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Reduction of epileptiform activity by valproic acid in a mouse model of Alzheimer's disease is not long-lasting after treatment discontinuation

Sofya Ziyatdinova[a], Jayashree Viswanathan[b], Mikko Hiltunen[b], Heikki Tanila[a,c], Asla Pitkänen[a,*]

[a] A.I. Virtanen Institute, University of Eastern Finland, Kuopio, Finland
[b] Institute of Clinical Medicine-Neurology, University of Eastern Finland, Kuopio, Finland
[c] Department of Neurology, Kuopio University Hospital, Kuopio, Finland

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Summary Patients with Alzheimer's disease are at increased risk for unprovoked seizures and epilepsy compared with age-matched controls. Experimental evidence suggests that neuronal hyperexcitability and epilepsy can be triggered by amyloid-β (Aβ), the main component of amyloid plaques. Previous studies demonstrated that the administration of an anticonvulsant and histone deacetylase inhibitor, valproic acid, leads to a long-lasting reduction in Aβ levels. Here we used an APdE9 mouse model of Alzheimer's disease with overproduction of Aβ to assess whether treatment with valproic acid initiated immediately after epilepsy onset modifies the occurrence of epileptiform activity. We also analyzed whether the effect is long-lasting and associated with antiamyloidogenesis and histone-modifications. Male APdE9 mice (15 week old) received daily intraperitoneal injections of 30 mg/kg valproic acid for 1 week. After a 3-week wash-out, the same animals received injections of a higher dose of valproic acid (300 mg/kg) daily for 1 week. Long-term video-electroencephalography monitoring was performed prior to, during, and after the treatments. Aβ and total histone H3 and H4 acetylation levels were measured at 1 month after the final valproic acid treatment. While 30 mg/kg valproic acid reduced spontaneous seizures in APdE9 mice ($p < 0.05$, chi-square), epileptiform discharges were not reduced. Administration of 300 mg/kg valproic acid, however, reduced epileptiform discharges in APdE9 mice for at least 1 week after treatment discontinuation ($p < 0.05$, Wilcoxon test), but there was no consistent long-term effects on epileptiform activity after treatment

* Corresponding author at: Department of Neurobiology, A.I. Virtanen Institute for Molecular Sciences, University of Eastern Finland, PO Box 1627, FI-70211 Kuopio, Finland. Tel.: +358 50 517 2091; fax: +358 17 16 3025.
E-mail address: asla.pitkanen@uef.fi (A. Pitkänen).

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withdrawal. Further, we found no long-lasting effect on Aβ levels ($p > 0.05$, Mann—Whitney test), only a meager increase in global acetylation of histone H3 ($p < 0.05$), and no effects on H4 acetylation ($p > 0.05$). In conclusion, valproic acid treatment of APdE9 mice at the stage when amyloid plaques are beginning to develop and epileptiform activity is detected reduced the amount of epileptiform activity, but the effect disappeared after treatment discontinuation.

Introduction

Patients with Alzheimer's disease (AD) are at increased risk for unprovoked seizures and epilepsy as compared with age-matched controls (Amatniek et al., 2006; Bernardi et al., 2010; Friedman et al., 2012; Hauser et al., 1986; Pandis and Scarmeas, 2012). Seizures can occur at an early stage in both familial and sporadic AD (Vossel et al., 2013), as well as in advanced AD (Mendez et al., 1994; Romanelli et al., 1990). Seizures or even subclinical epileptiform activity are associated with cognitive decline, more rapid disease progression, and more severe neurodegeneration in AD patients (Aldenkamp and Arends, 2004; Hommet et al., 2008; Kleen et al., 2013; Volicer et al., 1995; Vossel et al., 2013). Moreover, a reduction in seizure frequency or severity during treatment with antiepileptic drugs (AEDs) results in cognitive improvement in some AD patients (Vossel et al., 2013). Taken together, these data suggest that rather than a mere co-occurrence, epileptogenesis and comorbidogenesis could have shared molecular mechanisms which result in pathologies compromising the outcome in AD.

Epileptiform activity and seizures are observed in several transgenic mouse models of AD (Born et al., 2014; García-Cabrero et al., 2013; Minkeviciene et al., 2009; Palop et al., 2007). Experimental evidence suggests that neuronal hyperexcitability and epilepsy in AD can be triggered by amyloid-β (Aβ), the main component of amyloid plaques (Minkeviciene et al., 2009). The most harmful Aβ species are not those that aggregate in plaques, but rather the soluble oligomeric-protofibrillar Aβ species that accumulate in synapses and cause functional impairment (Cleary et al., 2005; Selkoe, 2002). The accumulation of Aβ species in inhibitory synapses could be the initial cause of AD-related hyperexcitability (Palop et al., 2007; Palop and Mucke, 2009; Verret et al., 2012). Along with compromising inhibitory synaptic transmission, Aβ can also increase neuronal excitability, as previous studies demonstrated clusters of hyperactive neurons surrounding Aβ plaques in the cortex and hippocampus (Busche et al., 2012, 2008). Whereas high nanomolar concentrations of Aβ in brain slices suppress synaptic potentiation, low picomolar concentrations of Aβ enhance it (Puzzo et al., 2008). In addition, preincubation of brain slices with soluble profibrillar Aβ triggers neuronal hyperexcitability and reduces the resting membrane potential (Minkeviciene et al., 2009). Furthermore, in an APPswe/PS1dE9 mouse model of AD, the first seizures occur at the age of 3—4 months, when Aβ is still largely in a soluble form (Minkeviciene et al., 2009). These data suggest amyloidogenesis as a candidate mechanism for epileptogenesis in AD.

Qing et al. (2008) reported that valproic acid (VPA), a commonly used antiepileptic drug (AED), reduced the accumulation of Aβ and the number of amyloid plaques in APP23 (APPswe) and APP23/PS45 (presenilin-1 with G384A mutation) mouse models of AD. Notably, the effect on reducing plaque formation persisted for at least 2 months after treatment discontinuation (Qing et al., 2008). Our previous study with a 3—5 days drug administration paradigm showed that AEDs, including VPA reduced spontaneous seizures and epileptiform discharges (EDs) in APdE9 mice (Ziyatdinova et al., 2011). To test whether VPA would have an anti-amyloidogenic effect also in APdE9 mouse, and whether it would result in chronic reduction in epileptiform activity [suggesting antiepileptogenic (AEG) effect] in addition to acute AED effect, we administered VPA at the reported anti-amyloidogenic (30 mg/kg) as well as at anticonvulsive doses (300 mg/kg). Moreover, we continued the treatment for 1 week, and followed the persistence of the effect on epileptiform activity beyond the known biological half-life of VPA. Since VPA is a known inhibitor of histone deacetylase [HDAC; Monti et al. (2009)], we also assessed whether the putative long-term anti-amyloidogenic and AEG effects of VPA would be associated with a prolonged HDAC inhibition.

Materials and methods

Fig. 1 shows the study design.

Animals

Male heterozygous APPswe/PS1dE9 (APdE9) mice were used in the study ($n = 18$). At the time of electrode implantation, the mice were 12—13 week old (weight 25 ± 2 g). APdE9 colony founders were obtained from D. Borchelt and J. Jankowsky (Johns Hopkins University, Baltimore, MD, USA). Mice were created by coinjection of chimeric mouse/human APPswe and human PS1-dE9 (deletion of exon 9) vectors controlled by independent mouse prion protein promoter elements. The two transgenes cointegrate and cosegregate as a single locus (Jankowsky et al., 2004). The line was originally maintained in a C3HeJxC57BL/6J hybrid background. At the time of the present study, the mice had been backcrossed to C57BL/6J for 13 generations.

The mice were housed in individual cages in a controlled environment (constant temperature, 22 ± 1 °C, humidity 50—60%, and lights on 07:00—19:00 h). Food and water were available ad libitum.

All animal procedures were performed in accordance with the guidelines of the European Community Council