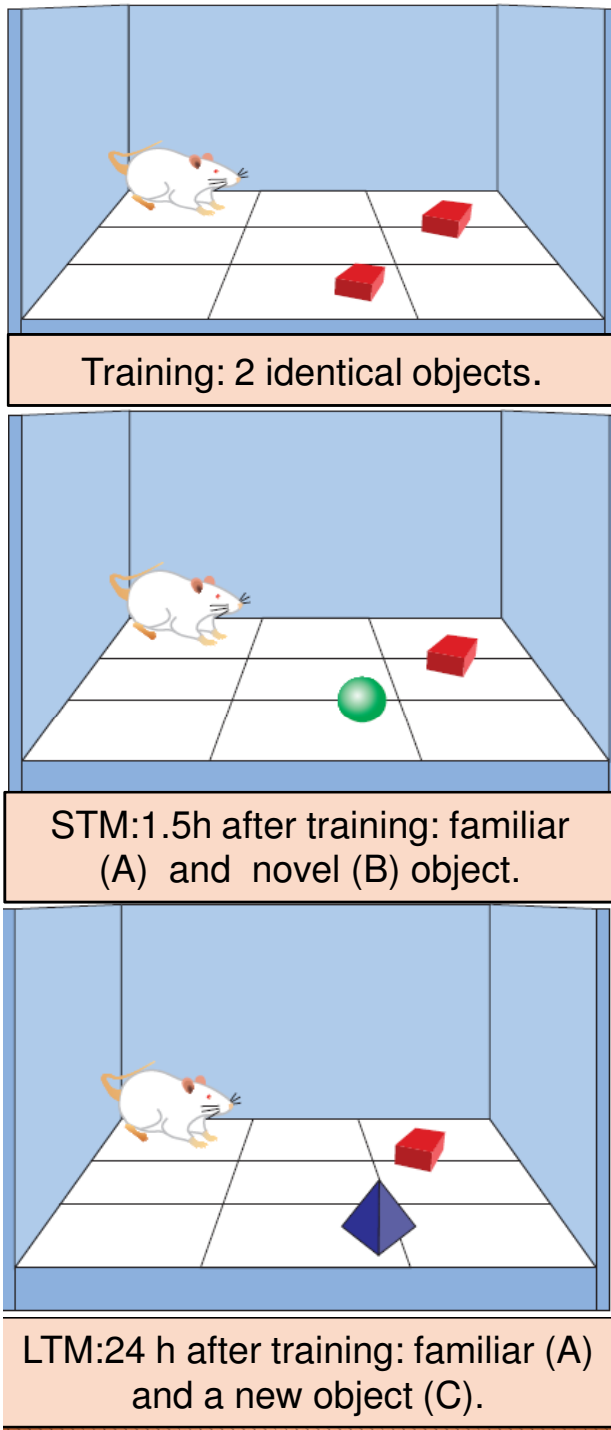
Step-down inhibitory avoidance task
1. Training: 5 min.
2. Test: 5 min/24 h after.



The cannabidiol prevented of aversive memory.



“Daptomycin” Prevents Cognitive Impairment

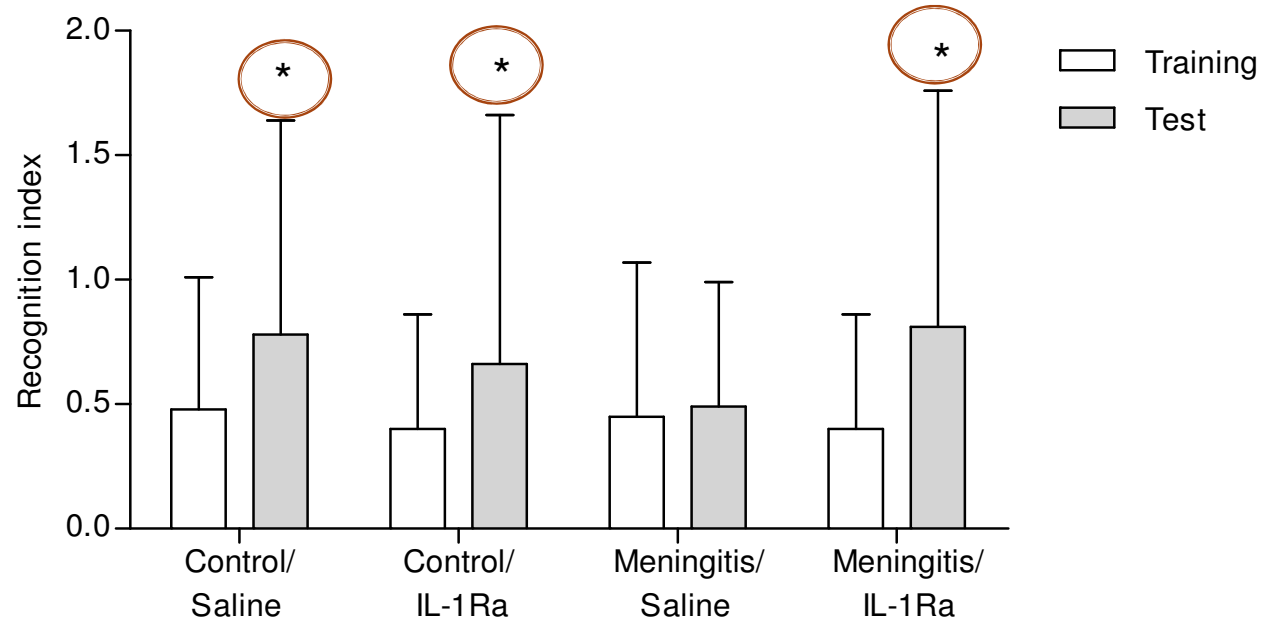
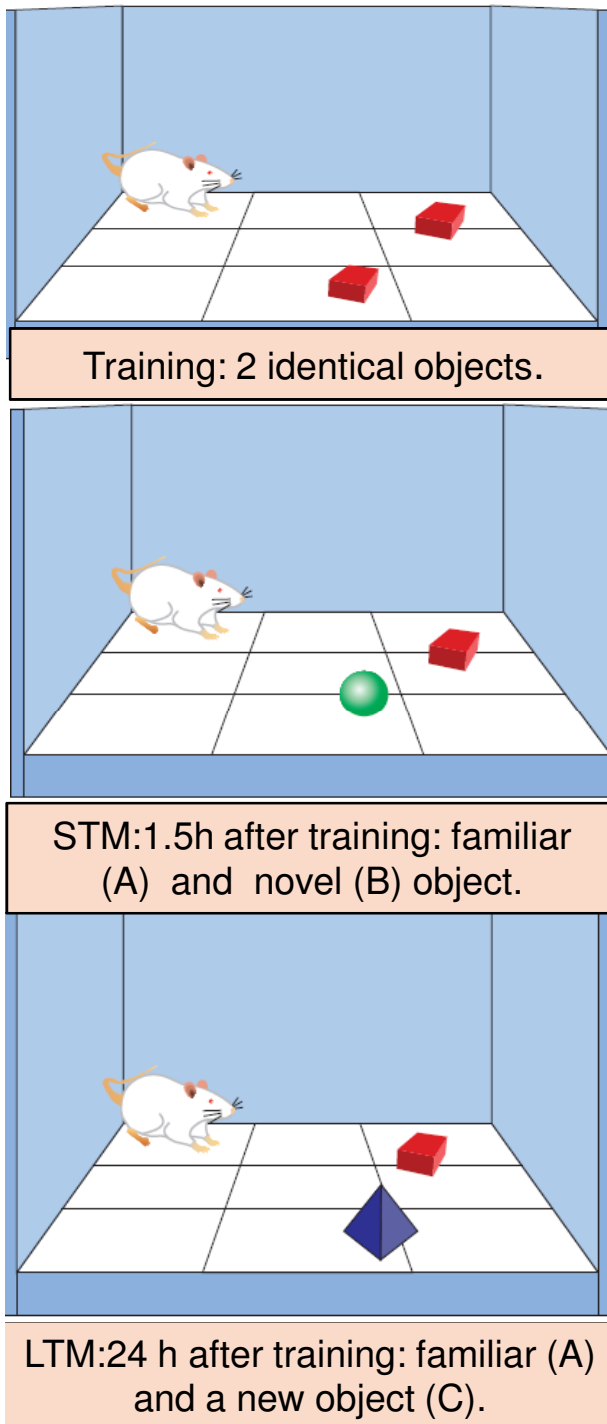


Demonstrating short- and long-term memory impairment for novel object recognition.

They did not spend a significantly higher percentage of time exploring the novel object.

Daptomycin reversed.

IL-1Ra: Object Recognition task



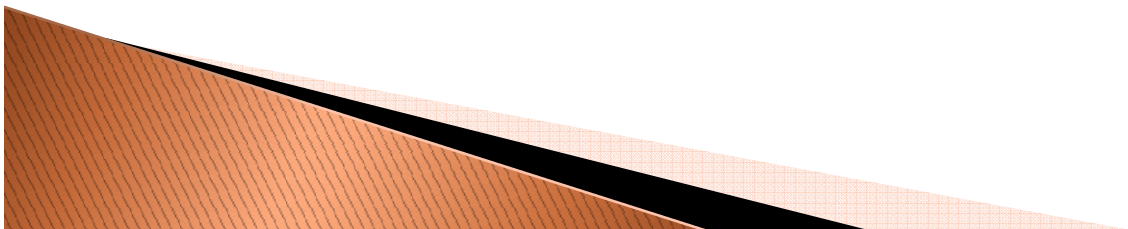
The meningitis/IL-1Ra groups showed difference between training and test sessions demonstrating long-term memory for novel object recognition.

Summary of Part I

The cytokines increase prior of BBB disruption.

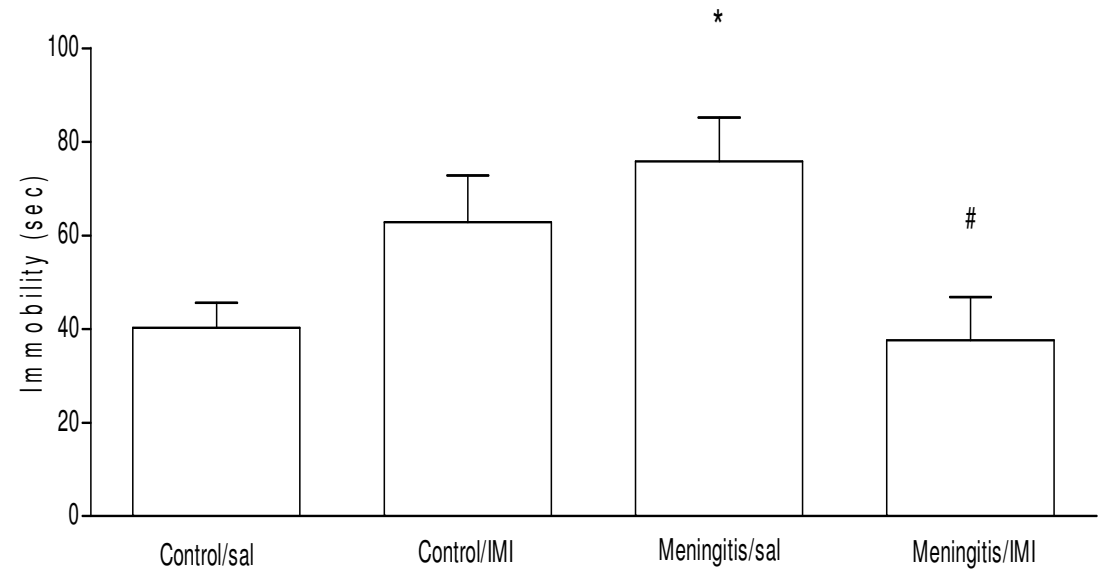
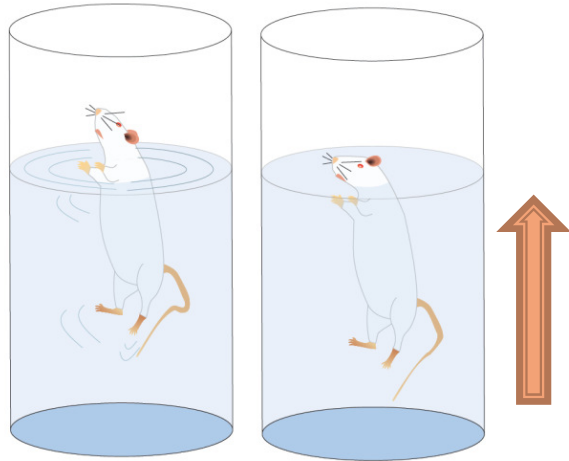
The rodents presented long-term cognitive impairment.

Kynurenine pathway, cytokines, non-bacteriolytic antibiotic prevented memory impairment.



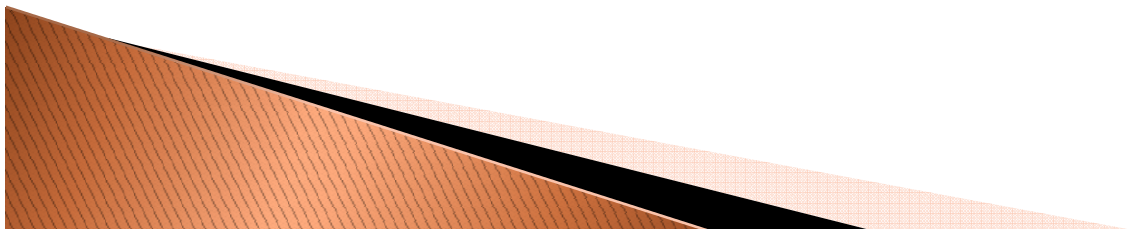
Depressive-like behavior

Forced Swimming task

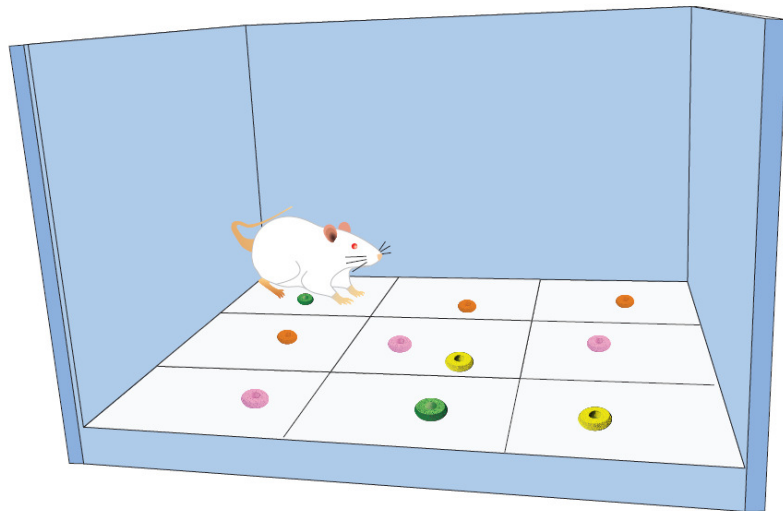


1. The training session: 5 min.
2. Test session after 24 h: 5 min.

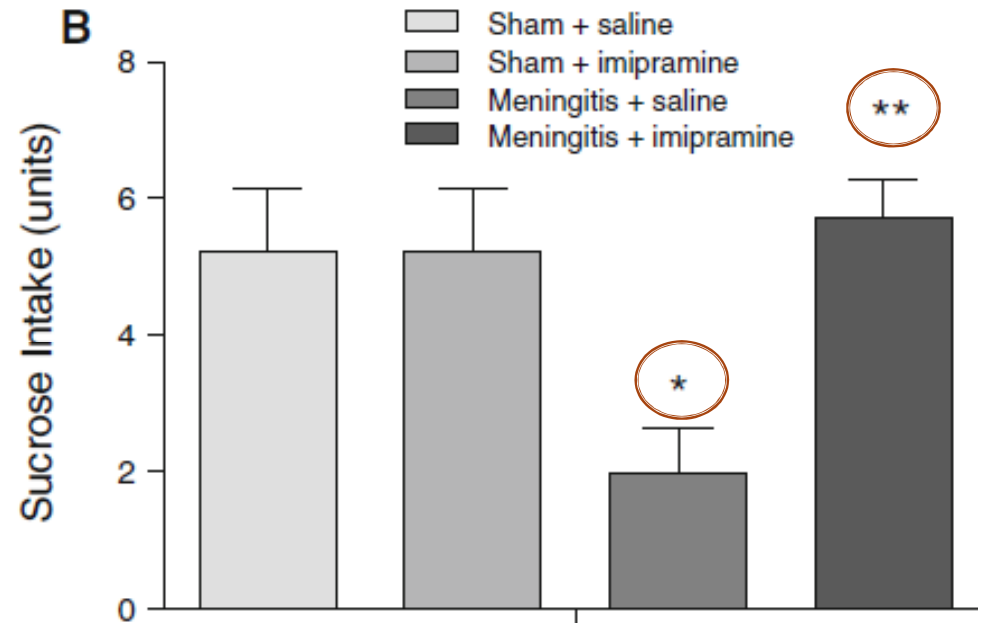
Imipramine treatment reversed depressive like-behavior.



“Imipramine” Prevented Depressive-like Behavior



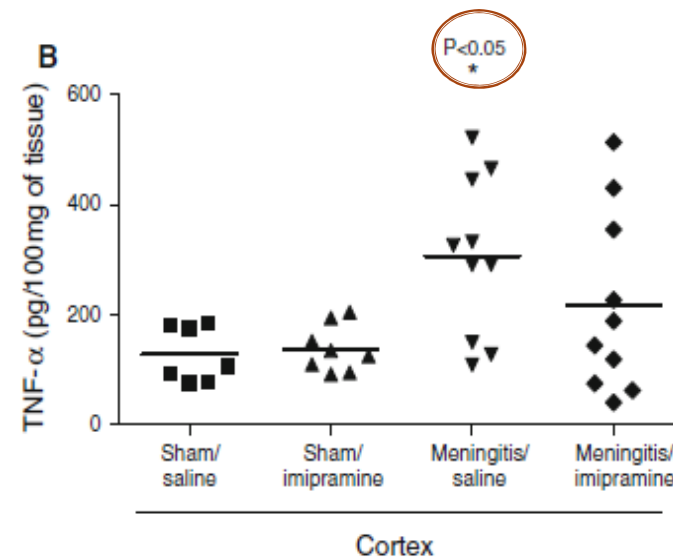
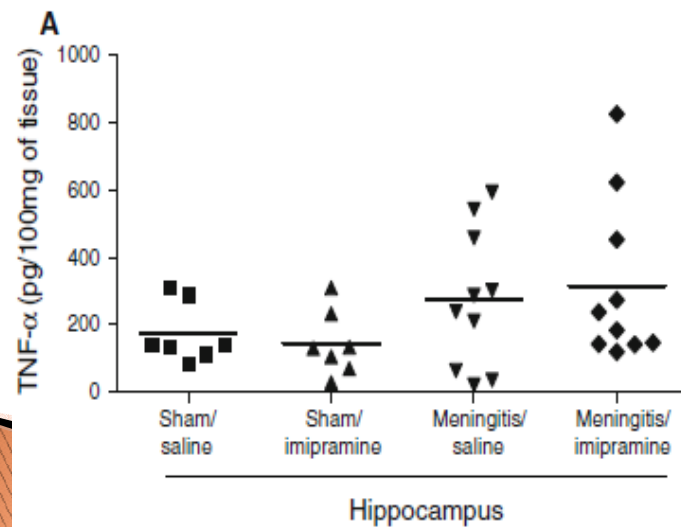
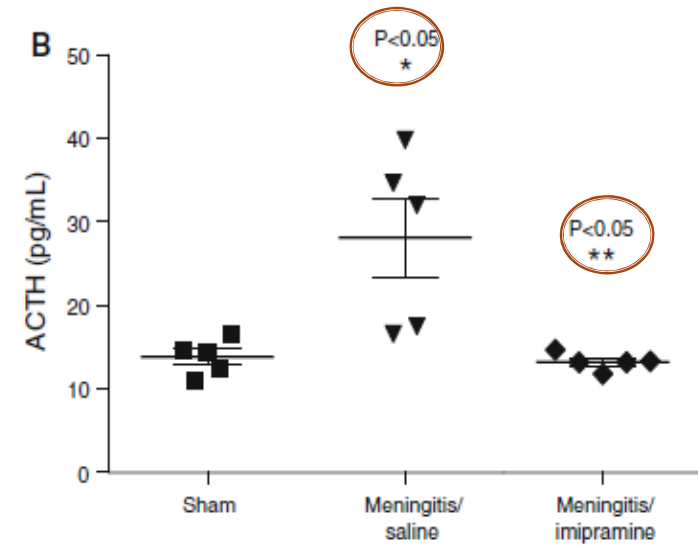
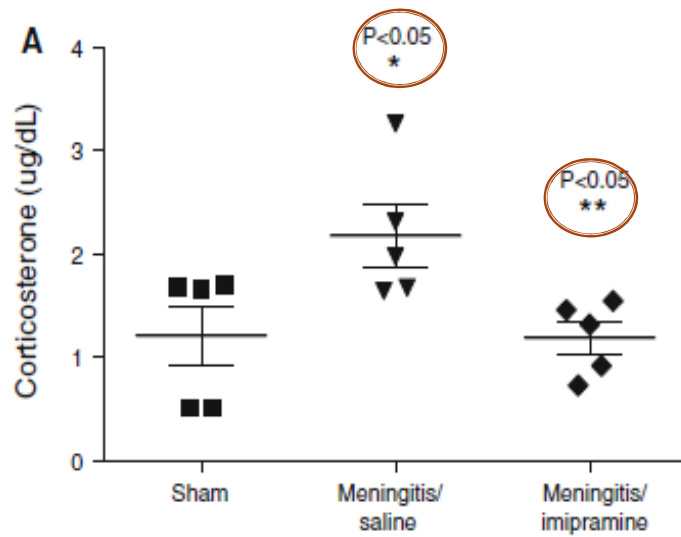
1. Trials: 5 days sessions/3 min.
2. Test: 2 test sessions/3 min.



Treatment with **imipramine** reverted the reduction of sweet food consumption when compared to meningitis/saline.

Imipramine prevented anhedonia-like behavior.

“Imipramine” decreased Corticosterone and ACTH levels

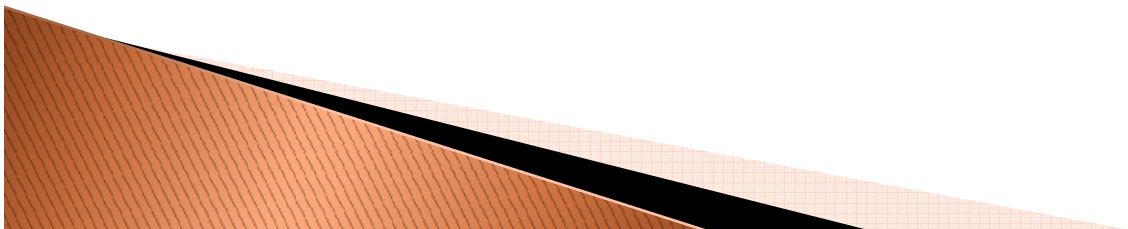


Summary of Part II

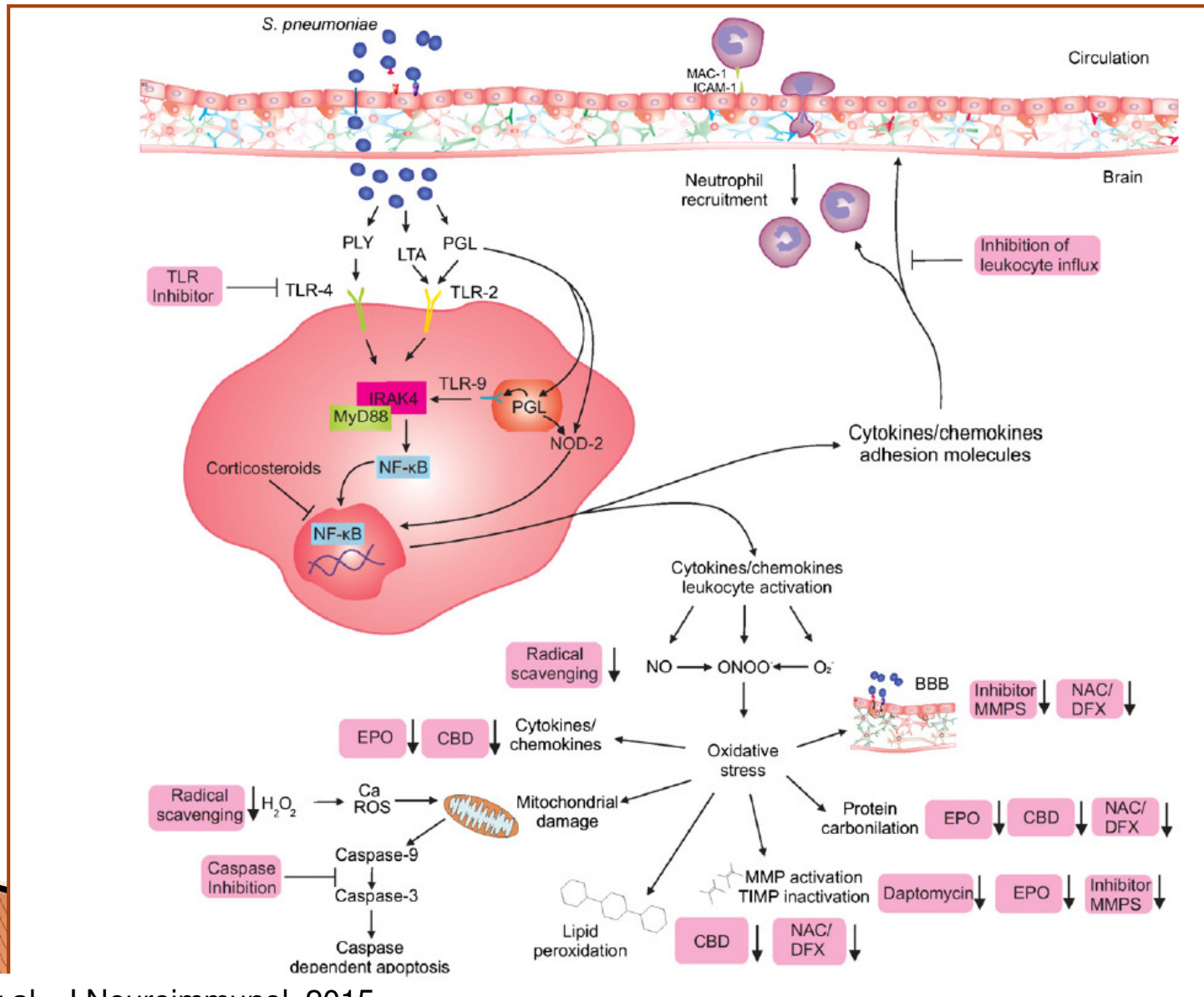
In the present research we showed experimental bacterial meningitis during childhood presented with depressive-like behaviour in adulthood.

The rodents also demonstrated pathophysiological findings similar to patients with depression.

They improved their behaviour in response to imipramine treatment.



New treatment options: a perspective from rodent model





The University of Texas
Health Science Center at Houston

Medical School



Neuroimmune Basis of Long-term Cognitive Impairment in Bacterial Meningitis

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