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Changes in Dopamine Signalling Do Not Underlie Aberrant Hippocampal Plasticity in a Mouse Model of Huntington's Disease

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Abstract Altered dopamine receptor labelling has been demonstrated in presymptomatic and symptomatic Huntington's disease (HD) gene carriers, indicating that alterations in dopaminergic signalling are an early event in HD. We have previously described early alterations in synaptic transmission and plasticity in both the cortex and hippocampus of the R6/1 mouse model of Huntington's disease. Deficits in cortical synaptic plasticity were associated with altered dopaminergic signalling and could be reversed by D1- or D2-like dopamine receptor activation. In light of these findings we here investigated whether defects in dopamine signalling could also contribute to the marked alteration in hippocampal synaptic function. To this end we performed dopamine receptor labelling and pharmacology in the R6/1 hippocampus and report a marked, age-dependent elevation of hippocampal D1 and D2 receptor labelling in R6/1 hippocampal subfields. Yet, pharmacological inhibition or activation of D1- or D2-like receptors did not modify the aberrant synaptic plasticity observed in R6/1 mice. These findings demonstrate that global perturbations to dopamine receptor expression do occur in HD transgenic mice, similarly in HD gene carriers and patients. However, the direction of change and the lack of effect of dopaminergic pharmacological agents on synaptic function demonstrate that the perturbations are heterogeneous and region-specific, a finding that may explain the mixed results of dopamine therapy in HD.

Keywords Synaptic plasticity · LTD ·
Electrophysiology · R6/1 · Neurodegeneration ·
Polyglutamine · Huntingtin

Introduction

Huntington's disease (HD) is a late-onset and fatal neurological disorder caused by the repetition of a CAG repeat codon in the first exon of the gene that codes for the protein huntingtin. This translates into a protein with an expanded polyglutamine repeat that confers a toxic gain of function, which induces neurodegenerative changes and neuronal cell death. A number of studies, including ours (Cummings et al. 2006; Dallérac et al. 2011, 2015; Milnerwood et al. 2006; Murphy et al. 2000), have demonstrated that neuronal dysfunction occurs prior to neurodegeneration. In particular, the loss of neuromodulatory receptors for dopamine, adenosine, and cannabinoids has been described in post-mortem human tissues (Glass et al. 2000), in prodromal and overt HD patients (Andrews et al. 1999; Antonini et al. 1998; Ginovart et al. 1997; Weeks 1997), as well as in several HD mouse models (André et al. 2010).

Dopaminergic signalling is involved in both cognition and the control of movement (Korchounov et al. 2010;

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Shohamy and Adcock 2010; Smith and Villalba 2008), processes that are affected in HD, though the aetiology is poorly understood. Many studies have demonstrated progressive loss of D1 and D2 dopamine receptor in striatal medium spiny neurones and cortical areas of symptomatic patients as well as asymptomatic HD gene carriers (André et al. 2010) demonstrating that striatal and cortical changes in the dopaminergic system are detected before clinical diagnosis and prior to gross neuropathological changes. Such findings support the notion that the early cognitive and emotional disturbances seen in HD gene carriers occur as a consequence of cellular dysfunction, rather than neuronal loss.

We have previously found that altered cortical plasticity in prodromal and symptomatic HD mouse models is attributable to dopaminergic dysfunction in the perirhinal as well as prefrontal areas, brain regions that are highly sensitive to dopaminergic neuromodulation (Cummings et al. 2006; Dallérac et al. 2011). Others have shown that long-term potentiation (LTP) is affected in the striatum of HD mice, a form of plasticity that is also modulated by dopamine (Kung et al. 2007). Strikingly, the impairment of perirhinal long-term depression (LTD) in R6/1 mice could be reversed by the administration of a D2R agonist (Cummings et al. 2006) whilst prefrontal long-term potentiation (LTP) was fully rescued by administration of a D1R agonist, suggesting that dopaminergic tone is altered in HD (Dallérac et al. 2011). Recent findings support further the view that dopaminergic modulation is abnormal in HD (Dallérac et al. 2015). Dopaminergic neuronal excitability was shown to be abnormally high in HD mice; importantly, evoked dopamine release from dopaminergic neurones was increased in the prodromal state and markedly decreased in symptomatic HD mouse models (Dallérac et al. 2015).

Cognition is altered in HD patients (Harper 1996), and the hippocampus plays a central role in memory formation (Colgin et al. 2008). A number of investigations have reported that hippocampal-dependent cognitive functions are modulated by midbrain dopaminergic inputs (González-Burgos and Feria-Velasco 2008; Hansen and Manahan-Vaughan 2014; Jay 2003). We and others have previously described markedly altered hippocampal synaptic plasticity in several HD mouse models (Hodgson et al. 1999; Milnerwood et al. 2006; Murphy et al. 2000; Usdin et al. 1999). In R6/1 and R6/2 mice this is manifest as impaired LTP and aberrant LTD (Milnerwood et al. 2006; Murphy et al. 2000). In light of the finding that alterations in cortical synaptic plasticity are highly sensitive to dopaminergic modulation in HD mice (André et al. 2010; Cepeda et al. 2014; Cummings et al. 2006; Dallérac et al. 2011, 2015), we hypothesized that abnormal dopaminergic signalling might also underlie the changes in synaptic plasticity seen in the hippocampus of HD mice. Therefore, using immunohistochemistry and electrophysiology, we have assessed the expression and regulatory functions of D1 and D2 receptors in the hippocampus of R6/1 mice.

Materials and Methods

Mice

Hemizygotic R6/1 males (Mangiarini et al. 1996) were mated with CBAxC57BL/6 females, resulting in ~50 % of the offspring being hemizygotic for the R6/1 transgene. At weaning (3 weeks), all mice were given identity marks and tail-tip samples were taken for genotyping by PCR (Mangiarini et al. 1996). R6/1 and aged-matched non-transgenic littermates (WT) mice were killed by cervical dislocation and immediate decapitation in accordance with the UK legislation (Animal (Scientific Procedures) Act 1986).

Immunohistochemistry

Brains were rapidly removed, and 400-μm coronal slices were prepared on a vibrating microtome (Campden Instruments Inc., USA). Slices were fixed in 4 % paraformaldehyde (PFA, Sigma-Aldrich, UK) then 2 % PFA overnight and transferred to 0.1 M phosphate buffered saline (PBS pH 7.4) and stored at 4 °C. Slices were temporarily mounted in 5 % agar and resectioned to 50 μm on a vibrating microtome (VT1000S; Leica, Milton Keynes, UK) washed in PBS, blocked/permeabilized (2 % Fish gelatine; 0.01 % sodium azide; 0.1 % TritonX-100 in PBS) for 2 h, and peroxidase quenched (3 % H_2O_2 30 min). Subsequently, sections were incubated with the relevant primary antibody (AB1765P, rabbit polyclonal anti-dopamine D1A receptor, or AB5840P rabbit polyclonal anti-dopamine D2 receptor; 1:1600 dilution of 1 mg/ml stock, Chemicon International Inc., UK) made up in 2 % blocking solution for 48 h. Next, sections were rinsed (PBS) prior to O/N incubation with peroxidase-conjugated anti-rabbit antibody (tyramide signal amplification kit, Molecular Probes Inc., USA). Sections were incubated in a 1:50 dilution of the amplification reagent and 0.0015 % H_2O_2 for 5 h, rinsed in PBS (3 × 15 min), coverslipped with fluorescence mounting medium, and left to dry for 48–62 h. Consecutive slices were visualized on an inverted confocal microscope (Leica DM IBRE scanning confocal microscope, Leica Microsystems, Heidelberg, Germany) under 568-nm excitation (PMT 907) with the TRIT-C channel optimized for emission at 576 nm. Transgenic and non-transgenic slices were processed and analysed in parallel. Image stacks (6 μm) of 12 sequential scans (0.5 μm) were performed and collected for each section using Leica

Confocal Software (version 2.5, Leica, Heidelberg, Germany). Fluorescence was calculated by manually selecting the three brightest scans from each stack and generating a composite average. Fluorescence was quantified by generating a mean fluorescence value (in arbitrary units) from three manually placed non-overlapping sampling boxes (2000 μm^2) in each region of interest (ROI) through the CA1 field of the hippocampus (capillaries were avoided). Fluorescence intensity was standardized between slices by imaging sections on the same day using the same laser and parameters, i.e. gain, offset, and PMT intensity. A minimum of three consecutive sections (three measurements were collected per slice, and slice values collapsed to an animal mean) were used per animal (WT, R6/1 $n = 3$ animals) and age (1, 3, and 7 months; three animals per genotype per time point). Negative control sections were included where the primary antibody was omitted. Antibody specificity was further confirmed on sections of the brain from mice deficient in D2 dopamine receptors (Kelly et al. 1997) that were a gift from Professor Michael Levine (Intellectual and Developmental Disabilities Research Center, UCLA, USA). Sections prepared from D2 knock-out brains were processed for D2 immunoreactivity together with control and R6/1 tissue. No immunoreactivity was observed in the D2 knock-out material or negative controls.

Electrophysiology

Transverse hippocampal slices (400 μm) were prepared as previously reported (Milnerwood et al. 2006), area CA3 was excised, and slices were transferred to an interface recording chamber (Scientific Systems Design Inc., USA) maintained at 28 °C and constantly perfused with oxygenated (95 % O_2, 5 % CO_2) artificial cerebrospinal fluid (ACSF; containing in mM: 120 NaCl, 3 KCl, 2 $MgSO_4$, 2 $CaCl_2$, 1.2 NaH_2PO_4, 23 $NaHCO_3$, 11 glucose) and left to incubate for a minimum of 1.5 h prior to experimentation. Hippocampal CA1 field potentials were evoked by constant current stimuli (40 μs) applied via monopolar stimulating electrodes (impedance 5 MΩ; AM Systems, USA) to CA3 Schaffer-collateral commissural projections. Field potentials were recorded via extracellular glass microelectrodes (impedance 5–8 MΩ, filled with 1 M NaCl and 2 % pontamine blue) placed in the stratum radiatum of CA1 using either a Neurolog AC-preamp or Axoclamp 2B amplifier (Digitimer, UK; Axon Instruments Inc., USA, respectively). Low frequency stimulation (LFS) consisted of 900 shocks at 1 Hz. For the purpose of assessing the probability of the induction of LTD it was defined as a stable reduction (>10 %) of the fEPSP slope 1 h post-conditioning. The fEPSP initial linear slope set at a fixed latency (software: A/Dvance 3.6) was used as an index of synaptic efficacy.

Data are presented as mean ± SEM ($n =$ slice/experiment), and statistical analysis is performed by one-way ANOVA. Stimulus intensity was set to produce a response just below the threshold for population spike activity detected in the fEPSP, and evoked at 0.033 Hz for at least 20 min, to ensure a stable baseline prior to conditioning. All drugs (purchased from Tocris Bioscience, UK, and Sigma-Aldrich Company Ltd.) were diluted in ACSF and perfused into the recording chamber for a minimum of 20 min prior to experimentation. The D2 dopamine receptor agonist quinpirole (10 μM, Cummings et al., 2006; Dallérac et al., 2015), the D2 dopamine receptor antagonist remoxipride (10 μM, Cummings et al. 2006), the D1 dopamine receptor antagonist SCH 23390 (10 μM, Huang et al. 2004), and the D1 dopamine receptor partial agonist SKF 38393 (10 μM, Dallérac et al. 2011) were used to investigate dopamine receptor activity.

Statistical Analyses

Data for each condition were pooled and are expressed as mean ± SEM. One- or two-way ANOVA were performed using Statistica 6.1 (StatSoft Inc.). Fisher's LSD test was used for post hoc analysis.

Results

CA1 Dopamine Receptor Expression Increases in R6/1 Transgenic Mice

In order to investigate the potential role of altered dopaminergic signalling in the R6/1 hippocampus, immunohistochemical investigation of the distribution of both D1 and D2 dopamine receptors was conducted. Representative confocal micrographs are shown in Figs. 1 and 2 for D1 and D2 receptor labelling, respectively. Regions of interest (ROIs: white matter, WM; stratum oriens, SO; stratum pyramidale, SP; stratum radiatum proximal to SP, SRp; stratum radiatum distal from SP, SRd; molecular layer, ML) were sampled for fluorescence quantification.

Two-way ANOVA demonstrated significant effect of age and genotype upon D1 receptor labelling ($p < 0.00001$, $F_{2,226} = 18.4$), relative to WT. At 1 month of age there was a trend towards less D1 receptor labelling in all ROIs in R6/1 sections (Fig. 1). D1 labelling was significantly lower in the SP (42.2 %, $p < 0.03$) and SRp (36.9 %, $p < 0.04$). By 3 months D1 labelling had increased relative to WT sections and significantly greater fluorescence was observed in the stratum radiatum (SRp, 62.9 %, $p < 0.03$ & SRd, 75.9 %, $p < 0.03$), suggesting that D1 receptor numbers are altered specifically in the R6/1 stratum radiatum. In the 7-months age group, D1 labelling also
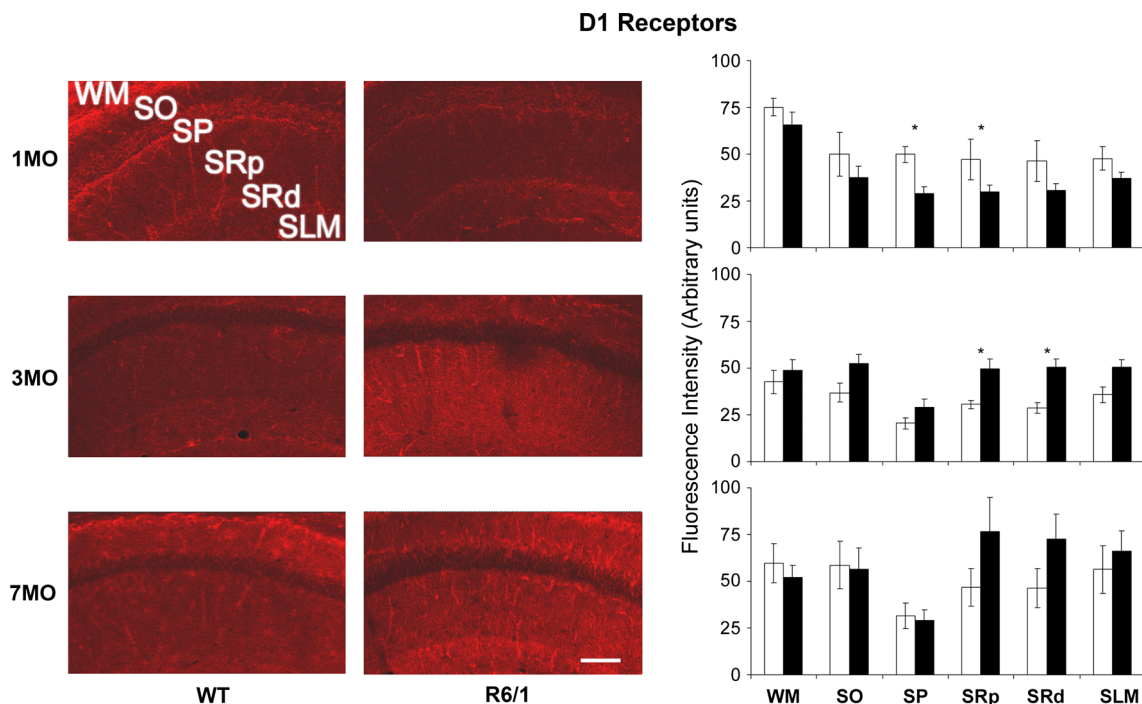
Fig. 1 Hippocampal CA1 D1 receptor labelling. Representative confocal micrographs (×40 objective) of D1 immunofluorescence in the CA1 area of the hippocampus of WT (*left*) and R6/1 (*right*) mice aged as indicated (months). Regions of interest are marked for reference (*top left*): *WM* white matter, *SO* stratum oriens, *SP* stratum pyramidale, *SRp/d*, stratum radiatum proximal/distal to SP, *SLM* stratum lanculosum-moleculare, *hf*, hippocampal fissure, *dg* dentate gyrus.

Bar = 100 μm. Quantification of D1 receptor immunofluorescence is also shown. R6/1 [$n = 8(3)$] sections had significantly less D1 receptor labelling than WT sections [$n = 9(3)$] in the SRp (*$p < 0.03$) and SP (*$p < 0.04$) at 1 month. At 3 months D1 receptor labelling was significantly increased in the R6/1 stratum radiatum [*$p < 0.03$. R6/1, $n = 9(3)$. WT, $n = 9(3)$]. R6/1 labelling was not significantly different from WT at 7 months [*$p > 0.1$. R6/1, $n = 5(2)$. WT, $n = 5(3)$]

appeared to be increased, although this did not reach significance.

Significant effects of age and genotype were also observed in D2 receptor labelling by ANOVA ($p < 0.00001$, $F_{2,220} = 22.9$). As detailed in Fig. 2, no significant difference between R6/1 and WT sections were observed at 1 month of age. At 3 months D2 labelling was significantly increased in the WM (32.9 %, $p < 0.02$), SR (SRp, 49.6 %, $p < 0.01$ & SRd, 63.9 %, $p < 0.001$), and SLM (47.4 %, $p < 0.01$). There was no significant difference between the degree of labelling in WT and R6/1 SP ($p = 0.4$) or SO, although the latter approached significance ($p = 0.06$). At 7 months of age there was a highly significant increase in D2 labelling in the WM (99.7 %, $p < 0.001$), SO (93.7 %, $p < 0.001$), SR (SRp, 83.1 %, $p < 0.001$ & SRd, 141.4 %, $p < 0.001$), and SLM (86.3 %, $p < 0.001$) relative to WT sections. The data suggest that D2 receptor numbers are greatly altered in the R6/1 CA1 field at 3 months and older. Taken together, these observations suggest that large alterations in D1 and D2 receptor expression occur in the R6/1 mouse hippocampus (albeit later for D2) compared to WT littermates, and furthermore

that these differences occur months prior to the onset of the overt motor phenotype.

Dopamine Signalling Does Not Underlie Aberrant Synaptic Function

Pharmacological manipulation of D1 and D2 receptors was employed to investigate whether altered dopaminergic transmission could account for the aberrant LTD observed in adult R6/1 mice (Milnerwood et al. 2006), which is normally down-regulated by 1 month in wild-type control mice (Milner et al. 2004). As shown in Fig. 3, neither D1 nor D2 receptor agonists nor antagonists (all delivered at 10 μM) altered the likelihood or magnitude of LTD induced by LFS in slices prepared from R6/1 mice aged 7–8 months. Indeed, as we reported previously (Milnerwood et al. 2006), in aged-matched untreated R6/1 slices, LFS induced significant LTD (-12.1 ± 1.4 %, $n = 41$, $p < 0.000001$). In the presence of the D1 receptor antagonist SCH 23390 (23), LTD was also induced (-9.3 ± 3.8 %, $n = 8$, $p < 0.04$) in 63 % of experiments. Similarly, LTD was induced (-14.5 ± 2.2 %, $n = 7$, $p < 0.001$) in the presence of the D2 receptor agonist
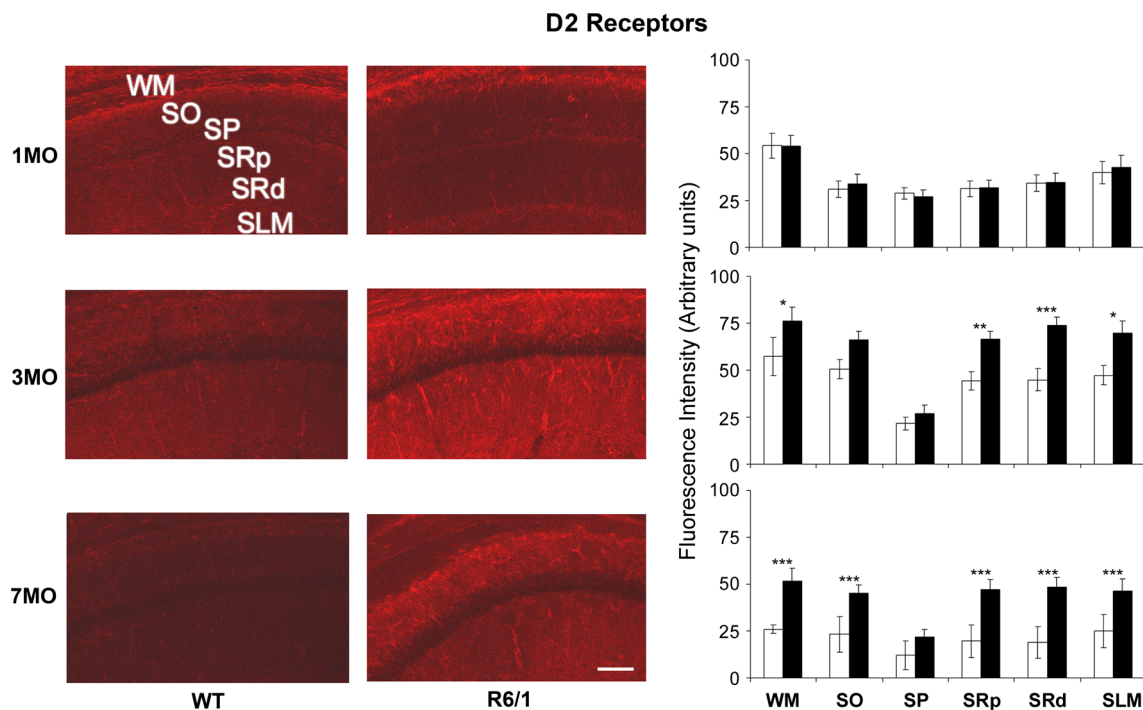
D2 Receptors

Fig. 2 Hippocampal CA1 D2 receptor labelling. Representative confocal micrographs (×40) of D2 immunofluorescence in the CA1 area of the hippocampus of WT (*left*) and R6/1 (*right*) mice aged as indicated. Regions of interest are marked for reference in the *top left panel*: *WM* white matter, *SO* stratum oriens, *SP* stratum pyramidale, *SRp/d* stratum radiatum proximal/distal to SP, *SLM* stratum lanculo-sum-moleculare, *hf* hippocampal fissure, *dg* dentate gyrus.

Bar = 100 μm. Quantification of D2 immunofluorescence is also shown. R6/1 [$n = 8(3)$] and WT [$n = 6(2)$] D2 receptor labelling is similar at 1 month. At 3 months D2 receptor labelling is significantly increased (with respect to WT) in the R6/1 stratum radiatum and WM. At 7 months a highly significant increase in R6/1 D2 labelling was observed in all ROIs except the SP [R6/1, $n = 8(3)$. WT, $n = 6(2)$, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$]

quinpirole (Cummings et al. 2006) in 86 % of experiments. The presence of the D1 receptor partial agonist SKF 38393 (Dallérac et al. 2011) did not alter LTD either as it was found to be induced (-14.0 ± 1.4 %, $n = 11$, $p < 0.00005$) in 82 % of experiments. Finally, the proportion of LTD induction (-12.4 ± 1.9 %, $n = 5$, $p < 0.02$) in the presence of the D2 receptor antagonist remoxipride (Cummings et al. 2006) reached an equally comparable 80 %. There were no significant differences in the mean LTD produced between activation and inhibition of either D1 ($p > 0.2$) or D2 receptors ($p > 0.3$), and none of the four drug conditions produced LTD that was significantly different from that seen in age-matched untreated R6/1 slices. Therefore the data suggest that, despite alterations to dopamine receptor expression, the mechanisms responsible for the induction of LTD in adult R6/1 mice is unperturbed by modulation of dopaminergic neurotransmission.

Discussion

Neither agonism nor antagonism of D1 or D2 dopamine receptors significantly altered LTD in R6/1 hippocampal slices (Fig. 3). This result is in stark contrast to the full rescue of LTP in the R6/1 prefrontal cortex by D1 receptor activation as well as restoration of LTD in the R6/1 perirhinal cortex by D2 agonist applied at similar concentrations (Cummings et al. 2006; Dallérac et al. 2011). The lack of effect upon hippocampal LTD is not attributable to a loss of dopamine receptors as we find an increase rather than a decrease in immunostaining for these receptors in R6/1 CA1 fields, with respect to wild-type controls. This indicates that although dopaminergic changes play an important role in HD, the aetiology of the disease is more complex and involves multiple mechanisms. Focusing on synaptic plasticity, alteration in brain-derived neurotrophic factor (BDNF) availability has for example been reported as an important modifier of synaptic efficacy (Lynch et al. 2007; Simmons et al. 2009; Zuccato et al. 2003). In this regard, two recent reports further indicate that in HD mice striatum (Plotkin et al. 2014) and hippocampus (Brito et al. 2014), signalling downstream the BDNF tyrosine-related kinase B (TrkB) receptors, and p75 neurotrophin receptors (p75NTR) would also be deficient. Other identified molecular abnormalities underlying synaptic dysfunction in HD include NMDA receptor composition with an increased NR2B function (Li et al. 2004; Milnerwood et al. 2006; Zeron et al. 2002) and cell adhesion molecules such as
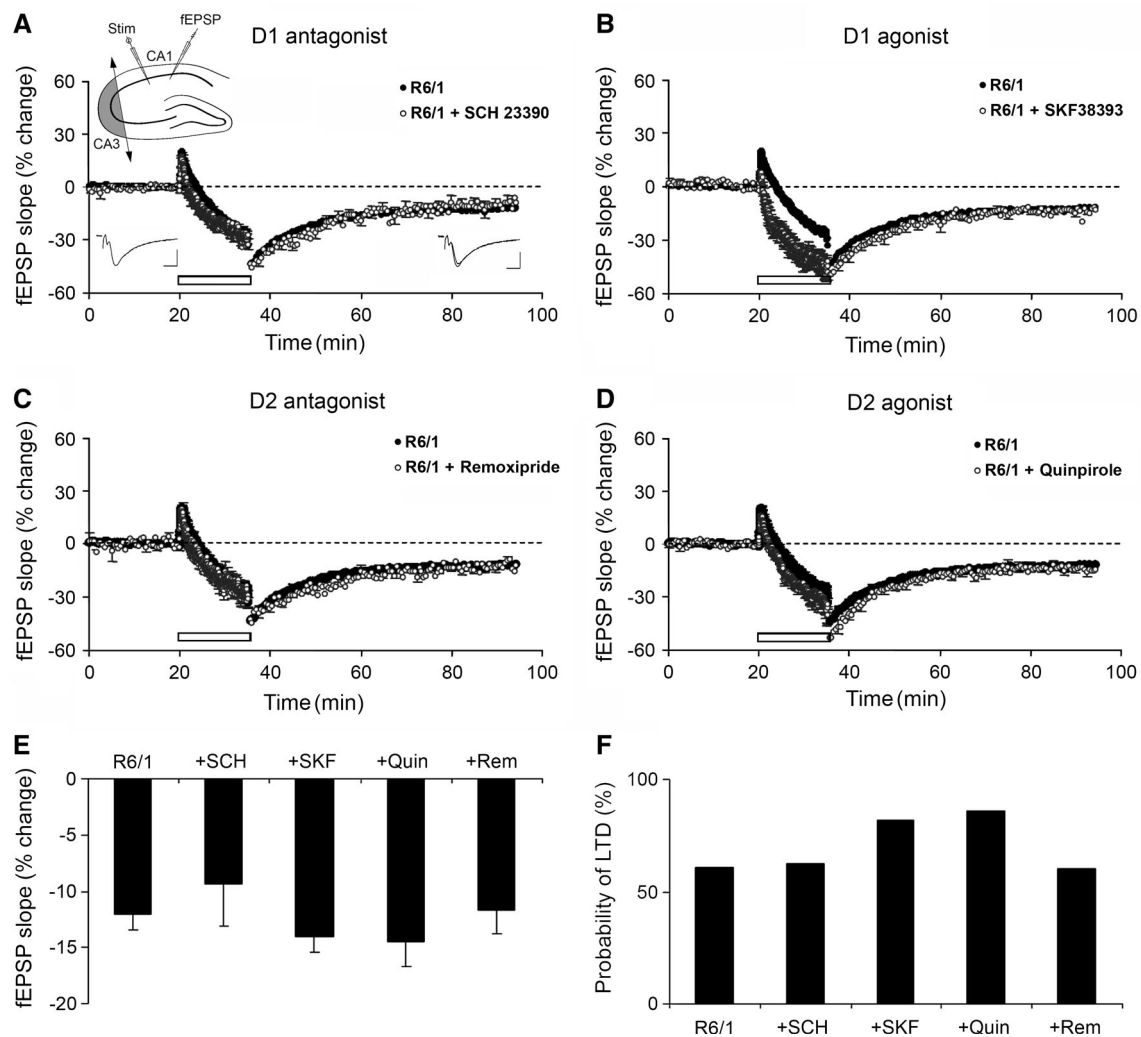
Fig. 3 LTD in R6/1 adults is not blocked by pharmacological manipulation of dopamine receptors. Neither D1 nor D2 receptor agonists nor antagonists (10 μM) significantly altered the magnitude (**a–e**) or probability (**f**) of LTD induction in slices prepared from R6/1 mice at 8 months of age. *Insert* in (**a**) shows the stimulating and recording electrode placement. *Double arrows* represent cutting of the CA3 area for which the excised part is depicted in *grey*

PSA-NCAM (van der Borght and Brundin 2007). Finally, a recent report indicates that astroglial Kir4.1 channels are deficient in HD (Tong et al. 2014); these astroglial channels are involved in the regulation of synaptic function (Dallerac et al. 2013) and are therefore also likely to contribute to abnormal neurotransmission in HD.

The significance of a large increase in dopamine receptor labelling is unclear, but it might reflect an up-regulation in dopamine receptors number in response to decreased dopaminergic innervation. Such a view is supported by a recent study reporting more than 30 % decrease in hippocampal dopamine content in 12 weeks old symptomatic R6/2 mice (Mochel et al. 2011). Another possibility is that the dopamine receptors are dysfunctional, thus leading to a compensatory increase in their expression levels. DA release has been found to be severely reduced in

both R6/1 and R6/2 HD mice (Dallérac et al. 2015; Johnson et al. 2006; Ortiz et al. 2011). Chemical enervation and depletion of the dopaminergic system in rats, by chronic treatment with 6-hydroxydopamine, result in behavioural hyperactivity in the case of limited destruction and hypoactivity with larger lesions (Koob et al. 1981), reminiscent of the behaviour of R6/1 mice as they age (Bolivar et al. 2004). This treatment causes a priming effect in intact rats; subsequent application of D1 and D2 agonists results in greatly exaggerated behavioural responses (e.g. explosive jumping) in comparison with the same agonism of non-treated animals (LaHoste and Marshall 1989). This priming effect is correlated with large increases in D2 receptor labelling (LaHoste and Marshall 1989; Savasta et al. 1992) and mRNA levels (Chritin et al. 1992). The lack of any observed effect of D1 and D2 agonism and

antagonism suggests that although there is an increase in number, the localization, activity, or downstream cascades resulting from DA receptors activation are either non-functional or severely impaired.

Interestingly, changes were not uniform for D1 and D2 labelling throughout hippocampal subfields, results reminiscent of the changes in dopamine receptors expression during ageing (Amenta et al. 2001). There is also an important heterogeneity between brain regions as reductions were seen in the cortex and striatum of various mouse models of HD including R6/1 and R6/2 mice (Ariano et al. 2002; Cummings et al. 2006; Heng et al. 2007) whereas we observe an augmentation in the hippocampus. We thus propose that dynamic modulations of dopamine receptors occur as a function of the changes in dopamine bioavailability (Dallérac et al. 2015) that results from transgene expression.

Dopamine therapy has long been used in the palliative treatment of HD with limited success (van Vugt and Roos 1999), likely because of the diverse actions of dopaminergic signalling in the brain. Our previous reports (Cummings et al. 2006; Dallérac et al. 2011, 2015) together with the data presented here demonstrate that pharmacological manipulations may have very different effects depending on the brain region in which they are active. The results of this study add weight to the suggestion that targeted dopamine therapy might better alleviate symptoms in HD.

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