Experimental Neurology 286 (2016) 69–82

Contents lists available at ScienceDirect

Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

Research Paper

Progressive gene dose-dependent disruption of the methamphetamine-sensitive circadian oscillator-driven rhythms in a knock-in mouse model of Huntington's disease

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ARTICLE INFO

Article history:
Received 23 May 2016
Received in revised form 29 August 2016
Accepted 14 September 2016
Available online 16 September 2016

Keywords:
Transgenic mice
Dopamine
Sleep
Preconditioning

ABSTRACT

Huntington's disease (HD) is a progressive genetic neurodegenerative disorder characterised by motor and cognitive deficits, as well as sleep and circadian abnormalities. In the R6/2 mouse, a fragment model of HD, rest-activity rhythms controlled by the suprachiasmatic nucleus disintegrate completely by 4 months of age. Rhythms driven by a second circadian oscillator, the methamphetamine-sensitive circadian oscillator (MASCO), are disrupted even earlier, and cannot be induced after 2 months of age. Here, we studied the effect of the HD mutation on the expression of MASCO-driven rhythms in a more slowly developing, genetically relevant mouse model of HD, the Q175 'knock-in' mouse. We induced expression of MASCO output by administering low dose methamphetamine (0.005%) chronically via the drinking water. We measured locomotor activity in constant darkness in wild-type and Q175 mice at 2 (presymptomatic), 6 (early symptomatic), and 12 (symptomatic) months of age. At 2 months, all mice expressed MASCO-driven rhythms, regardless of genotype. At older ages, however, there was a progressive gene dose-dependent deficit in MASCO output in Q175 mice. At 6 months of age, these rhythms could be observed in only 45% of heterozygous and 15% of homozygous mice. By 1 year of age, 90% of homozygous mice had an impaired MASCO output. There was also an age-dependent disruption of MASCO output seen in wild-type mice. The fact that the progressive deficit in MASCO-driven rhythms in Q175 mice is HD gene dose-dependent suggests that, whatever its role in humans, abnormalities in MASCO output may contribute to the HD circadian phenotype.

1. Introduction

Huntington's disease (HD) is an inherited neurodegenerative condition caused by an unstable expansion of CAG repeats in the Huntingtin (*HTT*) gene. The age onset of HD is inversely correlated to CAG repeat length (The Huntington's Disease Collaborative Research group, 1993) and is similar in homozygous (HOM) and heterozygous (HET) patients, although HD progresses more rapidly in HOM patients (Squitieri et al., 2003). HD is characterised by a progressive decline in locomotor and cognitive functions (see Bates et al., 2015 for references). As well, abnormalities in circadian rhythmicity and sleep have been described in HD patients (Arnulf et al., 2008; Lazar et al., 2015; Morton, 2013; Morton et al., 2005; Piano et al., 2015). These are recapitulated in multiple HD mouse models (Fisher et al., 2013, 2016; Jeantet et al., 2013; Kantor et al., 2013; Kudo et al., 2011; Lebreton et al., 2015; Morton et al., 2005). The hemizygous R6/2 transgenic mouse is the best characterised of these models of HD (Carter et al., 1999; Mangiarini et al., 1996; Menalled et al., 2009; Morton et al., 2005; Pouladi et al., 2012). With a transgene carrying ~250 CAG repeats, the R6/2 mouse has a rapid progression of disease with disruption in circadian behaviours at ~12 weeks and a lifespan of ~22 weeks (Wood et al., 2013). It is not known, however, how the gene mutation causes the circadian changes that occur in the R6/2 mouse.

Under normal physiological conditions, circadian rhythms are driven and coordinated by the suprachiasmatic nucleus of the hypothalamus (SCN). The SCN, however, is not the only oscillator that can regulate daily rhythms. For example, the methamphetamine-sensitive circadian oscillator (MASCO), is a putative circadian pacemaker that generates behavioural rhythms independent of the SCN (Honma et al., 1987, 1988). MASCO-dependent rhythms are induced by chronic low dose treatment of methamphetamine (MAP). When chronic treatment with MAP is given to SCN-intact wild-type (WT) mice placed in constant darkness (DD), a dissociation of the circadian locomotor activity rhythms can occur, leading to two rhythms, one that is driven by the SCN (~24 h), and a longer one that is driven by the MASCO (usually > 24 h; Cuesta et al., 2012; Honma et al., 1986; Tataroglu et al., 2006).

Abbreviations: ANOVA, analysis of variance; DA, dopamine; DD, constant darkness; HD, Huntington's disease; HET, heterozygous; HOM, homozygous; *HTT*, human Huntingtin gene; LD, 12:12 light-dark; MAP, methamphetamine; MASCO, methamphetamine-sensitive circadian oscillator; SCN, suprachiasmatic nucleus; WT, wild-type.

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http://dx.doi.org/10.1016/j.expneurol.2016.09.007
0014-4886/

The MASCO-driven rhythms are severely disrupted in R6/2 mice (Cuesta et al., 2012), and cannot be induced in ~95% of R6/2 mice, even at a presymptomatic age (2 months). Thus, MASCO output is disrupted several weeks before the locomotor circadian activity rhythms disintegrate (Cuesta et al., 2012). It is not clear what role the MASCO plays, if any, in humans. We suggest that whatever its role, since MASCO output is disrupted so early in R6/2 mice, MASCO disruption may contribute directly to the early symptoms of HD.

Since MASCO-dependent rhythms cannot be observed in R6/2 mice, they are unsuitable for detailed study of disruption of MASCO output. A number of 'knock-in' HD mouse models exist that have a slower progression of disease and more faithfully recapitulate the genetic context of HD mutation than does the R6/2 mouse (Menalled et al., 2009; Menalled, 2005). Here we used one such line, the Q175 mouse, to study MASCO output in HD, Q175 mice are a full length knock-in model expressing a chimeric mouse/human exon 1 with a CAG repeat expansion of around 188 (Menalled et al., 2012). HOM Q175 mice exhibit robust behavioural and molecular abnormalities (Menalled et al., 2012). They show locomotor hypoactivity and rotarod deficit by ~7 months of age and a lifespan of ~2 years. The locomotor deficits are preceded by a decrease in striatal gene markers from ~3 months of age. HET Q175 mice also exhibit behavioural deficits with a slower time course. Finally, it has recently been reported that Q175 mice have sleep and circadian deficits that recapitulate those seen in R6/2 mice and HD patients (Fisher et al., 2016; Loh et al., 2013), making the Q175 mouse line particularly suitable for studying MASCO-driven rhythms.

When we investigated circadian rhythms in Q175 mice, we found that circadian rhythms driven by both SCN and MASCO were disrupted in this line. As seen in R6/2 mice, induction of the MASCO output in Q175 mice was impaired long before the disruption of SCN-mediated rest-activity rhythms was seen. Disruption of MASCO-driven rhythms in Q175 mice were progressive and gene dose-dependent. The disruption or absence of the MASCO-driven rhythms in old Q175 mice can be explained by three possibilities. First, they may not be expressed in old Q175 mice. Secondly, their disruption may be due to a decrease in sensitivity to MAP, with the dose of 0.005% MAP no longer sufficient to induce the MASCO-driven behaviour rhythm in Q175 mice. Finally, MASCO-driven rhythms may be expressed in old Q175 mice, but their period may be shortened as aging progressed. If this is the case, they may be masked by the suprachiasmatic nucleus-driven rhythm, as seen in C3H mice (Tataroglu et al., 2006).

Our findings support the idea that disruption of MASCO output may contribute to early behavioural changes in Q175 mice. The HD gene dose-dependence of impairments of MASCO output expression is a strong indicator that abnormalities in MASCO output may contribute to the circadian phenotype in HD.

2. Materials and methods

2.1. Animals

All experiments were conducted under the UK Animals (Scientific Procedures) Act 1986 with the approval of the University of Cambridge

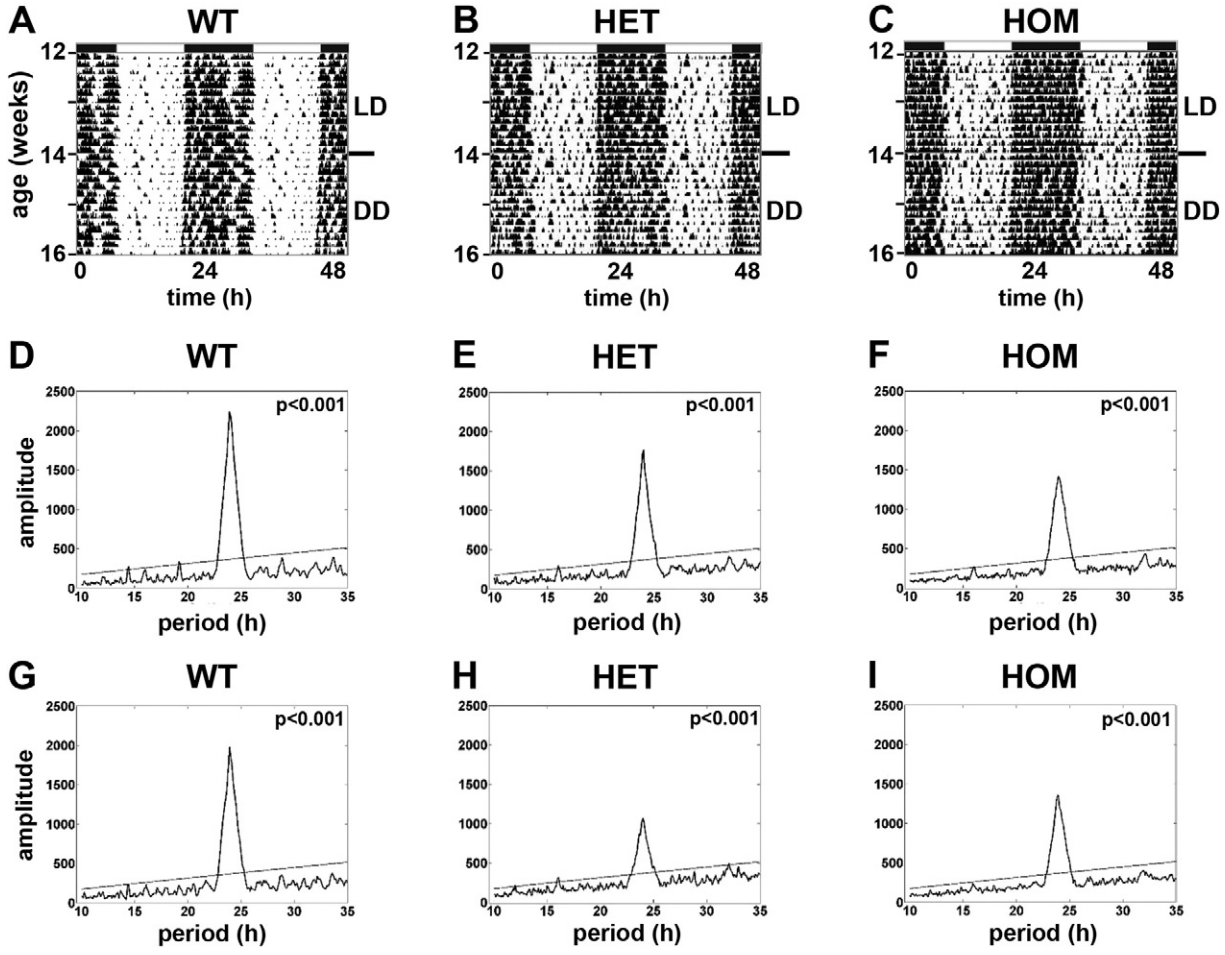

Fig. 1. Normal rest-activity patterns in young Q175 mice. Representative double-plotted actograms of wild-type (WT, A), heterozygous (HET, B) and homozygous (HOM, C) mice are shown from ~3 months (12 to 16 weeks) of age. Mice were placed in 12:12 light-dark (LD) for two weeks, followed by two weeks of constant darkness (DD). Chi-square periodograms are shown for LD (D–F) and DD (G–I) for WT (D, G), HET (E, H) and HOM (F, I) mice.