Protection against neurodegenerative disease on Earth and in space

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All living organisms have evolutionarily adapted themselves to the Earth’s gravity, and failure to adapt to gravity changes may lead to pathological conditions. This perspective may also apply to abnormal aging observed in bedridden elderly patients with aging-associated diseases such as osteoporosis and sarcopenia. Given that bedridden elderly patients are partially analogous to astronauts in that both cannot experience the beneficial effects of gravity on the skeletal system and may suffer from bone loss and muscle weakness, one may wonder whether there are gravity-related mechanisms underlying diseases among the elderly. In contrast to numerous studies of the relevance of microgravity in skeletal disorders, little attention has been paid to neurodegenerative diseases. Therefore, the objective of this paper is to discuss the possible relevance of microgravity in these diseases. We particularly noted a proteomics paper showing that levels of hippocampal proteins, including β-synuclein and carboxyl-terminal ubiquitin hydrolase L1, which have been linked to familial neurodegenerative diseases, were significantly decreased in the hippocampus of mice subjected to hindlimb suspension, a model of microgravity. We suggest that microgravity-induced neurodegeneration may be further exacerbated by diabetes and other factors. On the basis of this view, prevention of neurodegenerative diseases through ‘anti-diabetes’ and ‘hypergravity’ approaches may be important as a common therapeutic approach on Earth and in space. Collectively, neurodegenerative diseases and space medicine may be linked to each other more strongly than previously thought.

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INTRODUCTION

In our aging society, an increasing number of elderly people are becoming bedridden owing to frailty derived from age-related disorders, such as osteoporosis and sarcopenia. As these patients are forced to be in a supine-immobilized posture combined with no axial loading, they cannot experience the beneficial effects of gravity on the skeletal system. Accordingly, they are often compared with astronauts who suffer from muscle weakness and bone fragility upon return to Earth because their skeletal systems are not used to microgravity and degenerate in space. Thus, geriatrics and space medicine, two seemingly different fields, may be linked to each other.

There have been numerous studies of the effect of microgravity on degeneration of the skeletal system, but few on the relevance of microgravity to age-related neurodegenerative diseases, such as Alzheimer’s disease (AD) and Parkinson’s disease (PD). However, it is recognized empirically that dementia in elderly patients may accelerate after they become bedridden. If skeletal unloading in bedridden patients is partially analogous to the effect of microgravity in space, then there is a possibility that neurodegenerative disease may be accelerated in astronauts.

In this paper, we discuss the possible relevance of microgravity in neurodegenerative disease. First, neurons may be predisposed to degenerate under microgravity, based on a proteomics paper showing marked changes in protein expression levels in the hippocampus of mice subjected to hindlimb suspension. In addition, microgravity-induced neurodegeneration may be amplified by cosmic rays and other factors, such as alteration of behaviors and diabetes, in space. We propose that preventive strategies for neurodegenerative diseases will be important on Earth and in space.

MOUSE HINDLIMB SUSPENSION AS A MODEL FOR NEURODEGENERATION IN SPACE

To investigate the effect of microgravity on protein expression in the hippocampus, Sarkar et al. carried out a proteomic analysis on hippocampal tissues from mice subjected to hindlimb suspension. Interestingly, the levels of some proteins that are abundantly expressed in the normal hippocampus were significantly decreased (Figure 1a). These proteins included β-synuclein (βS), the non-amyloidogenic homolog of α-synuclein (αS), which has a central role in PD and related neurodegenerative diseases. Neurodegeneration in mice expressing αS is ameliorated by cross-breeding with mice expressing αS and βS, and viral delivery of βS reduces neurodegeneration in mice expressing αS. Moreover, the ratio of βS to αS at the mRNA level is significantly decreased in post-mortem brains of patients with PD, dementia with Lewy bodies, and AD, compared with the ratio in control brains. These results suggest that loss of function of βS may be involved in the pathogenesis of neurodegenerative diseases.

Expression of carboxyl-terminal ubiquitin hydrolase L1 (UCHL1) was also decreased in mice after hindlimb suspension (Figure 1a). UCHL1 is a deubiquitinating enzyme that is critical in recycling of ubiquitin, and impairment of this molecule has been implicated in various neurodegenerative diseases, including AD, PD, and...
Impairment of vestibular function is a serious symptom stimulated by time in space\(^1\) and is also a neuropathological feature of AD.\(^{16}\) Vestibular dysfunction may influence multiple biological processes, including bone integrity,\(^{17}\) sense of self,\(^{18}\) and even cognition in space;\(^{19}\) therefore, it is difficult to distinguish cognitive dysfunctions due to vestibular effects from neurodegenerative diseases on Earth and in space.

It is also possible that cognitive dysfunction may be stimulated by other non-dementia conditions. These include the relative lack of mental stimulation and motor activity during bed rest, and the relative monotony of sensory stimulation while in a spacecraft, both of which might contribute to neural decline, especially in the cognitive area. Thus, differential diagnosis of dementia is important in space.

**DIFFERENTIAL DIAGNOSIS OF COGNITIVE DYSFUNCTION**

Impairment of vestibular function is a serious symptom stimulated by time in space\(^2\) and is also a neuropathological feature of AD.\(^{16}\) Vestibular dysfunction may influence multiple biological processes, including bone integrity,\(^{17}\) sense of self,\(^{18}\) and even cognition in space;\(^{19}\) therefore, it is difficult to distinguish cognitive dysfunctions due to vestibular effects from neurodegenerative diseases on Earth and in space.

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**EXACERBATION OF NEURODEGENERATION BY OTHER FACTORS IN SPACE**

It may be argued that the effects of microgravity on neurodegenerative diseases are too small to be observed as a disease in astronauts. However, even if neurodegeneration induced by microgravity is minimal by itself, it might be potentiated by cosmic rays,\(^7\) altered behaviors and diseases such as diabetes in space (Figure 1b).

Concerns have often been raised about the risk of cosmic rays in space.\(^1\) In particular, galactic cosmic radiation consisting of high-energy, highly charged particles may pose a significant threat to astronauts. Such cosmic rays may promote development of cancers, as well as neurodegenerative diseases. Indeed, cognitive impairment and Alzheimer plaque formation have been shown to be enhanced in an AD mouse model irradiated with high-energy\(^ {56}\) Fe particles.\(^7\) Furthermore, psychological and behavioral changes, such as depression and sleep disorders, are frequently associated with spaceflight.\(^{10}\) and various cohort studies have shown that depression may increase the risk of neurodegenerative diseases, including AD and PD.\(^{21,22}\) Sleep and neurodegenerative disease may influence each other,\(^{23}\) given that the circadian rhythm tends to be irregular in space.\(^1\) In this context, it is of a note that the sleep-wake cycle directly influences the Aβ level in the brain.\(^{24}\) An abnormal autonomic nerve reflex also occurs in space, including non-coordinated heart rates, reduction of blood pressure and syncope.\(^25\) These symptoms may predispose an individual to neurodegenerative diseases, and symptoms of abnormal autonomic nerve reflex have been described in α-synucleinopathies, such as PD and multiple system atrophy.\(^{26}\)

Other diseases might also exacerbate microgravity-induced neurodegeneration on Earth and in space. Among these, diabetes may be of a particular importance (Figure 1b), since it is associated with an increased risk of neurodegenerative diseases, including AD, PD, and HD.\(^ {27,28}\) Indeed, several studies suggest that neurodegenerative diseases have aspects of lifestyle diseases and are associated with metabolic dysfunction.\(^ {27,29}\) In space, microgravity may stimulate diabetes because it is predicted that muscle atrophy due to microgravity may result in a failure of energy consumption, leading to metabolic dysfunction.

**‘ANTI-DIABETES’ STRATEGIES TO PROTECT NEURONS**

Given the importance of diabetes on Earth and in space,\(^1\) an ‘anti-diabetes’ approach may be a common therapeutic strategy in neurodegenerative disease. In this regard, increasing attention has been paid to the therapeutic potential of anti-diabetic hormones, such as incretins and adiponectin (APN), for neurodegenerative disease. Glucagon-like peptide 1 (GLP-1) is a member of the incretin family that is secreted by the small intestine in response to food intake.\(^{30}\) GLP-1 improves insulin resistance without hypoglycemia,\(^{30}\) and thus may be useful to replace the neuroprotective
effects of insulin. Analogs of GLP-1, such as exenatide and liraglutide, have been shown to be effective in a pilot study in type II diabetes mellitus without any side effects.23

Accumulating evidence suggests that APN, a multifunctional adipocytokine, may be protective for brain disorders, such as ischemia and depression, in addition to other diseases, including type II diabetes, atherosclerosis, osteoporosis, and chronic pulmonary obstructive disease. Owing to the beneficial effects of APN on a wide range of diseases, APN signaling has been suggested as a mimetic of exercise. APN binds to APN receptors, AdipoR1 and AdipoR2, and exerts anti-diabetic effects via activation of signaling molecules, including AMPK and PPAR-α. As APN receptors are abundant in the brain, stimulation of APN signaling may be an approach to prevention of neurodegenerative diseases. In support of the therapeutic potential of APN, we recently showed that APN-ameliorated neuropathological features, such as aggregation of αS and impaired motor function, in a transgenic mouse model of α-synucleinopathies (Figure 2). Subsequently, osmotin, the plant homolog of APN, was shown to attenuate Aβ42-induced neurotoxicity and tau hyperphosphorylation in the mouse hippocampus. Furthermore, it is of note that AdipoRon, an AdipoR agonist, was isolated as a small molecule that ameliorates diabetes in a genetic mouse model, raising the possibility that AdipoR agonists may be promising as therapy for type II diabetes. Similarly, it will be intriguing to determine whether AdipoR agonists are effective for protection against neurodegenerative diseases on Earth and in space.

At this time, follow-up of a large number of astronauts who have been in space for long periods is required to determine whether neurodegenerative diseases are manifested or exacerbated by microgravity in space. Furthermore, it is unclear whether protective drugs against neurodegenerative diseases are needed on a regular basis in space. The astronaut population is thoroughly screened for preexisting conditions, such as diabetes, and regular exercise is successfully performed by most astronauts in space. However, it would be wise to have such an intervention on hand in an emergency or as a contingency, should there be an inability to exercise due to injury or equipment breakdown, or in excursions in small spacecraft without adequate exercise facilities.

**HYPERGRAVITY THERAPY** AGAINST NEURODEGENERATIVE DISEASES?

Given the negative effect of microgravity on aging-associated disorders, including osteoporosis, sarcopenia, and diabetes, it is possible that hypergravity may be beneficial for these disorders (Figure 3). Interestingly, such a concept goes back >200 years to Dr Erasmus Darwin, a British physician who was the grandfather of Charles Darwin. Metabolic rates may be upregulated because of increased energy consumption under hypergravity conditions, which may be compared with the beneficial effects of exercise. Therefore, ‘hypergravity therapy’ may be regarded as an ‘anti-diabetes’ strategy. Naturally, a similar view is applicable to prevention of neurodegenerative diseases on Earth and in space. Thus, now is the time for us to demonstrate Darwin’s hypothesis in the therapy of neurodegenerative diseases. In support of ‘hypergravity therapy’, it has been shown that hypergravity may be beneficial in aging diseases, such as bone atrophy and ischemia. However, hypergravity may also cause side effects, and it has been suggested that the circadian system is disrupted by chronic centrifugation, possibly due to hypergravity.

**CONCLUSIONS**

Given the possibility of long-term stays in space in the near future, improved understanding of microgravity-induced neurodegeneration is important. In particular, an ‘anti-diabetes’ strategy, a current paradigm for therapy of neurodegenerative diseases on Earth, may be applicable to protection against possible neurodegenerative diseases in space. In turn, hypergravity may be promising for

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Figure 2. APN ameliorates neurodegeneration in a mouse model of α-synucleinopathies. (a) Globular APN (gAPN, 0.1 mg/ml in 10 μl phosphate buffered saline (PBS)) or PBS alone (10 μl) was given intranasally to αS transgenic (tg) mice (male, 3 months old) or wild-type littermates every 3 days for 2 months. Motor performance was evaluated by the rotarod test (mean ± s.e.m., n = 8–9, *P < 0.05, **P < 0.01). (b) Mice were killed and their brains were analyzed immunohistochemically (anti-phospho-αS). Representative images of the cortex and olfactory bulb are shown. Insets show a higher magnification of the cortex. Reprinted from Sekiyama et al. APN, adiponectin.

Figure 3. A hypothetic model for the effects of gravity on aging-associated diseases. Aging-associated diseases, such as osteoporosis, sarcopenia, diabetes, and neurodegenerative diseases, may be exacerbated under microgravity conditions (e.g., bedridden patients and astronauts), whereas these diseases may be improved by hypergravity (e.g., therapeutic applications). G, gravity.
treatment of diseases of aging, including neurodegenerative diseases, in space and on Earth. Thus, geriatrics and space medicine may be mutually supportive in the context of treatment of neurodegenerative diseases.

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CONTRIBUTIONS

YT, WK and MH wrote the paper. TT, SS, JW, MW and KS discussed the idea of the paper. All authors have approved the manuscript.

COMPETING INTERESTS

The authors declare no conflict of interest.

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