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Presenilin and Alzheimer's disease interactions with aging, exercise and high-fat diet: A systematic review

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Abstract: Presenilin (*Psn*) protein is associated with organismal aging. Mutations in the *Psn* gene may lead to Alzheimer's disease (AD), dilated cardiomyopathy (DCM), and many age-dependent degenerative diseases. These diseases seriously affect the quality of life and longevity of the population and place a huge burden on health care and economic systems around the world. Humans have two types of Psn, presenilin-1 (PSEN1) and presenilin-2 (PSEN2). Mutations in the genes encoding PSEN1, PSEN2, and amyloid precursor protein (APP) have been identified as the major genetic causes of AD. *Psn* is a complex gene strongly influenced by genetic and environmental factors. The effects of exercise, training, and a high-fat diet on the *Psn* gene expressed in the heart and its related pathways are not fully understood. Fortunately, relevant aspects of the mutational effects on Psn can be studied experimentally in easily handled animal models, including Drosophila, mice, and other animals, all of which share orthologous genes of *Psn* with humans. Many previous studies have linked aging, exercise training, and a high-fat diet to the *Psn* gene. This review discusses the interrelationship between aging, exercise training, and a high-fat diet on the *Psn* gene and its associated disease, AD. The aim is to understand the adverse effects of *Psn* gene mutations on the body and the diseases caused by AD, find ways to alleviate the adverse effects and provide new directions for the improvement of treatment strategies for diseases caused by *Psn* gene mutations.

Introduction

Population aging phenomenon exists in most developed countries, even some developing countries. The world's aging population is increasing continuously at a high rate. The aging of the body is accompanied by a variety of age-dependent degenerative diseases such as Alzheimer's disease (AD) and dilated cardiomyopathy (DCM). Research has shown that mutations in the Presenilin (*Psn*) gene have been found in both AD and DCM (Li *et al.*, 2011a). Research has also shown that mutations in the *Psn* gene and a high-fat diet accelerate the development of aging-related diseases. On the contrary, exercise training and a balanced diet can delay the aging process and reduce the risk of aging-related diseases (Marcon *et al.*, 2009). However, there are few reports on the effects of exercise training and a high-fat diet on the *Psn* gene and related pathways.

Psn is a multichannel transmembrane protein, an intramembrane protease complex that catalyzes the intramembrane cleavage of intact membrane proteins such as Notch receptors (Guo *et al.*, 1999). Psn is located in the apical plasma membrane, late endosomes, and recycling endosomes. It is an integral component of the plasma membrane (Ankarcrona and Hultenby, 2002). It is expressed in multiple structures, including the anterior and posterior subdivision of the organism and the central nervous system, and is essential for the study of AD and DCM (Lehmann *et al.*, 1997). Psn is a γ-catalytic component of the secretase intramembrane protease complex; other non-catalytic Psn roles are also found in cellular signaling processes, including calcium homeostasis, lysosomal acidification, autophagy, and protein transport (Song *et al.*, 2013). Vertebrates have two *Psn* genes, presenilin-1 (*PSEN1*) and presenilin-2 (*PSEN2*). PSEN1 is a macromolecular protein on the endoplasmic reticulum and Golgi apparatus. PSEN1 is, additionally, a transmembrane protein that forms a complex with amyloid precursor protein (APP) in the cell and is involved in APP transport and post-synthesis processing (Raemaekers *et al.*, 2005). With age, PSEN1 increases in the human brain, thereby affecting memory in the elderly (Culvenor *et al.*, 2004). Mutations in the PSEN1 gene, which encodes this protein, are thought to be closely associated with the development of

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AD (Blanchard *et al*., 1997). Patients with hereditary AD carry PSEN1 and PSEN2 or APP. These disease-related mutations lead to an increase in amyloid-beta (Aβ) peptides (Villegas *et al*., 2007). Both PSEN1 and PSEN2 are proteins with anti-apoptotic effects.

Age-dependent neurodegenerative diseases affect millions of people worldwide (Arora and Ligoxygakis, 2020). *Psn* mutations are not only an important cause of age-dependent neurodegenerative diseases but also have many adverse effects on the body (Han *et al*., 2021). In this review, we will systematically explore the interaction of Psn and AD with aging, exercise training and a high-fat diet, hoping to find ways to alleviate the adverse effects through dietary changes and exercise training. Through this study, we aim to provide new directions for the improvement of complementary treatment strategies for *Psn* mutation-related diseases, thereby improving the quality of life and longevity and reducing the burden on the economy and health care systems around the world.

Psn in the brain and heart

PSEN1 and *PSEN2* genes are expressed in various human organs such as the brain and heart (Bruni, 1998). In the brain, Psn is found in neuronal cells in the hippocampus and cerebral cortex associated with learning and memory (Lee *et al*., 1996). Psn has a general and essential role in the survival of excitatory and inhibitory neurons during aging (Kang and Shen, 2020). Genetic studies in mice suggest that Psn regulates neurodevelopment in the developing brain through the Notch signaling pathway (Kim and Shen, 2008). Specific loss of PSEN1 in the forebrain of mice affects specific aspects of memory (Feng *et al*., 2001). PSEN1 plays an important role in brain development and neuronal function, which is related to the brain-specific pathological role of *PSEN1* mutations (Hartmann *et al*., 1997). PSEN1 and PSEN2 are expressed in the heart and its role in the heart has been discussed earlier (Levy-Lahad *et al*., 1996). Mutations in the *Psn* gene are thought to be involved in pathological changes in the heart (Yang *et al*., 2020). PSEN1 can act as an important regulator of cardiac Ca^{2+} pump function with complex stimulatory/inhibitory properties (Bovo *et al*., 2021). PSEN1 is associated with apoptosis and cardiac development, and *PSEN1* mutations trigger enlarged ventricular chambers and systolic dysfunction (Li *et al*., 2011b). Abnormalities in the dynamic regulation and function of PSEN1 lead to abnormal cardiomyocyte ultrastructure and cardiovascular disease (CVD) (Song *et al*., 2018). In contrast, PSEN2 is ubiquitous in various organ tissues, including the heart, and plays an important role in cardiac excitation-systole coupling by interacting with the cardiac ryanodine receptor (RyR2) (Takeda *et al*., 2005).

Psn and aging

PSEN1 and *PSEN2* genes are necessary for the survival of adult neurons, and mutation in this gene affects the aging of the organism. Aging is characterized by a deterioration of cellular function and physical health over time, accompanied by an increased susceptibility to disease (Goldsmith, 2014). Psn has a role in promoting neuronal activity in the brain, and the knockdown of *Psn* gene leads to an increase in the likelihood of neuronal death (Kang *et al*., 2017). AD is the most common form of dementia, accounting for more than half of dementia cases (Gaugler *et al*., 2022). AD is an age-related neurological disease that is one of the leading causes of death and disability worldwide (Small *et al*., 1997). It is an irreversible neurodegenerative disease characterized by insidious onset and slow progression (Hashimoto *et al*., 2005). In addition, AD is the most common type of chronic neurodegenerative disease among the elderly and is clinically characterized by progressive memory decline (Zhuang *et al*., 2020). In general, the clinical manifestations of AD are mainly characterized by anterograde episodic memory disorder. This condition is often accompanied by multiple cognitive impairments, such as visuospatial, language, and executive function (Chan et al., 2013). The combination of the above features can lead to global cognitive decline, eventually leading to a state of total dependence and, ultimately, death (Bowman and Quinn, 2008). The above studies show that AD can cause serious damage to the body, so it is crucial to study the treatment strategies for AD by exploring Psn-related literature.

AD caused by *Psn* mutations can have many adverse effects on the organism. Both AD and familial AD (FAD) are affected by changes in Psn levels. Studies on cultured nerve cells have shown that mutations in the *PSEN1* gene lead to disturbances in cellular calcium homeostasis, and many early-onset familial AD (EOFAD) is caused by mutations in this gene (Mattson *et al*., 2000). Studies have shown that mutations in a single copy of the Psn and APP may contribute to the development of FAD. Only normal Psn levels can maintain normal cognition throughout the lifespan. Therefore, the decrease in PSEN1 and PSEN2 functional activity may be related to the pathogenesis of FAD. A decrease in Psn function was found to lead to age-related cognitive deficits (Nagakura *et al*., 2013). Some aspects of FAD and AD may be caused by the decreased activity level of Psn (McBride *et al*., 2010). It is, hence, apparent that Psn is closely related to the generation of AD, and its low levels largely lead to memory deficit and cognitive impairment, resulting in the occurrence of FAD and AD.

A close relationship between Psn and aging can be found in studies using mice as a model. Psn plays an important role in the growth and development of embryos, and the inactivation of *PSEN1* may lead to developmental defects and eventual perinatal death in mice (Donoviel *et al*., 1999). Studies have shown that the interaction between the AD-associated protein PSEN1 and the synaptic vesicular protein SYT-1 is increased during normal aging of the mouse brain and neuronal aging *in vitro* (Keller *et al*., 2020). Therefore, studies on mice have found that changes in Psn level can affect normal learning and memory, growth and development, and even the conditions necessary for the survival of mice.

A study using Drosophila as a model found that Psn is extremely closely related to growth, development, and aging. In *Drosophila melanogaster*, Psn is expressed at different developmental stages, and the expression level in the adult is higher than that in the larvae, mainly in the central nervous system. Mutations in the *Psn* gene are the most common cause of EOFAD. *PSEN1* mutations account for 18%–50% of EOFAD cases, while *PSEN2* mutations are rare. *PSEN1* is

uniformly expressed, and *PSEN2* is confined to the heart, skeletal muscle, and pancreas (Zheng *et al.*, 2015). It is thus clear that Psn plays an important role in growth and development and mainly acts on mature individuals. The loss of Psn function in *D. melanogaster* increases the level of apoptosis in developing tissues (Ye and Fortini, 1999). It is evident that both *Psn* knockdown and overexpression can lead to apoptosis. RNA interference (RNAi) to stall the expression of the Drosophila ubiquitin homolog (dUbqln) enhances retinal degeneration caused by *Psn* overexpression (Li *et al.*, 2007). Overexpression of *Psn* in the retina leads to a smaller eye phenotype (Reynolds-Peterson *et al.*, 2020). Taking into account the aforementioned studies, it is, therefore, demonstrated that *Psn* gene mutations can alter the phenotype of Drosophila eyes and also lead to serious consequences such as apoptosis.

Psn and cardiac aging

PSEN1 and PSEN2 play an important role in the regulation of cardiovascular function. PSEN2 promotes heart excitation-contraction by directly coupling with RyR2 (Takeda *et al.*, 2005). The morphology of the heart in mice with *PSEN1* gene mutation exhibits ventricular septal defects and a double outlet of the right ventricular (Nakajima *et al.*, 2004). The incidence of heart dysfunction and arrhythmias in the hearts of senescent Drosophila increases significantly with age (Ocorr *et al.*, 2007). Cardiovascular stimulation in Drosophila revealed a negative correlation between age and maximum heart rate, that being smaller in older Drosophila (Paternostro *et al.*, 2001). It is thus clear that Psn plays an important physiological role in the heart.

Psn gene is closely related to the development and function of the heart. The mutations in the *Psn* gene lead to EOFAD and DCM, both of which accelerate cardiac aging (Cannon and Bodmer, 2016). The etiology of AD is mainly idiopathic, and in particular, autosomal dominant genetic disorders caused by mutations in the *PSEN1* and *PSEN2* genes are thought to be the main cause of FAD (Yang *et al.*, 2020). *Psn* knockdown can lead to a significant decrease in heart rate, while the opposite occurs with *Psn* overexpression (Li *et al.*, 2011a). Research has found a strong correlation between AD and heart insufficiency (Tublin *et al.*, 2019). Mutations in *PSEN1* and *PSEN2* may lead to an increased risk of cardiac systolic and diastolic dysfunction in patients with AD (Yang *et al.*, 2020). Research has shown that *PSEN1* and *PSEN2* mutations are associated with DCM and heart failure (Li *et al.*, 2006). Therefore, these studies suggest that mutations in the *Psn* gene lead to abnormal heart development, dysfunction, and accelerated cardiac aging.

Alzheimer's disease and muscle aging

Psn mutation-induced AD is often accompanied by muscle atrophy and aging. With age and muscle atrophy, the onset and progression of AD may be accelerated and accompanied by weight loss. One of the main features of aging is the progressive loss of skeletal muscle function and a gradual decrease in skeletal muscle mass called skeletal sarcopenia (Demontis *et al.*, 2013a). Studies have shown that muscle changes play an important role in common diseases (Wolfe, 2006). Muscle aging is associated with a gradual decline in muscle quantity and mass (Kim *et al.*, 2021). Clinical observation shows that skeletal muscle can affect central nervous system aging, and neurodegeneration of the central nervous system is a decisive characteristic of body aging affected by peripheral tissue (Rai *et al.*, 2021). With the increase in age, the function of multiple organ systems gradually declines, and skeletal muscle atrophy is one of the main physiological problems of the elderly. Studies have shown that elderly APP/PS1 double transgenic mice (APP/PS1 double transgenic mice is an AD transgenic animal model established by transferring amyloid precursor protein (APP) and *PSEN1* mutant genes into mice.) demonstrating phenotypes of lower body weight, less muscle tissue, increased myostatin expression, lower muscle strength, and reduced myostatin expression show AD-related memory impairment (Lin *et al.*, 2019). This progressive muscle wasting can lead to the progression of chronic diseases such as metabolic complexes, cancer, and AD (Ruiz *et al.*, 2008). Thus, as the organism gradually ages, the possibility of neurodegenerative pathologies of the central system, like AD, increases. The onset of these diseases is often accompanied by a progressive decrease in skeletal muscle function and quality.

Muscle levels, in turn, affect the progression of AD. People with higher muscle strength levels are at less risk of developing AD than those with lower muscle strength levels (Boyle *et al.*, 2009). Sudden weight loss is one of the signs of dementia in the elderly, often occurring in AD patients (Grundman, 2005), and weight loss can predict AD (Luchsinger and Gustafson, 2009). People with AD lose muscle at a faster rate than normal people (Burns *et al.*, 2010). Nutrition and stress perception in skeletal muscle affect the lifespan and overall aging of the body, and actin in the muscle affects the progression of age-dependent diseases, such as AD (Demontis *et al.*, 2013b). Therefore, weight changes are one of the signs to determine whether or not dementia is present. If an older person experiences a sudden loss of weight, it can be considered a sign of dementia onset.

Alzheimer's disease and exercise training

Exercise training can mitigate the adverse effects of AD on the organism. AD is a progressive neurodegenerative disease for which there are few effective treatments (Um *et al.*, 2008). Physical exercise is used to treat AD by eliciting positive neurophysiological effects (Garcia-Mesa *et al.*, 2011). Aerobic exercise can slow the progressive decline of older adults as they age (Young et al., 2015). Physical exercise improves cognitive performance (da Silva *et al.*, 2018). Therefore, active physical exercise can reduce the likelihood of cognitive impairment in older adults (de la Rosa *et al.*, 2020). Exercise also slows the progression of AD by improving mitochondrial function and REDOX homeostasis (Teglas *et al.*, 2020). Regular running is beneficial for people who have traditional cardiovascular risk factors (Tapia-Rojas *et al.*, 2016). Studies have shown that exercise may also affect Aβ levels by modulating the immune response of AD patients (Nichol *et al.*, 2008). Exercise training improves

cognitive function in AD patients (Zhang *et al*., 2017). Hence, regular exercise training has a series of positive effects on AD.

Evidence shows that exercise training can enhance heart function and is beneficial in delaying cardiac aging and reducing the occurrence of heart failure (Lai *et al*., 2014). Physical exercise can also improve cardiac diastolic dysfunction, reduce lipid overaccumulation, reduce oxidative damage, and to some extent, improve the mobility and life span of Drosophila (Wen *et al*., 2019). Endurance exercise promotes health and longevity, while chronic endurance training also prevents disease, improves heart, skeletal muscles, and brain functions, and reduces obesity, heart disease, and cognitive decline (Sujkowski *et al*., 2020). Running is an effective way to delay cardiac aging (Wen *et al*., 2021). Thus, exercise training may alleviate cardiac aging and its adverse effects.

In animal models of AD, studies conducted on mice have shown the protective effect of exercise training on the organism (Kim *et al*., 2019). Exercise improved short-term recognition memory and spatial learning and memory ability, and restored neuronal excitability of APP/PS1 double transgenic mice (Tan *et al*., 2020). Exercise also improves the exploration ability (Li *et al*., 2019). And running reduced brain inflammation (Falkenhain *et al*., 2020) in APP/PS1 double transgenic mice. In addition, voluntary exercise prevented mitochondrial dysfunction in AD, enhanced mitochondrial autophagic activity in the hippocampus, and effectively improved the pathological phenotype of APP/PS1 transgenic mice (Zhao *et al*., 2020). Regular treadmill exercise plays a neuroprotective role in age-related memory loss (Zeng *et al*., 2020). In conclusion, exercise training alleviates age-dependent degenerative diseases such as AD and improves cognitive and neural activities.

A combined intervention of treadmill exercise and dietary polyphenols improves cognitive loss in APP/PS1 double transgenic mice and has a therapeutic effect on AD (Zhang *et al*., 2016). Running has been found to inhibit the deposition of Aβ plaques in the hippocampus, one of the main pathological markers of AD in APP/PS1 double transgenic mice (Xia *et al*., 2019). Treadmill exercise reduces hippocampal neuron loss in APP/PS1 double transgenic mice (Zhang *et al*., 2019). Running also improves the structure and function of the hippocampus and amygdala-related neurons in APP/PS1 double transgenic mice (Lin *et al*., 2015). In addition, exercise combined with probiotic supplementation can further delay the progression of AD in APP/PS1 double transgenic mice (Abraham *et al*., 2019).

Sports training is categorized into voluntary and passive exercises that bring about different degrees of training effect; besides, their impact on AD is also not the same. In a transgenic mouse model of AD, voluntary exercise significantly reduced Aβ load (Adlard *et al*., 2005). Long-term treadmill exercise can better delay the progression of AD neuropathology in the hippocampus of APP/PS1 double transgenic mice (Liu *et al*., 2013). The effect of voluntary exercise in improving memory impairment due to AD is better than passive exercise training (Yuede *et al*., 2009). Long-term treadmill exercise also had positive effects on cognitive function and synaptic plasticity in APP/PS1 double transgenic mice (Zhao *et al*., 2015). The above-mentioned studies prove that exercise training, especially voluntary exercise training, has a certain therapeutic effect on delaying the progression of AD. However, the relationship between exercise training and Psn is unclear.

Alzheimer's disease and a high-fat diet

A high-fat diet is also one of the main causes of AD. High-fat diets have been shown to induce elevated insulin and blood glucose in the body and lead to the development of fatty liver (Oliveira *et al*., 2014). Research data suggest that high-fat diets have a detrimental effect on the brain, increasing the prevalence of AD and damaging the structure and function of the hippocampus, which impact consequently learning and memory (Stranahan *et al*., 2008). Obesity induced by a high-fat diet is one of the main risk factors for cognitive impairment in AD (Sah *et al*., 2017). The high-fat diet causes significant increases in plasma cholesterol (TC), triacylglycerol (TG), and low-density lipoprotein (LDL-C) (Park *et al*., 2018). Long-term high-fat diets can cause the body to produce more cholesterol and lead to other adverse effects on the body, increasing the risk of developing AD.

Studies reveal that a high-fat diet produces a series of negative effects on APP/PS1 double transgenic mice, who exhibited a phenotype of significantly impaired glucose tolerance (Hiltunen *et al*., 2012). Genetic and diet-induced insulin resistance affects the pre-pathological manifestations of AD in APP/PS1 double transgenic mice (Bruning *et al*., 2000). Both episodic and spatial memory were found to be impaired in mice fed on a high-fat diet for just one day (McLean *et al*., 2018). Further, APP/PS1 double transgenic mice fed on a high-fat diet exhibited increased body weight, decreased number of age spots in the hippocampus, and significant lipid droplets deposition in the liver (Guo *et al*., 2021). High-fat diets also promoted Aβ production (Perdoncin *et al*., 2021). Moreover, a high-fat diet resulted in memory and motor dysfunction and impaired socialization in APP/PS1 double transgenic mice (de Souza *et al*., 2019). Bad dietary habits can also cause many adverse effects. Short-term western diets are sufficient to induce an increase in oxidative stress in young APP/PS1 double transgenic mice (Studzinski *et al*., 2009). Feeding a high-fat diet to triad transgenic mice (including PSEN1 transgenic mice) impaired memory capacity, exacerbated memory deficits in AD mice, and impaired mitochondrial morphology (Martins *et al*., 2017). A high-fat diet leads to altered APP and PSEN1 protein levels and thus affects Aβ metabolism (Spagnuolo *et al*., 2020). Other studies have found that ethyl acetate (EAE) can prevent memory loss and reduce the progressive development of neurological disorders in AD patients (Jara-Moreno *et al*., 2018). A study found that high-fat diet-fed obese mice exhibit reversible impairment of hippocampal function (Hao *et al*., 2016). Even in the absence of obesity, an unbalanced diet with prolonged high-fat diets and continuous intake of excessive fat can cause cognitive impairment in mice (Cifre *et al*., 2018). High-fat diets can also have a range of negative effects on the heart; it is one of the major factors contributing to CVD (Stobdan *et al*., 2019). Obesity caused by a chronic high-fat diet also accelerates the aging of the body's heart function and exercise capacity (Wen *et al*., 2018). Studies have shown that a high-fat diet can lead to the accumulation of heart lipids, decrease heart contractility,

block the conduction, and cause serious structural lesions (Birse *et al.*, 2010). A high-fat diet can also induce hereditary heart dysfunction, such as lipotoxic cardiomyopathy (Guida *et al.*, 2019). It is thus clear that a high-fat diet can adversely affect the heart function of Drosophila and damage the integrity of heart structure and function. However, the relationship between a high-fat diet and heart Psn awaits further investigation.

Conclusion

In this review, we have systematically explored many articles on the interaction of the *Psn* gene and AD with aging, exercise training, and high-fat diets. Based on these, we show that the *Psn* gene is not only closely associated with aging but is also necessary for adult neuronal survival and normal heart function. *Psn* mutations can have many adverse effects on the body, and regular exercise training combined with good dietary habits can alleviate the adverse effects of *Psn* mutation-induced AD, such as heart dysfunction and muscle atrophy. However, the relationship between exercise training, a high-fat diet, and the *Psn* gene warrant further investigation. For example, further studies should focus on whether exercise training can improve cardiac aging caused by *Psn* overexpression or knockdown, a subject poorly examined. Therefore, the study of the relationship between exercise training, a high-fat diet, and Psn can provide a more comprehensive understanding of the prevention and treatment mechanism of aging.

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