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Annals of Neurodegenerative Disorders

Short Communication

Alterations in Striatal Survival Signaling Pathways in the YAC128 Transgenic Mouse Model of Huntington's Disease

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Submitted: 22 August 2016

Accepted: 10 September 2016

Published: 13 September 2016

Keywords
- Brain-derived neurotrophic factor (BDNF)
- Extracellular signal-regulated protein kinase (ERK)
- Huntington's disease
- Protein kinase B (PKB/Akt)
- Yeast artificial chromosome (YAC) 128 transgenic mice

Abstract

Huntington's disease (HD) is an autosomal dominant neuropathology characterized by a degenerative process in the basal ganglia (namely the striatum) and associated with progressive cognitive and motor dysfunctions. This neurological condition is caused by a mutation in the gene that encodes the protein huntingtin (HTT). The YAC128 is a transgenic mouse model that expresses the full-length human *HTT* gene with 128 CAG repeats. This animal model reproduces several features of HD including age-dependent striatal neurodegeneration and a decline in cognitive and motor processes. Considering that behavioral and cognitive impairments have been reported before the onset of motor dysfunction and striatal degeneration in YAC128 mice, the present study investigated whether alterations in striatal levels of brain-derived neurotrophic factor (BDNF) and pro-survival signaling may contribute to these abnormalities during the early symptomatic stages of disease progression. Our results show no alterations in BDNF levels in the YAC128 striatum both at 3 and 6 months of age. The analysis of pro-survival signaling detected an increase in protein kinase B (PKB/Akt) and extracellular signal-regulated protein kinase-2 (ERK2) signaling but not in extracellular signal-regulated protein kinase-1 (ERK1) in this brain region. Together, these data suggest the occurrence of a compensatory response in the early stages of disease progression, which is likely a consequence of the increased excitability and excitotoxicity that other studies have previously reported in young YAC128 mice.

ABBREVIATIONS

PKB/Akt: Protein Kinase B; BCA: Bicinchoninic Acid; BDNF: Brain Derived Neurotrophic Factor; CAG: Cytosine-Adenine-Guanine; ERK: Extracellular Signal-Regulated Protein Kinase; HD: Huntington's Disease; HTT: Huntingtin; mBDNF: mature BDNF; NMDAR: *N*-methyl-D-aspartate Receptors; p-Akt: phosphorylated Akt; p-ERK: phosphorylated ERK; polyQ: Polyglutamine; WT: Wild-Type; YAC: Yeast Artificial Chromosome

INTRODUCTION

Huntington's disease (HD) is an autosomal dominant neuropathology caused by a mutation in the gene encoding huntingtin (HTT). This alteration leads to an unstable expansion of cytosine-adenine-guanine (CAG) repeats and a consequent polyglutamine (polyQ) stretch in the NH_2-terminal region of HTT [1]. HD is characterized by a neurodegenerative process in the basal ganglia (particularly caudate nucleus and putamen) and several other brain structures including the hippocampus, cerebral cortex, and hypothalamus [2]. The first symptoms of HD comprise psychiatric disturbances and cognitive impairment (i.e. affective disorders and deficits in memory formation), which can manifest up to a decade before the onset of the classical motor deficits. With the progression of disease, patients develop movement abnormalities such as chorea (involuntary movements) and dystonia, which gradually increases over the years until death (usually within 15 years) [3]. This degenerative process is related both to loss of function of normal HTT as well as a toxic gain of function of mutant huntingtin (mHTT) [4]. Indeed, normal HTT is thought to play a role in critical processes

of the central nervous system including endocytosis, vesicle transport, synaptic signaling and transcriptional regulation [5, 6]. Furthermore, normal HTT is also known to promote neuronal survival by regulating the transcription and vesicular transport of brain derived neurotrophic factor (BDNF) [7,8], and by modulating neuronal sensitivity to excitotoxicity [9]. In addition to the loss of function of normal HTT, the conformational alterations induced by excessive polyQ expansions is thought to result in a toxic gain of function of the mutant HTT, which also contributes to the pathophysiology of HD. Indeed, the conformational alteration of mHTT is associated with the formation of insoluble intracellular aggregates and neuronal intranuclear inclusions of mHTT, which form pathogenic protein-protein interactions with several intracellular proteins [10-12] thus impairing several aspects of cell function [13,14]. Additionally, there is also evidence suggesting that the toxicity of this mutant protein may also derive from its soluble fragments [15].

The survival of neurons is mediated by the activation of pro-survival cascades such as the protein kinase B (PKB/Akt) and extracellular signal-regulated protein kinases (ERKs) [16,17]. These signaling pathways mediate the activity of growth factors, protecting the brain from insults and stimulating its regenerative mechanisms [18-21]. Interestingly, previous studies have reported abnormalities in Akt and ERK content and activity in both HD animal models and HD patients. These signaling alterations might contribute to the neurodegenerative process in the HD brain by exacerbating mHTT toxicity and/or reducing pro-survival signaling [22-24].

The YAC128 transgenic mouse model, which expresses the full-length human *HTT* gene with 128 CAG repeats, reproduces several HD features including age-dependent striatal neurodegeneration, behavioral impairments and a decline in cognitive and motor processes [25,26,27]. YAC128 mice present early manifestations of the disease such as a hyperkinetic phenotype and depressive-like behavior at 3 months of age, followed by progressive motor deficits at 6 months with striatal and cortical degeneration becoming evident after 9 months of age [26,28,29]. Despite the occurrence of phenotypic alterations that precede cell death in this transgenic model, it is still not clear whether pro-survival alterations occur in early stages of disease progression. Therefore, the present study evaluated whether levels of BDNF and proteins involved in pro-survival signaling (Akt, ERK-1 and ERK-2) are altered in the striatum of early symptomatic YAC128 mice at 3 and 6 months of age.

MATERIALS AND METHODS

Transgenic mice

Transgenic mice expressing the human *HTT* gene with 128 CAG repeats (YAC128) were used to model HD in this study [30]. YAC128 mice were donated by the Michael Hayden Laboratory, Department of Medical Genetics, University of British Columbia (Vancouver, BC, Canada). The following primers were used to test for genotype: LYA1 = 5' CTGCTCGCTTCGCTACTTGGAGC 3', LYA2 = 5' GTCTTGCGCCTTAAACCAACTTGG 3', RYA1 = 5' CTTGAGATCGGGCGTTCGACTCGC 3', RYA2 = 5' CCGCACCTGTGGCGCCGGTGATGC 3'. Polymerase chain reaction (PCR) products were run on a 1.5% agarose gel with 10,000x SYBR-safe and visualized under a BioRad trans-illuminator (BioRad, Mississauga, ON, Canada). YAC128 and wild-type (WT) mice were housed according to sex and age at the Division of Medical Sciences, University of Victoria (Victoria, BC, Canada) in groups with a maximum of five mice per cage, with *ad libitum* access to food and water and under a normal 12-hour light/dark cycle. All procedures were performed in accordance with the University of Victoria and the Canadian Council for Animal Care policies.

Sample collection and tissue lysate preparation

After reaching the appropriate age (3 or 6 months of age), animals were anesthetized with isoflurane (Abbott Laboratories, North Chicago, IL, USA) and sacrificed by rapid decapitation. Striata were quickly dissected and snap-frozen with liquid nitrogen prior to storage at -80°C until use. Individual samples were homogenized in lysis buffer [137 mM NaCl, 20 mM Tris-HCl pH 8.0, 1% NP40, 10% glycerol, protease and phosphatase inhibitor cocktails (Thermo Scientific, Rockford, IL, USA)] by sonicating four times for 5 seconds. Total protein concentration for each individual sample was determined by the bicinchoninic acid (BCA) assay using a BCA Assay Kit (Thermo Scientific, Rockford, IL, USA) according to the manufacturer's instructions.

Measurement of total BDNF levels

Levels of total (including pro- and mature) BDNF were measured by antigen-capture enzyme-linked immunosorbent assay (ELISA) using a Promega BDNF Emax® ImmunoAssay System ELISA kit (Promega, Madison, WI, USA) according to the manufacturer's instructions. This ELISA kit included all antibodies and reagents used and can detect BDNF levels in samples from a variety of species, including mouse (see BDNF Emax® ImmunoAssay System Technical Bulletin for further details). Briefly, 96-well polystyrene plates (Thermo Scientific, Rockford, IL, USA) were coated with anti-BDNF monoclonal antibody overnight without agitation at 4°C, washed with Tris-buffered saline (TBS), and blocked using the supplied block and sample buffers for one hour at room temperature. Following blocking, tissue lysates or BDNF standards (serially diluted in halves to prepare a standard curve from 500 pg/mL to 7.8 pg/mL) were incubated for 2 hours at room temperature to allow BDNF binding by the coating antibody. Wells were then incubated with the (primary) polyclonal anti-human BDNF antibody for 2 hours at room temperature. Wells were subsequently incubated with the (secondary) anti-IgY polyclonal antibody conjugated to horseradish peroxidase, for one hour at room temperature. Wells were then incubated with TMB One Solution for 10 minutes at room temperature. The reduction of hydrogen peroxide in TMB One Solution was stopped by the addition of HCl, and the diimine product of TMB oxidation was measured spectrophotometrically at 450 nm. Levels of total BDNF in tissue lysates were determined by interpolation from the standard curve, and results were expressed in pg BDNF / mg protein.

Western-blot analyses

Equal amounts of protein were separated on a 10% sodium dodecyl sulfate - polyacrylamide gel electrophoresis (SDS-PAGE) and transferred at 4°C onto Polyvinylidene Fluoride (PVDF) membranes (Perkin Elmer, Boston, MA, USA). Membranes were

probed with primary antibodies against Akt, phosphorylated Akt (p-Akt), ERK1/2, phosphorylated ERK1/2 (p-ERK1/2) (Cell Signaling, Danvers, MA, USA), and actin (loading control; Sigma-Aldrich, Oakville, ON, Canada) and were detected with the appropriate secondary antibodies conjugated to horseradish peroxidase (HRP), and then developed by enhanced chemiluminescence (ECL; GE Healthcare, Buckinghamshire, UK). Data were quantified by densitometric analysis using the Quantity One Software program (BioRad, Hercules, CA). Immuno content levels of ERK1, p-ERK1, ERK-2, and p-ERK2 were calculated as a ratio to the levels of the loading control (β-actin) and were expressed as a percentage of the WT signal.

Statistical analyses

All statistical analyses were performed using Statistica 7.0 software (StatSoft, Tulsa, OK, USA). Data are presented as mean ± SEM. For all analyses, no significant differences between sexes were obtained (data not shown) and therefore data from males and females were combined and compared using two-factor analysis of variance (ANOVA), for genotype and age followed by Tukey's post-hoc analysis when appropriate. A value of $p<0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

The progression of HD is accompanied by a decrease in the expression of BDNF in the brain of HD patients [31,32]. BDNF is a trophic factor crucial for the survival of striatal neurons [33]. Since normal HTT has been shown to regulate the transcription [7] and vesicular transport [8] of this neurotrophin, the loss of function of normal HTT in HD may affect these processes, thus resulting in the decreased levels of BDNF seen in HD brains [31,32]. The role of BDNF in the degenerative progression of HD is further supported by experimental findings showing that the onset and severity of cognitive and motor dysfunctions in the R6/1 HD transgenic mouse model are associated with an endogenous deficit in this neurotrophic factor [34,35]. In addition, it is also known that YAC128 mice have reduced levels of BNDF in the striatum at an advanced stage of the disease (16 months of age) [36]. However, it is still not clear whether a decline in BDNF levels contribute to the early behavioral and cognitive alterations observed in this transgenic model. Thus, the present study evaluated BDNF levels in the striatum of YAC128 mice at 3 and 6 months of age (i.e., early symptomatic stages).

Our findings demonstrated that YAC128 mice did not present alterations in striatal levels of BDNF when compared to their age-matched WT controls at both these time points [two-factor ANOVA; main effect of genotype: $F_{(1,22)}=0.68$, $p=0.42$; no significant main effect of age and no significant interaction genotype versus age; Figure 1], suggesting that alterations in the striatal total levels of this neurotrophin are not involved in the abnormalities observed at the early stages of disease progression in this transgenic mouse model. One possible explanation for this finding is the fact that YAC128 mice have a biphasic pattern of corticostriatal activity, presenting hyper excitability and susceptibility to excitotoxicity at early stages and a markedly decrease when motor dysfunction starts to develop [37,38]. Therefore, considering that BDNF found in the striatum is dependent on anterograde transport from other brain structures, particularly

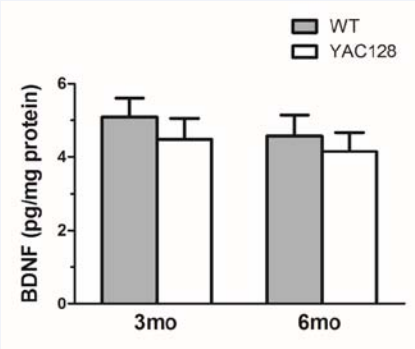

Figure 1 Levels of total BDNF in the striatum of YAC128 mice compared to WT mice at 3 and 6 months of age, as determined by ELISA. Levels of BDNF were expressed as pg per mg protein. Results are presented as means ± SEM (n=6-7/group).

from the cerebral cortex [39], it is possible that this age-dependent corticostriatal disconnection may cause a reduction in BDNF levels in subsequent time points (i.e. after 6 months of age). Of note, the BDNF ELISA procedure used in this study does not discriminate between pro-BDNF and mature BDNF (mBDNF) and therefore, we should not rule out the possibility that a potential flaw in the processing of pro-BDNF to mature BDNF could still occur during these early symptomatic stages. Further analyses by Western-blotting with antibodies selective for pro- and mature forms of BDNF at each stage of disease progression may aid in elucidating whether a defect in pro-BDNF processing (and a consequent increase in pro-BDNF with a concomitant reduction in mBDNF levels) may play a role in striatal neuropathology in YAC128 mice.

We also evaluated the immunocontent and phosphorylation status of proteins implicated in pro-survival signaling (Akt/p-Akt, ERK1 / p-ERK1, ERK2 / p-ERK2) of YAC128 mice in comparison to their age-matched WT counterparts. With regards to Akt, a two-factor ANOVA revealed a significant main effect of genotype [$F_{(1,22)}= 17.44$, $p<0.01$] but no main effect of age and no interaction between these two variables (Figure 2A). With regard to p-Akt, a significant main effect of genotype was also found [$F_{(1,22)}= 24.80$, $p<0.01$], although no main effect of age and no interaction between these two variables were encountered (Figure 2B). Finally, no main effects of genotype or age and no interaction between these two variables were found with regards to the p-Akt/Akt ratio (Figure 2C). Further post-hoc analyses confirmed that YAC128 mice display increased levels of Akt and p-Akt at both 3 ($p<0.01$) and 6 months of age ($p<0.05$).

When analyzing ERK1 levels, no significant alterations were found with regards to genotype, age, and interaction genotype versus age (Figure 3A). Similarly, no main effects of genotype and age, and no interaction genotype versus age were found with regards to p-ERK1 immunocontent (Figure 3B). Finally, no main effects of genotype, age, and no interaction between these two variables were found with regards to the p-ERK1/ERK1 ratio (Figure 3C). Similarly, a two-factor ANOVA revealed no main effects of genotype and age and no interaction between these two variables with regards to the levels of ERK-2 (Figure 4A). However, with regards to p-ERK2 immunocontent, a significant

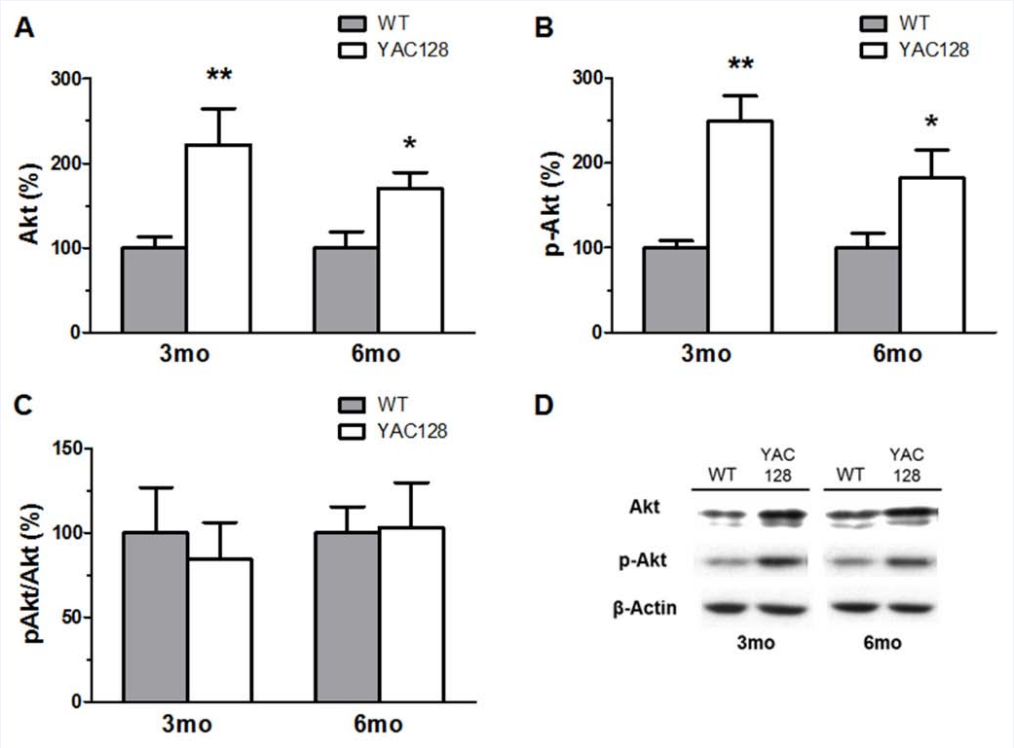

Figure 2 Western-blot analysis of Akt in the striatum of YAC128 mice at 3 and 6 months of age. Quantification of Akt (A) and p-Akt (B) revealed a significant increase in their immunocontent at both time points, but no alteration was found in the ratio p-Akt/Akt (C). Representative western-blots showing Akt, p-Akt, and ß-actin (loading control) immunoreactivity in early symptomatic YAC128 mice and their age-matched WT controls (D). Values are presented as mean ± SEM (n=6-8/group). **p<0.01 or *p<0.05 in comparison to age-matched WT animals.

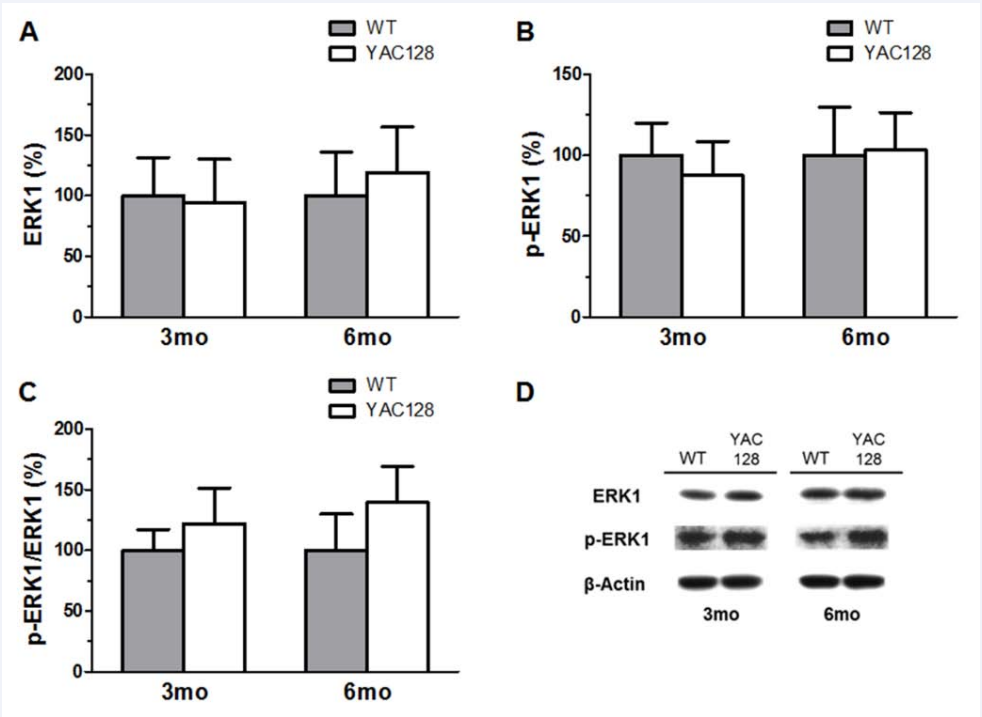

Figure 3 Western-blot analysis of ERK1 in the striatum of YAC128 mice at 3 and 6 months of age. Quantification of ERK1 (A), p-ERK1 (B) and the ratio p-ERK1/ERK1 (C) did not reveal significant alterations when compared to age-matched WT animals. Representative western-blots showing ERK1, p-ERK1, and ß-actin (loading control) immunoreactivity in early symptomatic YAC128 mice (D). Values are presented as mean ± SEM (n=6-8/group).

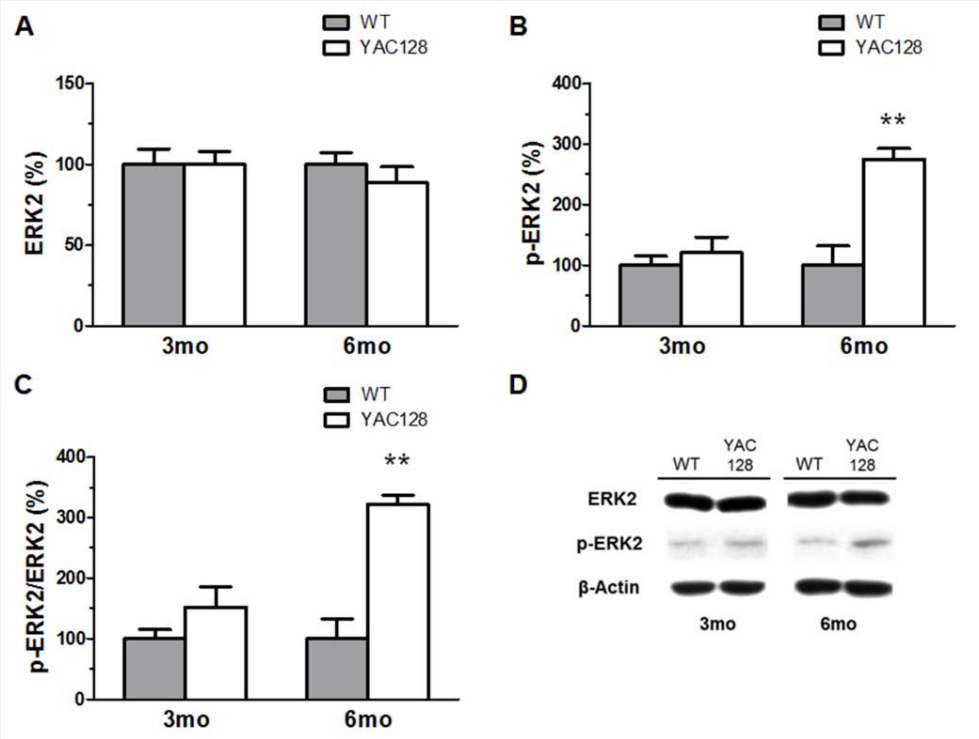

Figure 4 Western-blot analysis of ERK2 in the striatum of YAC128 mice at 3 and 6 months of age. Quantification of ERK2 immunocontent did not reveal a significant alteration in comparison to age-matched WT mice (A). However, a significant increase in p-ERK2 (B) and in the ratio p-ERK2/ERK2 (C) was found in the striatum of YAC128 mice at 6 months of age. Representative western-blots showing ERK2, p-ERK2, and ß-actin (loading control) immunoreactivity in early symptomatic YAC128 mice (D). Values are presented as mean ± SEM (n=6-8/group). **p<0.01 in comparison to age-matched WT animals.

main effect of genotype [$F_{(1,24)}$= 14.97, p<0.01], and a significant interaction between genotype and age [$F_{(1,24)}$= 9.26, p<0.01] were found (Figure 4B). Finally, a significant main effect of genotype [$F_{(1,24)}$= 25.17, p< 0.01], and a significant interaction between genotype and age [$F_{(1,24)}$ = 9.69, p<0.01] were found with regards to the p-ERK2/ERK2 ratio (Figure 4C). Post-hoc analysis evidenced that YAC128 mice have increased ERK2 striatal phosphorylation (p<0.01) at 6 months of age.

One possible explanation for this up-regulation of Akt, p-Akt, p-ERK2 and ERK2 phosphorylation in the YAC128 striatum may be related with the occurrence of a compensatory pro-survival response in the striatum of early symptomatic YAC128 mice to counteract the toxicity of mHTT. Similarly to our findings, a previous study provided compelling evidence for the activation of the Akt pathway in the striatum of $Hdh^{Q111/Q111}$ knock-in mouse model of HD [40]. Interestingly, this effect was associated with increased activation of glutamate *N*-methyl-D-aspartate receptors (NMDAR) and mitochondrial deficits, suggesting that Akt signaling may occur in response to the HTT-induced dysregulation of glutamate NMDARs functioning and resulting excitotoxicity during the early stages of disease progression [40]. Indeed, the occurrence of striatal hyperexcitability in pre-symptomatic stages of HD is also reproduced in YAC128 mice, as evidenced by electrophysiological findings showing increased glutamate release and synaptic response in corticostriatal projections [37]. Moreover, a similar pattern of increased excitability was demonstrated in the subthalamic nucleus [41] and in the hippocampus [42] of young YAC128 mice, suggesting that synaptic abnormalities may be causing alterations in the function of other brain structures. Therefore, similarly to other findings using distinct transgenic models of HD [40,43-45], the increased pro-survival signaling found in our study (i.e. increased Akt levels and ERK2 phosphorylation) may be a response to the occurrence of excitotoxic events. As a matter of fact, in a study conducted by Xie et al., (2010), no alterations were found in striatal Akt and ERK1/2 signaling of middle-aged YAC128 mice [36], supporting the hypothesis that our results may be related to the age-dependent biphasic pattern of excitability that occurs in this transgenic model.

CONCLUSION

Our study provided evidence that alterations in key signaling molecules involved in pro-survival pathways (namely Akt and ERK2) occur early on in the course of the disease. These alterations are likely to reflect a pro-survival compensatory response that occurs during the early symptomatic stage, as an attempt to counteract the deleterious and toxic effects of mHTT. Further studies are warranted to clarify the relationship between this putative compensatory response and the excitotoxic events that take place in striatal neurons in the YAC128 brain.

ACKNOWLEDGEMENTS

P.S.B. and J.G.M. acknowledge funding from the Ciência Sem Fronteiras/CNPq funding program (Science Without Borders, Brazil). P.S.B. also acknowledges funding from Edital Universal CNPq no. 480176/2013-2. E.M. received a Jamie Cassels

Undergraduate Research Award (JCURA) from the University of Victoria (Victoria, BC, Canada) and an Undergraduate Student Research Award (USRA) from the Natural Sciences and Engineering Research Council of Canada (NSERC, Canada). B.R.C. is a Michael Smith Senior Scholar and is supported by grants from NSERC, the Canadian Institutes of Health Research (CIHR), the Michael Smith Foundation for Health Research (MSFHR), and the Canada Foundation for Innovation (CFI).

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Cite this article

Bettio LEB, Brocardo PS, McGinnis E, Vetrici M, Christie BR, et al. (2016) Alterations in Striatal Survival Signaling Pathways in the YAC128 Transgenic Mouse Model of Huntington's Disease. Ann Neurodegener Dis 1(3): 1012.