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Preventive and therapeutic types of environmental enrichment counteract beta amyloid pathology by different molecular mechanisms

Arne Herring [a,*,1], Lars Lewejohann [b,c,1], Anna-Lena Panzer [b], Anja Donath [a,d], Oliver Kröll [d], Norbert Sachser [b,c], Werner Paulus [d], Kathy Keyvani [a]

[a] Institute of Pathology and Neuropathology, University Hospital Essen, Hufelandstr. 55, 45122 Essen, Germany
[b] Department of Behavioural Biology, University of Muenster, Badestr. 13, 48149 Muenster, Germany
[c] Otto Creutzfeldt Center for Cognitive and Behavioral Neuroscience, University of Muenster, Muenster, Germany
[d] Institute of Neuropathology, University Hospital Muenster, Domagkstr. 19, 48149 Muenster, Germany

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ABSTRACT

Combined preventive and therapeutic physical/cognitive stimulation starting before disease onset and continuing over its progression reduce Alzheimer-related pathology in transgenic mice. We now report that exposure of TgCRND8 mice to an enriched environment as either a preventive or therapeutic approach is also capable to reduce Aβ burden, though with different plaque and cerebral amyloid angiopathy (CAA) morphology. Preventive treatment resulted in fewer and smaller plaques without affecting CAA, whereas in therapeutically treated mice beside reduction of CAA extent, numerous plaques of strongly diminished size were found, so that total plaque loads declined as well. These effects seemed to be mediated by distinct molecular pathways. In preventive but not therapeutic group a shift of $A\beta_{42/40}$ ratio towards $A\beta_{40}$ and up-regulation of Aβ clearing and degrading molecules were found. Contrariwise anti-oxidative defense mechanisms were induced only in therapy but not preventive group. We hypothesize that preventive enrichment lowers the amounts of plaque seeds and decelerates plaque growth by degradation and clearance of Aβ, while therapeutic enrichment mitigates growth and fusion of plaque seeds to large plaques by inhibiting further Aβ aggregation. This study provides an experimental basis for application of physical/cognitive training in both prophylaxis and therapy of Alzheimer's disease.

Introduction

Alzheimer's disease (AD) is morphologically characterized by cerebral parenchymal and vascular beta amyloid (Aβ) deposits and neurofibrillary tangles composed of hyperphosphorylated tau protein (Duyckaerts et al., 2009; Selkoe, 2001; Walsh and Selkoe, 2004), whereby the latter seems to be a better indicator for the clinical expression of the AD (Gong et al., 2010). Aβ peptides arise from the sequential β- and γ-secretase triggered amyloidogenic processing of the ubiquitously expressed *trans*-membranous amyloid precursor protein (APP). Under pathologic conditions, the homophilic Aβ misarranges into soluble synaptotoxic oligomers (Haass and Selkoe, 2007; Lesne et al., 2006; Shankar et al., 2007; Shankar et al., 2008; Walsh and Selkoe, 2007) and insoluble, pre-fibrillar and fibrillar aggregates that finally precipitate as senile plaques (Le et al., 2001; Meyer-Luehmann et al., 2009; Walsh and Selkoe, 2004). Further, the harmful Aβ compositions interact with inflammatory responses (Salminen et al., 2009; Vasto et al., 2008), oxidative stress (Ansari and Scheff, 2010; Manczak et al., 2006; Miranda et al., 2000; Sultana et al., 2009) and neurovascular dysfunction (Bell and Zlokovic, 2009; Zlokovic, 2005), ultimately resulting in cerebral atrophy. The brain combats deleterious imbalance of Aβ metabolism by the removal of surplus amyloid load, engaging various neuronal, microglial and neurovascular Aβ clearance and degradation mechanisms (Bell et al., 2007; Boche et al., 2010; Boche and Nicoll, 2008; Doi et al., 2009; Miners et al., 2008).

Voluntary physical exercise and cognitive stimulation in form of environmental enrichment starting before disease onset and continuing over its progression antagonize cognitive decline and anxiety-related behavior in transgenic mice with Alzheimer-like pathology (Adlard et al., 2005; Costa et al., 2007; Görtz et al., 2008; Pardon et al., 2009). Additionally, we and others have demonstrated that enrichment is able to reduce Aβ plaque burden and the extent of cerebral amyloid angiopathy (CAA) (Adlard et al., 2005; Ambrée et al., 2006; Lazarov et al., 2005; Pardon et al., 2009), probably mediated by induction of Aβ clearance and disrupted amyloid aggregation,

* Corresponding author. Fax: +49 2017235927.
E-mail addresses: arne.herring@uk-essen.de (A. Herring), ljohann@phenotyping.de (L. Lewejohann), anna-lena.panzer@gmx.de (A.-L. Panzer), anja.donath@uk-essen.de (A. Donath), olli.kr@web.de (O. Kröll), sachser@uni-muenster.de (N. Sachser), werner.paulus@uni-muenster.de (W. Paulus), kathy.keyvani@uk-essen.de (K. Keyvani).
[1] A.H. and L.L. contributed equally to this work.
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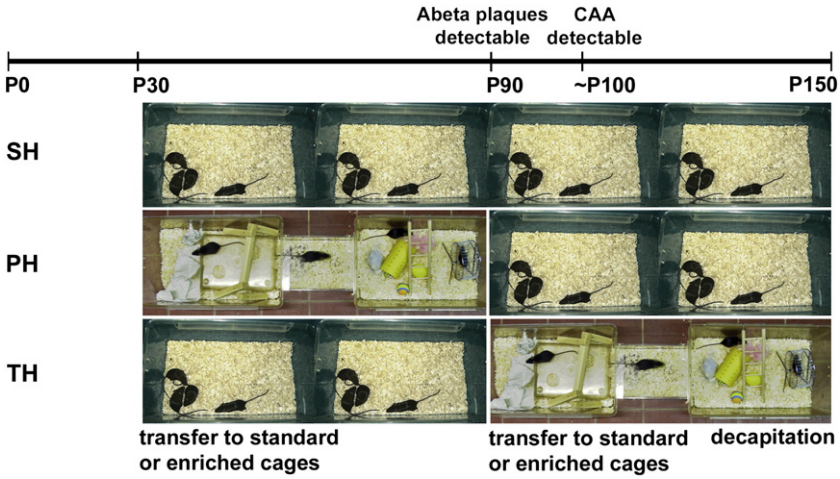

Fig. 1. Animal housing. Female TgCRND8 mice were transferred at 30 days to their experimental housing condition. Control mice were kept in standard housing from P30-P150 (SH, $n = 12$). Animals of the preventive housing group were kept in enriched cages supplied with physically and cognitively stimulating objects before disease onset from P30–P90 (PH, $n = 13$) and afterwards transferred to SH cages from P90–P150. Reciprocally, mice with therapeutic stimulation were housed in SH cages until P90 and thereafter conveyed to enriched cages until P150 (TH, $n = 13$). P = postnatal; SH = standard housing; PH = preventive enriched housing; TH = therapeutic enriched housing; CAA = cerebral amyloid angiopathy.

utilizing increased activation of the Aβ degrading endopeptidase neprilysin (Lazarov et al., 2005), reduced inflammation and oxidative stress (Ambrée et al., 2006; Herring et al., 2010), enhanced microglial phagocytosis (Ambrée et al., 2006), as well as boosted angiogenesis and modulated expression of Aβ receptor/transporter systems facilitating Aβ efflux across the blood–brain barrier (Herring et al., 2008). Furthermore, increased hippocampal neurogenesis and cellular plasticity following enriched housing supports the brain to compensate for abnormal hippocampal neurogenesis and neuronal loss occurring in transgenic models of AD (Herring et al., 2009; Mirochnic et al., 2009; Wolf et al., 2006).

In previous investigations, enriched housing was administered before disease onset and lasted over disease progression. Here we asked whether preventive environmental enrichment alone, presented before the disease onset (P30–P90) or therapeutic enrichment, provided only after disease onset (P90–P150) are also able to reduce AD-related pathology in TgCRND8 mice and if yes, whether this shift in the stimulation time frame also results in morphology differences and/or alterations of the underlying molecular mechanisms.

Materials and methods

Animals and experimental housing

We investigated 38 female TgCRND8 mice encoding the human APP 695 transgene including the “Swedish” and “Indiana” mutations, regulated by the Syrian hamster prion protein promoter, on a hybrid C57BL/6-C3H/HeJ background. TgCRND8 mice are characterized by

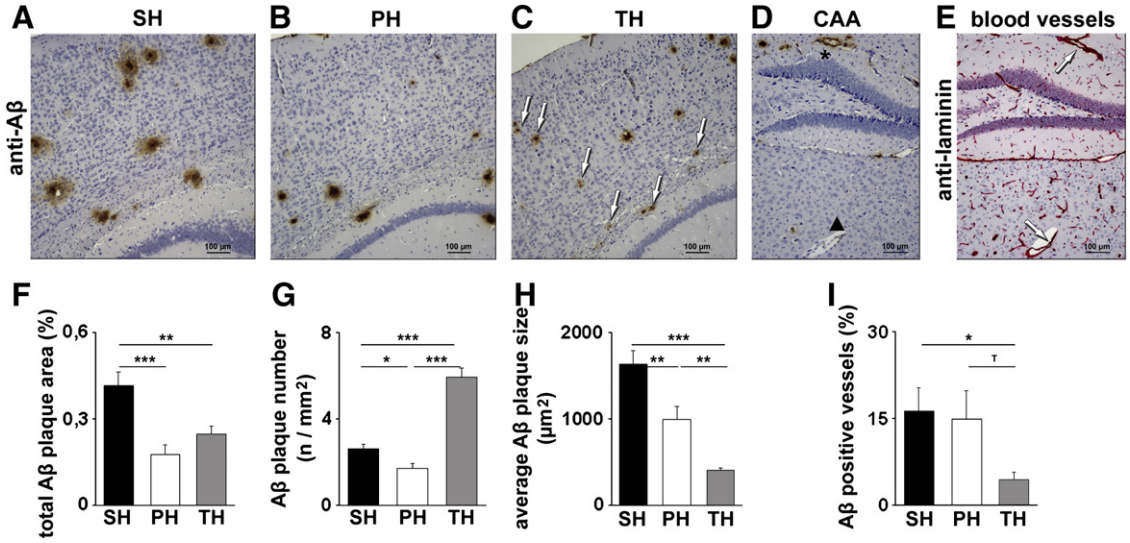

Fig. 2. Preventive and therapeutic environmental enrichment both reduce cerebral Aβ plaque burden. (A–C) Representative figures of cerebral Aβ plaque morphology in SH (A), PH (B) and TH mice (C) after immunohistochemical staining against Aβ using 6F/3D antibody. (D) Representative figure of a blood vessel with CAA (indicated by an asterisk) and an unaffected vessel (indicated by a triangle). The number of Aβ positive vessels was set in relation to laminin labeled vessels indicated by arrows in (E). Nonbiased morphometric quantification uncovered in preventive enrichment a decrease in total Aβ plaque area (F) as a result of plaque number (G) and plaque size (H) reduction without affecting the severity of CAA (I) when compared to SH animals. Therapeutic enrichment reduced also the total plaque area (F) due to a strong decline of the average plaque size (H) and despite higher plaque number (G); note numerous small-sized aggregates as indicated by arrows in (C). Furthermore, the CAA extent was diminished in the therapy group (I). Data are given as mean ± SEM; statistics ANOVA and LSD post hoc analysis. $T = 0.1 > P \geq 0.05$; $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$; SH = standard housing; PH = preventive enriched housing; TH = therapeutic enriched housing; CAA = cerebral amyloid angiopathy.