Review

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Review

Homocysteic Acid Causes Alzheimer's Disease, Promotes Cancer Growth, and Induces Various Aging Processes

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Abstract

It has been 125 years since Dr. Alzheimer of Germany first announced Alzheimer's disease to the world in 1900, yet the causative agent of this disease remains unidentified to this day. Through the efforts of many researchers, deposits of amyloid beta protein outside nerve cells and tau protein within nerve cells have been identified as the pathological hallmarks. These proteins have been suggested as the cause of Alzheimer's disease. However, even when amyloid is reduced through amyloid therapy, no recovery of cognitive function is observed. Currently, attention is focused on whether treatment targeting tau protein might lead to cognitive recovery. Yet, the reason why this tau protein accumulates within nerve cells remains unknown. We previously published in the 2010 issue of PLOS ONE that homocysteic acid (HCA), generated by the super-oxidation of the amino acid methionine via OH radicals, is a causative agent that produces amyloid and tau proteins and further induces cognitive decline. This time, we comprehensively reviewed how this HCA is related to various lifestyle-related diseases associated with aging, and is a factor determining lifespan beyond Alzheimer's disease, cancer, and aging itself. By reducing this HCA, we will explore the potential to extend healthy lifespan and curb the escalating costs of healthcare.

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1. Introduction

Currently, the causative agents for diseases such as Alzheimer's disease, Parkinson's disease, Lewy body dementia, and frontotemporal dementia remain unknown. Particularly for Alzheimer's disease (AD), despite over a century having passed since Alzheimer presented his findings at a conference, the causative agent remains unidentified. Pathologically, it has been established that deposits of amyloid beta protein and tau protein are the pathological hallmarks of this disease [1]. Unfortunately, however, anti-amyloid antibody therapy for early Alzheimer's disease has been successful in removing amyloid accumulated in the brain, slightly reducing tau, and slightly slowing the progression of dementia, but has not improved cognitive function or even stopped the disease [2,3]. Although it remains possible that tau causes cognitive decline, the substance responsible for causing cognitive impairment has yet to be identified.

On the other hand, significant progress has been made in prevention. Regarding diet, the journal Neurology recently reported a link between regularly consuming processed red meat products—such as hot dogs, sausages, salami, bologna, and bacon—and an increased risk of developing dementia [4]. This suggests that causative agents may exist within these processed red meat products. Supporting this, studies indicate that restricting the amino acid methionine may help prevent the onset of AD [5]. This methionine is abundant in red meat [6]. Processing this methionine has been

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reported to generate homocysteic acid (HCA) by the production of oxygen radicals [7], suggesting HCA may be involved in AD.

This review examines the role of blood HCA as a potential cause of AD and various other age-related illnesses.

2. HCA Is a Physiologically Active Substance

HCA is a substance which is originally produced by glial cells in the brain, and exists in extremely small amounts (picomolar concentrations) [8]. It is an isomer of glutamate [9]. Although its physiological activity is still unknown, it has been found to transmit certain types of pain [10]. This may sometimes be related to pain complaints in Alzheimer's patients [11].

When HCA acts on cells, most cells undergo cell death due to oxidative stress [12]. This oxidative stress is associated with the aging process [13]. Based on this cell death effect of HCA, it is thought to be related to the recombination of nerve cells in the brain.

HCA is a strong agonist of glutamic acid [9]. Note that homocysteine and homocysteic acid are entirely different molecules (Figure 1).

3. Metabolism of HCA

HCA is synthesized only in glial cells [8]. The parent substance of this HCA is the amino acid methionine. Marshall et al. reported that HCA is produced when this methionine is oxidized by OH radicals ([7], Figure 2). Because HCA is an isomer of glutamate, it has been clarified that it seems to be metabolized by enzymes related to glutamate metabolism. It is metabolized by glutamate dehydrogenase, an enzyme present in the blood whose activity declines with age, which seems to be associated with the aging process. Blood HCA is primarily excreted into urine via kidneys [14].

Furthermore, a study published in Nature Aging [15] reported that the diuretic bumetanide suppresses disease onset in APOE4 Alzheimer's patients, though the mechanism remained unclear. We observed that high HCA concentrations are more common in APOE4 carriers (manuscript in preparation) and, as a result, discovered the mechanism by which APOE4 promotes disease onset. Consequently, we understood that the diuretic effect of bumetanide lowers blood HCA concentrations, thereby suppressing the APOE4-promoted disease onset phenomenon.

Exercise has also been reported to have a significant effect in preventing dementia [16]. It has been reported that exercise promotes the excretion of various substances in the blood into the urine [17]. From this effect, exercise may also increase the excretion of HCA.

4. The Causative Agent of Alzheimer's Disease

Recently, presenilin, the gene responsible for familial AD, has been reported to show aging-dependent neurodegeneration [18,19]. The implication of these reports are that the causative gene of familial AD induces an aging-dependent neurodegenerative phenomenon. These reports raise the following questions. What is the causative agent that induces the aging dependence? Several reports have shown that limiting methionine intake prolongs life span and inhibits the onset of Alzheimer's disease and the growth of cancer [20–25]. Although the mechanism underlying this phenomenon has not yet been conclusively reported, these may be explained by HCA as follows.

The 3xTg-AD mouse is a mouse that incorporates the APP, Presenilin, and Tau genes, which are the causative genes of familial AD [26]. T.H. one of the authors of this article published a paper showing that anti-HCA vaccine administration clearly improved memory impairment in these mice [10]. The method of HCA vaccine is briefly described [27]. This result proves that HCA is the cause of memory impairment in the model mice. However, it is unclear from these results which gene, presenilin or APP is responsible for the HCA-increasing effect. The altered responses to apoptotic stimuli in cells carrying presenilin mutations include increased intracellular calcium concentrations and enhanced production of reactive oxygen species [28,29]、which induce methionine super-oxidation to produce HCA from methionine [7].

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The trisomy 21 in Down's syndrome patients results in the overproduction of genes products on these chromosomes, including amyloid precursor protein (APP) [29,30]. The APP protein interacts with mitochondria to promote the generation of oxygen radicals [31], which in turn promote the hyperoxidation of methionine and the production of HCA [7]. Taken together, these reports suggest that people with familial AD genes and trisomy 21 seem to have high HCA levels in their blood, resulting in an higher incidence of AD.

These results suggest that people with familial AD and Down syndrome have high HCA levels in their blood, resulting in an abnormally high incidence of AD and abnormal aging. It is intriguing to see the photo of the first Alzheimer's patient, showing that she looks very aged.

5. HCA and Cognitive Functions in AD

In our earlier study, we saw a positive correlation between urinary HCA and MMSE scores [14]. In other words, the lower the urinary HCA level, the lower the MMSE score. In our later study, we have seen a significant correlation of high blood HCA levels and low MMSE scores (Figure 3). The method for measurement of HCA is briefly described [33]. Although it is difficult to say anything definitely because HCA levels in urine and blood were not measured simultaneously, it is assumed that people with poor renal function have poor urinary excretion of HCA, resulting in high HCA levels in the blood and low levels in the urine.

The HCA vaccine is only applicable to mice and cannot be used in humans. Therefore, we have developed a supplement [34] that can be used in humans. Glutamate dehydrogenase activity will be stimulated by NAD from niacin [35] and ferulic acid will compete with HCA at NMDA receptor [36]. Volunteers took the supplement for one month and blood HCA was examined before and after. Blood HCA concentrations in individuals who actually took the supplements for one month were all lower compared to those before taking the supplements (Figure 4). It is interesting to note that anti-HCA vaccines and anti-HCA supplements have the same effect as that of methionine restriction.

6. The Pro-Aging Effects of HCA

HCA is produced by the hyperoxidation of the methionine [7]. Limitation of methionine has been reported to prolong the life span of many organisms and prevent cancer and AD [20–25]. This phenomenon is consistent with Naked Mole Rats [37,38], which show super longevity. It was shown that the level of methionine was extremely low in the blood of the rats [39].

The senescence-promoting phenomenon of HCA is related to the recently reported anti-aging effect of glutaminase enzyme inhibition reported in Science [40]. Glutaminase catalyzes the formation of glutamic acid and ammonia from glutamine. The ammonia promotes the survival of senescent cells, but at the same time, glutamate itself also promotes senescence [41]. A potent agonist of glutamate is HCA [8]. As a result, it can be understood that HCA also produces oxygen radical [42] and promotes aging.

These facts indicate that both presenilin and APP, the causative genes of familial AD and Down syndrome, exhibit senescence-promoting effects through promotion of HCA production, which potentiates the neuronal cell-killing effects of amyloid [43]. As a result, reduction of amyloid causes a decrease in the toxic effect of HCA and thus prevents cognitive decline speed, but elimination of amyloid does not prevent cognitive decline because HCA is still present.

Animals fed a methionine-restricted diet have been reported to have extended lifespans, halted cancer growth, prevented Alzheimer's disease, and improved brain function in model mice with frontotemporal dementia (FTD) [44]. However, there are currently no reports of extended lifespans or prevention of Alzheimer's disease or FTD in humans.

7. Parkinson Disease and HCA

Parkinson's disease affects the second-largest number of patients after Alzheimer's disease. While the cause of this disease also remains unknown, we investigated whether alpha-synuclein

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protein—which is closely associated with Parkinson's disease—is generated by HCA, in order to explore the relationship between HCA and Parkinson's disease. The results confirmed that, similar to Alzheimer's disease, alpha-synuclein is generated by HCA [45].

8. Frontotemporal Dementia and HCA

This disease also affects a large number of patients, second or third only to Alzheimer's disease, but its causative agent has not been identified. Recent reports indicate that restricting methionine intake improved cognitive function in a mouse model of this disease, suggesting that HCA is involved in its pathogenesis [44].

9. Cancer Proliferation Effect

Let us consider why HCA induces Alzheimer's disease and promotes cancer proliferation. Neurons have ceased cell division, while cancer cells actively divide. Why are these two opposite phenomena regulated by a single HCA molecule?

Regarding neurons, their activity is regulated by NMDA receptors.

There are two types of NMDA receptors: synaptic NMDA receptors and extrasynaptic NMDA receptors [46]. HCA acts on both types of NMDA receptors, but HCA is an extracellular substance. Therefore, it acts on extrasynaptic NMDA receptors rather than synaptic NMDA receptors. This activation of the receptor induces neuronal cell death.

Cancer cells keep proliferation, and the signal to stimulate cell division is regulated by NMDA receptors on the cell membrane [47]. HCA binds to these NMDA receptors on the cell membrane, thereby activating cancer cell proliferation.

Through these NMDA receptors, HCA can activate both neuronal cell death and cancer proliferation, which are completely opposite processes.

The activation of Alzheimer's disease and cancer has been a phenomenon discussed for a long time, but the recent discovery of HCA provides a sufficient explanation.

10. Various Age-Related Diseases and HCA

10.1. Diabetes

Pancreatic β-cells are in the pancreatic islets that synthesize and secrete insulin and amylin. NMDA receptors are known to suppress the activity of pancreatic β-cells responsible for insulin secretion [48]. Blood HCA activates these NMDA receptors. Therefore, an increase in blood HCA concentration contributes to the progression of diabetes.

10.2. Hypertension

The onset of hypertension has been implicated in the activation of NMDA receptors involved in the sympathetic nervous system, and the involvement of HCA in the blood as an activator of these NMDA receptors has been suggested [49].

10.3. Obesity

Activation of NMDA receptors in the hypothalamus has drawn attention as a regulator of appetite that induces obesity. Blood HCA is implicated in this NMDA receptor activation [50].

10.4. Heart Disease

The relationship between heart function, which is directly linked to our lives, and NMDA receptors is crucial. It is noteworthy that blood HCA causes abnormal activation of these NMDA receptors [51].

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10.5. Kidney Disease

Blood HCA is involved in the activation of NMDA receptors that affect kidney function [52].

Thus, HCA in the blood activates NMDA receptors present in various organs, leading to the onset of lifestyle-related diseases. We also explained that it is involved in the proliferation of cancer cells in those organs. Until now, we believed that functional abnormalities in each organ arose from distinct causes. However, the role of blood HCA has revealed that abnormal activation of NMDA receptors is the underlying cause of a unified set of organ dysfunctions, particularly those related to aging.

10.6. Lifespan Reduction

As mentioned above, high blood HCA linked to all kind of lifestyle-related diseases, cancer, and dementia. Super longevity Naked Mole rats show extremely low levels of methionine in blood. Blood HCA is thus a substance vital to our lives. Since methionine, an amino acid, is its precursor of HCA, we can understand that our various illnesses stem from food. Food originates from the natural world of this Earth. We have come to understand the importance of carefully cultivating this life-sustaining food, and of lowering blood HCA levels through plant-based protein intake rather than meat consumption, thereby enjoying longevity.

We investigated whether HCA could be used as a biomarker for detecting mild cognitive impairment (MCI). Unfortunately, both sensitivity and specificity were not high enough, making it somewhat difficult to use as a biomarker for detecting MCI. This is understandable, as HCA is involved not only in dementia but also in lifestyle-related diseases and aging [53].

11. Conclusions

The HCA molecule is originally produced by astrocytes in the brain and functions as a physiological substance involved in the reorganization of nerve cells and the transmission of pain signals. However, beyond this physiological function, it has been revealed that HCA is also produced non-physiologically from the foods we consume, specifically through the action of OH radicals on the amino acid methionine. This non-physiologically generated HCA triggers aging phenomena. Consequently, it leads to Alzheimer's disease in the brain and various diseases in other organs, including diabetes, hypertension, obesity, and abnormalities in the heart and kidneys. Ultimately, it has been shown to bring about the end of our lifespan.

Furthermore, since aging phenomena manifest based on blood HCA concentration, differences in individual blood HCA levels appear to account for why some people age while others remain youthful. Therefore, suppressing aging becomes possible by keeping this blood HCA concentration as low as possible.

A rapid increase in Alzheimer's disease patients is currently being reported worldwide. This is because the causative agent of this disease remains unclear. However, it has been understood that Alzheimer's disease is not a special disease, but rather a disease accompanying the aging process. Furthermore, it has been understood that even if cancer occurs, HCA molecules promote the proliferation of those cancer cells. The methionine-restricted diet has a major issue. Since methionine is an essential amino acid, implementing this diet clinically may lead to nutritional problems.

If we could remove this HCA molecule from our bodies, we could eliminate the various adverse effects associated with aging and enjoy a healthy lifespan. To achieve this, we need to develop drugs that distinguish between physiological HCA and non-physiological HCA. If it were possible to develop an anti-HCA vaccine that indiscriminately removes both physiologically functional HCA and disease-causing HCA, it might even be possible to create a body that never experiences pain, suffering, or sorrow.

Author Contributions: T. Hasegawa is the PI of all the work and the corresponding author of this review. C. Kudo and T. Tabira are collaborators of a part of the work.

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L of PBS, and 100 μ L of labeled antibody solution were mixed and incubated, initially at 37°C. Next, the mixed solution was added to the antigen-binding polystyrene plate and incubated at 37°C. After washing with wash buffer, we added luminescent substrate and measured the decrease in light emission with a plate reader. BSA-bound HCA was used as a standard solution, and light emission was converted to a measured value. In our preliminary experiment, the coefficient of variation of HCA measurement was within 15%, and the error of the sample concentration was within 20%, when measurement was done immediately after thawing, or done after keeping at 4°C or 25°C for 24 h after thawing. Thus, HCA in plasma is stable during sample processing, and we expected that it is stable in frozen conditions.

38. Supplement ingredient contents cannot be disclosed at this time, because of business activity, but it contains niacin, ferulic acid, vitamin C, coral calcium and ginseng.
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