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Research report

Seizure susceptibility in the APP/PS1 mouse model of Alzheimer's disease and relationship with amyloid β plaques

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ABSTRACT

Alzheimer's disease is a common age associated neurodegenerative disorder associated with an elevated risk of seizures that may be fundamentally connected to cognitive dysfunction. We used 4–9 month-old mice of the APP/PS1 mouse model of Alzheimer's disease to study the presence of epileptiform-like discharges and to establish if the amyloid-β plaques affect their generation. The EEG of the APP/PS1 transgenic mice revealed a higher incidence of epileptiform-like discharges i.e. seizure events (interictal spikes, sharp waves, or polyspikes) than in the controls. Also, APP/PS1 mice showed a lower latency to evoke seizure events than in the control animals when pentylenetetrazole (60 mg/kg; i.p.) was injected. Moreover, physostigmine injection (1 mg/kg; i.p.) also increased the frequency of spontaneous epileptiform-like discharges in the APP/PS1 mice. We also found a correlation between the frequency of epileptiform-like discharges and the number of amyloid-β plaques. Application of N-(2-chloroethyl)-N-ethyl-bromobenzylamine (50 mg/kg) generated amyloid-β plaques in the cortex and seizure activity appeared. Taken together, these data indicate that deposits of amyloid-β plaques may be responsible for the epileptiform-like discharges recorded in the APP/PS1 mice and could be responsible for the elevated risk for seizures of Alzheimer's patients.

1. Introduction

Alzheimer's disease (AD) is the most common age associated neurodegenerative disorder and is characterized by the deterioration of memory and cognition. AD is currently the leading cause of dementia and its incidence is set to increase (Sloane et al., 2002; Norton et al., 2013). Currently there are no effective therapies that can prevent, delay or stop the progression of AD, which causes a severe burden for the patients (Sperling et al., 2012; Cowley et al., 2013). AD is only diagnosed after patients show cognitive deficits. However, disease progression before diagnosis lasts for decades, which represents a valuable window for therapeutic intervention before irreversible neurodegenerative changes and consequent cognitive loss occur (Lesne et al., 2013).

AD is associated with an elevated risk of seizures and this association may be fundamentally connected to cognitive dysfunction. It is known that people with AD are ten times more likely to develop epilepsy than the age-matched general population (Hauser et al., 1986; Amatniek et al., 2006; Pandis and Scarmeas, 2012; for a review see Born, 2015). Late-onset sporadic AD is associated with a threefold increase in seizure incidence compared with the general population, whereas early-onset familial AD is linked to an 87-fold rise (Amatniek et al., 2006). This supports the notion that seizures can be a part of the natural progression of AD, ranging from 5 to 67% of AD patients (Risse et al., 1990; Lehtovirta et al., 1996). Recent studies suggest that an excitatory-inhibitory imbalance may contribute to the cognitive deficits in AD, and serve as a target for clinical intervention (Palop and Mucke, 2009). Furthermore, these seizures may be a critical part of AD pathogenesis (Scarmeas et al., 2009; Vossel et al., 2013).

The mechanism by which AD increases the risk of seizure has only recently been explored using mouse models. A growing number of studies have documented abnormal electrical activity in APP-transgenic mouse models of AD. Spontaneous seizures and sharp wave discharges have been observed in several transgenic animal models expressing mutations in amyloid precursor protein (APP) (Lalonde et al., 2005; Palop et al., 2007; Westmark et al., 2008; Minkeviciene et al., 2009; Ziyatdinova et al., 2011; Sanchez et al., 2012; Verret et al., 2012; Corbett et al., 2013). The seizure

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid-β; APP, amyloid precursor protein; DSP4, N-(2-chloroethyl)-N-ethylbromo-benzylamine; GABA, γ-aminobutyric acid; PTZ, pentylenetetrazole; WT, wild-type.

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phenotype is most often noted in models carrying the Swedish mutation, including Tg2576 (Westmark et al., 2008), APP23 (Lalonde et al., 2005), hAPPJ20 (Lesne et al., 2013) and APP/PS1dE9 (Palop et al., 2007).

Although neurodegeneration and age-related co-factors may contribute to the development of seizures in AD, recent data obtained using transgenic mice expressing human APP in neurons have indicated that high levels of the amyloid-β (Aβ) peptide are sufficient to elicit epileptiform activity and seizures even in the early stages of the disease process, and in the absence of evident neuronal loss (Palop et al., 2007). Notably, experimental manipulations that prevent seizure activity in hAPP mice have also prevented cognitive deficits in these models (Roberson et al., 2007). In addition, Aβ enhances epileptic activity in the dentate gyrus of mice hippocampal slices (Costa et al., 2016).

Consequently, we have been experimenting with the APP-double transgenic mouse model to identify the relationship between Aβ production and epileptiform activity to ascertain if there is a causal relationship between them. Furthermore, electroencephalography (EEG) would be useful in determining the early diagnosis of this pathology. The aim of this study is to improve the understanding of the relationship between AD pathology and seizure susceptibility by using a transgenic animal model. We used 4–9 month-old APP/PS1 mice when the first plaques appear in the cortex (Garcia-Alloza et al., 2006) to establish if Aβ plaques may affect the EEG.

2. Results

2.1. EEG activity in APP/PS1 mice

We studied the proportion of delta (1–4 Hz), theta (4–8 Hz) and alpha (8–12 Hz) frequency bands in the EEG power spectrum of WT and APP/PS1 mice. We did not study fast activities because they were absent in anesthetized mice. In spontaneous conditions (5 min EEG recording), we did not find any differences in the delta, theta or alpha frequency bands recorded in the wild-type (WT) or the APP/PS1 mice (Fig. 1A). The percentage of delta waves in the power spectrum was higher than other EEG frequencies due to the anesthetic (92.5 ± 1.9% and 92.7 ± 1.4% of total EEG in WT and APP/PS1 mice, respectively). By contrast, we found differences in the EEG as a result of the i.p. injection of physostigmine. Physostigmine is a reversible cholinesterase inhibitor which increases the ACh level in the brain and induces EEG activation (Enz et al., 1993). A 1 mg/kg physostigmine I,p. injection mainly increased the percentage of alpha activity and reduced delta and theta frequency bands with respect to the control period i.e. the mean of 15 min prior to the physostigmine injection. In the 4–6 month-old WT mice (n = 8) alpha activity increased from 1.4 ± 0.1% in the controls to 5.2 ± 0.3% 15 min post physostigmine injection ($P < 0.001$; ANOVA plus Dunnett's test), returning to the control values 30 min post injection (Fig. 1B). The alpha activity also increased in the 4–6 month-old APP/PS1 mice (n = 8), but in a lower proportion than in the control animals (from 1.5 ± 0.06% in control to 3.4 ± 0.1% 15 min post physostigmine injection; $P < 0.001$; ANOVA plus Dunnett's test; n = 8). Theta activity was reduced in both the WT and APP/PS1 mice post physostigmine injection, but the differences were only statistically significant in the APP/PS1 mice at 15 min ($P = 0.043$; ANOVA plus Dunnett's test; n = 8). These findings suggest that the APP/PS1 mice show a lower response to cholinergic agonists than the WT animals at alpha frequencies, while the lower frequencies were reduced in these animals.

Epileptiform-like discharges i.e. seizure events were observed in spontaneous EEG recordings of APP/PS1 mice. They consisted of (i) interictal spikes, (ii) sharp wave discharge or (iii) polyspikes (Fig. 2A). The epileptiform-like discharge definition was based on

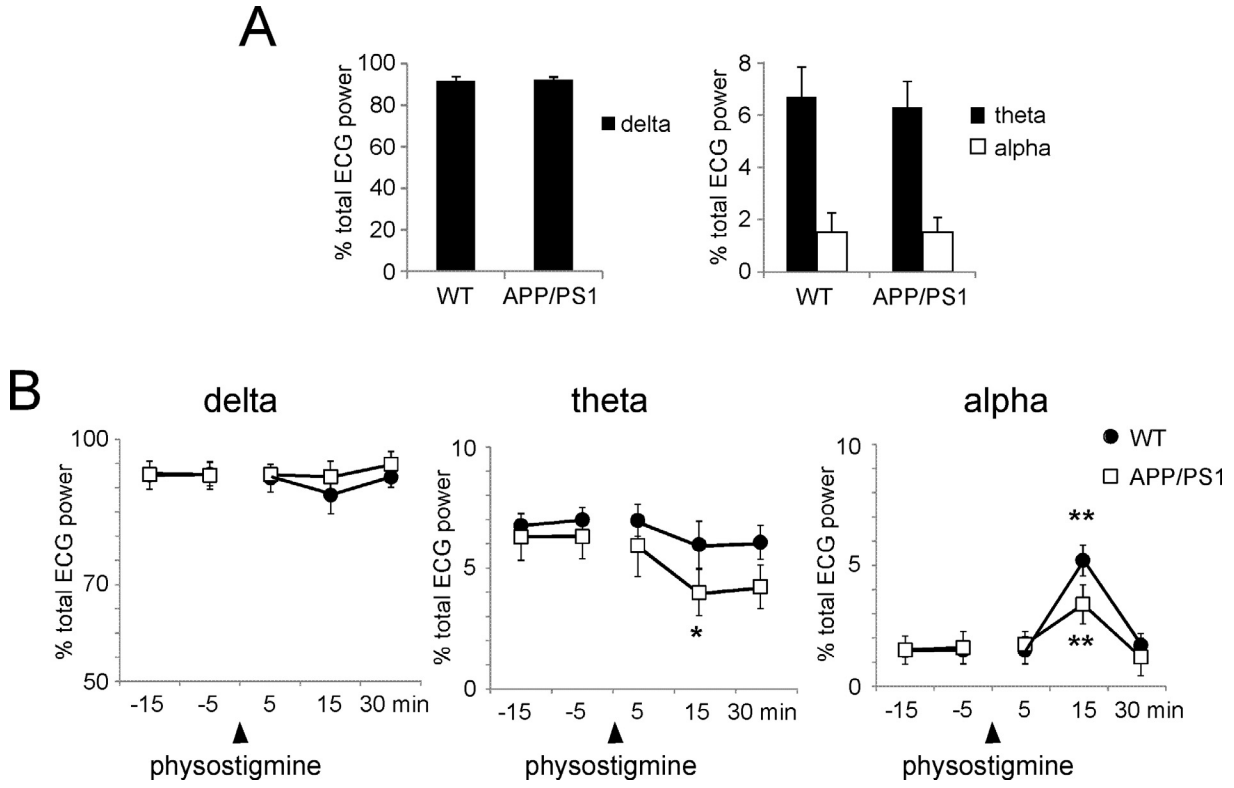

Fig. 1. EEG characteristics of APP/PS1 and WT mice. A, percentages of delta, theta, and alpha waves in the total power spectrum. The power spectrum was calculated from 5 min periods of spontaneous activity. No differences were observed between both animal types. B, physostigmine i.p. injection (1 mg/kg) increased alpha activity in the EEG of WT and APP/PS1 mice. The change was lower in APP/PS1 mice. Theta activity was also decreased in APP/PS1 mice.