Name of research institute or organization:

Institute of Veterinary Physiology, University of Zürich (UZH)
Department of Medicine, Unit of Anatomy, University of Fribourg

Title of project:

Effects of enriched environment (EE) including exercise and Vascular Endothelial Growth Factor (VEGF) on rats' memory performance at high altitude (3450 m)

Project leader and team:

Dr. Enrike G. Argandoña, project leader (University of Fribourg)
Dr. Edith Schneider Gasser, project coordinator (UZH)
Dr. Markus Thiersch (UZH)
Dr. Lavinia Alberi (University of Fribourg)
Ms. Maria Alvarez Sanchez (UZH)
Ms. Caroline Leuenberger (UZH)
Mr. Dmitry Kosenkov (guest)
Prof. Max Gassmann (UZH)

Project description:

The 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 oxygene and energy demand changes, VEGF 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 funtions 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. Furthermore we investigated whether EE before ascent to high altitude can be sufficient to prevent memory impairement.

MATERIAL AND METHODS

Long Evans rats were housed in Zürich (400 m) from ages P40 to P49 and then transported to the Jungfraujoch High Altitude Research Station, Jungfraujoch (3450 m.a.s.l.) on a trip of 250 minutes. We used the following cohorts of 8 rats each: rats housed in Zürich and Jungfraujoch in standard laboratory conditions (SC) (SC-SC), rats housed in Zürich in SC and at Jungfraujoch in EE (SC-EE), rats housed in Zürich in EE and at Jungfraujoch in SC (EE-SC); and rats housed in Zürich in SC and at Jungfraujoch in EE, treated orally with a VEGF inhibitor (Vandetanib) (VANDE). After two days of acclimatization and three days of adaptation to the open field arena (diameter 1 m; height 0.5 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. The spatial test is tested by the ability of an animal to recognize the change in the quadrant position of one object (Object C).
During the training phase, each rat is allowed to three times freely explore the arena 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 in the same position replaces object C (figure 1C lower schema). The time spent exploring the familiar objects and the novel object is recorded and expressed as a percentage of the total exploration time.

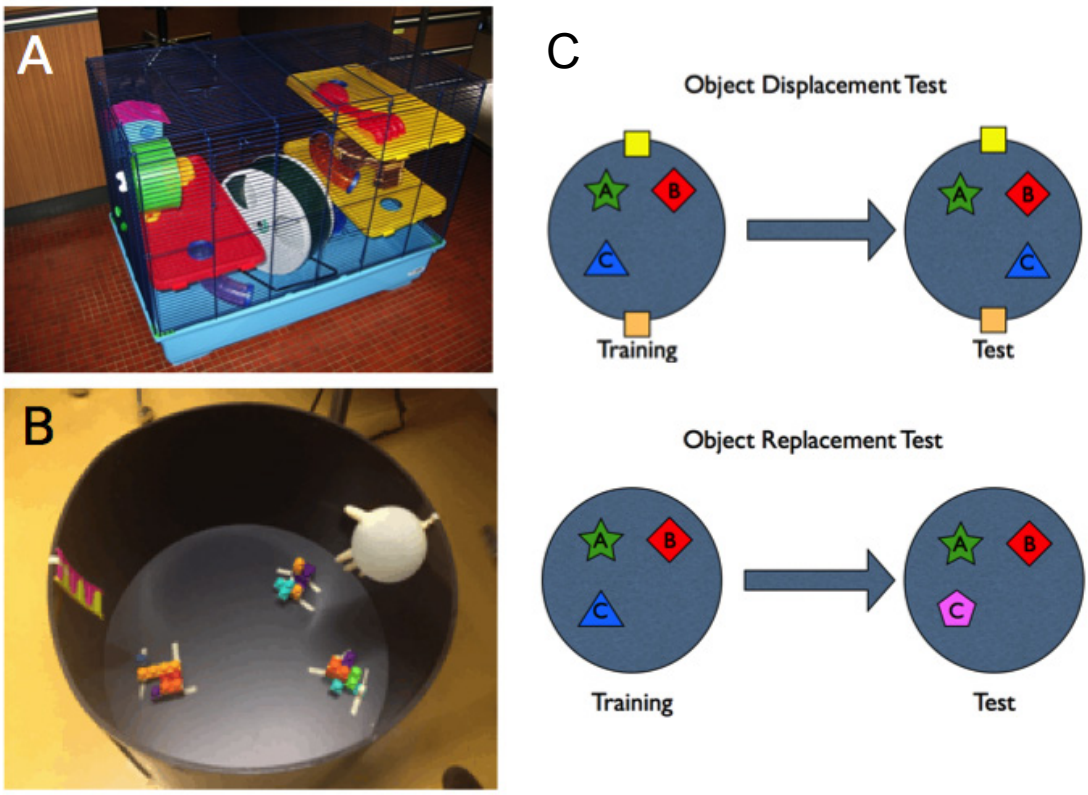

Figure 1. Pictures of the cage used for Environmental Enrichment (A) and of the open field arena arranged for an ODT (B). Schemas of Object Displacement Test (ODT) (upper schema) and Object Replacement Test (ORT) (lower schema) (C). ODT reflects Spatial Learning and Memory and ORT visual learning and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

RESULTS

Rats that were housed in EE at Jungfraujoch (SC-EE) showed a general decrease exploratory behaviour. However spatial and visual learning was improved compared to rats of the same age raised at JFJ at SC (Figure 2 second group). When rats were raised between days P40 to P49 in EE at mild altitude (400 m, Zürich) and then hosted between P49 and P59 at Jungfraujoch in SC (EE-SC), exploratory behaviour and spatial learning was increased as compared to SC-SC rats, but visual learning was not different from SC rats (Figure 2 fourth group). This result indicated that EE, including exercising before ascending to high altitude, can improve spatial learning skills. The group of rats that took a VEGF inhibitor, although they showed an increased exploratory behavior during the tests, failed to recognize the displaced or replaced object; therfore we can conclude that EE mediated memory improvement in high altitude is, at least in part, mediated by VEGF.

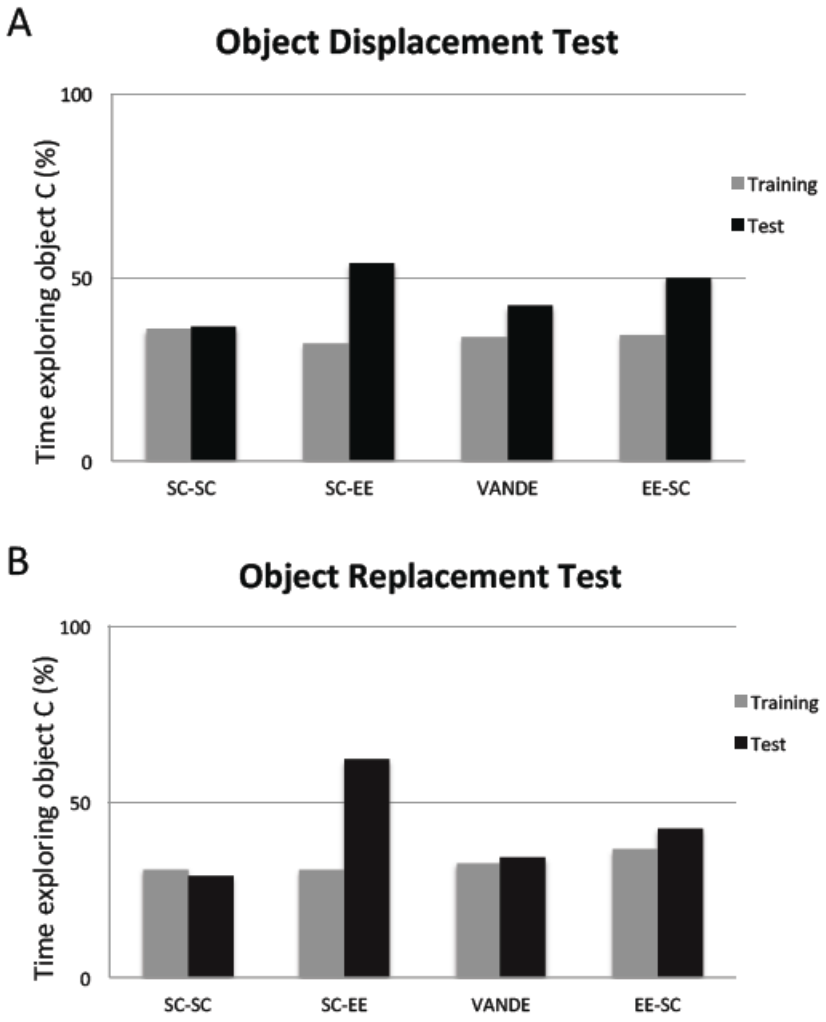

Figure 2. Percentage of time rats spent exploring the displaced (A) or the replaced (B) object. The test is positive when the animal explores object C more than 50% of the total time.

In conclusion our results show that exercise and EE can play a protective role to memory impairment in high altitude, through adaptive VEGF mediated angiogenesis. Exercise and EE before ascending to high altitude can also partially protect from memory loss, but whether VEGF is also playing a role in this preconditioning still has to be investigated. Our results are from high relevance to understand the neuroprotective effects of VEGF in hypoxic conditions and to validate the importance of EE and sport in preconditioning and during high altitude exposition.

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 Fribourg in Zürich.

Scientific publications and public outreach 2013:

Conference papers

Argandoña, E.G., H. Bengoetxea, S. Bulnes, R. Ledezma, N. Ortuzar, I. Rico-Barrio, J.V. Lafuente, Environmental enrichment reverts the cognitive effects of altitude hypoxia inducing changes at the neurogliovascular unit, Annual Meeting of the Swiss Society of Neuroscience, Geneva, Switzerland, February 2, 2013.

Argandoña, E.G., S. Marathe, L. Alberi, Environmental enrichment reverts the cognitive effects of altitude hypoxia, 75th Annual Meeting of the Swiss Society for Anatomy, Histology, and Embryology, Fribourg, Switzerland, September 6, 2013.

Argandoña, E.G., S. Marathe, L. Alberi, Environmental enrichment reverts the cognitive effects of altitude hypoxia, Neurogune 2013, Basque Neuroscience Meeting, Bilbao, Spain, July 8, 2013.

Schneider Gasser, E.M., M. Alvarez Sánchez, M. Thiersch, L. Alberi, D. Kosenkov, C. Leuenberger and E.G. Argandoña, Environmental enrichment including physical exercise reverts high-altitude induced impairment of spatial and visual memory in rats, Annual Meeting of the Swiss Society of Neuroscience, Bern, Switzerland, January 25, 2014.

Schneider Gasser, E.M., M. Alvarez Sánchez, M. Thiersch, L. Alberi, D. Kosenkov, C. Leuenberger and E.G. Argandoña, Environmental enrichment including physical exercise reverts high-altitude induced impairment of spatial and visual memory in rats, FENS Forum, Milano, Italy, July 5-9, 2014.

Address:

Edith M. Schneider Gasser
Institute of Veterinary Physiology
University of Zürich
Winterthurerstrasse 260
CH-8750 Zürich

Contacts:

Edith Schneider Gasser
Tel.: +41 63 588 17
Fax: +41 63 589 32
e-mail: edith.schneidergasser@uzh.ch

Enrike G. Argandoña
Tel.: +34 946015606
e-mail: eg.argandona@ehu
URL: http://www.ehu.es/ehusfera/lance/