Metabotropic glutamate receptor 5 knockout promotes motor and biochemical alterations in a mouse model of Huntington’s disease

Fabiola M. Ribeiro1,†,*, Rebecca A. DeVries2,†, Alison Hamilton2, Isabella M. Guimaraes1, Sean P. Cregan2, Rita G. W. Pires3 and Stephen S. G. Ferguson2,*

1Departamento de Bioquimica e Imunologia, ICB, Universidade Federal de Minas Gerais, Belo Horizonte 31270-901, Brazil 2J. Allyn Taylor Centre for Cell Biology, University of Western Ontario, London, ON, Canada N6A 5K8 3Departamento de Ciencias Fisiologicas, CCS, Universidade Federal do Espirito Santo, Vitoria 29043-910, Brazil

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Huntington’s disease (HD) is an autosomal-dominant neurodegenerative disorder caused by a polyglutamine expansion in the amino-terminal region of the huntingtin protein, which promotes progressive neuronal cell loss, neurological symptoms and death. In the present study, we show that blockade of mGluR5 with MTEP promotes increased locomotor activity in both control (HdhQ20/Q20) and mutant HD (HdhQ111/Q111) mice. Although acute injection of MTEP increases locomotor activity in both control and mutant HD mice, locomotor activity is increased in only control mice, not mutant HD mice, following the genetic deletion of mGluR5. Interestingly, treatment of mGluR5 knockout mice with either D1 or D2 dopamine antagonists eliminates the increased locomotor activity of mGluR5 knockout mice. Amphetamine treatment increases locomotor activity in control mice, but not mGluR5 null mutant HD mice. However, the loss of mGluR5 expression improves rotarod performance and decreases the number of huntingtin intranuclear inclusions in mutant HD mice. These adaptations may be due to mutant huntingtin-dependent alterations in gene expression, as microarray studies have identified several genes that are altered in mutant, but not wild-type HD mice lacking mGluR5 expression. qPCR experiments confirm that the mRNA transcript levels of dynein heavy chain, dynactin 3 and dynein light chain-6 are altered following the genetic deletion of mGluR5 in mutant HD mice, as compared with wild-type mutant HD mice. Thus, our data suggest that mutant huntingtin protein and mGluR5 exhibit a functional interaction that may be important for HD-mediated alterations in locomotor behavior and the development of intranuclear inclusions.

INTRODUCTION

Huntington’s disease (HD) is an autosomal-dominant neurodegenerative disorder caused by a progressive neuronal cell loss in the caudate-putamen, which leads to involuntary body movement, loss of cognitive function, psychiatric disturbance and death (1,2). HD patients typically exhibit hyperkinesia such as chorea, which is characterized by involuntary, abrupt and irregular movements (1−3). The mutated form of the huntingtin (Htt) protein, exhibiting >37 polyglutamines in the amino-terminal region, is proposed as the cause of the neuronal cell loss observed in the caudate-putamen (striatum in rodents) and neocortical regions of HD patients (4). The striatum is composed mainly (85%) of medium-sized spiny neurons (MSNs), which are GABAergic neurons, but also of interneurons, including cholinergic neurons (5). Although MSNs are the first neurons to be affected during HD progression, cholinergic neurons are spared (6,7).

Striatal neurons receive input from different areas of the basal ganglia and also glutamatergic input from thalamus and cortex (8,9). Moreover, dopaminergic neurons from the substantia

†F.M.R. and R.A.D. contribute equally for this manuscript.

*To whom correspondence should be addressed at: Robarts Research Institute, University of Western Ontario, 100 Perth Dr., London, ON, Canada N6A 5K8. Tel: +519 9315706; Fax: +519 9315706; Email: ferguson@robarts.ca (S.S.G.F.); Universidade Federal de Minas Gerais, Ave. Antonio Carlos 6627, Belo Horizonte, MG, CEP: 31270-901, Brazil. Tel: +55 3134092655; Email: fmribeiro@icb.ufmg.br (F.M.R.)

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RESULTS

To test whether mGluR5 had a role in locomotor activity, we submitted mGluR5 knockout (mGluR5<sup>−/−</sup>) mice to an open-field arena. mGluR5<sup>−/−</sup> mice were more active in the arena than mGluR5<sup>+/+</sup> mice as evidenced by the total distance traveled (Fig. 1A and B), confirming that mGluR5 was important for movement control. Moreover, the locomotor activity lines for wild-type and mGluR5 knockout mice have the same slope (Fig. 1A), which indicates that both mouse lines habituate at the same rate.

Abnormal movements including hyperkinesia and chorea are the most typical symptoms observed in HD patients, and we previously demonstrated that mGluR5 signaling was altered in mutant HD (Hdh<sup>Q111/Q111</sup>) mice (1–3,20). Therefore, to further study the role of mGluR5 in HD, we investigated the locomotor activity of control (Hdh<sup>Q20/Q20</sup>) and mutant HD mice that were crossed with mGluR5 knockout mice. At 3 months of age, mGluR5 null control mice (Hdh<sup>Q20/Q20</sup>/mGluR5<sup>−/−</sup>) traveled much further in the open-field arena than wild-type control mice, wild-type mutant HD mice or mGluR5 null mutant HD mice (Hdh<sup>Q111/Q111</sup>/mGluR5<sup>−/−</sup>) (Fig. 2A). To determine whether the hyperlocomotor phenotype was influenced by age, we also submitted the same groups of mice at the ages of 6, 9, 12, 15, 18, 21 and 24 months to the open-field arena (Fig. 3B). Statistical analysis [two-way analysis of variance (ANOVA)] indicated that there is an interaction between age and genotype [F(6, 132) = 2.04, P < 0.001] and age [F(6, 132) = 2.66, P = 0.0115] affect locomotor activity, although age did not seem to play a major role. Locomotor activity of mGluR5 null control mice remained higher than that of mGluR5 null mutant HD mice, and Bonferroni posttests indicated that this difference was significant at the ages of 3, 6, 15 and 24 months (Fig. 2B). Moreover, the locomotor activity of the mGluR5 null mutant HD mice was significantly different from that of wild-type control mice at the ages of 9, 12 and 15 months (Fig. 2B). Interestingly, although the distance traveled by mGluR5 null control mice was higher than that of mGluR5 null mutant HD mice, time spent in the center of the arena was not different between the two lines of mice (Fig. 2C and D), indicating that mutant huntingtin affects locomotor activity specifically, but did not appear to affect anxiety behavior. Moreover, the four tested mouse lines did not display differences in

Figure 1. mGluR5<sup>−/−</sup> mice exhibit increased locomotor activity. Graph shows total distance traveled by wild-type (mGluR5<sup>+/+</sup>) (n = 11) and mGluR5 knockout (mGluR5<sup>−/−</sup>) (n = 12) mice measured at 5-min intervals (A) or cumulatively >120 min (B). Each animal was monitored for 120 min in open-field apparatus. Data represent the means ± SEM. * indicates significant difference as compared with mGluR5<sup>+/+</sup> mice (P < 0.05).
Figure 2. Mutant huntingtin abrogates mGluR5<sup>−/−</sup>-induced increased locomotor activity. Graphs show total distance traveled (A) and time spent in the center of the apparatus (C) by control (Hdh<sup>Q20/Q20</sup>/mGluR<sup>5+/−</sup>) (n = 11), mGluR5 null control (Hdh<sup>Q20/Q20</sup>/mGluR<sup>5−/−</sup>) (n = 11), mutant HD (Hdh<sup>Q111/Q111</sup>/mGluR<sup>5+/−</sup>) (n = 12) and mGluR5 null mutant HD (Hdh<sup>Q111/Q111</sup>/mGluR<sup>5−/−</sup>) mice (n = 11) at 3 months of age measured at 5-min intervals. Each animal was monitored for 120 min. Data represent the means ± SEM. Graphs show total distance traveled (B) and time spent in the center (D) by Hdh<sup>Q20/Q20</sup>/mGluR<sup>5+/−</sup> (n = 9–11), Hdh<sup>Q20/Q20</sup>/mGluR<sup>5−/−</sup> (n = 6–11), Hdh<sup>Q111/Q111</sup>/mGluR<sup>5+/−</sup> (n = 9–12) and Hdh<sup>Q111/Q111</sup>/mGluR<sup>5−/−</sup> mice (n = 6–11) tested at 3, 6, 9, 12, 15, 18, 21 and 24 months of age. Each animal was monitored for 120 min in the open-field apparatus. Data represent means ± SEM. * indicates significant differences as compared with Hdh<sup>Q111/Q111</sup>/mGluR<sup>5−/−</sup> mice (P < 0.05).

Figure 3. Acute MTEP injection induces increased locomotor activity in both Hdh<sup>Q20/Q20</sup> and Hdh<sup>Q111/Q111</sup> mice. (A and B) Graphs show total distance traveled by control (Hdh<sup>Q20/Q20</sup>/MTEP n = 8 and saline n = 7) and mutant HD (Hdh<sup>Q111/Q111</sup>/MTEP n = 8 and saline n = 7) mice. Animals were placed in the open-field box and injected at an injection point of 5 min with either saline or MTEP (i.p. 5 mg/Kg). Each animal was monitored for 120 min, and total distance was measured at 5-min intervals (A) or cumulatively >120 min (B). (C and D) Graphs show total distance traveled by Hdh<sup>Q20/Q20</sup>/MTEP (MTEP n = 8 and saline n = 7) and Hdh<sup>Q111/Q111</sup>/MTEP (MTEP n = 8 and saline n = 7) mice. Animals were placed in the open-field box and injected at an injection point of 60 min with either saline or MTEP (i.p. 5 mg/Kg). Each animal was monitored for 120 min, and total distance was measured at 5-min intervals (C) or cumulatively >120 min (D). Data represent the means ± SEM. * indicates significant differences as compared with matched genotype injected with saline (P < 0.05).
weight gain (data not shown) or in huntingtin mRNA and protein expression levels (Supplementary Material, Fig. S1). In addition, the tested mouse lines did not exhibit any kind of stereotypical behavior when allocated either in their home cage or in the open-field arena (Supplementary Material, Fig. S2). Together, these data suggest that the expression of mutated huntingtin protein in mGluR5 null mutant mice might be activating compensatory mechanisms that prevented the increase in locomotor activity.

To test whether the observed increase in locomotor activity caused by mGluR5 knockout could be recapitulated pharmacologically in control and mutant HD mice, we assessed the effects of mGluR5 antagonist MTEP on the locomotor activity of both mouse lines. To do this, we injected mice with MTEP (i.p. 5 mg/kg) 10 min after introducing the mice to the open-field arena. Both control and mutant HD mice injected with MTEP traveled much further in the arena than saline-injected mice, and no differences in the locomotor activity of both mouse lines was observed following acute pharmacological blockade of mGluR5 (Fig. 3A and B). However, it was not clear whether mGluR5 blockage caused hyperactivity or a lack of habituation. In order to investigate this, we introduced control and mutant HD mice to the open-field arena, waited 60 min for habituation to the new environment and then injected the mice with MTEP (i.p. 5 mg/kg). Both mouse lines showed an increase in locomotor activity, measured by distance traveled, following MTEP injection, indicating that mGluR5 blockage promotes hyperactivity as opposed to prevention of habituation (Fig. 3C and D).

The mechanism underlying the increase in locomotor activity promoted by mGluR5 blockage is unknown. Therefore, we investigated whether this increase in locomotor activity was dopamine dependent. Thus, mGluR5 null control and mutant HD mice were injected with either saline or the D2 dopamine receptor antagonist haloperidol (i.p. 0.5 mg/kg). Haloperidol caused the levels of locomotor activity, as measured by total distance, in the mGluR5 null control mice to go down to levels observed for mGluR5 null mutant HD mice (Fig. 4A and B). Similar results were observed when mGluR5 null control mice were injected with the D1 dopamine receptor antagonist SCH23390 (i.p. 0.5 mg/kg), as the levels of distance traveled by mGluR5 null control mice treated with SCH23390 were not different than those of mGluR5 null mutant HD mice (Fig. 4C and D). Interestingly, the distance traveled by mutant HD following either haloperidol or SCH23390 treatment was not different than that of saline-treated mutant HD mice that express mGluR5 (Fig. 4A–D). In addition, amphetamine (i.p. 2 mg/kg) treatment promoted a further increase in locomotor activity for mGluR5 null control mice, but had no effect on the locomotor activity of mGluR5 null mutant HD mice (Fig. 4E and F). These data suggested that the increase in locomotor activity observed following genetic deletion of mGluR5 in control mice was dopamine dependent. The lack of effect of amphetamine treatment on mGluR5 null mutant HD mice suggested that polyglutamine-expanded mutant huntingtin protein might activate a developmentally compensatory mechanism that appears to block the hyperactivity induced by both mGluR5 deletion and dopamine stimulation.

Previously, rotarod performance of mutant HD (Q111) mice was shown to not be impaired when compared with that of control mice (21). Moreover, it was shown that MTEP had no effect on rotarod performance (22). To determine whether mGluR5 knockout could alter control and mutant HD mouse motor coordination, mice were trained and submitted to testing sections on the rotarod. Rotarod learning curves were not different from one another (Fig. 5C). The knockout of mGluR5 did not change the performance of control mice on the rotarod (Fig. 5C). However, genetic deletion of mGluR5 significantly improved the performance of mutant HD mice on the rotarod, when compared with all other genotypes (Fig. 5C). Statistical analysis (two-way ANOVA) indicates that both genotype [±(3.3) = 27.6, P < 0.0001] and age [±(7.3) = 20.1, P < 0.0001] affected rotarod performance. Moreover, Bonferroni posttests indicate that the rotarod performance of mGluR5 null mutant HD mice was better than that of wild-type control mice at the ages of 3, 6 and 21 months (Fig. 5C). These data further support the notion that mGluR5 is intrinsically implicated in the motor alterations promoted by mutated Htt protein.

To further characterize the consequences of polyglutamine-expanded huntingtin expression in an mGluR5 null genetic background, we performed immunohistochemistry experiments using EM48 antibody to determine the pattern of mutated huntingtin aggregation in the striatum of 12-month-old mice. Control mice that either express or do not express mGluR5 did not display any huntingtin aggregates (Fig. 6A and B). However, mutant HD mice that express mGluR5 exhibited high levels of diffuse EM48 labeling in the striatum, as well as darkly stained puncta (Fig. 6C and E), which has been characterized as ubiquitin-positive intranuclear inclusions (23). Interestingly, although diffuse EM48 labeling could be observed in the striatum of mGluR5 null mutant HD mice, intranuclear inclusions were mostly absent in the striata of these mice (Fig. 6D and F). Quantification of these data and statistical analysis demonstrate that both diffuse EM48 labeling (Fig. 6G) and intranuclear inclusions (Fig. 6H) were robustly reduced in mGluR5 null mutant HD mouse striatum as compared with that of wild-type HD mutant mice (Fig. 6E), strongly indicating that mGluR5 is involved in huntingtin aggregation. Statistical analysis (unpaired t-test) indicates a significant effect of genotype (P < 0.0001).

To further investigate the mechanism behind the observed adaptive phenotype of mGluR5 null mutant HD mice, we decided to analyze whether mutated huntingtin expression in an mGluR5 null background was altering the expression of genes that might be involved in the pattern of huntingtin aggregation and HD-related locomotor alterations. Thus, we performed a microarray assay to compare mRNA expression levels between wild-type control mice, mGluR5null control mice, wild-type mutant HD mice and mGluR5null mutant HD mice. As expected, mGluR5 expression was down-regulated in both mouse lines lacking mGluR5 expression when compared with wild-type control and mutant HD mice (data not shown). These data support the assumption that the microarray assay was performed properly and was capable of detecting gene expression variations. To identify pathways and networks of genes significantly altered in mGluR5 null mutant HD mice versus wild-type mutant HD mice, we analyzed the microarray data using ingenuity pathway analysis (IPA). The microarray
analysis indicated that the expression of many genes encoding for animal motility, cell transport, vesicular trafficking proteins, brain development and protein aggregation was altered in mGluR5 null mutant HD when compared with wild-type mutant HD mice (Tables 1 and 2 and Supplementary Material, Fig. S3). The expression of these genes was neither different nor altered when we compared wild-type control and mutant HD mice (data not shown).

In order to confirm the microarray results, we performed quantitative real-time PCR (qPCR) to determine the expression of genes of interest, including the mGluR5 null mutant HD mouse up-regulated genes, dynein heavy chain 6 (Dnahc6) and dynein light Tctex chain-type 1B (Dynlt1), and the mGluR5 null mutant HD mouse down-regulated gene dynactin 3 (Dctn3). The qPCR results confirmed that Dnahc6 and Dynlt1 were up-regulated in mGluR5 null mutant HD mouse versus mGluR5 null control mice (Fig. 7A and B). Moreover, in agreement with the microarray results, Dctn3 was down-regulated in mGluR5 null mutant HD mouse versus mGluR5 null control mouse (Fig. 7C).
alterations were gene specific, we performed qPCR to measure expression levels of related genes that did not appear altered in the microarray assay. The microarray results did not indicate any changes in dynein light chain LC8-type 1 (Dynll1) and dynactin 6 (Dctn6) expression levels in mGluR5 null mutant HD mouse versus mGluR5 null control mice. Supporting these results, qPCR data also indicated that the expression of Dynll1 and Dctn6 was not different between mGluR5 null mutant HD mouse versus mGluR5 null control mice (Fig. 7D and E).

DISCUSSION

Chorea-like movements are the most characteristic symptoms of HD patients. Currently, these abnormal hyperkinetic movements are treated with antidopaminergic neuroleptic drugs, which are not very efficacious in the case of HD and may promote extrapyramidal side effects (24,25). A better understanding of the neural circuits and alterations promoted by mutated huntingtin will help to develop new therapeutic strategies to treat chorea-like HD symptoms. In the present study, we demonstrate that mGluR5 blockage promotes increased locomotor activity and that this increase is abrogated by D1 and D2 dopamine antagonists. mGluR5 null control (Q20/Q20) mice, as well as wild-type control mice treated with MTEP, exhibit increased locomotor activity as compared with control. However, although MTEP acute injection increases mutant HD mouse locomotor activity, knockout of mGluR5 in mutant HD mice does not promote augmented locomotor activity. Moreover, mGluR5 null mutant HD mice exhibit improved rotarod performance as compared with that of wild-type control, mGluR5 null control and mutant HD mice. In addition to these behavioral alterations, mutated huntingtin aggregation appears to be influenced by mGluR5 as huntingtin intranuclear inclusions observed in mutant HD mouse striatum are significantly reduced in mGluR5 null mutant HD mice. It is possible that mutated huntingtin protein could alter gene expression differently in the absence of mGluR5, which could account for these adaptations. Supporting this hypothesis, our microarray study indicates that mutated huntingtin protein can alter the expression of a number of genes that could be important for the locomotor adaptations and decrease in huntingtin intranuclear inclusions observed in mGluR5 null mutant HD mice. Importantly, qPCR experiments confirmed that the mRNA transcript levels of Dnahc6 and Dynlt1, and dynactin 3 are altered in mGluR5 null mutant HD mice, as compared with mGluR5 null control mice.
although these alterations are not observed when we compare wild-type control and mutant HD mice.

mGluR5 is highly expressed in the striatum, which is the main region affected in HD (26,27). Our group has established a link between mGluR5 and HD by showing that group I mGluRs interact with the huntingtin protein (17). Moreover, mutant huntingtin protein can alter mGluR5 signaling, decreasing inositol-1,4,5-triphosphate (IP3) formation and increasing ERK1/2 and AKT activation (20). A number of reports have demonstrated that mGluR5 blockage can induce hyperkinetic movements (12,13). In agreement with these findings, our data demonstrate that mGluR5 knockout or mGluR5 blockage induce hyperkinesia in mice, suggesting that mGluR5 could contribute to HD chorea.

It is still unknown how mGluR5 blockage induces hyperkinesia and which neuronal circuits are involved in this regulation. We show that the hyperkinesia exhibited by the mGluR5 knockout mice is abolished by D1 and D2 dopamine receptor antagonists, haloperidol and SCH23390, respectively. It is well known that the glutamatergic and dopaminergic systems physically interact in certain brain regions, including the striatum, nucleus accumbens and prefrontal cortex, and that this interaction is important for the control of both cognition and movement (28–31). Interestingly, striatum and cortex are the primary affected areas in HD (6,7). Importantly, our data demonstrate that mutated Huntingtin expression abolishes increased locomotor activity promoted by both mGluR5 knockout and amphetamine, further supporting the idea that mGluR5 blockade in the striatum and cortex could be involved in hyperkinesia. The striatum is mainly composed of GABAergic inhibitory MSNs, which express high levels of mGluR5 and project to different areas of the brain, including the SNc, which is mainly composed of dopaminergic projection neurons that up-regulate locomotor activity via cortical and nigrostriatal stimulation (10,32). We hypothesize that the increase in locomotor activity observed in mGluR5 knockout mice is because of the decreased stimulation of MSNs by glutamatergic cortical projection neurons, which in wild-type mice can occur via mGluR5 activation (8,9). Decreased stimulation of MSNs lessens the inhibition of SNc neurons, leading to dopaminergic disinhibition and increased thalamocortical stimulation, which can increase locomotor activity. Further experiments, including brain region-specific injections of MTEP, will be important to confirm this hypothesis.

Figure 6. The number of huntingtin (EM48) intranuclear inclusions is reduced by the knockout of mGluR5 in Hdh/Q111/Q111/mGluR5−/− mice. Shown are representative images for EM48 immunostaining from (A) control (Hdh/Q20/Q20/mGluR5+/+), (B) mGluR5 null control (Hdh/Q20/Q20/mGluR5−/−), (C) mutant HD (Hdh/Q111/Q111/mGluR5−/−) and (D) mGluR5 null mutant HD (Hdh/Q111/Q111/mGluR5−/−) striatal slices. Previous panels were enlarged to show intranuclear inclusions present in Hdh/Q111/Q111/mGluR5+/+ (E) and Hdh/Q111/Q111/mGluR5−/− (F) striatal slices. Graphs show quantification of diffuse EM48 staining (G) and number of Huntingtin aggregates (intranuclear inclusions) (G) found per 900 × 900 μm². Data represent the means ± SEM for three independent experiments. Asterisks indicate significant differences (unpaired t-test) as compared with Hdh/Q111/Q111/mGluR5+/+ mice (P < 0.05). Scale bar = 150 μm.
Motor coordination deficit can be typically observed in HD patients, and this feature is also present in most HD mouse models, such as R6/2, YAC128 and BACHD, which can be assessed by submitting the animals to the rotarod task (21). However, knock-in mouse models of HD with <150 polyglutamines, such as HdhQ111/Q111 mice, do not exhibit any impairment in rotarod performance, as compared with control (21,33). It has also been shown that mGluR5 blockage with MTEP does not improve rotarod performance (22). However, we show here that the knockout of mGluR5 in a mouse expressing mutated huntingtin, but not wild-type huntingtin, improves rotarod performance. One potential hypothesis to explain these finding is that mGluR5 blockage facilitates motor coordination but that improvement in motor coordination in mGluR5 null control mice is abrogated by hyperactivity. Thus, because the mGluR5 null mutant HD mice do not exhibit increased locomotor activity, improvement in rotarod performance can be detected in these mice. Further experiments, including crossing a HD mouse model that exhibit rotarod deficiency to mGluR5 knockout mice, will be necessary to test this hypothesis and determine whether mGluR5 blockage can improve motor coordination in HD. Moreover, the knockout of mGluR5 in a HD mouse model that has a short life span will be important to determine whether the lack of mGluR5 could increase mouse longevity.

MTEP acute injection was sufficient to augment locomotor activity in both control and mutant HD mice. However, lack of mGluR5 expression during the whole life span as in mGluR5 knockout mice fails to increase locomotor activity in mutant huntingtin expressing mice, although mGluR5 null control mice exhibit increased locomotor activity. These data indicate that following the developmental loss of mGluR5 expression, the mutated huntingtin protein might activate compensatory mechanisms that abrogate mGluR5-induced hyperkinesia. Understanding these mechanisms could contribute to a better comprehension of mutant Huntington-induced chorea. A number of reports indicate that the mutated Huntington protein can alter gene expression (34,35). Moreover, mGluR5 stimulation can also modify gene expression (36,37). Thus, we investigated whether mutated Huntington-induced gene expression alterations in an mGluR5 null background could help to explain the lack of hyperkinesia, improved rotarod performance and decreased intranuclear inclusions observed in mGluR5 null mutant HD, as compared with mGluR5 null control mice. In agreement with this hypothesis, we found that the mRNA transcript levels correspondent to a number of genes were altered in mGluR5 null mutant HD, as compared with mGluR5 null control mice. Mutation and/or altered expression of proteins prone proteins, such as mutated Huntingtin, leading to increased dynein function impairs autophagic clearance of aggregate-prone proteins, such as mutated Huntingtin, leading to increased huntingtin toxicity and enhanced phenotype in mouse and fly models of HD (40). A mouse model of HD expressing mutated

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<td>Ectonucleoside triphosphate diphosphohydrolase 2</td>
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<td>Rho GTPase activating protein 4</td>
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<td>Tubby like protein 4</td>
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Table 2. Genes down-regulated in HdhQ20/Q20/mGluR5−/− versus HdhQ111/Q111/mGluR5−/− mice that are not down-regulated in HdhQ20/Q20/mGluR5+/+ versus HdhQ111/Q111/mGluR5+/− mice

<table>
<thead>
<tr>
<th>Gene name</th>
<th>Gene symbol</th>
<th>RefSeq</th>
<th>Transcript ID</th>
<th>Fold change</th>
<th>P-value</th>
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<tr>
<td>Dybindin 3</td>
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<td>Retinol binding protein 1</td>
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<td>Chromoblastomannosidase</td>
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<td>Nucleoporin 35</td>
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<td>Carboxypeptidase D2</td>
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<tr>
<td>Holiday junction recognition protein</td>
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<td>Hydroxysteroid (17-beta) dehydrogenase 7</td>
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<td>Abhydrolase domain containing 10</td>
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<td>Disintegrin-like and metalloepitidase (reprolysin)</td>
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<td>PTPRF interacting protein, binding protein 1 (liprin)</td>
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<td>Formin 2</td>
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<td>Serine peptidase inhibitor, Kazal, type 8</td>
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<td>Cysteine-rich secretory protein LCCL domain containing</td>
<td>Crisp1d</td>
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<td>Leucine carboxyl methyltransferase 2</td>
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<td>FAT tumor suppressor homolog 4</td>
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<td>Purkinje cell protein 4-like 1</td>
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<td>Glutamate receptor, metabotropic 7</td>
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<td>Deoxynucllosine kinase</td>
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<td>Protein tyrosine phosphatase, receptor, type B</td>
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In conclusion, our data indicate that mutated huntingtin protein and mGluR5 exhibit a functional interaction that might be implicated in HD-related symptoms. Both mutated huntingtin and mGluR5 can regulate gene expression levels, which could account for the changes in motor behavior and pattern of huntingtin aggregation observed in mGluR5 null mutant HD mice. However, although mGluR5 knockout in mutant HD mice decreased huntingtin aggregation, it is still not clear whether mGluR5 antagonists could ameliorate HD-related symptoms. Future experiments will be important to further investigate the mechanisms underlying the alterations observed in mGluR5 null mutant HD mice.

MATERIALS AND METHODS

Materials
TRIZol, Nuclease-Free Water and Power SYBR® Green PCR Master Mix were purchased from Life Technologies (Foster City, CA, USA). Mouse anti-Huntingtin EM48 antibody was
purchased from Millipore (Billerica, MA, USA). MTEP was kindly provided by Merck & Co., Inc. (Rahway, NJ, USA), haloperidol (Cat. H1512) was purchased from Sigma–Aldrich (St. Louis, MO, USA), SCH23390 (cat. 0925) and D-amphetamine (cat. 2813) were purchased from Tocris Bioscience (Bristol, UK). All other biochemical reagents were purchased from Sigma–Aldrich.

Mouse model

STOCK-Htt\textsuperscript{tm2Mcm/3} \textit{(Hdh\textsuperscript{Q20/Q20})} and STOCK-Htt\textsuperscript{tm5Mcm/3} \textit{(Hdh\textsuperscript{Q111/Q111})} knock-in mice (43) and mGluR5 knockout mice B6:129-Grm\textsuperscript{tm1Rod/J} \textit{(mGluR5\textsuperscript{+/+})} (44) were purchased from Jackson Laboratory (Bar Harbor, ME, USA). \textit{Hdh\textsuperscript{Q111/Q111}/mGluR5\textsuperscript{-/-}} and \textit{Hdh\textsuperscript{Q111/Q111}/mGluR5\textsuperscript{+/+}} mice were obtained by crossing \textit{Hdh\textsuperscript{Q111/Q111}} and \textit{mGluR5\textsuperscript{+/+}} mice. \textit{Hdh\textsuperscript{Q20/Q20}/mGluR5\textsuperscript{-/-}} and \textit{Hdh\textsuperscript{Q20/Q20}/mGluR5\textsuperscript{+/+}} mice were obtained by crossing \textit{Hdh\textsuperscript{Q20/Q20}} and \textit{mGluR5\textsuperscript{-/-}} mice. Mice were housed in an animal care facility at 23°C on a 12 h light/12 h dark cycle with food and water provided \textit{ad libitum}. Animal care was in accordance with The University of Western Ontario Animal Care Committee.

Open field

Eight VersaMax Animal Activity Monitors (AccuScan Instruments, Inc., Columbus, OH, USA) were used to measure locomotor activity. Experiments were performed during the light cycle of the mice and between the hours of 08:00 and 14:00. Mice were allowed to explore the open-field boxes (20 × 20 cm) for 120 min during which time movement was measured at 5-min intervals using beam breaks converted to cm. During
drug studies, mice were allowed to explore the open-field boxes for 10 min after which an injection of either saline or drug was administered and the activity was monitored for additional 110 min. Measurement of total activity and time spent in the center of the arena were calculated, and statistical analyses were performed using GraphPad Prism software.

Rotarod test

The training and testing of the mice on the rotarod treadmill system (Diego Instruments, Sand Diego, CA, USA) occurred during the light cycle between the hours of 08:00 and 14:00. Mice were habituated to the testing room for 15–20 min. To introduce the mice to the rotarod apparatus, mice were placed on the rotarod and left at rest for 5 min on the first day of training before beginning the accelerating protocol. Mice were then trained for a maximum of 10 min in six trials at an accelerating speed (from 4 to 40 RPM in 600 s) for five consecutive days with 10-min breaks between each trial. If mice fell in the first 20 s of training, they were placed back on the apparatus immediately, up to three times. Mice were returned to their home cages at the end of training day 5 and rested for 2 days. On day 8, mice were tested in three trials with accelerating speed separated by a 30-min inter-trial interval. The latency to fall from the rod was recorded, and the average obtained from the three trials was used for analysis. Mice remaining on the rod for >600 s were removed and their time scored as 600 s.

EM48 immunohistochemistry

Mice were transcardially perfused with 4% paraformaldehyde (PFA) in PBS. Brains were then dissected out and stored in 4% PFA in PBS. Prior to sectioning, brains were put into 30% sucrose in PBS overnight at 4°C. Brains were dissected into left and right hemisphere, with the right hemisphere used for histology. Brains were coronally sectioned through the striatum, from +1.18 to −0.4 mm bregma. Immunohistochemistry was performed on 40-μm free-floating sections using a peroxidase-based immunostaining protocol. In brief, endogenous peroxidase activity was quenched using 0.1% hydrogen peroxide, after which the membranes were permeabilized using 1% Triton X-100. Non-specific binding was blocked using 1.5% normal horse serum, followed by incubation in primary antibody (1:100, anti-Huntingtin protein, mouse monoclonal EM48 antibody) overnight at 4°C. Sections were washed in PBS and then incubated in secondary antibody (biotinylated horse anti-mouse; Vector Elite ABC kit mouse) for 90 min at 4°C. Finally, sections were incubated in an avidin–biotin enzyme reagent (Vector Elite ABC kit mouse, PK-6102, Vector Laboratories). Immunostaining was visualized using a chromogen (Vector SG substrate). Sections were mounted on slides and visualized using a Zeiss LSM-510 META multiphoton laser scanning microscope with a Zeiss 10× lens, representative 900 × 900-μm areas of striatum were imaged for analysis. The number of EM48-positive cells was analyzed using the multi-threshold plugin on Image J, whereas the number of EM48-positive puncta per image was counted using the cell counter tool in Image J (NIH, USA). The difference in numbers between genotypes was analyzed using unpaired t-test.

Microarray hybridization and analysis

Microarray labeling and hybridization were performed at the London Regional Genomics Centre (Robarts Research Institute, London, ON, CA). To prepare 5.5 μg of cDNA using GeneChip® WT Terminal Labeling Kit (Affymetrix, Santa Clara, CA, USA), 20 μg of isolated RNA from striatum extracts was used. cDNAs were then labeled and hybridized in Mouse Gene 1.0 ST chips using GeneChip® WT Terminal Labeling Kit and GeneChip® Hybridization Wash and Stain kit (Affymetrix). The arrays were incubated for 17 ± 1 h, scanned with the GeneChip Scanner 3000 7G (Affymetrix) using Command Console v1.1, and probe set signals were calculated with the multi-array average algorithm. We used Partek Genomics Suite v6.5 (Partek, St. Louis, MO, USA) to determine differences in gene expression levels. Networks were generated through the use of IPA software (Ingenuity Pathway Analysis, Ingenuity Systems). Genotype effects were considered significant based of the following criteria: (i) ANOVA P-values < 0.05 and (ii) 1.5-fold increase or decrease. Considering that Hdh(G111) is a knock-in mice, we used mGluR5 expression as an internal control for the microarray assay.

Quantitative RT-PCR

RNA was isolated using Trizol reagent as per manufacture’s instructions (Invitrogen, Burlington, ON, USA). RNA was re-suspended in 20 μl of RNase-free water, and its concentration and quality were analyzed by NanoDrop™ (Thermo Scientific, Wilmington, USA) and gel electrophoresis, respectively. cDNAs were prepared from 40 ng of total RNA extracted in a 20 μl final reverse transcription reaction. Quantitative PCR was performed using the Power SYBR® Green PCR Master Mix and the ABI PRISM 7900HT Sequence Detection System platform (Applied Biosystems, Foster City, CA, USA). Quantitative RT-PCR (qPCR) was performed to quantify mRNA levels of the following genes: dynine light chain LC8-type 1—Dynll1 (NM_019682); dynactin 6—Dctn6 (NM_011722); dynactin 3—Dctn3 (NM_016890); dynein light chain axonemal 6—Dnahc6 (NM_001164609); dynactin 3—Dctn3 (NM_016890); dynein light Tctex chain-type 1B—Dynlt1b (NM_009342). Primers were designed using Primer3Plus Program: Dynll1 (forward: 5′-TTTGTCCTCCTGCAAGTACTG-3′; reverse: 5′-CTTACTGCTCATCTGTGTC-3′); Dctn6 (forward: 5′-TGATCCACCATGCAAGCAG-3′; reverse: 5′-ATAGGTTGCGCTGTCTGTC-3′); Dnahc6 (forward: 5′-CCAGAACAGATGACA-3′; reverse: 5′-TGAGAGGACGCTACTGAC-3′); Dctn3 (forward: 5′-CAGATCCACATCAGCA-3′; reverse: 5′-ACCTTCTCAGGCAATGCTA-3′); Dynlt1b (forward: 5′-CTAGCCAAGAAGCCT-3′; reverse: 5′-TCTGTGGAGCTTAC-3′). Samples were prepared in triplicate, and changes in gene expression were determined with the 2−ΔΔCt method using actin for normalization. All RT-qPCRs showed specific binding and proper melting curves as verified by the serial dilution method.

Data analysis

Means ± SEM are shown for the number of independent experiments indicated in Figure Legends. GraphPad Prism software
was used to analyze data for statistical significance and for curve
fitting. Statistical significance was determined by ANOVA
testing followed by post hoc Multiple Comparison testing.

SUPPLEMENTARY MATERIAL
Supplementary Material is available at HMG online.

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Conflict of Interest statement. None declared.

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