CRH and CRHR1 mediate acute stress-induced prefrontal cortex dysfunctions


INTRODUCTION

The prefrontal cortex (PFC) constitutes a key area for the execution of complex behaviors, plays a fundamental role in adaptive responses and has been ascribed to the cognitive hallmarks that characterize different psychiatric disorders. Stress has been shown to affect the function of the PFC, and prolonged stress exposure has been associated with different neuropsychiatric conditions, such as depression. Among numerous candidates CRH, through the activation of CRHR1 receptors, constitutes one of the main effector systems by which stress unchains deleterious effects upon different brain regions. Furthermore, the persistent activation of this system has been regarded as a risk factor for depression. However, the contributions of this system to the effects of stress in the PFC are still unclear. The present project therefore aims to characterize the role of the CRH-CRHR1 system on the impact of stress in the PFC.

1. EFFECTS OF ACUTE STRESS IN TEMPORAL ORDER MEMORY

Acute Social Defeat

- 5.5 h

5 min

Sample Phase I

60 min

60 min

A) Control

B) Stressed

Diagram of a Coronal section depicting the Cingulate, Prelimbic and Infralimbic regions of the PFC (C).

Figure 1. Effects of acute stress on the percentage of exploration of an old and recent object (A), and the discrimination ratio between both objects in the Test Phase of the temporal order memory task.

2. EFFECTS OF ACUTE STRESS IN REVERSAL LEARNING

Day 1

Training

Day 2

Retention

Acute social defeat

Day 3

Reversal

1.5 h

A) Control

B) Stressed

Figure 2. Effects of acute stress on Perseverative Errors (A) and number of Trials to Reach Criteria (B) during the reversal phase of a reversal learning task.

3. EFFECTS OF ACUTE STRESS ON CRHR1 mRNA LEVELS IN THE PFC

Acute Social Defeat

5 Min

Home cage

Brain Extraction

Stress

CRHR1

Figure 3. Effects of acute stress on CRHR1 mRNA levels in the PFC (A and B).

4. EFFECTS OF INTRA-PFC CRH MICROINJECTION IN TEMPORAL ORDER MEMORY

7 d

CRH 1.5ug/0.5ul

ACSF

5.5 h

Sample I

60 min

60 min

Test

A) Control

B) Stressed

Figure 4. Effects of intra-PFC CRH microinjections on the percentage of exploration of an old and recent object (A) and the discrimination ratio between both objects (B) in the temporal order memory task.

5. EFFECTS OF INTRA-PFC CRH MICROINJECTION IN REVERSAL LEARNING

7 d

Day 1

Training

Day 2

Retention

ACSF

CRH 1.5ug/0.5ul

Day 3

Reversal

1.5 h

A) Control

B) Stressed

Figure 5. Effects of intra-PFC CRH microinjections on Perseverative Errors (A) and number of Trials to Reach Criteria (B) during the reversal phase of a reversal learning task.

6. EFFECTS OF PFC CRHR1 KO ON THE IMPACT OF ACUTE STRESS IN TEMPORAL ORDER MEMORY

4 wk

Social Defeat

5.5 h

Sample I

60 min

60 min

Sample II

10 Min

A) Control

B) Stressed

Figure 6. Effects of PFC CRHR1 KO on the impact of acute stress on the percentage of exploration of an old and recent object (A) and the discrimination ratio between both objects (B) in the temporal order memory task.

CONCLUSION

• A single episode of social defeat stress increases CRHR1 mRNA levels in the PFC and induces PFC-mediated cognitive alterations that are mimicked by intra-PFC CRH microinjections and are fully rescued by the selective PFC CRHR1 knockout.

• The CRH-CRHR1 system constitutes an attractive therapeutic target for the cognitive dysfunctions that characterize different stress-related diseases.

OUTLOOK

• Ongoing experiments now focus on the downstream signalling pathways activated by acute stress and CRH microinjections in the PFC.

• Employing RT-PCR, current experiments aim to establish changes in CRH levels in the PFC 8 hours after Acute Stress.
Corticotropin-releasing hormone and corticotropin-releasing hormone receptor 1 mediate acute stress-induced prefrontal cortex dysfunctions

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The prefrontal cortex (PFC) plays a fundamental role in adaptive responses and has been ascribed to the cognitive hallmarks that characterize different psychiatric disorders. Furthermore, stress has been shown to affect the function of the PFC [1] and is also associated with neuropsychiatric conditions such as depression. Among numerous candidates corticotropin releasing hormone (CRH), through the activation of CRH receptor 1 (CRHR1), constitutes one of the main effector systems by which stress unchains deleterious effects upon different brain regions [2,3]. However, the contributions of this system to the effects of stress in the PFC are still unclear.

The present project aims to characterize the role of the CRH-CRHR1 system on the impact of stress in the PFC.

In all experiments, C57Bl6 mice were employed. In experiment 1, animals were submitted to a single episode of social defeat stress and 8 hours later were sacrificed. PFC sections of these animals were submitted to an in situ hybridization protocol to assess changes in CRHR1 mRNA levels. In experiment 2, animals underwent acute social defeat stress and were tested 8 hours later either in a temporal order memory task (TOM) or a reversal learning task. In experiment 3, a guide cannula was implanted in the PFC and animals received intra-PFC microinjections of either vehicle or CRH, and 8 hours later were submitted to either the TOM or reversal learning task. In experiment 4, CRHR1lox/lox mice received intra-PFC microinjections of either empty-AAV or Cre-AAV to induce a PFC-specific CRHR1 KO. One month later, they were submitted to an acute social defeat stress and after 8 hours were tested in either the TOM or reversal learning tasks.

The results obtained show that an acute episode of stress significantly increased CRHR1 mRNA levels in the prelimbic \( t(22)=2.592, p<0.05 \), infralimbic \( t(22)=3.009, p<0.01 \), and cingulate \( t(22)=2.978, p<0.01 \) regions of the PFC. Acute stress also disrupted the discrimination between objects with different recency in the TOM \( t(21)=4.193, p<0.001 \) and increased the trials to reach criteria \( t(18)=1.783, p<0.05 \) in a reversal learning task. Furthermore, intra-PFC CRH microinjections induced significant impairments in the discrimination ratio between objects with different recency \( t(16)=3.567, p<0.01 \) in the TOM, and increased the trials to reach criteria \( t(19)=2.114, p<0.05 \) in the reversal learning task, mimicking the effects of acute stress. Additionally, the PFC-specific CRHR1 KO fully recovered acute stress-induced deficits in the discrimination ratio \( F_{1,33}=12.91, p<0.01 \) in the TOM, and trials to reach criteria \( F_{1,29}=17.29, p<0.001 \) in reversal learning.

The present findings suggest that an acute stressor is able to induce intra-PFC increases in CRHR1 mRNA together with functional impairments in PFC-mediated cognition, which are mirrored by intra-PFC CRH microinjections and rescued by the CRHR1 KO in the PFC. Taken together, our results suggest a molecular mechanism that links stress to behavioral dysfunctions, thereby opening new intervention strategies for patients suffering from stress-related diseases, such as depression.


Citation: Eur Neuropsychopharmacol. 2014;24(Suppl 2):S368

Keywords
Stress
Behavioural pharmacology
Animal models