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Review Article

Cell Therapy Products in Alzheimer Disease

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We are rapidly becoming an aging society, with the ongoing increase in challenges of the elderly. The age-related cognitive decline in accordance with aging society is of major importance in public health. Recent studies have proved the impacts of sex-steroid hormone on the brain; compliant with aging, menopause and decrease in estrogen have an effect on the occurrence and prevention of Alzheimer's disease. A new hypothesis states that Alzheimer's disease is a postmenopausal dementia, and is a negative form of estrogen deficiency. In this review article, we reckoned the cause of postmenopausal Alzheimer's disease. We further investigated new cell therapies for postmenopausal Alzheimer's disease, which are under development in some pharmaceutical companies. One remedy is cell therapy that inhibits the amyloid beta formation, and the other is the umbilical cord blood derived mesenchymal stem cell therapy. **(J Menopausal Med 2017;23:1-4)**

Key Words: Alzheimer's disease · Cell- and tissue-based therapy · Menopause · Stem cells

Introduction

The population of Republic of Korea is aging at an unprecedented fast rate. And per capita medical utilization due to geriatric illness has increased since 2002 in accordance with an aging society. Among geriatric diseases in women, there are some diseases related to menopause in this aging society.[1] Average menopause age and average life expectancy is 49.7 and 85.5, respectively in Korean women, which means that they almost suffer from postmenopausal symptoms for two-fifth of their lives. The postmenopausal period in women has increased in accordance with increase in average life expectancy. Therefore, healthcare and management for postmenopausal women has become important issues recently.[2] Incidence of Alzheimer's disease, one of postmenopausal diseases, rapidly increases after 65 years old in women, which is 1.5 to 3 times higher than men's incidence. And cognitive function is decreased more when bone loss is occurred fast, which implies that there is a strong relevance between endogenous estrogen and Alzheimer's disease.[3] Appropriate brain action is controlled by estrogen in women. Therefore, disorder in mood, memory, and cognitive function can be happened when estrogen level is dropped under estrogen setting point: For some reason, or at any time or at any age, the brain's estrogen levels are decreased below estrogen setting point which defined as brain's estrogen requirement level needed to modulate the brain activity.[3] Cholinesterase inhibitors, donepezil, rivastigmine, N-methyl-D-aspartate (NMDA)-glutamate receptor, and memantine, are mainly used for

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the treatment of Alzheimer's disease generally. Although these drugs can improve cognitive function of patients with Alzheimer's disease temporally, adverse effects and toxicity can be occurred in case of long-term use. Because of these problems, interests toward hormone therapy and cell therapy have been increased.[1] Cell therapy can compensate the defects and limitations of existing chemical medicines and become newly developed treatment for Alzheimer's disease. Besides Alzheimer's disease, it can be used as treatment for other perimenopausal symptoms. Therefore, we will figure out trend of studies about cell therapy for Alzheimer's disease.

Alzheimer's Disease and Estrogen Deficiency

Estrogen deficiency caused by menopause is related to heart disease, stroke, colon cancer, osteoporosis, fracture, and Alzheimer's disease, etc. Also, serotonin extinction induced by low progesterone and norepinephrine causes depression and gives negative effects on mood, sleep, and appetite. Alzheimer's disease affects patients' daily lives and causes disorders such as decrease in memory, linguistic ability, intellectual capacity and changes in personality, depression, dromomania, anxiety, aggression, unstable sleep, dromomania at night, etc. These behavioral and mental disorders are strongly related to malfunction of neurochemicals such as gamma-aminobutyric acid (GABA), norepinephrine, dopamine, serotonin.[4] Sex steroid hormones like estrogen affect brain in two different ways in accordance with development process of central nervous system (CNS): Organizational effect, activational effect. Estrogen receptor in the CNS is expressed in multiple regions like hippocampus, hypothalamus, pituitary, etc. CNS is representative target organ of sex-steroid hormone. According to animal experiment and clinical studies, it negatively affects pathological pathways and estrogen production, consequently lead to behavioral disorders and diseases such as changes in mood, function of sensory organ, convulsion and pain sensitivity and Parkinson's disease, etc. Especially, appropriate brain action in postmenopausal women depends on estrogen level. Estrogen is associated with the activation of acetylcholine which modulates cognition, learning and memory. When estrogen level is dropped below the estrogen setting point, which is brain's estrogen requirement level needed to modulate the brain activity, malfunction in brain center occurred. Finally, it probably causes disorder in mood, memory, and cognitive function regardless of reasons, stages and ages. Generally, rapid loss of estrogen below the estrogen setting point is occurred physiologically in postmenopausal women.[3] And significant changes are seen in estrogen receptors in the CNS under estrogen setting point, accordingly, behavioral changes are observed as well. Estrogen controls neurotransmitters in the CNS and it improves mood, triggers irritability. And it increases dendritic spine and synapse of neuron by stimulating neuron formation in brain. On the other hand, progesterone, estrogen antagonist, maintains balance of the CNS. There is no obvious study of whether estrogen levels in all postmenopausal women fall below the estrogen setting point. However, studies on relationship between estrogen and Alzheimer's disease suggest that aging and estrogen loss in postmenopausal women are possible risk factor for Alzheimer's disease: the incidence of Alzheimer's disease is particularly high in women aged over 65. Body weight has also been suggested as a risk factor of Alzheimer's disease: higher body weight increases the level of blood estrogens, and lower body weight is common among patients with Alzheimer's disease. Recently, a hypothesis that Alzheimer's disease is a type of postmenopausal estrogen deficiency has been raised. Regarding this hypothesis, some studies suggested that postmenopausal estrogen deficiency damages specific part of the CNS related to the factors affecting neuropathic changes and causing aging and Alzheimer's disease.[5]

Alzheimer Disease and Melatonin

Melatonin, known as sleep-inducing hormone, is effective in treating Alzheimer's disease and autism, etc. Usually, daily sleeping time decreases as people gets older. The problem is that if this insufficient sleep status lasts for a long time, cognitive functions and immune functions are getting lower and lead to high risk of neurologic diseases emergence including Alzheimer's disease. At the same time,

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inflammatory cell response in the brain hippocampus and increased level of oxidative stress are shown. And fragile X mental retardation protein (FMRP), preventing mental retardation and autism, is decreased. Lack of sleep induces oxidative stress, inflammatory response in brain cell and decreases FMRP expression, which prove that it is highly related to decreased cognitive function, neurologic diseases like Alzheimer's disease.[6]

Cell Therapy Development

When introducing cell therapy technology and its value to the general populations, diabetes mellitus and Alzheimer's disease are mainly suggested as examples that easily applicable and has a big possibility of success, although these are inveterate diseases. There is a limitation to differentiate neuron for treating Alzheimer's disease only by using biological knowledge. Because of this situation, studies on adult stem cell, fetal nerve tissue in Alzheimer's disease are rarely performed, unlike in other diseases. Despite that Alzheimer's Association tried to verify if it is possible to replace damaged neuron with neural stem cells differentiated from bone marrow mesenchymal stem cells and apply this to Alzheimer's disease in 2002, its effectiveness in Alzheimer's disease hasn't been proved yet. However, it is expected that stem cells are well worth applying to Alzheimer's disease patients for treating. Also Alzheimer's disease cell therapy using embryonic stem cells and Alzheimer's disease related mutant genes (amyloid precursor protein [APP], tau, presenilins) is currently under development. If further studies about embryonic stem cells are performed, neuroembryological and neurobiological understanding of Alzheimer's disease and its therapeutic clues can be discovered.[7]

When adipocyte stem cells are administrated intravenously to animal models with Alzheimer's disease, it pass through blood-brain-barrier (BBB) and move into brain. Consequently, positive neuropathological effects such as improvement in scholastic skills, memory were shown. In this mechanism, up-regulated interleukin-10 and neurotrophic factors, which both are neuroprotective, were shown.[8] Also, level of amyloid beta and C-protein that destroying brain cells were significantly decreased due to the effect of stem cell administration, and this is because toxoprotein proteolytic enzyme were increased. Also, stem cells grafted on brain induce neuronal differentiation, proliferation of endogenous neural precursor cell and its surrounding cells in hippocampus and improve dendrite safety.[9]

Summary

Therapeutics for Alzheimer's disease have usually been developed to improve patients' cognitive functions so far. The problem is that it just delays aggravation of symptoms, and it is impossible to expect complete recovery of Alzheimer's disease. Most of therapeutic companies around the world are developing therapeutics for Alzheimer's disease. Also, variety of therapeutics for Alzheimer's disease such as natural product, stem cell therapy have been developed in South Korea as well. For example, sex-steroid hormone including estrogen is expected to act on brain as well as used in the treatment of osteoporosis, breast cancer, etc.[10] Another example is flibanserin, which is act on brain. It controls dopaminergic and serotonergic activity neurotransmitter metabolites in brain areas including prefrontal cortex, nucleus accumbens, hypothalamus, brain stem.[11,12] However, it is expected that it takes long time to achieve good results. These days, research and development associated with Alzheimer's disease have been widely performed, and considerable efforts have been devoted to investigate the risk factors of Alzheimer's disease: It is mainly about neuron damages such as acetylcholine (neurotransmitter) composition decrease, amyloid beta deposition, tau protein hyper-phosphorylation. Decrease in choline acetyltransferase activation in cerebral cortex, hippocampus induces decrease in acetylcholine, and causes disorder in anamnesis, cognitive function. Perivascular invasion of beta-amyloid protein causes neurofibroma, nerve cell loss, blood vessel lesion, etc. secondarily, and finally lead to brain dysfunction.[13] There are two kinds of drugs for Alzheimer disease which got an approval from United States Food and Drug Administration: Cholinergic neuron control drug like donepezil and NMDA receptor antagonist drug. However, these are only effective in relieving the symptoms, whereas

it is impossible to cure underlying causes of Alzheimer's disease and prevent aggravation of symptoms. Recently, pharmaceutical companies in South Korea are promoting research and development (R&D) programs associated with Alzheimer's disease therapeutics using natural substances and stem cells. R&D about natural product drug, and its clinical tests have been proceed in large pharmaceutical companies. Not only natural product drug, but R&D about umbilical cord blood originate mesenchymal stem cell therapy, and its clinical tests are in progress. However, causes of Alzheimer's disease, which is the most important thing, haven't been proved clearly so far. Accordingly, adequate therapies haven't been developed and applied to patients with Alzheimer's disease. Therefore, not merely basic clinical study, but further specialized studies and R&D are required until therapeutics for Alzheimer's disease are commercialized.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

References

1. Jeon WK, Han CH, Kang JS, Heo EJ, Han JS, Lee YJ. Research performance evaluation based on quantitative information analysis in the field of herbal medicine for dementia treatment. J Oriental Neuropsychiatry 2011; 22: 101-13.
2. Kim IK, Choi HM, Kim MH. Menopausal knowledge and management in peri-menopausal women. J Korean Soc Menopause 2012; 18: 124-31.
3. Kim T. The effects of estrogen on the cognitive function and dementia. J Korean Soc Menopause 2006; 12: 103-12.
4. Lee KB. The difference in neurotransmitter & depression scale and the sleep effect following aroma therapy in postmenopausal women and dementia patients [dissertation]. Seoul: Sookmyung Women's University; 2013.
5. Park HM. Role of estrogen in senile dementia of alzheimer type. J Korean Soc Menopause 1997; 3: 99-109.
6. Kwon KJ, Lee EJ, Kim MK, Jeon SJ, Choi YY, Shin CY, et al. The potential role of melatonin on sleep deprivation-induced cognitive impairments: implication of FMRP on cognitive function. Neuroscience 2015; 301: 403-14.
7. Roh SI, Lee JY. Embryonic stem cell therapy for neurodegenerative brain diseases. Dement Neurocogn Disord 2005; 4: 68-75.
8. Lee HM, Joo BS, Lee CH, Kim HY, Ock JH, Lee YS. Effect of glucagon-like peptide-1 on the differentiation of adipose-derived stem cells into osteoblasts and adipocytes. J Menopausal Med 2015; 21: 93-103.
9. Kim S, Chang KA, Kim J, Park HG, Ra JC, Kim HS, et al. The preventive and therapeutic effects of intravenous human adipose-derived stem cells in Alzheimer's disease mice. PLoS One 2012; 7: e45757.
10. Shin JH, Kang AR. Estetrol, E4. J Korean Soc Menopause 2009; 15: 1-7.
11. Ferger B, Shimasaki M, Ceci A, Ittrich C, Allers KA, Sommer B. Flibanserin, a drug intended for treatment of hypoactive sexual desire disorder in pre-menopausal women, affects spontaneous motor activity and brain neurochemistry in female rats. Naunyn Schmiedebergs Arch Pharmacol 2010; 381: 573-9.
12. Sang JH, Kim TH, Kim SA. Flibanserin for treating hypoactive sexual desire disorder. J Menopausal Med 2016; 22: 9-13.
13. Kim JH. Alzheimer's disease and estrogen. J Korean Soc Menopause 2000; 6: 3-11.