Name of research institute or organization:

Institute of Veterinary Physiology, University of Zürich (UZH)

Title of project:

Effects of enriched environment (EE) including exercise in recovery of high-altitude induced memory impairment

Part of this program:

University of the Basque Country, Bilbao

Project leader and team:

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† In memoriam of Enrike G. Argandoña. Deceased on December 23rd, 2014.

Project description:

Successful survival of mammals to hypoxic environments depends on efficient O_2-sensing mechanisms, including rapid adaptive cellular, tissular and systemic responses. Acute hypoxia, e.g. during a rapid ascent to high altitude (over 2500 m.a.s.l.), is associated with memory impairment. In the brain, the microvascular environment is fundamental in adapting to oxygen and energy demand changes, VEGF (Vascular Endothelial Growth Factor) being the main hypoxia-inducible factor that induces angiogenesis. We have previously reported that environmental enrichement (EE), housing rats in cages specially designed to provide an environment to play and exercise, leads to an increase in VEGF and angiogenesis. In this work we studied the interplay between the vascular and the neuronal networks in cognitive functions in Long Evans rats exposed to high altitude (3450 m.a.s.l.). We addressed whether high altitude can interfere with spatial and visual memory in Long Evans rats and whether EE and exercise can rescue this effect under conditions when VEGF is present and when it is blocked.

Long Evans rats were housed in Zürich (400 m) from ages P40 to P49 and then tested either in Zürich (normoxia groups) or transported to the High Altitude Research Station Jungfraujoch (3450 m.a.s.l.) on a trip of 250 minutes and tested there (hypoxia groups). We used the following cohorts of at least 8 rats each: rats housed in Zürich in standard laboratory conditions (SC), rats housed in Zürich in enriched environment (EE), rats housed in Zürich in EE treated orally with VEGF inhibitor (Vandetanib) (EE_{inh}); rats housed in Zürich and at Jungfraujoch in standard laboratory conditions (SC), rats housed in Zürich in SC and at Jungfraujoch in EE (EE), rats housed in Zürich in SC and at Jungfraujoch in EE treated orally with VEGF inhibitor (Vandetanib) (EE_{inh}). After two days of acclimatization to high altitude and three days of adaptation to the open field arena (diameter 1 m; height 0.9 m), behavioral tests were performed in a dimly lit room. Three different exploration objects for the tests were constructed from toy bricks. Spatial memory was measured via the Object Displacement Test (ODT) and visual memory was measured via the Object Replacement Test (ORT).

a) Object Displacement Test (ODT)
For this test two spatial cues are placed on the walls of the arena and three objects are fixed to the floor, each in the middle of one quadrant. Spatial test is tested by the ability of an animal to recognize the change in quadrant position of one object (Object C).

During the training phase, each rat is allowed to explore in the arena freely three times for 5 minutes, with an inter-trial rest period of 5 minutes. The time that each object is explored during each interval is measured in seconds and the sum of the three intervals represented as a total exploration time per object. For the testing phase, object C is moved from its original position to the empty quadrant and rats are reintroduced to the open field 24 hours post-training during 5 minutes (see Figure 1C upper schema). The time spent exploring the displaced object (object C) is expressed as a percentage of the total exploration time.

b) Object Replacement Test (ORT)
Visual learning is tested by the ability of the animal to recognize a new object (Object C) in the arena. For this test, no spatial cues are used and three new objects are positioned in the open field as described before. Training is equal as before. For the testing phase, a novel object replaces object C in the same position (Figure 1C lower schema). The time spent exploring the familiar objects and the novel object are recorded and expressed as a percentage of the total exploration time.

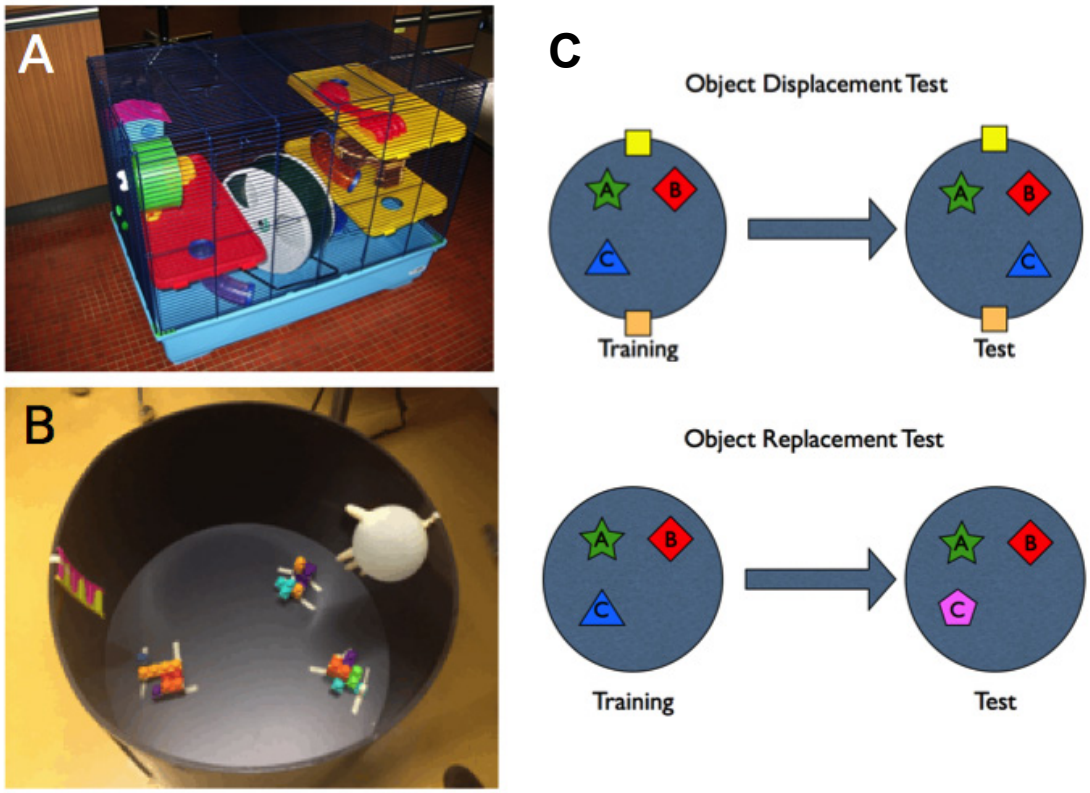

Figure 1. Pictures of the cage used for Environmental Enrichment (A) and of the open field arena arranged for an ODT (B). Schema of Object Displacement Test (ODT) (upper schema) and Object Replacement Test (ORT) (lower schema) (C). ODT reflects Spatial Learning and Memory and ORT visual learning and memory. Exploration time to the displaced or changed object (C) is measured and represented in percentage of total exploration time. The more time spent in exploring object C, the better the memory performance.

RESULTS

The total exploration time of rats during training and test was similar between the different housing groups. A slight decrease in exploration time was observed when rats were housed in EE (Figure 2).

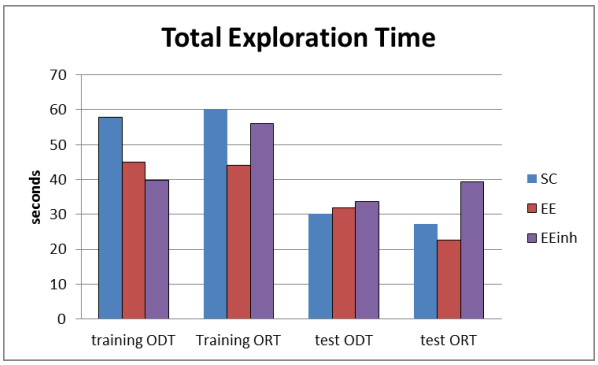

Figure 2. Total exploration time in different housing groups. No significant change in exploratory behavior was observed between groups.

In Zürich (normoxia), spatial and visual learning was observed in rats housed in SC and EE (Figure 3). EE improved visual recognition in rats. Animals in EE that took VEGF inhibitor (EE-inh) failed to recognize the displaced object but kept recongizing the replaced changes; therefore in normoxic conditions VEGF plays a role mainly in spatial learning.

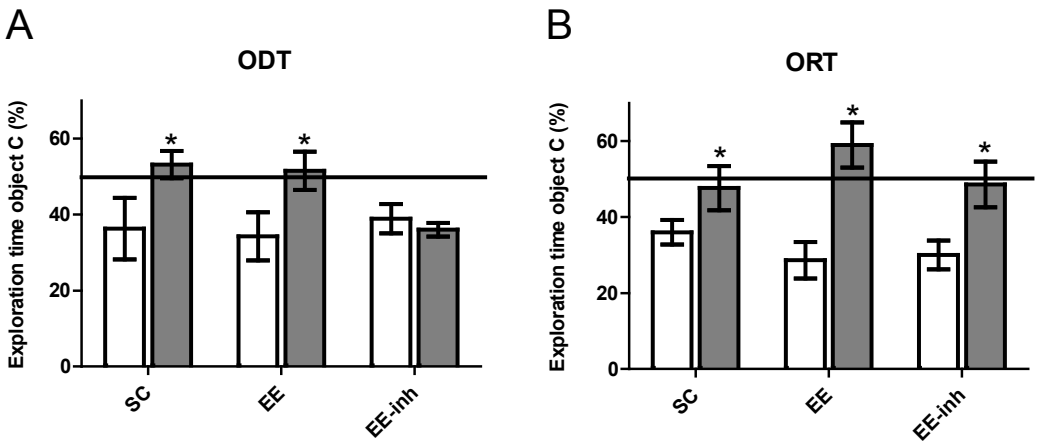

Figure 3. Percentage of time that rats spent exploring the displaced (A) or the replaced (B) object in normoxic conditions (Zürich). Line at 50% of the total exploration time represent a significant recognition of change. $P \geq 0.05$.*

At Jungfraujoch (hypoxia), all animals housed in SC lost completely their spatial (Figure 4, A) and visual (Figure 4, B) learning skills. EE allowed the recovery of spatial and visual learning and this recovery was not posible if animals in EE were treated with VEGF inhibitor (EEinh).

Quantification of total number of neurons (nerve cells) revealed a reduction in number in all groups that were exposed to high altitude; however an increase in neurogenesis (new born neurons) was observed in groups housed in EE.

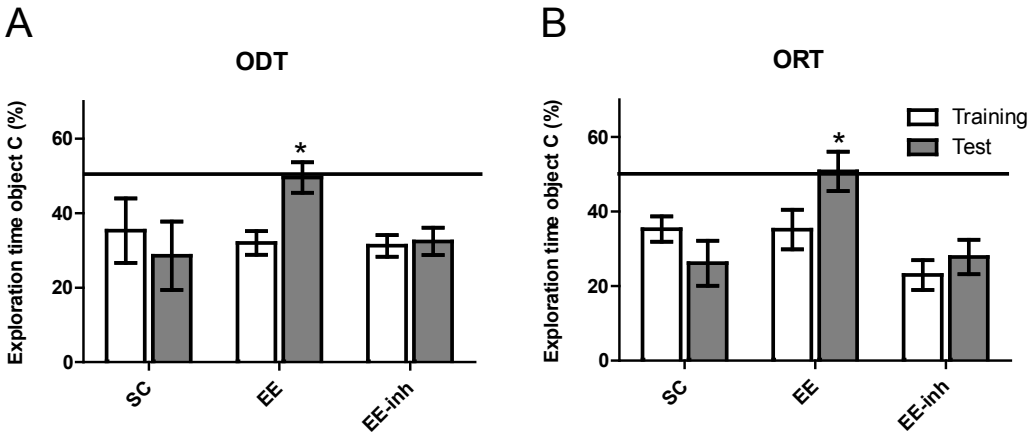

Fig. 4. Percentage of time that rats spent exploring the displaced (A) or the replaced (B) object in hypoxic conditions (Jungfraujoch). Line at 50% of the total exploration time represent a significant recongnition of change. P ≥ 0.05.*

In conclusion, high-altitude impairs memory learning in rats. This memory loss can be recovered with EE and exercise, showing a tight interplay between activity induced blood flow (VEGF mediated angiogenesis) and neural activity modulation. Angiogenesis is not only crucial in memory recovery in high-altitude but also for keeping spatial memory at normoxic conditions. Our work shows the tight interplay between the vascular and the neural network in information processing.

Key words:

VEGF, angiogenesis, environmental enrichment, altitude-hypoxia, spatial memory, visual memory

Collaborating partners/networks:

The work has been done in collaboration between the Institute of Veterinary Physiology at the University of Zürich, Switzerland and the University of Bilbao, Spain.

Scientific publications and public outreach 2014:

Conference papers

Schneider Gasser, E.M., H. Bengoetxea, D. Kosenkov, M. Alvarez Sánchez, M. Thiersch, B. Canto Matorrel and E.G. Argandoña, Environmental enrichment including physical exercise revert high-altitude induced impairment of spatial and visual memory in rats, Annual Meeting of the Swiss Society of Neuroscience, Fribourg, Switzerland, January 24, 2015.

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