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Research Report

# Antidepressant-Like Effect of the Norepinephrine-Dopamine Reuptake Inhibitor Bupropion in a Mouse Model of Huntington's Disease with Dopaminergic Dysfunction

Thibault Renoir[a,*], Andrew Argyropoulos[a,b] and Anthony J. Hannan[a,b]
[a]*Florey Institute of Neuroscience and Mental Health, Melbourne Brain Centre, University of Melbourne, Melbourne, Australia*
[b]*Department of Anatomy and Neuroscience, University of Melbourne, Melbourne, Australia*

**Abstract**.
**Background:** The pre-motor stages of Huntington's disease (HD) are commonly associated with psychiatric manifestations including depression. Recent clinical data indicate that dopaminergic dysfunction is common in both symptomatic and pre-manifest HD gene carriers. There is also increasing evidence implicating catecholamine dysfunction in the pathophysiology of depression.
**Objective:** In this study, we aimed to functionally investigate the dopaminergic system in the R6/1 mouse model of HD prior to onset of motor symptoms.
**Methods:** We assessed the effects of acute administration of bupropion (a dopamine-norepinephrine reuptake inhibitor) on spontaneous locomotor activity and depression-like behaviour (using the forced-swim test).
**Results:** Here we show that the bupropion-induced increased locomotor activity found in wild-type animals was no longer observed in HD mice. We also found that acute administration with bupropion rescued depressive-like behaviours in HD animals, possibly through dopamine D2/D3 receptor mechanisms.
**Conclusion:** Our present data are the first *in vivo* evidence of an impaired dopamine D1 receptor-dependent function in pre-motor symptomatic R6/1 HD mice. Moreover, our findings suggest clinical potential for bupropion to alleviate depressive symptoms in HD.

Keywords: Huntington's disease, mouse model, depression, behaviours, dopamine, bupropion

## INTRODUCTION

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by an abnormal expansion of CAG repeats in exon 1 of the huntingtin gene [1]. Clinical diagnosis of HD is

*Correspondence to: Dr. Thibault Renoir, Florey Institute of Neuroscience and Mental Health, Melbourne Brain Centre, University of Melbourne, VIC 3010, Melbourne, Australia. Emails: thibault.renoir@unimelb.edu.au; tibo.renoir@gmail.com.

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determined on the basis of motor symptoms; however, the pre-motor stages of the disease are commonly associated with psychiatric manifestations including depression [2–5]. Interestingly, longitudinal studies suggest that the clinical syndrome of apathy is fundamental to the evolution and progression of HD [6, 7], arising as a direct consequence of damage to frontostriatal pathways. Pathological processes affecting mainly the striatum are likely to lead to alterations in dopamine activity in frontostriatal circuitry, resulting in behavioural, cognitive and motor symptoms characteristic of HD. Recent clinical data indicate that dopaminergic dysfunction is common in both symptomatic and pre-manifest HD gene carriers [8–10], suggesting that this early event in HD pathophysiology could contribute to neuropsychiatric disorders.

Our group was the first to demonstrate that expression of the mutant huntingtin (HTT) gene was sufficient to cause depression-like behaviours in an animal model of HD, R6/1 transgenic mice [11], and this has since been replicated in other independent models, YAC128 transgenic mice [12] and knock-in Hdh(Q111) animals [13]. In agreement with other animal models of affective-like disorders [14, 15], we recently reported serotonin system dysregulation in R6/1 HD animals [11, 16–18] as well as beneficial effects of treatment with the selective serotonin reuptake inhibitor sertraline [11, 17]. However, there is also increasing evidence implicating catecholamine dysfunction in the pathophysiology of depression [19, 20] and recent clinical data suggest that antidepressants which enhance noradrenergic and dopaminergic activity such as bupropion may afford a therapeutic advantage over serotonergic antidepressants, especially in regard to the treatment of apathy [21] or symptoms associated with a reduction in positive affect [22].

Dopaminergic signalling proteins (e.g. D1 and D2 dopamine receptors) as well as catecholamine brain levels have been previously reported to be decreased in several animal models of HD [23–26], including the R6/1 HD mice [27, 28]. However, those studies were all conducted at mid-late stages of the disease. In that regard, the dopaminergic system in pre-motor symptomatic HD animals has not been previously investigated in the context of associated affective- or depression-like behaviors. The present study aimed to functionally investigate the dopaminergic system of motorically asymptomatic R6/1 HD mice using the dopamine and norepinephrine reuptake inhibitor, bupropion. We assessed the effects of acute administration of bupropion on spontaneous locomotor activity and depression-like behaviour.

## MATERIALS AND METHODS

### *Animals*

R6/1 transgenic hemizygote males [29] were originally obtained from the Jackson Laboratory (Bar Harbor, ME, USA) and bred with CBB6 (CBA6C57/B6) F1 females to establish the R6/1 colony at the Howard Florey Institute (HFI). The CAG repeats length of transgenic mice in the colony at the time of cohort generation was within the range 127–135 (Pathology Department, University of Melbourne, Australia). After weaning, animals were grouped housed (4 mice per cage with 2 of each genotype) and maintained on a 12 h light/dark cycle with access to food and water *ad libitum*. All experiments were performed on female wild-type (WT) and R6/1 (HD) mice at 12 weeks of age in accordance with the guidelines of the HFI Animal Ethics Committee. Each animal was only exposed to a unique behavioral test.

### *Exploratory activity assessment*

Mice (44WT/48HD) were acclimatised to the room for 1 h prior to testing. Animals were then individually placed in a square clear acrylic box ($26 \times 26 \times 38$ cm) for another 30-min habituation period and then intraperitoneally (i.p.) injected with either saline solution (0.9% NaCl, 1 ml/100 g body weight) or bupropion (10 and 20 mg/kg). Total distance travelled (in the horizontal plane) was assessed using locomotor cells (TruScan Photobeam Arenas E63-12, Coulbourn Instruments, Allentown, PA, USA) [30]. The selective dopamine D1 receptor antagonist SCH-23390 (SCH, 0.3 mg/kg, i.p.) was administrated 30-min before bupropion.

### *Forced-swim test (FST)*

Mice (43WT/43HD) were acclimatised to the room for 1 h prior to testing. Mice were then individually placed into a glass beaker (13 cm diameter) filled with 12 cm deep water (25–26°C) and video recorded for 300 secs. Total immobility time was manually scored by an experienced experimenter blind to treatment and mouse genotype. Mice were injected intraperitoneally (i.p.) with either saline solution (0.9% NaCl, 1 ml/100 g body weight) or bupropion (10 mg/kg) 30 mins before FST [11]. The D2/3 receptor antagonist haloperidol (Halo, 0.3 mg/kg, i.p.) was administrated 30-min before bupropion.

*Statistical analysis*

Analyses of variance (ANOVAs) were used to examine main effects and/or interactions. A 2-way ANOVA was used to analyse the effects of bupropion treatment and HD genotype on total distance travelled (expressed in cm as an index of spontaneous locomotor activity) and immobility time (expressed in seconds as an index of "despair-like behavior" in FST). To determine specific group differences in case of significant main effects (or interaction), the ANOVAs were followed by Fisher's LSD or Bonferroni *post-hoc* tests. In all cases, the significance level was set at $p < 0.05$. Statistical analyses were performed using Prism5.

## RESULTS

*Locomotor activity*

Statistical analysis of the 10-min time-point after drug injection (Fig. 1), revealed effects of bupropion treatment ($F_{3,74} = 6.46$, $P < 0.001$) and HD mutation ($F_{1,74} = 12.5$, $P < 0.001$) as well as a significant treatment × genotype interaction ($F_{3,74} = 3.54$, $P < 0.05$). *Post-hoc* analysis found that bupropion 20 mg/kg (but not 10 mg/kg) increased locomotor activity in WT mice ($P < 0.001$). This response was reduced in HD animals ($P < 0.001$) and blocked by pre-treatment with the selective dopamine D1 receptor antagonist SCH-23390 (SCH, 0.3 mg/kg, i.p.) while SCH pre-treatment alone did not significantly alter locomotion when compared to saline groups.

*Forced-swim test*

Statistical analysis of the forced-swim test (FST) performances (Fig. 2), revealed effects of bupropion treatment ($F_{2,68} = 6.39$, $P < 0.05$) and HD mutation ($F_{1,68} = 4.96$, $P < 0.05$) as well as a significant treatment × genotype interaction ($F_{2,68} = 2.78$, $P < 0.05$). *Post-hoc* analysis found that control saline-injected HD mice exhibited a higher immobility time when compared to WT animals ($P < 0.05$). This HD mutation-induced difference in FST performance was no longer observed after treatment with bupropion (10 mg/kg). Finally, the decreased immobility time induced by bupropion in HD mice ($P < 0.01$) was blocked by pre-treatment with the D2/3 receptor antagonist haloperidol (Halo, 0.3 mg/kg, i.p.). Haloperidol pre-treatment alone did not significantly alter immobility time when compared to saline groups.

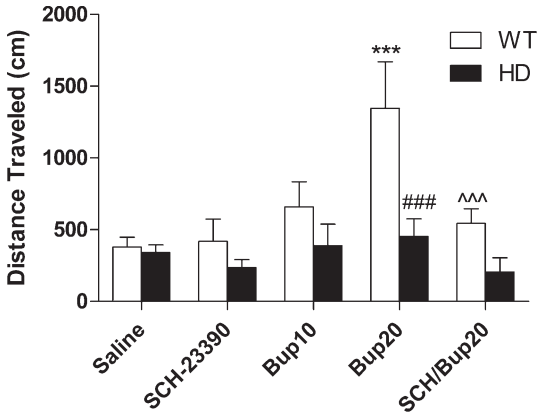


Fig. 1. Effect of HD mutation on maximal bupropion-induced locomotor activity. We found a significant interaction between genotype and treatment when analysing maximal bupropion-induced locomotor response 10 min after drug injection. There was no genotype difference in the saline-treated animals ($n = 13$WT/15HD). Bupropion 20 mg/kg (Bup20) increased locomotor activity in WT mice ($n = 10$). This response was reduced in HD animals ($n = 13$) and blocked by pre-treatment with the selective D1 receptor antagonist SCH-23390 (SCH, $n = 10$), which has no effect *per se* ($n = 5$). Values represent means (±SEM). Saline vs. bupropion20: (***) $p < 0.001$; WT vs. HD: ($^{###}$) $p < 0.001$; Saline/Bup20 vs. SCH/Bup20: ($^{\wedge\wedge\wedge}$) $p < 0.001$.

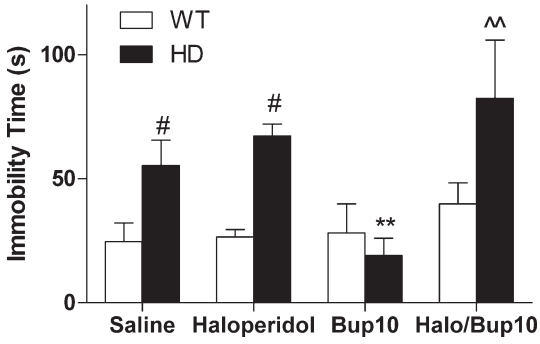


Fig. 2. Effect of HD mutation and acute bupropion administration on immobility time in mice exposed to the forced-swim test (FST). We found a significant interaction between genotype and treatment when analysing the effect of bupropion 10 mg/kg (Bup10) on FST performance. Control saline-injected HD mice ($n = 18$) exhibited a higher immobility time when compared to WT animals ($n = 16$). This HD mutation-induced depression-like behaviour was no longer observed after treatment with bupropion ($n = 13$). Interestingly, the bupropion-induced antidepressant-like response observed in HD mice was blocked by pre-treatment with the D2/3 receptor antagonist haloperidol (Halo, $n = 7$), which has no effect *per se* ($n = 7$WT/5HD). Values represent means (±SEM). Saline vs. Bup10: (**) $p < 0.01$; WT vs. HD: ($^{\#}$) $p < 0.05$; Saline/Bup10 vs. Halo/Bup10: ($^{\wedge\wedge}$) $p < 0.01$.

## DISCUSSION

The dopaminergic system in pre-motor symptomatic HD animals had never been investigated

before in the context of associated affective- or depression-like behaviours. Overall our data demonstrated that, although HD animals exhibited impaired dopaminergic functions, bupropion was still able to correct the depressive-like behaviour of HD mice. Since we previously found that pre-motor symptomatic R6/1 HD mice displayed a female-specific depressive-related phenotype [11, 18], only female R6/1 HD animals were used in the present study. Whether our present findings could be extrapolated to males, as well as the possible relationship between dopamine molecular changes (i.e. D1 versus D2 receptors) and affective-related behaviours remain to be addressed in the future. This report is the first *in vivo* assessment of the effects of bupropion in a mouse model of HD.

Here we show that the bupropion-induced increased locomotor activity found in wild-type (WT) animals, was no longer observed in HD mice. Since the locomotor effect of bupropion displayed by WT animals was blocked by pre-treatment with the selective dopamine D1 receptor antagonist SCH-23390, our data suggest an impaired D1 receptor-dependent function in pre-motor symptomatic R6/1 HD mice. Interestingly, bupropion acts primarily on the dopamine transporter (DAT), therefore further work dissecting more specifically DAT-functioning as well as the whole dopaminergic cascade would be required. In addition, we did not measure dopamine receptors expression in this present study. Whether any reduction in D1/D2 dopamine receptors levels directly correlates with the impaired locomotor response to bupropion displayed by HD mice remains to be established. However using quantitative autoradiography, previous studies [31, 32] reported that striatal D1 and D2 receptors binding were decreased in R6/1 HD mice from 12 weeks of age. Our results also extend a previous study showing an attenuation of dopaminergic signalling cascade (through a reduction in D1 dopamine receptor level) in striatal slices from pre-symptomatic R6/2 animals [33]. Furthermore using *in situ* hybridization, Cha et al. (1998) [34] found that D1 dopamine receptor mRNA was altered as early as 4 weeks of age in R6/2 mice. Finally, examining the effect of acute administration with the D1 receptor agonist SKF-82958 on immediate early gene (IEG) expression, a previous study in symptomatic R6/2 animals unexpectedly reported an enhanced D1-related dopaminergic signal transduction in HD mice despite a parallel decreased in D1 receptor expression [35]. The authors concluded that this hyperresponsiveness of D1-containing neurons might be a reflection of a compensatory mechanism for decreased dopaminergic input, suggesting that similar functional studies in pre-symptomatic HD animal models were needed.

The FST (in which animals are individually placed into a beaker filled with water and scored for their time remaining immobile), is widely used on the basis of its strong predictive validity (for the screening of compounds with potential antidepressant-like effects) as well as good reliability and some face validity [36]. Originally, Porsolt et al. (1978) [37] described the state of immobility as a behavioural despair "reflecting a state of lowered mood". Further complementing the characterization of depressive-like behavior in HD animals using the FST, we now show that acute administration with the dopamine-norepinephrine reuptake inhibitor bupropion, reduced immobility time in HD animals. This is the first study assessing the behavioral effect of bupropion in an animal model of HD and therefore the first evidence of a positive behavioral outcome, especially in terms of affective-like disorders at early stage of the disease (prior the onset of locomotor impairment). To avoid potential confounds on locomotor effects in FST, we used a low dose of bupropion (10 mg/kg) previously shown as ineffective on locomotor activity (Fig. 1), especially at the 30-min post-injection time-point used for our FST assessment. The bupropion-induced antidepressant-like effects in HD mice we report here are likely to involve D2/3 receptor-dependent mechanisms since they were blocked by pre-treatment with haloperidol. Interestingly, dysregulation of the dopamine D2 receptor has recently been suggested as a sensitive measure for HD pathology in mouse models [38]. Furthermore, abnormalities in cortical synaptic plasticity have also been found reversed by the introduction of the D2 receptor agonist quinpirole [39]. However, since the impaired long-term potentiation observed in the prefrontal cortex of HD animals was also rescued by the D1 receptor agonist SKF38393 [40], further pharmacological studies specifically targeting D1 versus D2 receptors would be worthwhile in the context of affective endophenotypes and depression-like disorders in HD. Functional imaging studies suggest that, despite displaying reduced striatal dopamine D2 receptor binding, asymptomatic mutation carriers may show apparently normal brain function for a long period of life [41]. Another recent study reported that D2 receptors extrinsic to the striatum are well preserved in early to mid stage patients with HD [42], providing a potentially viable target for the treatment of HD symptomatology. Interestingly, the dopaminergic stabilizer pridopidine shows promise as a treatment for

some of the symptoms of HD including affective and motor disorders [43], supporting a role for DA in the pathogenesis of these co-morbidities.

Bupropion, which is an effective antidepressant [44, 45], has been trialled in other neurodegenerative disorders [46], but not in HD. Further controlled clinical trials are required to objectively determine the therapeutic potential of antidepressant treatments in HD. To our knowledge, the sole clinical trial to date addressing this specific question has only assessed the potential effectiveness of treatment with venlafaxine (a serotonin-norepinephrine inhibitor) in HD patients with major depression [47]. Our present findings suggest clinical potential for bupropion to alleviate depressive symptoms in HD. Furthermore, the new insights into dopaminergic dysfunction in HD may also inform the development of other therapeutic approaches.

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## CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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