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Transient enriched housing before amyloidosis onset sustains cognitive improvement in Tg2576 mice

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Abstract

Levels of educational and occupational attainment, as components of cognitive reserve, may modify the relationship between the pathological hallmarks and cognition in Alzheimer's disease (AD). We examined whether exposure of a Tg2576 transgenic mouse model of AD to environmental enrichment (EE) at a specific period during the amyloidogenic process favored the establishment of a cognitive reserve. We found that exposure to EE during early adulthood of Tg2576 mice—before amyloidogenesis has started—reduced the severity of AD-related cognitive deficits more efficiently than exposure later in life, when the pathology is already present. Interestingly, early-life exposure to EE, while slightly reducing forebrain surface covered by amyloid plaques, did not significantly impact aberrant inhibitory remodeling in the hippocampus of Tg2576 mice. Thus, transient early-life exposure to EE exerts long-lasting protection against cognitive impairment during AD pathology. In addition, these data define the existence of a specific life time frame during which stimulatory activity most efficiently builds a cognitive reserve, limiting AD progression and favoring successful aging.

Keywords: Alzheimer's disease; Transgenic mice; Enriched environment; Amyloid; Learning and memory; Hippocampus; Brain cognitive reserve; Tg2576; Calbindin; Neuropeptide Y

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia and is characterized by inexorable deficits in memory and other cognitive functions. Environmental factors have been suggested to modulate the risk and the development of AD. In particular, physical activity and cognitive occupational attainment during midlife have been associated with a reduced risk of AD (Friedland et al., 2001; Stern et al., 1994). The finding that highly-educated individuals have a reduced risk for AD has fostered the concept of a cognitive reserve that provides a better brain capacity to cope with pathological insults so that those individuals display delayed clinical expression of the disease (Katzman et al., 1988; Reed et al., 2010; Stern, 2006). Given the large population of aging individuals and the financial burden on caretakers, finding effective therapeutic strategies to mitigate the cognitive dysfunction seen in AD pathology is critical. Thus understanding the neurobiological mechanisms that underlie the cognitive reserve—which are referred to as brain reserve—is of particular importance for the development of effective strategies in treating AD.

In rodents, a promising manipulation to study the neurobiological underpinnings of the cognitive reserve is the

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environmental enrichment (EE) paradigm, where the complexity of the social, cognitive, and sensorial environments can be manipulated (Nithianantharajah and Hannan, 2006; Rosenzweig and Bennett, 1996), and its effects on cognitive function can be evaluated. Indeed, a large body of evidence indicates that EE not only improves learning and memory performance in healthy animals (Bruel-Jungerman et al., 2006; van Praag et al., 2000), but it can also enhance recovery from lesion-induced memory deficits (Dahlqvist et al., 2004; Pacteau et al., 1989; Wolf et al., 2006). These studies demonstrate the potential of environmental stimulation to improve or restore cognitive function as either a preventive or a rehabilitative strategy in disease or injury models. In addition, EE induces structural and biochemical modifications of neurons (Escorihuela et al., 1995; Rampon et al., 2000b), stimulates adult hippocampal neurogenesis (van Praag et al., 1999), and triggers profound changes in the transcription of specific genes (Griffin et al., 2009; Rampon et al., 2000a; Thiriet et al., 2008), indicating that profound neurobiological changes may underlie the improvements in behavioral and cognitive functions. These quantitative changes, referred to as brain reserve, are likely to reflect the building of the cognitive reserve, which elevates the threshold of pathology required to render clinical deficits visible. Importantly, it was also reported that EE is able to mitigate cognitive decline in transgenic models of familial AD (Arendash et al., 2004; Costa et al., 2007; Cracchiolo et al., 2007; Hu et al., 2010; Jankowsky et al., 2005; Valero et al., 2011; Wolf et al., 2006), demonstrating the potential effectiveness of this paradigm as a strategy for reducing AD-related cognitive impairments. Though these studies demonstrated the utility of EE paradigm on improving cognitive function in AD models, they were not designed to examine whether exposure to EE at a specific time frame—either prior to or during AD progression—would most efficiently lead to the establishment of a cognitive reserve. Indeed in these reports, AD mice were placed in EE either continuously from weaning to an age when cognitive deficits manifest (Cotel et al., 2012; Cracchiolo et al., 2007; Herring et al., 2009; Hu et al., 2010; Jankowsky et al., 2003, 2005; Lazarov et al., 2005; Wolf et al., 2006), or when the full range of amyloid pathology symptoms are already present (Arendash et al., 2004; Valero et al., 2011). Therefore, to define this specific period we investigated at which stage, in the course of the amyloid pathology, exposure to EE is more prone to trigger optimal functional compensation and alleviate age-related memory dysfunction and neuropathological hallmarks in Tg2576 mice, a well-established mouse model of AD (Hsiao et al., 1995, 1996).

Transgenic mice were transiently exposed to EE at specific time periods of the amyloidosis process (i.e., prior to, at, or after amyloid onset). At 13 months of age, long-lasting behavioral and neuropathological effects of EE were analyzed in Tg2576 mice and nontransgenic littermates, as a function of the age of the mice during exposure to EE. We found that transient exposure to EE prior to plaque formation improved spatial and nonspatial memory performance in Tg2576 mice later in life, at an age when these mice normally show strong memory deficits. This effect was associated with a reduction of neocortical senile plaque formation during aging. Moreover, we report that a subpopulation of standard-housed 13.5-month-old Tg2576 mice display an ectopic expression of the neuropeptide Y (NPY) in their mossy fibers. These findings further extend previous reports of hippocampal alterations of synaptic activity-related proteins associated with amyloid β (Aβ)-dependent network dysfunction in other mouse models of AD (Chin et al., 2005; Harris et al., 2010; Minkeviciene et al., 2009; Palop et al., 2003, 2007; Vogt et al., 2011). Such abnormal expression of NPY in Tg2576 mice is highly suggestive of seizure activity and remained limited in mice exposed to EE at older age. Our data support the hypothesis that environmental and social stimulation occurring before the formation of amyloid aggregates is able to robustly enhance brain capacity to cope with the disease.

2. Methods

2.1. Animals and experimental groups

One hundred twelve female mice from the transgenic line Tg2576 (Hsiao et al., 1995, 1996), were used. Two Tg2576 (HuAPP696swe in a C57BL6/SJL genetic background) male mice created by K. Hsiao Ashe were generously gifted by Mayo Foundation for Medical Education and Research to J.M. Lassalle. Tg2576 mice carry a double mutation (Lys670-Asn, Met671-Leu [K670N, M671L]), driven by a hamster prion protein promoter, and overexpress human APP695. Tg2576 males were bred with C57B6/SJL F1 females (Charles River, L'Arbresle, France) and the offspring was genotyped for the human amyloid precursor protein (hAPP) transgene using DNA obtained from postweaning tail biopsies. Polymerase chain reaction products were analyzed to confirm the presence of hAPP DNA sequence in offspring.

2.1.1. Housing conditions

Transgenic mice (Tg2576) and age-matched nontransgenic littermate control mice (NTg) were maintained on a 12 hours light/12 hours dark cycle with free access to food and water. Transgenic mice and their NTg littermates were randomly assigned to either standard housing (nonEE) or environmental enrichment (EE) (Fig. 1A and B). Mice were exposed to the EE for 10 weeks starting at the age of 3 months (EE3m), 5 months (EE5m), or 10 months (EE10m) (Fig. 1B). These specific ages were chosen because they correspond to milestones in the development of the amyloid pathology along the lifespan of these transgenic mice (Arendash and King, 2002; Hsiao et al., 1996; Kawarabayashi et al., 2001; King and Arendash, 2002; Lesné et al., 2006; Westerman et al., 2002). At 3 months of age, a presymp-