Alzheimer's Disease and Prenatal Maternal Stress

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Abstract: The pathogenesis of Alzheimer’s disease (AD) remains largely unknown. As a chronic disease, AD is probably best considered in a life-course framework, with important influences beginning at conception and early life. Excess prenatal maternal stress could affect brain development and long-term functional maintenance, and subsequently increase the risk of neurologiological disorders during the later life stage. The mechanisms underlying these negative effects may include alterations in the hypothalamus-pituitary-adrenal axis, hippocampal development and postpartum breast feeding.

Keywords: Alzheimer’s disease, prenatal maternal stress, brain development

1. Introduction

Alzheimer’s disease (AD), including familial AD and sporadic AD, is the most common form of dementia among the elderly. As a chronic neurodegenerative disease, the major symptoms of AD are progressive memory impairment and cognitive dysfunction. At the neuro pathological levels, AD is characterized by extracellular deposits of amyloid-β (Aβ) peptide, and neurofibrillary tangles consisting of hyperphosphorylated microtubule associated with tau proteins, found in the brain areas responsible for learning and memory [1].

The pathogenesis of AD remains largely unknown. The known risk factors of AD include age, limited education, head trauma, dietary cholesterol, gender, family history, lifestyle, socioeconomic conditions, occupation, cerebrovascular diseases and so on. Specific genetic mutations in the amyloid precursor protein (APP), presenilin 1 (PS1), and presenilin 2 (PS2) genes have been proven to be sufficient to cause familial AD [2]. However, the etiopathogenesis of sporadic AD remains unknown.

Like many other chronic diseases, AD is probably best considered in a life-course framework, with important influences beginning at conception and early life. While most cases of AD usually present clinically at older ages and are diagnosed after the emergency of clinical symptoms, increasing evidences support the notion that the origins and neuropathology of AD likely predate its clinical manifestation by many decades. Since the publication of the NINCDS-ADRDA criteria in 1984 [3], functional neuroimaging techniques such as PET or SPECT and the elucidation of the biological basis of AD have advanced greatly, allowing an unprecedented understanding of the disease process [4]. Especially, a new diagnostic criterion for preclinical states of AD including asymptomatic at-risk state for AD and presymptomatic AD has been established recently [5].

Both genetic factors and environmental factors are involved in the onset of AD [6]. Any hypothesis to explain the etiology of AD must take into account not only neuropathological features, but also the various environmental factors, for example prenatal maternal stress (PMS). Psychological stress is a multifactorial process at a core of cognition. Moderate psychological stress is necessary and useful, while excess psychological stress can cause health damage [7]. Excess PMS may result in continuous long-term effects to offspring, more than change birth outcomes, such as premature birth and low birth weight [8, 9]. Animal studies have shown that PMS can increase the risk of neurological disorders to offspring, and this risk is independent from genetic factors [10].

In addition, mouse models during various stages of the life have demonstrated that stress exposure can alter the neuropathological process, causing reduction of neurons in the memory regions, more deposits of Aβ peptide and hyperphosphorylated microtubule associated protein tau [11, 12, 13]. Compared to infancy and adulthood mouse models, studies on embryonic mouse models of stress exposure are relatively few. Thus, there is still considerable space for further research.

2. AD and early-life stage of development

In 1966, Roth reported that dementia doesn’t occur until a critical number of Alzheimer lesions or critical volume of brain softening (secondary to strokes) is evident [14]. This ‘threshold’ theory has been further developed by later researchers. Satz [15] and Mortimer [16] have proposed that the clinical expression of AD requires two elements: (1) the accumulation of AD lesions over the life span, (2) the attainment of a critical threshold of ‘brain reserve’ below which normal cognitive function can’t be sustained.

It’s observed that infants, with low birth weight and small head circumference, are at higher risk of suffering coronary heart disease, hypertension, stroke, insulin resistance, diabetes and other diseases in adulthood [17]. According to this phenomenon, Barker proposed a hypothesis, called ‘fetal origins hypothesis’, that the intrauterine environment has significant impact on the development of chronic diseases [18]. Changes of intrauterine environment, such as metabolism, hormones, and re-distribution of cardiac output, chronic diseases may result in slow fetal growth during the critical gestational period, permanently affecting the body's structure and function in the late-life stage.

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It is clear that there is a gender difference in the relation between PMS and the neurodevelopment in early-life stage [33, 34]. It has been reported that PMS causes a reduction in hippocampal glial count in the pyramidal layer and an increase in depressive-like behavior with cognitive deficits in female offspring only [35]. On the other hand, it is also well known that women have a higher incidence of AD [36]. Consistently, many AD mouse models display a sex-dependent pattern of cognitive deficits and neuropathology [37, 38, 39]. A recent study reported that repetitive restraint stress during the first week of gestation exerted a sex-dependent effect on the cognition, affect, and AD-related neuropathology in APPswe/PS1dE9 mice. Male PMS mouse offspring showed spatial memory deficits and a blunted hypothalamus-pituitary-adrenal axis response, while female offspring showed increased depressive-like behavior and improved spatial memory performance with a decrease in hippocampal plaque load [40]. Further studies are necessary to explore the underlying mechanisms for the sex-specific responses to PMS in AD patients as well as AD animal models.

4. Mechanism that PMS influences the neurodevelopment

4.1 Altered HPA axis

A central feature of the stress response is the activation of the HPA axis, resulting in increased plasma levels of glucocorticoids (GCs). Studies have shown that PMS can alter the set points of the HPA axis [41]. Changes of HPA axis in embryonic stage could influence offspring’s postnatal regulation of stress, thereby cause a lesion of anti-injury and repairing ability of cells in the later life stage [42, 43].

GCs regulate tissue programming in the utero by acting at cellular and molecular levels to alter cell function by changing the expression of receptors, enzymes, ion channels and transporters, making a negative regulation in the fetal development [44]. There is a linear positive correlation of the concentrations of GCs between the fetus and expectant mother [45]. An excess stress in the pregnant women can lead to increase the levels of GCs in the fetus. As a placental barrier, enzyme 11β-HSD2 could metabolises GCs and protects fetus from excess concentration of GCs. However, 11β-HSD2 activity could be greatly reduced by excess PMS, diminishing this protection [46, 47]. Furthermore, in the long term, prenatal GCs exposure can permanently reset endocrine systems, such as the somatotrophic and HPA axis [48]. In turn, these changes contribute to the pathogenesis of adult diseases including AD.

4.2 The abnormal development of hippocampus

The hippocampus is an important region of learning and memory in the brain, and the atrophy of hippocampus is one of pathological hallmarks of AD. The developing hippocampus is highly vulnerable to alterations induced by PMS-induced elevations in GCs because of high expression of GCs receptors [49, 50].

GCs have shown to affect the growth and maturation of hippocampal cells GCs, via activation of their receptors, which can reduce the dendritic complexity of developing hippocampal CA1 neurons of rats [51]. PMS affects the morphological development of the hippocampus in an intensity-dependent manner [52]. Short-lasting, mild prenatal stress enhances neonatal neurogenesis and differentiation processes of hippocampal neurons via activation of mineralocorticoid receptor. In contrast, long-lasting, severe stress impairs the morphology of
hippocampal neurons via glucocorticoid receptor [52]. Consistently, the varying effects of short-term and long-term corticosterone injections on depression-like behavior in mice have been observed [53]. In addition, a considerable body of work has shown that both stress and corticosterone treatment induce enhancement of activity-dependent glutamate release that also plays an important role in the maturation of the hippocampal circuit during the development [54]. Taken together, increased GCs by PMS perturb the normal development of the hippocampus via multiple mechanisms, contributing its vulnerability to Aβ plaque deposits in the late stage.

4.3 Insufficient postpartum breast feeding

Duration of breast feeding is positively related to young children's neurodevelopment, largely independently from parental psychosocial factors [55, 56]. Pregnant women who suffer excess PMS are more likely to experience delayed onset of lactation, which could result in an earlier breastfeeding termination [57, 58]. Animal studies further reveal that PMS affects lactation directly by controlling secreting prolactin and oxytocin, two hormones most relative to the production and secretion of breast milk [59].

Nutritional restriction, causing by insufficient breast milk, isn’t amenable to catch-up growth, thereby failing to produce sufficient numbers of cells at the correct time and causing a permanent deficit to brain structures and functions. It is not difficult to propose that the cerebral dysplasia during the lactating period should accelerate brain aging and neurodegeneration process, causing the occurrence of AD.

5. Conclusion and perspective

The exact pathogenesis of AD is complex and still unknown. Combined with the current views [15-16, 19-22], we have proposed that AD occurrence is a consequence of reaching an imbalance threshold between brain reserve established during the development and decreased during the aging process. Normal individuals lost their brain reserve with aging at a low rate and without clinical manifestations of AD. Individuals with specific genetic mutations are of a high rate of decreasing brain reserve and suffer familial AD finally. Individuals with environment factors in utero, for example PMS, have less brain reserve and vulnerability to AD occurrence during the later life stages (Figure 1).

![Figure 1](http://www.researchpub.org/journal/and/and.html)

**Figure 1** Individuals with excess PMS reach a critical threshold easily below which normal cognitive function can’t be sustained and AD is manifest.

Based on this, AD is probably best considered in a life-course framework, with important influences beginning at conception and early development. Excess PMS could affect the brain development and increase the risk of AD in the later life stage. The main mechanisms may be due to excess PMS altering the set points of the HPA axis of the offspring, which subsequently affects the development of brain, especially the hippocampus, during the fetus. In addition, excess stress during the pregnant also affects the postpartum breast feeding, which in turn impairs brain growth and maturation during the early postnatal development.

Although the effects of PMS on brain development and AD occurrence have been extensively accepted, there is still lack of unified and recognized evaluation criteria of PMS. Different types, degrees and period of PMS have different impacts on the neurodevelopment of offspring, which make it difficult to compare these results. In addition, epidemiological investigations in a large time span between exposure and clinical manifestation of AD is not precise enough and able to be controlled accurately. By using animal models, environmental exposure can be strictly controlled and AD-related behavior and neuropathology can be monitored. However, the results of animal studies aren’t suitable...
completely for human because of species difference. Furthermore, the gender-difference should be considered carefully in the experimental design. Further studies are necessary to explore effects and mechanisms of maternal lifestyle factors during pregnancy on the risk of AD in the offspring. These studies will highlight a new strategy for preventing and treating the devastating neurodegeneration.

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References


