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Neurobiology of Aging 33 (2012) 1045–1053

NEUROBIOLOGY OF AGING

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Prepulse inhibition in patients with fragile X-associated tremor ataxia syndrome

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Received 7 April 2010; received in revised form 23 August 2010; accepted 5 September 2010

Abstract

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a late onset neurodegenerative disorder that affects carriers of the fragile X premutation, typically after age 50. Common symptoms include intention tremor, ataxia, neuropathy, autonomic dysfunction, cognitive decline, and dementia. The objectives of this study were to determine if patients with FXTAS have altered prepulse inhibition (PPI; a measure of sensorimotor gating), and to study possible correlations between PPI, molecular status, and cognitive performance. A passive acoustic PPI paradigm was applied in 163 subjects; 121 carriers of the fragile X premutation, and 42 healthy controls. There were significant differences in PPI between premutation carriers with FXTAS and controls at PPI 60 ms, and at 120 ms. This effect was more prominent in the male FXTAS patients. There was a tendency to an impaired PPI in female premutation carriers at the 120 ms condition. There was a significant correlation between the PPI deficit and a higher CGG repeat number. The results show an impairment in sensorimotor gating processes in male carriers of the fragile X premutation, which is more prominent in patients with FXTAS.

Keywords: PPI; Prepulse inhibition; Fragile X premutation; Sensorimotor gating; FXTAS

1. Introduction

Prepulse inhibition (PPI) of the human startle response is a neurobiological measure that is used to investigate sensorimotor gating and information processing (Buckland et al., 1969; Cadenhead et al., 1999; Hoffman and Ison, 1980; Swerdlow et al., 2005). The startle response is an involuntary contraction of facial and skeletal muscles after a sudden intense stimulus that can occur in different sensory modalities (Larsson, 1956). If a nonstartling stimulus (pre) is presented 30–500 ms before a strong startle-inducing stimulus (pulse), the amplitude of the startle response is reduced (inhibition). The modulation of the startle response (PPI) is believed to reflect preattentive central inhibitory mechanisms that protect initial processing of sensory stimuli (Li et al., 2009; Swerdlow et al., 1991).

PPI research, mostly in mice and rats, provide insights in the neuroanatomical and neurochemical mechanism of PPI (Geyer, 1999; Geyer et al., 2002; Larrauri and Schmajuk, 2006; Schmajuk and Larrauri, 2005). The information processing following an auditory stimulus elicits a response over the dorsal cochlear nucleus, inferior colliculus to the auditory cortex. Parallel to this process and depending on the startle intensity, the cochlear root neurons project to the caudal pontine reticular nucleus and then to the motor neurons, mediating the startle response (Blumenthal, 1988; Wu et al., 1988). If a prepulse precedes the startle stimulus, the startle processing circuit in the pons is regulated by connections between limbic cortico-striato-pallido-pontine and

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doi:10.1016/j.neurobiolaging.2010.09.002

thalamic circuits (Li et al., 1998, 2009; Ornitz and Guthrie, 1989; Swerdlow et al., 2001). A functional magnetic resonance imaging (fMRI) study by Kumari et al. reported the structural brain correlates, especially gray matter volumes in the hippocampus, striatum, and thalamus to PPI in healthy human volunteers (Kumari et al., 2005). A twin study by Anokhin et al. showed a significant heritability rate for PPI of over 50% (Anokhin et al., 2003).

PPI has been established as a reliable measure for abnormal sensorimotor gating in fragile X syndrome (FXS), the most common genetic cause for intellectual disability and autism (Hessl et al., 2009). In an earlier study by Frankland and colleagues with 10 boys with FXS and 7 age-matched controls, the authors demonstrated significant PPI deficits in FXS that correlated with several clinical measures including IQ, attention, and autistic symptoms (Frankland et al., 2004).

A study in the FMR1 knockout mouse model, the molecular genetic equivalent to FXS in humans, could show impaired PPI using the eyeblink startle response (de Vrij et al., 2008). Interestingly, the PPI deficit in the knockout mouse could be restored to wild-type levels by MPEP (2-methyl-6-(phenylethynyl) pyridine), an mGluR5 (metabotropic glutamate receptor 5) antagonist (de Vrij et al., 2008).

In neurodegenerative diseases, PPI changes are seen in dementia, most severely in the Alzheimer type and less impaired in Lewy body dementia (Perriol et al., 2005; Ueki et al., 2006). The PPI findings in milder forms of dementia vary. A study by Hejl et al. did not find any significant PPI differences between subjects with mild cognitive impairment or mild Alzheimer's dementia (Hejl et al., 2004). In Huntington disease and transgenic mice expressing the Huntington disease related CAG repeat expansion, the PPI decrease mechanism is considered to be related to the degeneration of striatal GABAergic neurons (Carter et al., 1999; Munoz et al., 2003; Swerdlow et al., 1995; Valls-Sole et al., 2004).

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a neurodegenerative disorder that affects carriers of a mutation in fragile X mental retardation 1 (*FMR1*) gene with a CGG repeat expansion from 55 to 200 (Hagerman et al., 2001; Jacquemont et al., 2003). Typically, the onset of FXTAS symptoms occurs after age 50 with a distinct phenotype of cerebellar ataxia, intention tremor, peripheral neuropathy, white matter disease, and cognitive decline (Berry-Kravis et al., 2007; Grigsby et al., 2008; Hagerman et al., 2007). On magnetic resonance imaging (MRI), white matter hyperintensity in the middle cerebellar peduncles is a common neuroanatomical finding. Postmortem cellular pathology shows intranuclear inclusions in the hippocampus and neocortex, both in neurons and astrocytes (Greco et al., 2003, 2006; Iwahashi et al., 2006; Tassone et al., 2004). The cognitive decline presents initially with frontal executive dysfunction, attention problems, and short term memory deficits (Grigsby et al., 2006, 2008).

The objectives of this study are to determine if individuals with the FMR1 premutation demonstrate PPI impairments, and if so, whether an alteration in PPI is associated only with FXTAS disease or also in carriers without overt neurological symptoms. Based on the findings in other neurodegenerative disorders, we expect PPI to be impaired in FXTAS, because the intranuclear inclusions mostly occur in the hippocampus, an area that is involved with PPI regulation. In addition, if a PPI deficit associated with the permutation or FXTAS could be documented, we wished to further investigate the potential use of PPI as a central nervous system (CNS)-based outcome measure for use in clinical trials of neuroprotective agents being developed for this disorder.

Authors of earlier studies showed a clear correlation between PPI, IQ, and attention measures in fragile X syndrome full mutation carriers. We expect a correlation of PPI with measures of cognitive function, attention, and motor control in FXTAS, because these are the main symptoms of neurodegeneration in this patient population.

To the best of our knowledge, PPI has not previously been investigated in patients with FXTAS.

2. Methods

The study protocol was approved by the Institutional Review Board at the University of California at Davis, and all participants signed a written consent. Because the participants were also required to stay awake during the approximately 20-minute duration of the protocol, a silent movie showing natural scenes and landscapes was shown. This method was primarily essential in our studies of individuals with fragile X syndrome and intellectual disability, and significantly improves compliance and reduces movement and other types of artifact, and yet retains excellent test-retest reliability (Frankland et al., 2004; Hessl et al., 2009; Ornitz and Guthrie, 1989). Although compliance is less of an issue in premutation carriers, we decided not to alter the procedure in order to maintain a consistent protocol in our laboratory allowing comparisons across samples.

2.1. Stimuli

The PPI protocol was administered using the James Long presentation and psychophysiology recording system (James Long Company, Caroga Lake, NY, USA). The auditory stimuli were presented binaurally through high-impedance headphones Telephonics TDH-49P (Monitor Instruments, Inc., Hillsborough, NC, USA). The psychophysiology laboratory has a constant environmental background noise of 62 db. The PPI protocol included startle pulses of 105 db white noise for 50 ms. The prepulse stimuli were 1 KHz tones at 75 db for 25 ms. The protocol included 4 trial types: startle pulse alone, prepulse 60 ms prior to the startle, prepulse 120 ms prior to the startle, and prepulse 240 ms prior to the startle. These trials are presented 8 times each at a random order with intertrial intervals from 25 to 45 seconds. Before the start of the first