Hypergravity-induced molecular and biochemical changes in the rat central nervous system

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Abstract

In the present study, we aimed to clarify the mechanisms responsible for the adaptation to altered gravity and space motion sickness through examining the molecular, biochemical and behavioral changes seen in the rat following exposure to hypergravity (2G). Hypergravitational environment was produced by a centrifuge device.

The most striking difference between space and ground is a lack of gravity in space. Linear acceleration including gravity is sensed by otolithic pathways. Therefore, it could be assumed that possible plastic changes which have influences on the otolithic pathways from the level of the vestibular periphery to the level of neurotransmission in the central vestibular system might be responsible for the adaptation to altered gravity. For this purpose, we investigated the changes in morphology and synthesis of otoconia and mRNA expression of various glutamate receptor subunits/subtypes in the vestibular ganglion cells, vestibular nucleus and vestibulocerebellum following hypergravity using real-time quantitative PCR methods. Not only the above mentioned peripheral and central vestibular systems but also the limbic systems (amygdala and hippocampus) and hypothalamus, which have a role in emotion, spatial information processing and regulation of the autonomic nervous system, would be important for the development of space motion sickness. To explore the key areas in the brain responsible for the space motion sickness, we performed immunohistochemistry using antibody against Fos protein as a marker of neuronal activation following hypergravity. We also performed lesion-studies of these areas to test whether these areas are important for the development of space motion sickness using pica, a behavioral marker of emesis. Lastly, we measured glutamate release from these areas during hypergravity exposure in freely behaving rats using microdialysis methods.

The results showed that neither morphology nor synthesis of otoconia was affected by hypergravity, suggesting that otoconia itself has only minor role in the adaptation to altered gravity. The mRNA expression of GluR2 and NR1 receptors in the uvula/nodulus increased in animals exposed to 2 hs-hypergravity, and it decreased gradually to the control level. The mRNA expression of GluR2 receptors in vestibular ganglion cells decreased in animals exposed to 1 week-hypergravity. It is suggested that the animals adapted to the hypergravity by enhancing the cerebellar inhibition of the vestibular nucleus neurons through activation of the NR1 and GluR2 receptors on the Purkinje cells in uvula/nodulus especially at the early phase following hypergravity. In the later phase following hypergravity, the animals adapted to the hypergravity by
reducing the neurotransmission between the vestibular hair cells and the primary vestibular neurons via down-regulation of the post-synaptic GluR2 receptors in the vestibular periphery. Marked Fos expression was induced in the central nucleus of amygdala following hypergravity and the lesion of the amygdala suppressed the pica behavior, a marker of emesis, following hypergravity. It is suggested that amygdala was activated by hypergravity and was important for the development of space motion sickness. In contrast, glutamate release from the hippocampus examined by microdialysis methods was not affected by hypergravity, and lesion of the hippocampus and vestibulocerebellum did not affect the pica behavior induced by hypergravity, suggesting that neither hippocampus nor vestibulocerebellum was involved in the development of space motion sickness.

In this study, we found some significant changes using multimodal methods including molecular, biochemical and behavioral techniques. These results would account for the mechanisms responsible for the adaptation to gravity changes and space motion sickness, however, we have to pay attention that these studies were simulation tests performed on the ground using a centrifuge device to produce hypergravity and that it is not a real experiment performed in space. Further studies to repeat the same experiments in space are necessary to clarify the mechanisms for the adaptation to altered gravity and space motion sickness seen in the exposure to minor gravity.

List of publication
Nakagawa, A., Uno, A., Horii, A., Uno, Y., Nishiike, S., Kitahara, T., Takeda, N., Kubo, T.: cFos expression in the amygdala by hypregravity and its relation to motion sickness
in rats, *Brain Res.* (submitted)