doi:10.1093/brain/awp006 Brain 2009: 132; 919–932 | 919

BRAIN
A JOURNAL OF NEUROLOGY

Prevention of depressive behaviour in the YAC128 mouse model of Huntington disease by mutation at residue 586 of huntingtin

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Huntington disease is a neurodegenerative disorder caused by an expanded CAG repeat in the Huntington disease gene. The symptomatic phase of the disease is defined by the onset of motor symptoms. However, psychiatric disturbances, including depression, are common features of Huntington disease and recent studies indicate that depression can occur long before the manifestation of motor symptoms. The aetiology of depression in Huntington disease is not fully understood and psychosocial factors such as the knowledge of carrying a mutation for an incurable disease or adverse social circumstances may contribute to its presentation. Due to the difficulties in discriminating between social and biological factors as contributors to depression in clinical Huntington disease, we chose to assess whether a model for Huntington disease not subject to environmental stressors, namely the YAC mouse model of Huntington disease, displays a depressive phenotype. Indeed, the YAC transgenic mice recapitulate the early depressive phenotype of Huntington disease as assessed by the Porsolt forced swim test as well as the sucrose intake test as a measure of anhedonia. The YAC model mirrors clinical Huntington disease in that there were no effects of CAG repeat length or disease duration on the depressive phenotype. The depressive phenotype was completely rescued in YAC transgenic animals expressing a variant of mutant huntingtin that is resistant to cleavage at amino acid 586 suggesting that therapies aimed towards inhibition of huntingtin cleavage are also likely to have beneficial effects on this aspect of the disease. In conclusion, our study provides strong support for a primary neurobiological basis for depression in Huntington disease.

Keywords: Huntington disease; depression; CAG repeat; proteolysis; mouse model

Received August 6, 2008. Revised December 27, 2008. Accepted December 29, 2008. Advance Access publication February 18, 2009

Introduction

Huntington disease is an incurable autosomal dominant neurological disorder characterized by a triad of motor, cognitive and affective disturbances (Hayden, 1981). The disease is caused by a trinucleotide CAG expansion in exon 1 of 67 axons comprising the Huntington disease gene leading to an extended polyglutamine tract in the huntingtin protein. The cardinal and early neuropathological feature of Huntington disease is atrophy of the caudate nucleus and the putamen (the neostriatum), with selective loss of medium-sized spiny neurons within the striatum.

Although onset of Huntington disease is clinically determined on the basis of motor performance, prominent affective abnormalities, particularly depression are common features of the disease. Depression has been reported to occur in as many as 40–50% of Huntington disease patients and may predate onset of motor symptoms by >10 years (Heathfield, 1967; Folstein and Folstein, 1983; Pflanz *et al*., 1991; Kirkwood *et al*., 2001; Duff *et al*., 2007). Indeed, the prevalence of depressive symptoms has been demonstrated to be increased in pre-symptomatic mutation carriers compared with non-mutation carriers (Julien *et al*., 2007; Marshall *et al*., 2007).

The aetiology of depression in Huntington disease is thought to be multifactorial with both psychosocial and neurobiological contributions. The realization of the intransigent nature of this fatal illness, along with increased functional disability and loss of capacity to carry out daily functions are considered to be important precipitating factors. Also, social upheaval in families with Huntington disease with significant discord and stress may contribute. There is evidence, however, that biological factors do contribute independently to depression in Huntington disease. Indeed, depression in Huntington disease often antedates motor and cognitive impairments by many years (Folstein and Folstein, 1983; Pflanz *et al*., 1991; Duff *et al*., 2007). Further, depression is often observed in other disorders of the basal ganglia such as Parkinson's disease and corticobasal degeneration, where it may also predate other symptoms (Litvan *et al*., 1998; Lieberman, 2006), implicating disruptions of neural circuits involving the basal ganglia as the precipitating factor leading to depression in these disorders.

As a first step towards unraveling the pathogenic mechanisms underlying the affective disturbances in Huntington disease, we examined whether the depression state observed in patients is modelled in the transgenic YAC Huntington disease animals. The YAC Huntington disease animals express the entire human Huntington disease gene under the control of the endogenous huntingtin promoter and regulatory elements and recapitulate many features of the human condition, including motor and cognitive, and selective neuronal deficits (Hodgson *et al*., 1999; Slow *et al*., 2003; Van Raamsdonk *et al*., 2005*b*). The Porsolt forced swim test (FST) and a sucrose intake test were used to assess depressive behaviour in the YAC Huntington disease animals compared with their littermates in the same environment. The Porsolt FST is one of the most widely employed paradigms for assessing 'depression' phenotypes and antidepressant action in rodents (Porsolt *et al*., 1977*a*, *b*; Cryan *et al*., 2002). The test model is based on the observation that a rodent, when forced to swim in a restricted space where there is no possibility for escape, will cease to struggle after an initial period of activity and simply float. Increased immobility is interpreted as a depressive state, representing signs of psychomotor retardation and/or despair (Porsolt *et al*., 1977*a*, *b*; Cryan *et al*., 2002). The sucrose intake test assesses one of the major symptoms of depression, anhedonia (inability to experience pleasure). Reduced sucrose consumption and preference is interpreted as a decreased sensitivity to reward (Willner *et al*., 1987). Our results indicate that early depressive phenotypes are indeed present in the YAC Huntington disease animals, independent of disease duration and CAG repeat length, and closely mirror the symptoms observed in patients with Huntington disease.

Materials and methods

Animals

The experiments were performed on wild-type (WT) animals and transgenic YAC animals expressing the entire human Huntington disease gene under the control of the endogenous huntingtin promoter and regulatory elements on the FVB/N strain background. YAC18 animals express human WT huntingtin with 18 CAG repeats (Hodgson *et al*., 1996). YAC46, YAC72 and YAC128 express human mutant huntingtin with 46, 72 and 120 CAG repeats, respectively (Hodgson *et al*., 1999; Slow *et al*., 2003). The most characterized of these is the YAC128 line which recapitulates several features of human Huntington disease including progressive cognitive deficits starting at 2 months of age, motor dysfunction by 3 months of age, followed by selective neuropathology with striatal atrophy clearly evident by 8 months of age (Slow *et al*., 2003; Van Raamsdonk *et al*., 2005*b*, *c*; Lerch *et al*., 2008). C6R YAC transgenic animals express human mutant huntingtin with 133 CAG repeats that has been mutated at amino acid 586 to prevent cleavage by caspase-6 (Graham *et al*., 2006). All animals were bred at the animal facility of the Centre for Molecular Medicine and Therapeutics at the University of British Columbia and were group-housed in numerical birth order with littermates of mixed genotype. Mice were maintained on a 12-h light:dark light cycle (lights on at 23 h) and behavioural testing was conducted during the dark phase. Experimenters were blind to the genotype of the mice. Food and water were provided *ad libitum*. Unless stated otherwise, experiments were performed on 3- to 4-month-old and 8- to 9-month-old mice and their non-transgenic littermates. Experiments were performed with the approval of the Animal Care Committee at the University of British Columbia.

Forced swim test procedure and scoring

Immobility in the FST is a commonly used measure of depression in rodents (Cryan *et al*., 2002; Porsolt *et al*., 1977*a*, *b*). The FST was conducted by placing mice in individual cylinders (25-cm tall × 19-cm wide) filled with room temperature water (23–25°C) to a depth of 15 cm for a period of 6 min. The test sessions were recorded by a video camera placed directly above the cylinders. The sessions were examined blind and the last 4 min of the test session was scored using a time-sampling technique to rate the predominant behaviour over 5-s intervals. The following behaviours were measured and

recorded at the end of every 5 s: swimming, immobility and climbing. Independent cohorts of animals were used throughout the study, and no repeat testing was performed. The number of animals tested for each genotype and time point is stated in the figure legend. As no significant difference was observed in climbing behaviour between the genotypes in any of the comparisons made throughout the study, climbing behaviour data will not be shown for the sake of clarity.

Simple test of swimming ability

To assess whether the ability to swim in YAC128 Huntington disease animals is impaired, animals were tested in a simple swimming test. In this test, mice were placed at one end of a linear swimming chamber (76 x 13 cm; water depth, 9 cm; platform, 6 x 13 cm) and trained to reach a platform at the other end of the chamber in the shortest amount of time to escape from the water. Mice were trained with three consecutive sessions 5 min apart. Mice were tested with seven successive trials and swimming speed for each mouse was recorded for each trial.

Test of motor function

Training for the test of motor function was carried out at 2 months of age. Mice were trained for 3 days with three trials per day on a fixed-speed rotarod (UGO Basile, Comerio, Italy). Training sessions ran for 120 s at 18 r.p.m. and were spaced 1 h apart. Testing took place during the dark cycle and was carried out at 3 and 12 months of age. Motor coordination and balance were assessed using the accelerating rotarod task. In this test, the rotarod accelerated from 5 to 40 r.p.m. over 4 min and performance was assessed by the amount of time that a mouse could remain running on the rotarod; the maximum score is 300 s. Rotarod scores are the average of three trials spaced 2 h apart.

Sucrose consumption measurement

A modified sucrose consumption test based on that described by Strekalova *et al*. (2004) was performed. Briefly, individually housed animals were given *ad libitum* access to food and two bottles of water. On the day preceding intake measurements, one of the water bottles was replaced with a bottle containing 2% sucrose solution was introduced. After 24 h, the amount of sucrose solution and water intake by each animal was estimated by weighing the bottles. The sucrose preference was calculated as the ratio of the amount of 2% sucrose solution consumed to the total amount of solution consumed [(2% sucrose solution)/(2% sucrose solution + water)] normalized to kilogram body weight.

Stress-induced hyperthermia test procedure

The procedure for the stress-induced hyperthermia (SIH) test of anxiety was adapted from Van der Heyden *et al*. (1997). Measurement of the basal temperature in mice with a rectal probe represents a stressor that causes an increase in the rectal temperature and that can be inhibited by anxiolytics (Zethof *et al*., 1994). The rectal temperature of individually housed mice was measured twice in each mouse to the nearest 0.1°C: at $t = 0$ min (T1) and $t = +10$ min (T2). The SIH was calculated as the difference $\Delta T = T2 - T1$. The number of animals tested is $n = 18$ for WT, 20 for YAC128.

Antidepressant treatment

Mice were treated with two commonly used antidepressants: fluoxetine, a selective serotonin reuptake inhibitor and imipramine, a tricyclic antidepressant.

Animals were treated with fluoxetine hydrochloride (Sigma, St Louis, MO, USA) at 4 months of age, daily for 21 days. Fluoxetine hydrochloride was dissolved in 0.9% saline and administered intraperitoneally (i.p.) at a dose of 20 mg/kg in a volume of 10 ml/kg. Control animals received 0.9% saline in a volume of 10 ml/kg, i.p (Duncan *et al*., 1996). The number of animals tested is $n = 9$ per treatment.

Animals were treated with imipramine (Sigma, St Louis, MO, USA) daily for 21 days. Imipramine was dissolved in 0.9% saline and administered i.p. at a dose of 10 mg/kg b.i.d. in a volume of 10 ml/kg. Control animals received 0.9% saline in a volume of 10 ml/kg, i.p. b.i.d (Przegalinski *et al*., 1995). The number of animals tested is $n = 5$ per treatment.

Statistical analysis

Data are expressed as means ± SEM. Whenever suitable, results were interpreted using one-way ANOVA with a Tukey test. Pair-wise comparisons between genotypes or treatments at individual time points were assessed with a Student's *post hoc* test. Linear regression analyses for r^2 and *P*-values were performed with GraphPad Prism version 4.02. Differences were considered statistically significant when $P < 0.05$.

Results

YAC128 Huntington disease animals display depressive behaviour

To determine whether YAC128 exhibit depressive behaviour, 3-months-old YAC128, YAC18 and WT animals were subjected to the FST. YAC128 animals spent a significantly longer time in an immobile state compared with YAC18 ($P = 0.027$) and WT animals ($P = 0.008$) (Fig. 1). Consistent with the increased immobility displayed, YAC128 animals spent significantly less time swimming compared with YAC18 ($P < 0.001$) and WT animals ($P = 0.002$). No significant differences in immobility or swimming behaviours between YAC18 and WT animals were observed ($P = 0.986$, and $P = 0.733$, respectively) (Fig. 1).

The severity of the depressive behaviour does not increase over time in the YAC128 Huntington disease animals

The severity of depressive symptoms in Huntington disease patients has been shown not to correlate with the duration of disease (Craufurd *et al*., 2001). To examine whether the severity of depressive behaviours in YAC128 animals worsened with time, the performance of YAC128 animals and WT littermates in the FST at 3, 8 and 12 months of age were compared. As seen at 3 months of age, YAC128 animals spent a significantly longer time in an immobile state compared with their WT littermates

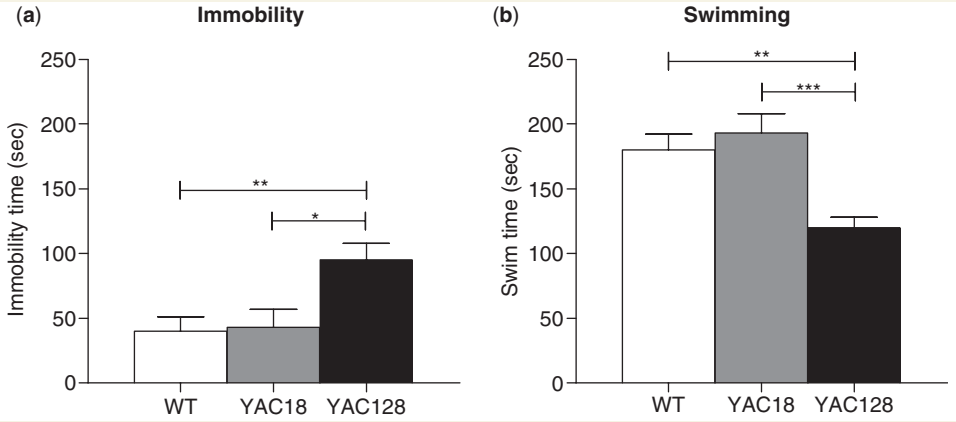

Figure 1 YAC128 Huntington disease animals display depressive behaviour. YAC128, YAC18 and WT animals were subjected to the forced swim test at 3 months of age. YAC128 animals spent a significantly longer time in an immobile state compared with YAC18 ($P = 0.027$) and WT animals ($P = 0.008$). Consistent with the increased immobility displayed, YAC128 animals spent significantly less time swimming compared with YAC18 ($P < 0.001$) and WT animals ($P = 0.002$). No significant differences in immobility or swimming behaviours between YAC18 and WT animals were observed ($P = 0.986$, and $P = 0.733$, respectively). Data are represented as means ± SEM; $n = 12$ (WT), $n = 8$ (YAC18) and $n = 12$ (YAC128); females. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

($P = 0.002$ and 0.0187 for 8- and 12-months-old mice, respectively) (Fig. 2A) and significantly less time swimming ($P = 0.001$ and 0.0295 for 8- and 12-months-old mice, respectively) (Fig. 2B). Consistent with the findings in Huntington disease patients, no significant differences were observed in depressive behaviour as signified by immobility between 3-, 8- and 12-months-old YAC128 animals ($P = 0.965$) or swimming times ($P = 0.885$) (Fig. 2A and B). Similarly, no significant differences were noted in immobility or swimming times between 3-, 8- and 12-months-old WT animals ($P = 0.218$ and $P = 0.267$, respectively) (Fig. 2A and B). These results are in contrast to the progressive nature of motor and neuropathological features in these mice.

The depressive behaviour is observed to the same extent in male and female animals

To examine whether a gender difference exists in the performance of animals in the forced swim test, immobility time of males was compared with that of females at 8 months of age. Similar to female YAC128 animals, male YAC128 animals spent a significantly longer time in an immobile state compared with male WT littermates (96 ± 21 s for YAC128 and 24 ± 9 s for WT, $n = 10$ for YAC128 and 8 for WT, $P = 0.011$). However, no significant difference in immobility between male and female YAC128 animals were observed (96 ± 21 s for males and 90 ± 21 s for females, $n = 10$ for males and 9 for females, $P = 0.844$). Similarly, no significant difference in immobility between male and female WT animals were observed (24 ± 9 s for males and 11 ± 5 s for females, $n = 8$ for males and 9 for females, $P = 0.228$). As no gender differences were observed, all the subsequent cohorts of animals employed in this study are of mixed gender.

The extent of the depressive behaviour is independent of animal body weight

The body weight of 3-months-old YAC128 animals does not differ from that of WT littermates ($P = 0.135$), while increased body weight is observed in 8- ($P < 0.001$) and 12-months-old YAC128 animals ($P < 0.01$) compared with WT littermates (Fig. 2C). To examine whether increased body weight may contribute to immobility in the forced swim test, immobility time of 3-, 8- and 12-months-old animals was plotted against body weight. Regression analysis revealed no correlation between body weight and immobility time ($r^2 = 0.0317$, $P = 0.159$) (Fig. 2D).

The ability to swim is not impaired in the YAC128 Huntington disease animals despite motor dysfunction

To assess whether the ability to swim in YAC128 Huntington disease animals is impaired, animals were tested in a simple swimming test. In this test, mice were placed at one end of a linear swimming chamber and trained to reach a platform at the other end of the chamber to escape from the water. Mice were tested on seven successive trials and the swimming speed (distance travelled per second) for each mouse was assessed for each trial. There was no significant difference in the swimming speed of YAC128 animals compared with WT animals at either 3 or 12 months of age in any of the trials (Fig. 3A). Further, the average swimming speed over the seven trials was not significantly different between YAC128 and WT animals at either 3 or 12 months of age (Fig. 3B), despite significantly lower performance in the rotarod test of motor function by YAC128 animals compared with WT animals at these time points (Fig. 3C).

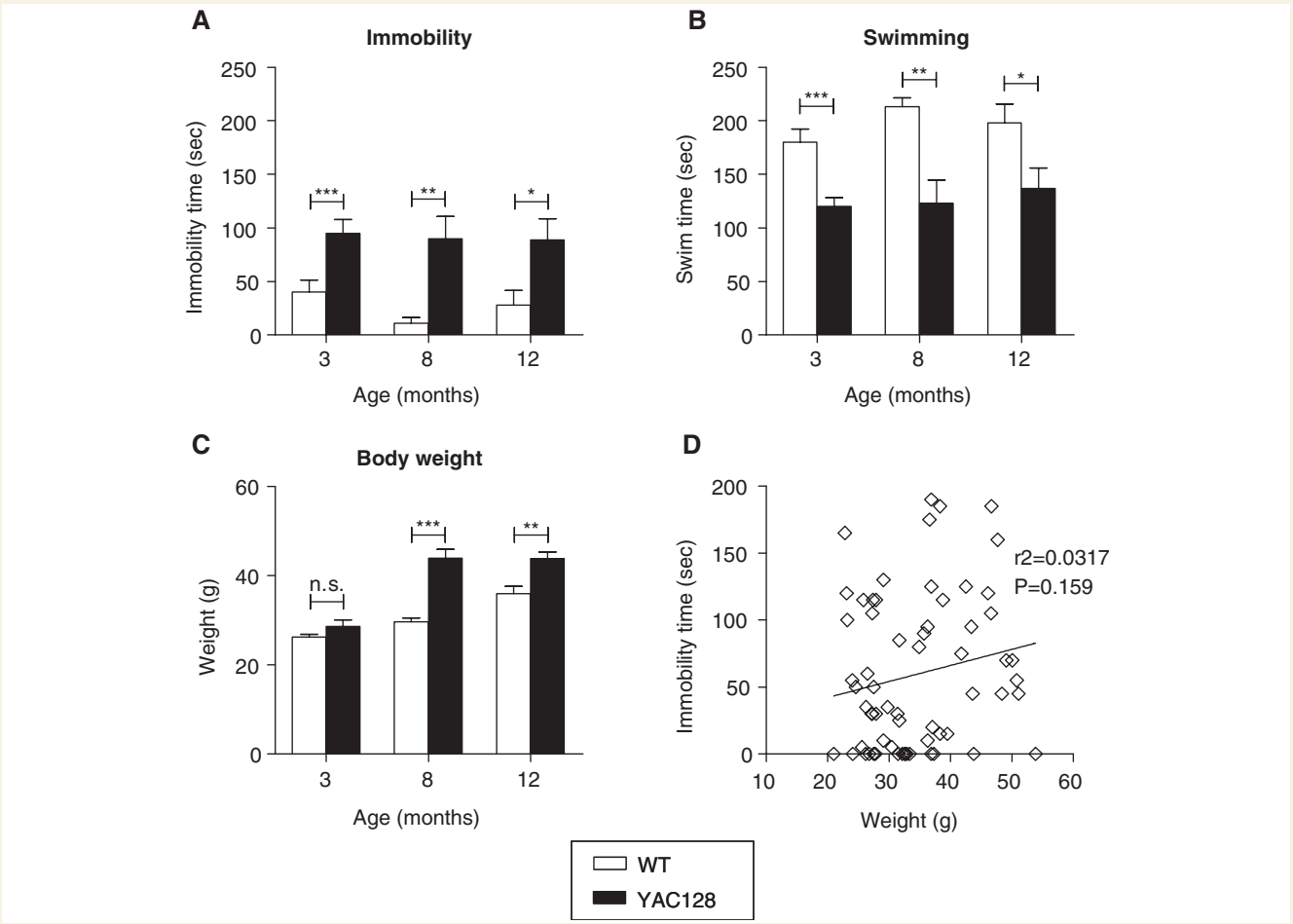

Figure 2 The severity of the depressive behaviour does not increase over time and is independent of animal body weight. YAC128 animals and WT littermates were subjected to the forced swim test at 8 and 12 months of age. (**A**) As seen at 3 months of age, YAC128 animals spent a significantly longer time in an immobile state compared with WT littermates ($P = 0.002$ and 0.0187 for 8- and 12-months-old mice, respectively) and (**B**) significantly less time swimming ($P = 0.001$ and 0.0295 for 8-and 12-months-old mice, respectively). No significant differences were observed between 3-, 8- and 12 months-old YAC128 animals in immobility ($P = 0.965$) or swimming times ($P = 0.727$). Similarly, no significant differences were observed between 3-, 8- and 12 months-old WT animals in immobility ($P = 0.218$) or swimming times ($P = 0.267$) (**C**) The body weight of 3-months-old YAC128 animals does not differ from that of WT littermates ($P = 0.135$), while increased body weight compared with WT littermates is seen in 8- ($P < 0.001$) and 12-months-old YAC128 animals ($P = 0.0026$). (**D**) To examine whether increased body weight may contribute to immobility in the forced swim test, immobility time of 3-, 8- and 12-months-old animals was plotted against body weight. Regression analysis revealed no correlation between body weight and immobility time ($r^2 = 0.0317$, $P = 0.159$). Data are represented as means ± SEM; for (A–C) $n = 12$ (3 months), $n = 9$ (8 months), $n = 11$ (12 months); for (**D**) Individual animals are represented by diamond shapes. $n = 64$. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, NS = no significant difference.

The severity of the depressive behaviour in YAC transgenic Huntington disease animals is independent of CAG repeat length

The severity of depressive symptoms in Huntington disease patients has been shown to be independent of CAG length (Zappacosta *et al*., 1996; Berrios *et al*., 2001; Craufurd *et al*., 2001). To assess whether the severity of the depressive behaviour correlated with CAG repeat length, WT, YAC46, YAC72 and YAC128 animals were subjected to the FST. Similar to YAC128 animals, YAC46 and YAC72 animals were immobile for significantly longer times than WT animals (versus WT: $P = 0.026$ for YAC46, $P < 0.001$ for YAC72 and $P < 0.001$ for YAC128) (Fig. 4). No difference in the extent of immobility between YAC46, YAC72 and YAC128 animals was observed (YAC46 versus YAC72 and YAC128: $P = 0.054$ and 0.828, respectively; YAC72 versus YAC128: $P = 0.125$) (Fig. 4). YAC46, YAC72 and YAC128 animals also spent less time swimming compared with WT animals, although the difference did not reach statistical significance in the case of the YAC46 animals (versus WT: $P = 0.067$ for YAC46, $P < 0.001$ for YAC72, and $P < 0.001$ for YAC128) (Fig. 4).

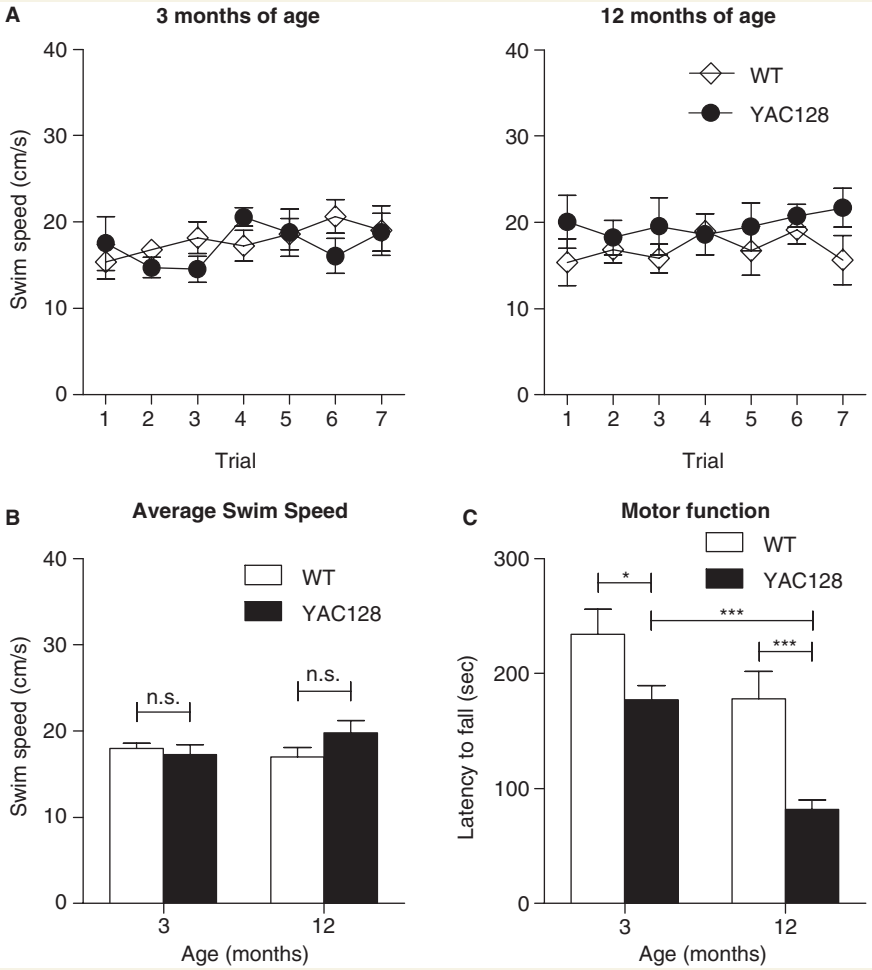

Figure 3 The ability to swim is not impaired in the YAC128 Huntington disease animals despite motor dysfunction. To assess whether the ability to swim in YAC128 Huntington disease animals is impaired, animals were tested in a simple swimming test. In this test, mice were placed at one end of a linear swimming chamber and trained to reach a platform at the other end of the chamber to escape from the water. Mice were tested with seven successive trials and the swimming speed for each mouse was recorded for each trial. (**A**) There was no significant difference in the swimming speed of YAC128 animals compared with WT animals at either 3 or 12 months of age in any of the trials. (**B**) The average swimming speed over the seven trials was not significantly different between YAC128 and WT animals at either 3 or 12 months of age, despite significantly lower performance by YAC128 animals in the rotarod test of motor function compared with WT animals (**C**). Data are represented as means ± SEM; for (**A** and **B**) $n = 5$ WT and 8 YAC128 (3 months time point) and $n = 8$ WT and 8 YAC128 (12 months time point); for (**C**) $n = 12$ WT and 17 YAC128; NS = no significant difference. $^{*}P < 0.05$, $^{***}P < 0.001$.

YAC128 Huntington disease animals display anhedonic behaviour

Anhedonia (inability to experience pleasure) is a major component of depression. Reduced sucrose intake and preference are considered a measure of anhedonia in mice (Willner *et al*., 1987). To determine whether YAC128 Huntington disease animals display anhedonic behaviour, the sucrose intake and preference of 3- to 4-months-old YAC128 Huntington disease animals was measured over a 24-h period. Consistent with anhedonic behaviour, YAC128 Huntington disease animals have a reduced sucrose intake compared with WT animals ($P = 0.0045$) (Fig. 5A). Furthermore, YAC128 animals exhibit reduced preference for sucrose compared with WT animals (Fig. 5B), suggesting that the reduced sucrose consumption observed in these animals is not the result of generalized reduction in fluid intake. Indeed, there is no difference in the amount of water consumed between YAC128 Huntington disease and WT animals (Fig.5C).

YAC128 Huntington disease animals do not display anxiety-like behaviour

Anxiety or stress has been shown reproducibly to induce an acute increase in body temperature both in animals (Zethof *et al*., 1994; Bouwknecht and Paylor, 2002) and humans (Marazziti *et al*., 1992; Briese, 1995). This response, termed stress-induced hyperthermia, is well established as a measure of anxiety in animals (Zethof *et al*., 1994). This test was chosen as certain other tests of anxiety, such as the elevated plus/zero maze and the light/dark box, are influenced by visual

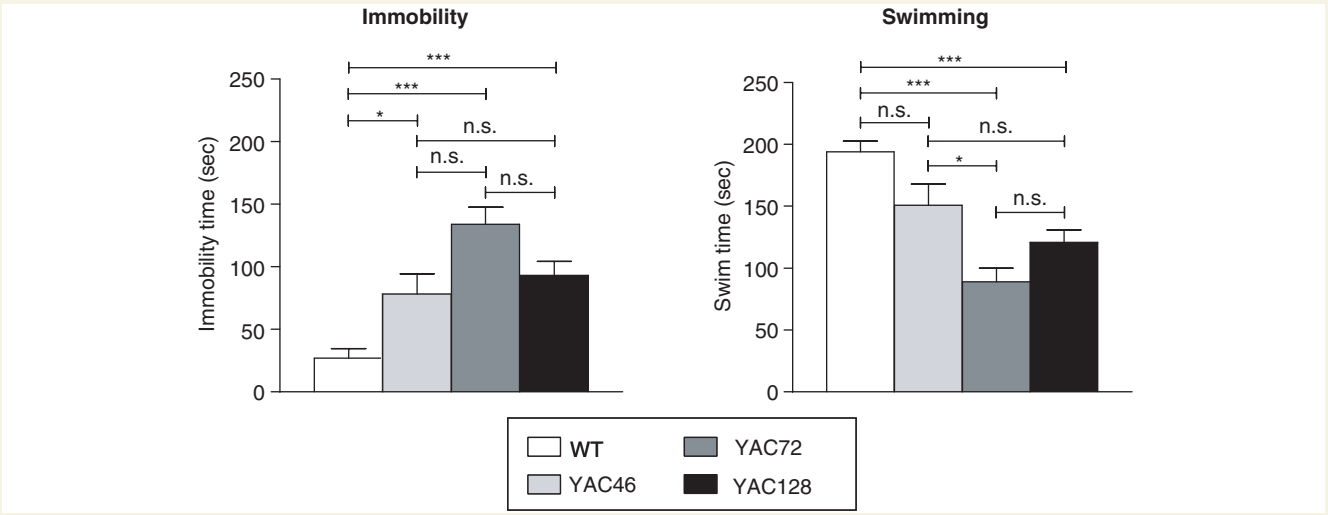

Figure 4 The severity of the depressive behaviour in YAC transgenic Huntington disease animals is independent of CAG repeat length. To assess whether the severity of the depressive behaviour correlated with CAG repeat length, WT, YAC46, YAC72 and YAC128 animals were subjected to the forced swim test. Similar to YAC128 animals, YAC46 and YAC72 animals were immobile for significantly longer times than WT animals (versus WT: $P = 0.026$ for YAC46, $P < 0.001$ for YAC72 and $P < 0.001$ for YAC128). No difference in the extent of immobility between YAC46, YAC72 and YAC128 animals was observed (YAC46 versus YAC72 and YAC128: $P = 0.054$ and 0.828, respectively; YAC72 versus YAC128: $P = 0.125$). YAC46, YAC72 and YAC128 animals also spent less time swimming compared with WT animals, although the difference did not reach statistical significance in the case of the YAC46 animals (versus WT: $P = 0.067$ for YAC46, $P < 0.001$ for YAC72 and $P < 0.001$ for YAC128). Data are represented as means ± SEM; $n = 21$ (WT), $n = 9$ (YAC46), $n = 8$ (YAC72) and $n = 21$ (YAC128). One-way ANOVA with Tukey *post hoc* test; $^{*}P < 0.05$, $^{***}P < 0.001$, NS = no significant difference.

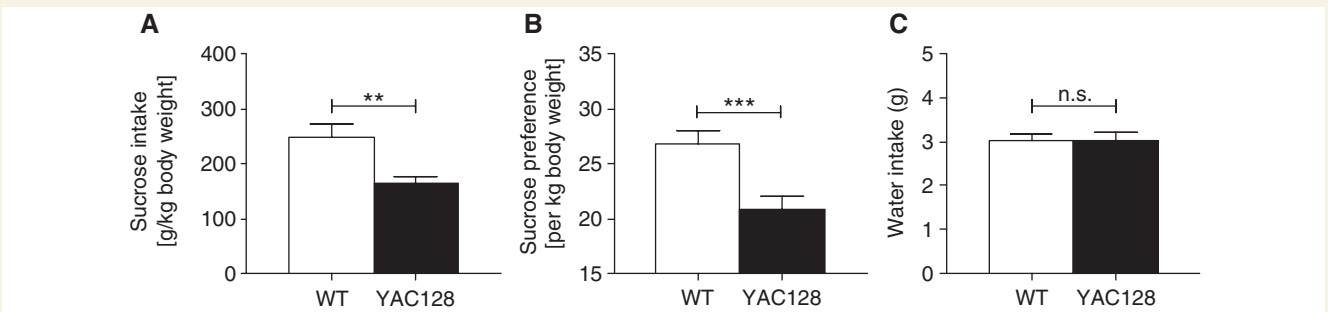

Figure 5 YAC128 Huntington disease animals display anhedonic behaviour. An inability to experience pleasure is considered a central aspect of depressive behaviour. To examine whether YAC128 animals display anhedonic behaviour, the sucrose intake of 3- to 4-months-old YAC128 animals over a 24-h period was measured. (**A**) YAC128 animals consumed significantly less sucrose solution compared with WT animals ($P = 0.0045$). (**B**) YAC128 animals exhibited significantly reduced preference for sucrose solution compared with WT animals ($P = 0.0004$). (**C**) No difference in water intake was observed between YAC128 HD and WT animals ($P = 0.492$). Data are represented as means ± SEM; $n = 26$ for WT, 23 for YAC128. $^{**}P < 0.01$; $^{***}P < 0.001$, NS = no significant difference.

cues (Cook *et al.*, 2001; Wong and Brown, 2006) and FVB/N animals develop retinal degeneration and are impaired visually by weaning age (Chang *et al.*, 2002). To examine whether YAC128 Huntington disease animals display anxiety-like behaviour, 3- to 4-months-old YAC128 Huntington disease and WT animals were subjected to the SIH test. The body temperature of YAC128 Huntington disease animals, measured rectally, was significantly increased during the SIH test ($T1 = 36.67 \pm 0.11$ versus $T2 = 37.04 \pm 0.09$, $P = 0.017$). Similarly, the body temperature of WT animals was significantly increased during the SIH test ($T1 = 36.88 \pm 0.40$ versus $T2 = 37.37 \pm 0.51$, $P = 0.003$). However, there was no difference in the SIH between YAC128 Huntington disease and WT animals ($\triangle T = 0.37 \pm 0.10$ for YAC128 and 0.49 ± 0.13 for WT, $P = 0.432$). This data suggest that depressive features, but not signs of anxiety are seen in these mice.

Preventing cleavage of mutant huntingtin at residue 586 ameliorates the depressive behaviour observed in YAC128 Huntington disease animals

Proteolysis of mutant huntingtin has been shown to play an important role in the pathogenesis of Huntington disease.

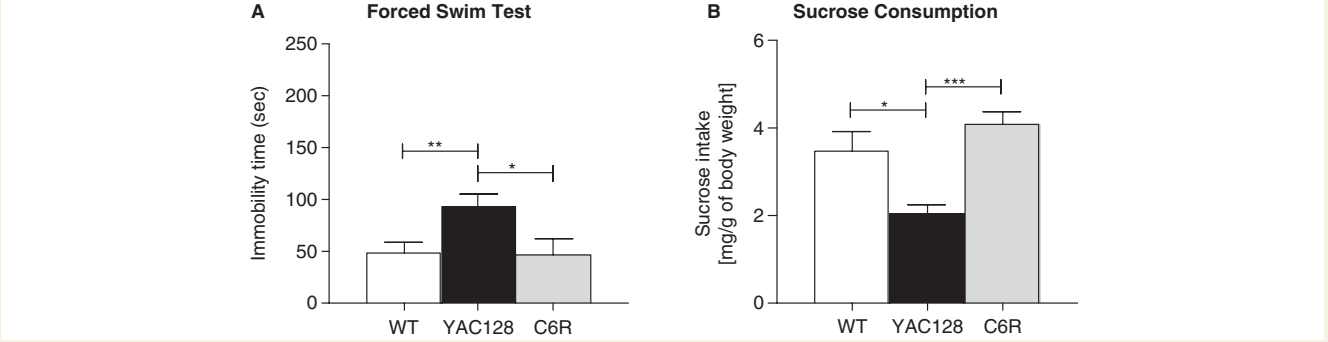

Figure 6 Preventing cleavage of mutant huntingtin at residue 586 ameliorates the depressive behaviour in YAC128 Huntington disease animals. To assess the effect of prevention of cleavage at residue 586 of mutant huntingtin on the depressive behaviour observed in YAC128 Huntington disease animals, WT and YAC128 animals along with YAC transgenic animals expressing a variant of mutant huntingtin that is resistant to cleavage at residue 586 (C6R) were subjected to the forced swim test and their sucrose consumption was measured at 3–4 months of age. (**A**) In the forced swim test, YAC128 animals spent a significantly longer time in an immobile state compared with WT animals ($P = 0.005$). In contrast, no significant difference in immobility between C6R and WT animals was observed ($P = 0.871$). Furthermore, C6R animals spent significantly less time in an immobile state compared with YAC128 animals ($P = 0.035$). (**B**) YAC128 animals consumed significantly less sucrose per gram of body weight compared with WT animals ($P = 0.010$). In contrast, no significant difference in sucrose intake per gram of body weight between C6R and WT animals was observed ($P = 0.116$). Furthermore, C6R animals consumed significantly more sucrose per gram of body weight compared with YAC128 animals ($P < 0.001$). Data are represented as means ± SEM; $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

Prevention of cleavage at residue 586 of mutant huntingtin has been demonstrated to result in amelioration of motor dysfunction and striatal pathology in the transgenic YAC Huntington disease mice (Graham *et al*., 2006). To assess the effect of prevention of cleavage of mutant huntingtin at residue 586 on the depressive behaviour observed in YAC128 HD animals, WT and YAC128 animals along with YAC transgenic animals expressing a variant of mutant huntingtin that is resistant at residue 586 (C6R) of 3–4 months of age were subjected to the FST and their immobility scored. YAC128 animals spent a significantly longer time in an immobile state compared with WT animals ($P = 0.005$) (Fig. 6A). In contrast, no significant difference in immobility between C6R and WT animals was observed ($P = 0.871$). Furthermore, C6R animals spent significantly less time in an immobile state compared with YAC128 animals ($P = 0.035$). Similarly, in the sucrose consumption test of anhedonia, while the intake of sucrose by YAC128 Huntington disease animals was significantly reduced compared with WT animals ($P = 0.010$), no significant difference in sucrose intake between C6R and WT animals was observed ($P = 0.116$) (Fig. 6B). Furthermore, C6R animals consumed significantly more sucrose compared with YAC128 Huntington disease animals ($P < 0.001$) (Fig. 6B).

Antidepressant treatment of YAC128 Huntington disease animals fails to ameliorate the depressive phenotype

To examine whether the depressive behaviour observed can be ameliorated by antidepressant treatment, 4-months-old YAC128 Huntington disease animals were treated with either fluoxetine or imipramine. Fluoxetine and imipramine treatment were used in the forced swim test and sucrose consumption test, respectively, since each is well established in the chosen concentration and the length of treatment as being efficacious in improving the depressive phenotype in the different tests (Przegalinski *et al*., 1995; Duncan *et al*., 1996). YAC128 animals were treated with saline or fluoxetine daily for 21 days and subjected to the forced swim test. Treatment of YAC128 animals with fluoxetine failed to decrease immobility time compared with saline-treated animals ($P = 0.544$) (Fig. 7A). Furthermore, there was no difference in the amount of time spent swimming or climbing by YAC128 Huntington disease animals following treatment with fluoxetine compared with saline (data not shown). Another group of YAC128 animals were treated with saline or imipramine daily for 21 days and their sucrose consumption was measured after 7, 14 and 21 days of treatment. There was no significant difference between saline- and imipramine-treated YAC128 Huntington disease animals in sucrose intake at any of the time points (Fig. 7B).

Discussion

Affective disturbances, including depression, are highly prevalent amongst at-risk and symptomatic Huntington disease patients and contribute considerably to the morbidity in Huntington disease (recently reviewed in van Duijn *et al*., 2007). While the aetiology of depression is thought to include pathophysiological changes caused by the mutation, this has not been directly examined in the absence of potential confounding psychosocial and environmental factors. Indeed, there is still controversy as to the nature and origin of depression in Huntington disease. In this respect, animal models provide the ideal tool in which to address this question under constant environmental conditions and in the absence of influence from psychosocial factors.

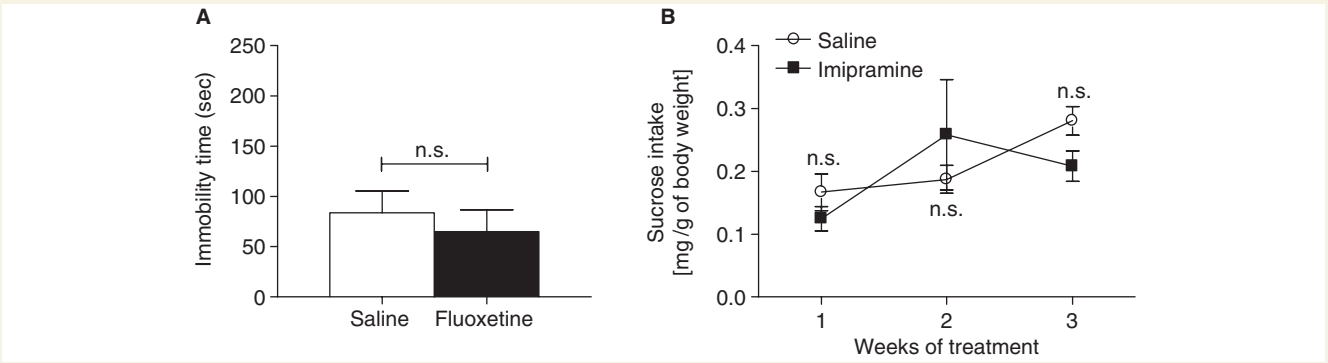

Figure 7 Antidepressant treatment fails to ameliorate the depressive phenotype in the YAC128 Huntington disease animals. To examine whether the depressive behaviour observed can be modulated, YAC128 animals were treated with the antidepressants. Fluoxetine and imipramine treatment were used in the forced swim test and sucrose consumption test, respectively, since each is well established as being efficacious in improving the depressive phenotype in the respective test. (**A**) YAC128 animals were treated with saline or 20 mg/kg of fluoxetine intraperitoneally, daily for 21 days and subjected to the forced swim test. Treatment of YAC128 animals with fluoxetine failed to decrease immobility time compared with saline-treated animals ($P = 0.544$). (**B**) YAC128 animals were treated with saline or 10 mg/kg of imipramine b.i.d. intraperitoneally, daily for 21 days and their sucrose consumption was measured after 7, 14 and 21 days of treatment. There was no significant difference between saline- and imipramine-treated YAC128 animals in sucrose intake at any of the time points. Data are represented as means ± SEM; $n = 9$ for (**A**), 5 for (**B**). NS = no significant difference.

While there are obvious limitations in modelling psychiatric diseases in rodents (Cryan *et al*., 2005), considerable progress has been made in defining the molecular and physiological underpinnings of depressive syndromes in humans where close parallels in rodent models of depressive behaviour have been established. That such parallels exist provides some validity to the use of rodents in the study of depression.

In this study, we sought to determine whether the depressive behaviour observed in Huntington disease patients is reproduced in the transgenic YAC128 mouse model of Huntington disease. We demonstrate that the YAC128 Huntington disease animals display depressive behaviour in the FST at an early stage of the disease which does not worsen over time and is independent of CAG repeat length. The depressive phenotype in the YAC128 Huntington disease animals was further reproduced using a test of anhedonia, a key component of depression. We also demonstrate that YAC128 Huntington disease animals do not display anxiety-like behaviour. Furthermore, the depressive phenotypes are ameliorated in C6R animals expressing a variant of mutant huntingtin that is resistant to cleavage at residue 586. Finally, we demonstrate that treatment with antidepressants fails to ameliorate the depressive phenotype observed. Our findings provide strong support for a significant neurobiological contribution to depression in Huntington disease.

The severity of depressive behaviour is independent of disease stage and CAG repeat length

Unlike the Huntington disease-associated cognitive and motor deficits which worsen with the progression of the disease (Bamford *et al*., 1995; Harper, 1996; Lawrence *et al*., 1999; Ho *et al*., 2003), evidence from cross-sectional studies suggests that the severity of depression in Huntington disease is independent of disease progression (Berrios *et al*., 2001; Craufurd *et al*., 2001; Kingma *et al*., 2008). Consistent with findings in Huntington disease patients, we observed no significant difference in the severity of the depressive phenotype between 3-, 8- and 12-months-old YAC128 Huntington disease animals representing early and late phases of the illness in YAC128 mice (Slow *et al*., 2003; Van Raamsdonk *et al*., 2005*b*). This is in sharp contrast to the deficits in motor function observed in these animals which are progressive in nature and worsen with age (Slow *et al*., 2003; Van Raamsdonk *et al*., 2005*b*, *c*).

Furthermore, while distinguishing apathy from depression in rodents is difficult, our data show no worsening in performance in the FST in YAC128 animals over time which is consistent with these symptoms being reflective of depressive behaviour and not apathy. Indeed, apathy which is separable from depression (Levy *et al*., 1998) and is an important feature of Huntington disease (Folstein and Folstein, 1983) is found to correlate directly with disease stage and duration (Craufurd *et al*., 2001; Kingma *et al*., 2008).

The lack of correlation between depressive symptoms and disease severity in Huntington disease is markedly different from what is observed in other neurodegenerative disorders such as Parkinson's disease where depressive symptoms are significantly related to illness severity (Brown *et al*., 1988; Cole *et al*., 1996). Furthermore, the clinical severity of depressive symptoms in adult-onset Huntington disease patients is independent of CAG repeat length (Andrew *et al*., 1993; MacMillan *et al*., 1993; Weigell-Weber *et al*., 1996; Zappacosta *et al*., 1996; Berrios *et al*., 2001; Craufurd *et al*., 2001; Close Kirkwood *et al*., 2002). These findings were paralleled in the YAC Huntington disease animals where the severity of the depressive phenotype was independent of CAG repeat length.

Increased immobility in the FST and reduced sucrose intake by YAC128 Huntington disease animals are independent of the motor dysfunction

It may be argued that since YAC128 Huntington disease animals develop progressive motor dysfunction starting at 3–4 months of age (Slow *et al*., 2003; Van Raamsdonk *et al*., 2005*b*, *c*), that the increased immobility in the FST observed in the YAC128 Huntington disease mice may be the result of an impaired ability of YAC128 animals to swim. This possibility, however, is unlikely given that the ability of YAC128 Huntington disease animals to swim is not different from that of WT animals both in the early (3 months) and late (12 months) phases of disease, despite significant impairment in motor function (Fig. 3). Furthermore, this is in agreement with our previous findings demonstrating that the cognitive deficits in the YAC128 Huntington disease animals as assessed by the swimming T-maze test of cognition is not due to any motor dysfunction-related impairment in swimming ability (Van Raamsdonk *et al*., 2005*b*).

Similarly, the reduced sucrose intake observed in YAC128 animals could reflect generalized reduction in drinking/fluid intake due to motor dysfunction. However, this is not the case as YAC128 Huntington disease animals show no reduction in water intake compared with WT animals but only a specific reduction in sucrose intake, as indicated by the lower sucrose preference score (Fig. 4). Indeed, thirst has been shown to be increased in Huntington disease in advance stages of illness, and water consumption is significantly higher in late-stage R6/2 mice compared with WT animals, despite profound motor deficits (Carter *et al*. 1993; Wood *et al*., 2008).

Anxiety-like behaviour is absent in YAC128 Huntington disease animals

The stress-induced hyperthermia test of anxiety is thought to reflect an unconditioned physiological response related to anticipatory anxiety (Van der Heyden *et al*., 1997), and has been validated using pharmacological tools including benzodiazepine treatment and novel anxiolytic drugs (Borsini *et al*., 1989; Van der Heyden *et al*., 1997). Our finding of lack of anxiety-like behaviour in YAC128 Huntington disease animals is consistent with observations in other animal models of Huntington disease (File *et al*., 1998; von Horsten *et al*., 2003). However, it may also be due to effects of background mouse strain. Indeed, differences in the extent of induced hyperthermia in the SIH test in a panel of inbred mouse strains have been demonstrated (Bouwknecht and Paylor, 2002). Interestingly, of nine different animal strains tested, FVB/N mice showed the smallest induction of body temperature in this test, indicating least propensity to anxiety (Bouwknecht and Paylor, 2002). Thus, further assessment of anxiety-like behaviours in YAC128 animals on different animal strains could yield different results.

Prevention of cleavage of mutant huntingtin at residue 586 ameliorates the depressive behaviour in YAC128 Huntington disease animals

We have shown previously that eliminating cleavage of mutant huntingtin at residue 586 in C6R animals is sufficient to preserve striatal volume and rescue cognitive and motor function in the YAC128 mouse model of Huntington disease (Graham *et al*., 2006). We now show that the depressive phenotypes observed in the YAC128 Huntington disease animals are also ameliorated by preventing cleavage of mutant huntingtin at residue 586 in C6R animals. The cleavage of mutant huntingtin yielding a 586 amino acid fragment—which is detected in the nucleus and is an early event (Warby *et al*., 2008)—is associated with neuropathology and motor deficits *in vivo*. This fragment is absent in C6R animals, and therefore may be a key and rate limiting step underlying not only motor and neuronal deficits, but also the psychiatric disturbance observed in Huntington disease. Strategies aimed at modulating mutant huntingtin proteolysis may therefore also be of therapeutic value in the management of the psychiatric disturbance in Huntington disease.

Variability of expression of depression in Huntington disease

Depression has been reported to occur in about 40–50% of Huntington disease patients (Heathfield, 1967; Folstein and Folstein, 1983; Pflanz *et al*., 1991; Kirkwood *et al*., 2001; Duff *et al*., 2007). Development of depression can result from a broad range of genetic and environmental factors that together confer vulnerability. In the presence of psychosocial stressors, these factors precipitate depressive syndromes (Billings *et al*., 1983; Brown *et al*., 1986). This complex interaction of genetic and environmental susceptibility factors is likely to account for the variability of expression of depression in Huntington disease. Indeed, one may view mutant HTT as one important genetic risk factor predisposing individuals to increased risk of depressive behaviour, which in the presence of other precipitating genetic factors and environmental stressors leads to depression.

Early disruption of neural circuits likely underlies the psychiatric disturbances in Huntington disease

Increasing evidence points to alterations in neuronal plasticity and the consequent disruption in neural circuitry and gene expression as key mechanisms underlying major depressive disorders (Manji *et al*., 2001; McClung and Nestler, 2008; Pittenger and Duman, 2008). Several findings in Huntington disease patients and animal models of Huntington disease seem to suggest that a similar mechanism may account for the depression phenotype observed in Huntington disease. Indeed, multiple abnormalities in the dopaminergic, cholinergic and glutamatergic signalling systems, which are integral components of the synaptic plasticity machinery, have

been observed in Huntington disease (Li *et al*., 2003; Di Filippo *et al*., 2007). For example, YAC46 and YAC72 HD mice exhibit early electrophysiological abnormalities indicative of altered synaptic function, including NMDA receptor hyperactivity that can be detected prior to neurodegeneration (Hodgson *et al*., 1999). In addition, several abnormalities exist in NMDA and AMPA receptor-mediated corticostriatal synaptic signalling in YAC72 and YAC128 Huntington disease animals, which predate the detection of motor or cognitive deficits (Milnerwood and Raymond, 2007). These changes are consistent with the alterations in the NMDA receptor signalling machinery observed in Huntington disease patients (Young *et al*., 1988). Furthermore, the expression of dopamine and cAMP-regulated phosphoprotein of 32 kDa (DARPP-32)—a major component in dopaminergic signalling and a potential mediator of the molecular effects of the antidepressant fluoxetine (Svenningsson *et al*., 2002)—is significantly decreased in YAC128 HD animals (Van Raamsdonk *et al*., 2005*a*). This is in agreement with alterations in the dopamine signalling pathways in Huntington disease patients (Pavese *et al*., 2003; van Oostrom *et al*., 2005). Similar observations of altered synaptic plasticity have been observed in other animal models of Huntington disease (Di Filippo *et al*., 2007).

Perturbations in additional pathways known to influence synaptic plasticity are also well documented. These include alterations in the BDNF system (Castren *et al*., 2007; Martinowich *et al*., 2007) and neuroinflammatory activation (Dunn *et al*., 2005; Raison *et al*., 2006; Stellwagen and Malenka, 2006; Todd *et al*., 2006) which have been documents in Huntington disease patients and YAC128 animals (Ferrer *et al*., 2000; Zuccato *et al*., 2001; Dalrymple *et al*., 2007; Strand *et al*., 2007; Tai *et al*., 2007; Zuccato and Cattaneo, 2007; Bjorkqvist *et al*., 2008). Finally, overactivation of the hypothalamic-pituitary-adrenal (HPA) axis, which is thought to play a role in depression (Muller and Holsboer, 2006), has been observed in Huntington disease patients and is likely to contribute to the depressive phenotype (Bjorkqvist *et al*., 2006; Petersen and Bjorkqvist, 2006). These alterations may collectively contribute to disrupted synaptic plasticity and the psychiatric disturbances in Huntington disease.

Further evidence in support of disrupted neural circuitry in Huntington disease is provided by studies demonstrating significantly reduced glucose metabolism in the basal ganglia and cortical brain regions of Huntington disease patients compared with controls (Martin *et al*., 1992). Consistent with the early occurrence of depressive symptoms in Huntington disease, the hypometabolism is observed early and precedes neuronal loss (Kuhl *et al*., 1982; Hayden *et al*., 1986). In particular, selective hypometabolism in the paralimbic frontal lobe region was found in depressed patients with Huntington disease compared with non-depressed patients and normal controls, implicating dysfunction of neural circuits involving the paralimbic regions of the frontal lobes in the depressive symptoms in Huntington disease (Mayberg *et al*., 1992).

Thus it is likely that these multi-system alterations contribute to the disruption of neural circuitry and, in conjunction with predisposing environmental and genetic factors, lead to psychiatric disturbances in Huntington disease. The extent to which the neural circuitry is affected may account for the heterogeneity observed in the timing and nature of the psychiatric symptoms. Similar variations in perturbations of neural circuitry may also occur in depressive disorders in general. The YAC128 Huntington disease animals did not show improvement in depressive symptoms following antidepressant treatment, which is similar to what has been observed with the responsiveness of the depressive phenotype in certain other models of neurological disorder such as epilepsy (Mazarati *et al*., 2008). Indeed, only 50% of individuals with depression show full remission with optimized treatment with current available antidepressant therapy (Berton and Nestler, 2006). No definitive trial of antidepressant treatment in Huntington disease has been conducted. Furthermore, considerable variability in responsiveness to antidepressant treatment in Huntington disease patients has been reported (Leroi and Michalon, 1998).

Chronic treatment with antidepressants of the selective serotonin reuptake inhibitor (SSRI) class has been shown to lead to increased brain BDNF levels (Nibuya *et al*., 1995). In light of the deficits in brain BDNF levels in Huntington disease (Zuccato and Cattaneo, 2007), treatment with such SSRIs in Huntington

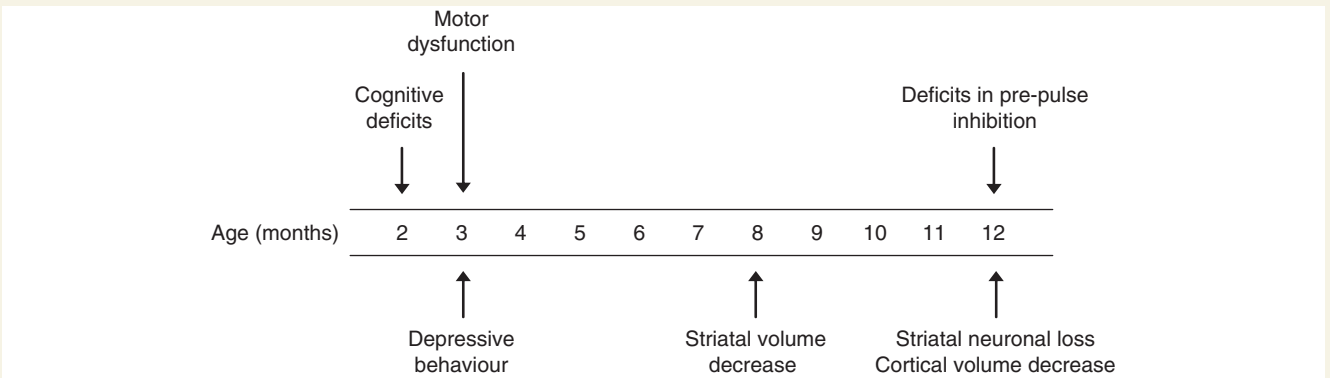

Figure 8 Time-course of behavioural and neuropathological correlates of Huntington disease in the YAC128 animals. YAC128 animals recapitulates several features of human Huntington disease including progressive cognitive deficits starting at 2 months of age, motor dysfunction and depressive behaviour by 3 months of age, followed by selective neuropathology with striatal atrophy clearly evident by 8 months of age and cortical volume loss by 12 months of age. Deficits in pre-pulse inhibition are seen at 12 months of age.

Table 1 Comparison of the characteristics of the depressive behaviour in Huntington disease patients and YAC128 Huntington disease animals

	Human Huntington disease patients	YAC128 Huntington disease mice
Time of presentation of depressive symptoms	Early (Heathfield, 1967; Folstein and Folstein, 1983; Duff *et al*., 2007)	Early (Fig. 1)
Severity in relation to disease (motor) stage/age	Independent/Does not worsen with age (Craufurd *et al*., 2001; Kingma *et al*., 2008)	Independent/Does not worsen with age (Fig. 2)
Relationship to CAG repeat length	Independent of CAG repeat length (Andrew *et al*., 1993; MacMillan *et al*., 1993; Weigell-Weber *et al*., 1996; Berrios *et al*., 2001; Craufurd *et al*., 2001; Close Kirkwood *et al*., 2002)	Independent of CAG repeat length (Fig. 4)

disease may be neuroprotective. Indeed, treatment with the SSRI sertraline has recently been shown to increase survival, improve motor deficits and attenuate the progression of brain atrophy in a mouse model of Huntington disease (Duan *et al*., 2008).

A study was published recently examining depressive behaviour in the R6/1 mouse model of Huntington disease (Pang *et al*., 2008). Female, but not male, transgenic R6/1 Huntington disease animals were found to exhibit depressive behaviour as assessed by the FST. Treatment with the antidepressant sertraline ameliorated the depressive phenotype in females. This is in contrast to our findings of depressive behaviour in male and female YAC128 animals and no improvement following antidepressant treatment. The two models express different constructs of huntingtin with R6/1 animals expressing exon 1 and YAC128 animals expressing full-length human huntingtin, which may partly account for these differences. Additional differences in the background strain may underlie these varying results.

Here, we demonstrate depressive behaviour in the transgenic YAC128 mouse model of Huntington disease that adds to the motor and cognitive deficits and selective neuropathology present in these animals (Fig. 8). The depressive behaviour occurs early, does not worsen with time, and is ameliorated by prevention of cleavage of mutant huntingtin at residue 586. The depressive behaviour recapitulates that observed in human Huntington disease (Table 1) and can be used as an outcome measure in therapeutic trials to assess the effect of potential treatments on depression.

Acknowledgements

We thank Wei-Ning Zhang for technical assistance. M.A.P. is the recipient of doctoral awards from the Canadian Institute of Health Research and the Michael Smith Foundation for Health Research. M.R.H. is a Killam University Professor and holds a Canada Research Chair in Human Genetics.

Funding

Michael Smith Foundation for Health Research (to R.K.G.); Heart and Stroke Foundation of Canada (to J.M.K.); Michael Smith Foundation for Health Research (to J.M.K.); Swedish Research Council (to Å.P.); Canadian Institutes of Health Research (to M.R.H.); the Huntington Society of Canada (to M.R.H.); the Hereditary Disease Foundation (to M.R.H.); the Huntington Disease Society of America (to M.R.H.); CHDI, Inc. (to M.R.H.); HighQ Foundation (to M.R.H.).

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