Name of research institute or organization:

Department of Medicine, Unit of Anatomy, University of Fribourg

Title of project:

Effects of physical exercise and Vascular Endothelial Growth Factor on the neurogliovascular adaption to hypoxia

Project leader and team:

Dr. Enrike G. Argandoña, project leader

Project description:

Microvascular environment plays a fundamental role in the adaptive response to increases in activity, involving an increase in energy demand. To punctual increases in demand, the response is effected by changes in local flow, but if demand remains high, angiogenic process is triggered through the formation of new capillaries from preexisting vessels. The trigger factor of angiogenesis is local neuronal hypoxia as result of increased activity, mediated by angioglioneurins whose main exponent is VEGF. There are situations in which hypoxia is not from an increased activity, but from a decrease in available oxygen, as occurs in the altitude exposure. Our goal is to study the changes underlying microvascular acute adaptation to moderate altitude and the possible effects of physical exercise and environmental enrichment and the behavioural effects of acute altitude hypoxia on spatial and visual memory.

MATERIAL AND METHODS

Long Evans Rats were bred at 600 m (P45) and transported to the Jungfraujoch High Altitude Research Station (3450m) in a trip of 150 minutes. We used the following cohorts of 5 rats each: a group was housed indoors in standard laboratory conditions, another group was housed in an enriched environment including free access to running wheel. Behavioural tests were performed from P49 to P56 after a 3 days adaptation to the arena. The environment used for the tasks consists of a black circular open field (diameter 1 m; height 0.5 m) in a dimly-lit room. The objects which have been subjected to exploration of rats are constructed from toy bricks and are fixed to the floor of the open field, 15 cm from the walls. A spatial cue is fixed to the wall. Spatial memory was measured by the Object Displacement Test (ODT), visual memory was measured by the Object Replacement Test (ORT).

a) Object Displacement Test (ODT)

For the training phase of the OD task, three objects are positioned in the open field with spatial cues. For training, each rat is allowed to explore the objects for 3 x 5 minute trials with an inter-trial rest period of 5 minutes. For the testing phase, object C is moved from its original position and rats are reintroduced to the open field 24 hours post-training, for a single 5 minutes trial for each series of experiments. The time spent exploring object C is expressed as a percentage of the total exploration time.

b) Object Replacement Test (ORT)

For the training phase of the OS task, three new objects are positioned in the open field without spatial cues. Training is same as OST with 2 days lap. For the testing phase, 24 hours later, object C is replaced with the novel object in the same position. Each rat is reintroduced to the open field for a single 5 minutes trial. The time spent exploring the familiar objects and the novel object is recorded and expressed as a percentage of the total exploration time.

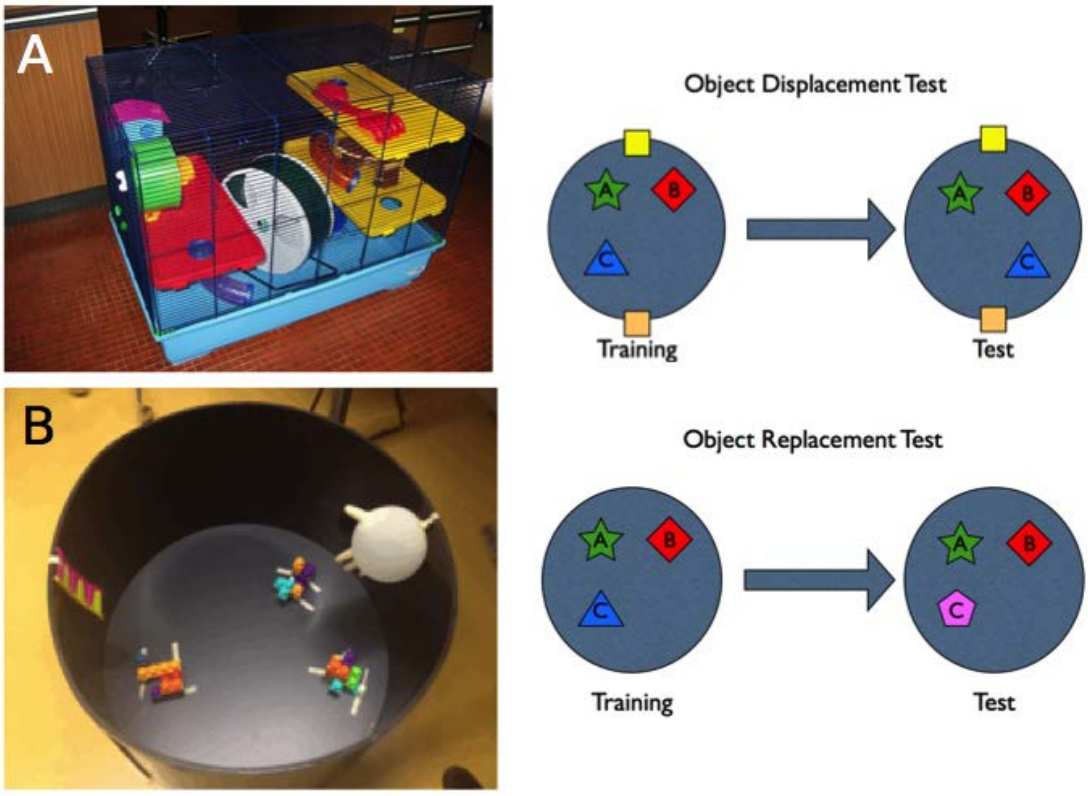

Fig. 1a: Pictures of the cage used for Environmental Enrichment (A) and for the arena used for Behavioural tests (B). Picture (B) shows the set for the Object Displacement Test with the three objects and the spatial cues. Fig. 1b: Schema of the Tasks for Object Displacement (ODT) and Object Replacement (ORT). First reflects Spatial Learning and Memory, second Visual Learning and Memory. After a training session composed by 3x5' exposure, the following day a unique session of 5 min. is done by changing the position of one of the objects (ODT) or by changing one of the objects in the same position (ORT).

RESULTS

Behavioural experiments show a trend towards a higher exploration activity in environmentally enriched rats, as well as a better performance in visual and spatial learning and memory, as transportation to altitude produced a significant deficit in spatial and non-spatial learning and memory.

*Fig. 2: The graph shows the total exploration time for behavioural tests (in seconds) and the percentage of time exploring the Displaced object (ODT) or the Replaced one (ORT). * shows significance between standard environment (std) and Environmental Enrichment (EE).*

The acute adaptation to moderate altitude is an increasingly relevant issue given the increase in displacements at moderate or high altitudes, with serious consequences such as acute mountain sickness, which in its most severe degree leads to brain edema. Our results show that exercise can play a protective role through adaptive angiogenesis. On the other hand, although exploration time did not differ significantly, altitude seems to have effects on both spatial and visual memory, which are compensated by rearing in a complex environment. More research on the role of angiogenesis in adaptive mechanisms should be performed.

Key words:

Angioglioneurins, neurogliovascular unit, environmental enrichment, altitude hypoxia, learning and memory

Collaborating partners/networks:

I have made a collaboration with the Institute of Veterinary Physiology, University of Zürich, Switzerland, and eventually we will try to finish the project all together. Also I started a collaboration with Dr. Juan Carlos López Ramos, División de Neurociencias, Universidad Pablo de Olavide, Sevilla, for a future collaboration on the same field of adaptation to altitude in rodents. Therefore a way to allow research from Spain has to be explored.

Scientific publications and public outreach 2012:

By now all scientific publications are in progress, and they are due for 2013, nevertheless, the advances have been presented at some conferences and can be accessed online. A paper with preliminary results on the same field, (but not at the HFSJG) can be consulted to understand the basis of the project.

Refereed journal articles and their internet access

Argandoña E.G., H. Bengoetxea, S. Bulnes, N. Ortuzar, I. Rico-Barrio, J.V. Lafuente, Vascular Endothelial Growth Factor: Adaptive changes in the neuroglialvascular unit, Current Neurovascular Research, **9**, 1, 72-81, doi: 10.2174/156720212799297119, 2012.
http://www.eurekaselect.com/76454/article

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, 74th Annual Meeting of the Swiss Society for Anatomy, Histology, and Embryology 2012, F1000 Posters 2012, 3: 1302, Zurich, Switzerland, September 7, 2012.
http://f1000.com/posters/browse/summary/1092456

Argandoña, E.G., H. Bengoetxea, S. Bulnes, R. Ledezma, N. Ortuzar, I. Rico-Barrio, J.V. Lafuente, Physical exercise mediates neuroprotective responses to the effects of altitude hypoxia at the neurogliovascular unit, 8th FENS Forum of Neuroscience 2012, F1000 Posters 2012, 3: 1043, Barcelona, Spain, July 14-18, 2012.
http://f1000.com/posters/browse/summary/1092145

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, 2013 Annual Meeting of the Swiss Society of Neuroscience, Geneva, Switzerland, February 2, 2013.

Radio and television

Arratoien garuna ikertzen 3.500 metrora (Investigating rat brains at 3500 m), Interview with neuroscientist Enrike G. Argandoña, University of Fribourg, Euskadi Irratia, "Mezularia" April 10, 2012.
http://www.eitb.com/eu/audioak/osoa/865531/arratoien-garuna-ikertzen-3500-metrora--mezularia/ (Basque)

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