OptoPath™

FEAR-RELATED MEMORY – PTSD

Using complementary behavioral and high tech *in vivo* electrophysiology procedures, with high face and construct validities, we evaluate the therapeutic potential of new compounds in the context of PTSD.

FEAR-PRODUCTS: THERAPEUTIC TESTS IN THE CONTEXT OF POST-TRAUMATIC STRESS DISORDER

TEST FEAR 1 - EVALUATION OF THE POTENTIAL OF NEW PSYCHOACTIVE COMPOUNDS IN NORMALIZING NEUROBIOLOGICAL MARKERS OF PATHOLOGICAL FEAR MEMORIES IN RODENTS

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ASSAY INFORMATION

Biological models	Mice
Methods	Extracellular recordings in vivo and behavior
Readouts	• Ability to reduce biological markers of fear memory • Ability to reduce long-lasting fear memories
Standard reference	
Animals per group	8-10 mice
Turn around time	8 to 10 weeks per test

BACKGROUND

Exposure to extreme traumatic events (e.g. genocides, terrorist attacks, military fights, rapes…) can induce anxiety disorders such as Post-Traumatic Stress Disorder (PTSD) which is notably characterized by long-lasting and recurrent traumatic memories and a high propensity to relapse after exposure therapies.
Our assay is based on the fact that **Persistent fear memories in humans and rodents are associated with specific oscillations in the medial prefrontal cortex and amygdala**.

ASSAY PRINCIPLE

Model: Pavlovian auditory fear conditioning and extinction learning

The method consist in recording the prefrontal local field potential in mice submitted to auditory fear conditioning and extinction learning to monitor the changes of a specific electrophysiological markers or fear memories upon the administration (systemic, intraventricular, intracerebral) of specific compounds. The test we specifically developed allows:

1- Testing the ability of compounds to reduce fear at the behavioral level

2- Testing the ability of compounds to alter the neurobiological markers of pathological fear memories

Test 1: Testing the ability of compounds to reduce fear at the behavioral level

Following auditory fear conditioning, mice are submitted to an extinction procedure that results in the significant reduction of conditioned fear responses. One week after extinction, mice challenged with the conditioned stimulus display an important heterogeneity in fear responses with half of the animals showing high fear recovery (vulnerable animals) and the other half low fear recovery (resistant animals). This bimodal distribution of conditioned fear responses after extinction is a measure of long lasting fear recovery.

This test allow to evaluate at the behavioral level if a specific compound can reduce long-lasting fear recovery and allow the switch from high fear recovery to low fear recovery in rodents.

Test 2: Testing the ability of compounds to alter the neurobiological markers of pathological fear memories

Long-lasting fear memories are associated with specific oscillatory activity in the medial prefrontal cortex and amygdala. These oscillations are causally related to the development of fear responses. Using local field potential recordings in these two neuronal structures we can monitor in behaving animals the changes occurring in these oscillations upon administration of specific compounds. Long-lasting changes in this oscillatory activity (up to several months post-treatment) can also be monitored.

REPRESENTATIVE RESULTS

Test 1: Testing the ability of compounds to reduce fear at the behavioral level

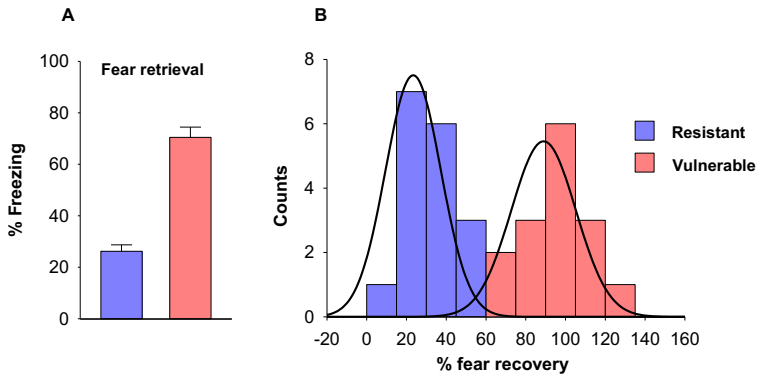

Figure 1: Behavioral model. A. Following fear conditioning and extinction, mice display either low (blue) or high (red) recovery of conditioned fear responses. **B.** Bimodal distribution of fear responses recovery in mice during the retrieval test revealing resistant (low fear recovery) and vulnerable (high fear recovery) individuals.

Test 2: Testing the ability of compounds to alter the neurobiological markers of pathological fear memories

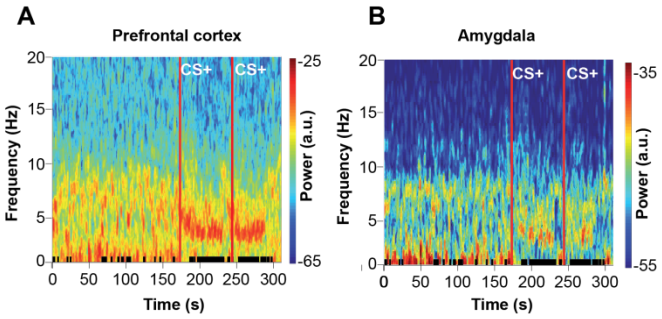

Figure 2: Specific oscillations during fear Local field potential recordings in the prefrontal cortex (**A**) or in the amygdala (**B**) following fear conditioning illustrating specific oscillatory activity in the 3-6 Hz band during fear episodes (blacks ticks at the bottom of each graph).

BIBLIOGRAPHICAL REFERENCES

Behavioral model: Herry, C., Ciocchi, S., Senn. V., Demmou, L., Müeller, C., and Lüthi, A., (2008). Switching on and off fear by distinct neuronal circuits. *Nature*, 454, 600-6

Local field potential recordings: Courtin J, Chaudun F, Rozeske, RR, Karalis, N, Gonzalez-Campo C, Wurtz H, Abdi A, Baufreton J, Bienvenu TCM, and Herry C. (2014) Prefrontal parvalbumin interneurons shape neuronal activity to drive fear expression. *Nature*, 505, 92-96