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Induced LC degeneration in APP/PS1 transgenic mice accelerates early cerebral amyloidosis and cognitive deficits

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ABSTRACT

Degeneration of locus ceruleus neurons and subsequent reduction of norepinephrine concentration in locus ceruleus projection areas represent an early pathological indicator of Alzheimer's disease. In order to model the pathology of the human disease and to study the effects of norepinephrine-depletion on amyloid precursor protein processing, behaviour, and neuroinflammation, locus ceruleus degeneration was induced in mice coexpressing the swedish mutant of the amyloid precursor protein and the presenilin 1 ΔExon 9 mutant (APP/PS1) using the neurotoxin N-(2-chloroethyl)-N-ethyl-bromobenzylamine (dsp4) starting treatment at 3 months of age. Norepinephrine transporter immunolabelling demonstrated severe loss of locus ceruleus neurons and loss of cortical norepinephrine transporter starting as early as 4.5 months of age and aggravating over time. Of note, dsp4-treated transgenic mice showed elevated amyloid β levels and impaired spatial memory performance at 6.5 months of age compared to control-treated APP/PS1 transgenic mice, indicating an accelerating effect on cerebral amyloidosis and cognitive deficits. Likewise, norepinephrine-depletion increased neuroinflammation compared to transgenic controls as verified by macrophage inflammatory protein-1α and -1β gene expression analysis. Exploratory activity and memory retention was compromised by age in APP/PS1 transgenic mice and further aggravated by induced noradrenergic deficiency. In contrast, novel object recognition was not influenced by norepinephrine deficiency, but by the APP/PS1 transgene at 12 months. Overall, our data indicate that early loss of noradrenergic innervation promotes amyloid deposition and modulates the activation state of inflammatory cells. This in turn could have had impact on the acceleration of cognitive deficits observed over time.

1. Introduction

The current prevalence of Alzheimer's disease (AD) comprises 18 million patients worldwide, and this number is assumed to double until 2025 (WHO). Due to the urgent nature of finding effective medication and specific diagnostic tools for AD several transgenic animal models have been developed which mimic the amyloid β (Aβ) and tau pathology as well as the neuroinflammatory component of the disease. Besides these main traits, human post-mortem studies have confirmed that an early and substantial degeneration of the locus ceruleus (LC), the main source of norepinephrine (NE) in the mammalian brain, strongly correlates with the progression and severity of dementia, with increase of Aβ plaque deposition as well as neurofibrillary tangle formation (Iversen et al., 1983; German et al., 1992; Marien et al., 2004; Bondareff et al., 1987). In order to model the human AD pathology in this study, APP/PS1 double transgenic mice were treated with dsp4. It has recently been suggested that dsp4's high-affinity uptake through the NET together with its completely irreversible mode of interaction with the NET contribute to its selectivity as noradrenergic neurotoxin (Wenge and Bönisch, 2009) leading subsequently to retrograde degeneration of the NE producing and containing neurons and axons of the LC while leaving other systems intact (Kalinin et al., 2007; Fritschy and Grzanna, 1989). Previously, NE-depletion has been shown to contribute to astroglial and microglial activation, upregulation of inflammatory markers such as macrophage inflammatory protein-1α and -1β (MIP-1α and MIP-1β), tumor necrosis factor alpha (TNFα), 'Regulated upon Activation, Normal T-cell Expressed, and presumably Secreted' (RANTES), glial fibrillary acidic protein (GFAP) and 'Cluster of Differentiation 11b' (CD11b) (Pugh et al., 2007), and elevated inducible nitric oxide synthase (iNOS) and nitric oxide levels in LC projection areas (Heneka et al., 2002, 2006). Secondary changes like the regulation of different adrenergic receptor

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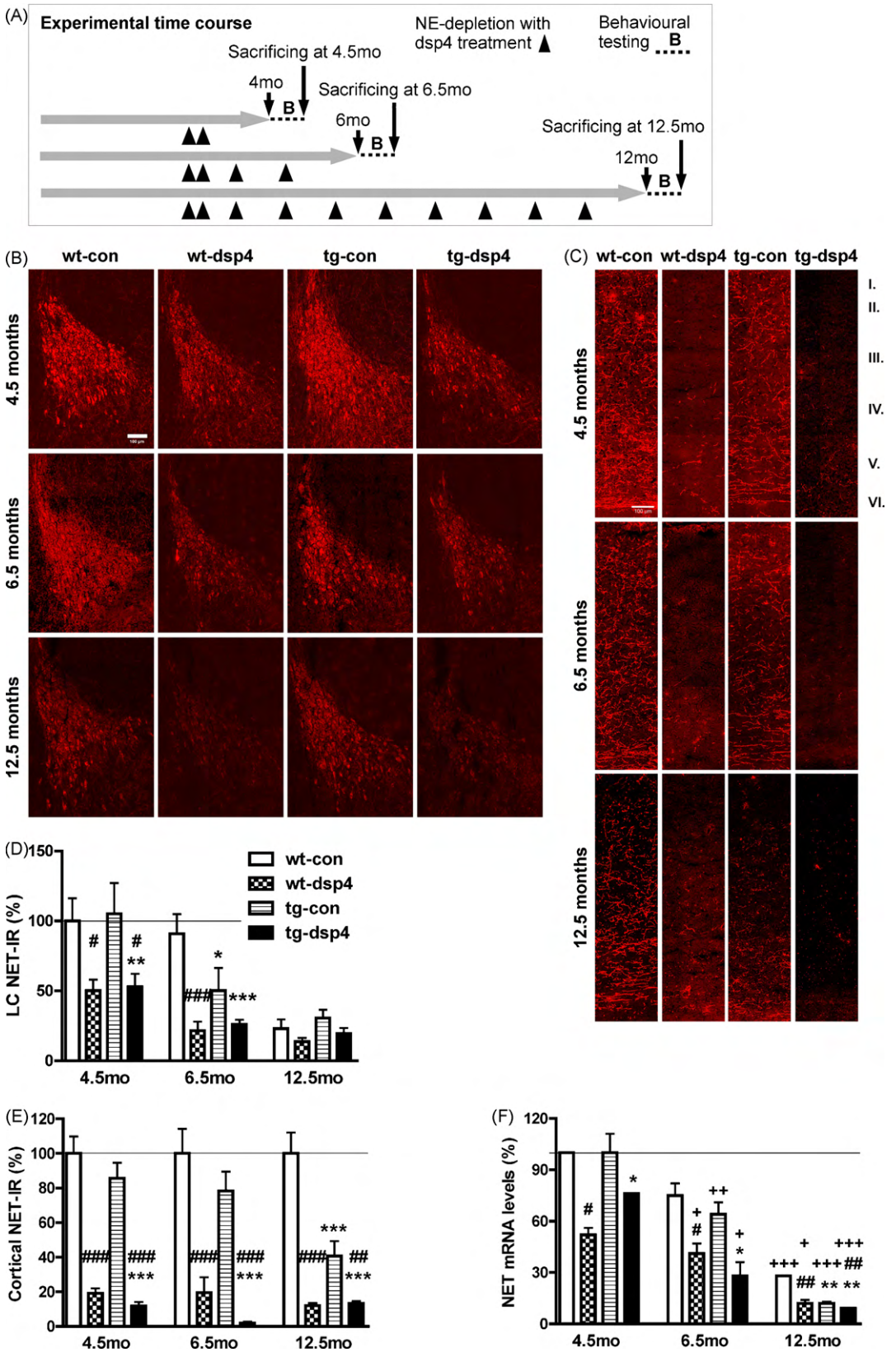

Fig. 1. Experimental time course. NE-depletion led to down-regulation of NET protein levels in the LC and the cortex as well as loss of NET mRNA expression. (A) Mice were treated (▲) with dsp4 to induce selectively degeneration of the locus ceruleus while control mice received saline treatment. Mice received first i.p. injections at 3 and 3.2 months of age followed by monthly administrations, which were stopped 1 month prior to behavioural testing at 4, 6 and 12 months of age. (B and C) NET-IR of 4.5, 6.5, 12.5 months old wild-type (wt) and APP/PS1 (tg) mice treated with dsp4 (dsp4) or saline (con). (B) Medial section of the LC at lat. 810 μm. (C) Retrosplenial granular and agranular cortices. Pictures depict a vertical segment of the retrosplenial granular and agranular cortices next to the hippocampus (Bregma: −1 to −3 mm). Roman numbers from I to VI point to the orientation of six cortical layers. Note the nearly absent NET-IR in the cortex of dsp4-treated mice. (D) Quantification of NET-IR in the LC. The NET-IR of dsp4-treated 4.5 months old mice was lower vs. wild-type and APP/PS1 controls ($p < 0.05$). By 6.5 month a further reduction of NET-positive areas were found in the LC due to transgenity ($p < 0.001$). Furthermore, 12.5-month-old mice of all groups demonstrated a severe LC NET loss as compared to 4.5 months old controls. (E) Quantification