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Research Report

YAC128 Huntington's disease transgenic mice show enhanced short-term hippocampal synaptic plasticity early in the course of the disease

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ABSTRACT

Huntington's disease (HD) is a progressive and fatal neurodegenerative disorder caused by a polyglutamine expansion in the gene encoding the protein huntingtin. The disease progresses over decades, but often patients develop cognitive impairments that precede the onset of the classical motor symptoms. Similar to the disease progression in humans, the yeast artificial chromosome (YAC) 128 HD mouse model also exhibits cognitive dysfunction that precedes the onset of the neuropathological and motor impairments characteristic of HD. Thus, the purpose of this study was to evaluate whether short- and long-term synaptic plasticity in the hippocampus, two related biological models of learning and memory processes, were altered in YAC128 mice in early stages of disease progression. We show that the YAC128 hippocampal dentate gyrus (DG) displays marked reductions in paired-pulse depression both at 3 and 6 months of age. In addition, significantly enhanced post-tetanic and short-term potentiation are apparent in YAC128 mice after high-frequency stimulation at this time. Early and late forms of long-term plasticity were not altered at this stage. Together these findings indicate that there may be elevated neurotransmitter release in response to synaptic stimulation in YAC128 mice during the

Abbreviations: AD, Alzheimer's disease; ANOVA, analysis of variance; CA1, *Cornu ammonis* 1; CS, conditioning stimulus; DG, dentate gyrus; E-LTP, early long-term potentiation; fEPSPs, field excitatory post-synaptic potentials; GABA, gamma-aminobutyric acid; HD, Huntington's disease; HFS, high-frequency stimulation; I/O, Input/Output; MPP, medial perforant path; nACSF, normal artificial cerebrospinal fluid; NMDA, N-methyl-D-aspartate; LFS, low-frequency stimulation; LTD, long-term depression; L-LTP, late long-term potentiation; LTP, long-term potentiation; PCR, polymerase chain reaction; WT, wild-type; YAC, yeast artificial chromosome

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initial phase of disease progression. These abnormalities in short-term plasticity detected at this stage in YAC128 HD transgenic mice indicate that aberrant information processing at the level of the synapses may contribute, at least in part, to the early onset of cognitive deficits that are characteristic of this devastating neurodegenerative disorder.

1. Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder that affects approximately 1 in 20,000 people worldwide (Harper, 1996). HD typically has an adult onset and is characterized by a variety of psychiatric, cognitive, and motor symptoms, culminating in death within 12–15 years of the time of onset (Folstein, 1989). The earliest symptoms of HD include mood swings, depression, irritability, and impaired learning and memory. As the disease progresses, concentration on intellectual tasks becomes increasingly difficult, and eventually patients may develop severe dementia (Harper, 1996). Interestingly, the cognitive deficits usually appear years before the onset of the classical motor symptoms. Furthermore, post-mortem studies suggest that the first cognitive symptoms appear in the absence of significant neurodegeneration and cell death (Vonsattel et al., 1985). Thus, it may be that impairments in cognition are caused by changes in neuronal communication preceding neuronal cell loss in non-striatal brain regions.

Changes in synaptic efficacy in the hippocampus are thought to underlie cognitive processes such as learning and memory (Bliss and Collingridge, 1993; Bruel-Jungerman et al., 2007a, 2007b; Citri and Malenka, 2008). Various studies have reported impairments in long-term potentiation (LTP) in the *Cornu ammonis* 1 (CA1) sub-region of the hippocampus of knock-in (Lynch et al., 2007; Simmons et al., 2009) and R6/2 transgenic (Murphy et al., 2000) HD mice, which express exon 1 of the human *HD* gene with approximately 150 CAG repeats (Mangiarini et al., 1996). Conversely, enhanced LTP has also been observed in the CA1 of yeast artificial chromosome (YAC) 72 HD mice (Usdin et al., 1999), which express the full-length human *HD* gene with 72 CAG repeats (Hodgson et al., 1999). This alteration was detected at 6 months of age, a time-point prior to the development of the behavioral phenotype. However, by 10 months, LTP could no longer be induced in these full-length HD transgenic mice, a deficit that appears to be associated with an increase in the resting levels of Ca^{2+} within YAC neurons (Usdin et al., 1999).

YAC128 HD transgenic mice express the full-length human *HD* gene with 128 CAG repeats (Slow et al., 2003) and faithfully recapitulate many features of the human condition (Gil-Mohapel, 2012). These mice develop behavioral abnormalities that follow a biphasic pattern with an initial phase of hyperactivity followed by the onset of motor deficits, which can be detected as early as 2 months and clearly by 4 months of age and finally by hypokinesis (Graham et al., 2006a, 2006b; Slow et al., 2003; Van Raamsdonk et al., 2007, 2005b, 2005c). Furthermore, YAC128 mice also develop mild cognitive deficits, which precede the onset of motor abnormalities and can be detected as early as 2 months of age and progressively deteriorate with the course of the disease (Van Raamsdonk et al., 2005c). These mice also develop a depressive-like behavior at the early stage of 3 months of age (Pouladi et al., 2009). At the neuropathological level, significant atrophy of the striatum, globus pallidus and cortex can be detected by stereological methods at 9 months of age (Slow et al., 2003; Van Raamsdonk et al., 2005a). However, subtle early striatal neuropathological changes can be observed with more sophisticated techniques (i.e., magnetic resonance imaging) as early as 3 months of age (Carroll et al., 2011). We have recently reported deficits in adult hippocampal neurogenesis, a form of structural plasticity, in this full-length HD transgenic mouse model (Simpson et al., 2011). Importantly, deficits in hippocampal neurogenesis can be detected as early as 3 months of age (Simpson et al., 2011), before the onset of overt motor symptoms and the appearance of striatal neuropathological deficits (Slow et al., 2003). As alterations in both structural and functional hippocampal plasticity might underlie some of the early cognitive deficits characteristic of this HD transgenic mouse model (Van Raamsdonk et al., 2005c), in the present study we examined whether functional (i.e., synaptic) short- and long-term plasticity were also altered during the early stages of the disease in YAC128 HD mice.

2. Results

2.1. *Normal basal synaptic transmission but reduced paired-pulse depression in the dentate gyrus of YAC128 mice during the early stages of disease progression*

We evaluated synaptic transmission in 3- and 6-month old YAC128 animals by constructing a field excitatory post-synaptic potential (fEPSP) Input/Output (I/O) curve in response to a series of ascending stimulus intensities. For both age groups, the slope of the fEPSP significantly increased with increasing stimulation [repeated measures analysis of variance (ANOVA); $F_{(1,806)}=1805.0$, $P=0.0000$]. There were no significant main effects for either genotype ($F_{(1,806)}=0.0006$, $P=0.98$), or age ($F_{(1,806)}=0.0005$, $P=0.98$), and no significant interaction was observed between age and genotype ($F_{(1,806)}=0.16$, $P=0.69$) (I/O curve; Figs. 1A and B). This data indicate that synaptic transmission is not significantly altered in the dentate gyrus (DG) of YAC128 HD mice at the early stages of disease progression, and that at this time they retain a normal capacity to exhibit single evoked responses in response to synaptic stimulation.

In addition to single pulse stimulation, paired-pulse plasticity was also assessed. To isolate excitatory responses, in these experiments the hippocampal slices were bathed in normal artificial cerebrospinal fluid (nACSF) containing the gamma-