Cellular Toxicity*

Nuclear Localization of a Non-caspase Truncation Product of Atrophin-1, with an Expanded Polyglutamine Repeat, Increases Cellular Toxicity

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Dentatorubral and pallidolysian atrophy (DRPLA) is an autosomal dominant neurodegenerative disorder similar to Huntington’s disease, with clinical manifestations including chorea, incoordination, ataxia, and dementia. It is caused by an expansion of a CAG trinucleotide repeat encoding polyglutamine in the atrophin-1 gene. Both patients and DRPLA transgenic mice have nuclear accumulation of atrophin-1, especially an ~120-kDa fragment, which appears to represent a cleavage product. We now show that this is an N-terminal fragment that does not correspond to the previously described caspase-3 fragment, or any other known caspase cleavage product. The atrophin-1 sequence contains a putative nuclear localization signal in the N terminus of the protein and a putative nuclear export signal in the C terminus. We have tested the hypothesis that endogenous localization signals are functional in atrophin-1, and that nuclear localization and proteolytic cleavage contribute to atrophin-1 cell toxicity. In transient cell transfection experiments using a neuroblastoma cell line, full-length atrophin-1 with 26 (normal) or 65 (expanded) glutamines localized to both nucleus and cytoplasm, with no significant difference in toxicity between the normal and mutant proteins. A construct with 65 glutamine repeats encoding an N-terminal fragment (which removes an NES) of atrophin-1 similar in size to the truncation product in DRPLA patient tissue, showed increased nuclear labeling, and an increase in cellular toxicity, compared with a similar fragment with 26 glutamines. Full-length atrophin-1 with 65 polyglutamine repeats and mutations inactivating the NES also yielded increased nuclear localization and increased toxicity. These data suggest that truncation enhances cellular toxicity of the mutant protein, and that the NES is a relevant region deleted during truncation. Furthermore, mutating the NLS in the truncated protein shifted atrophin-1 more to the cytoplasm and eliminated the increased toxicity, consistent with the idea that nuclear localization enhances toxicity. In some of the experiments were inclusions visible in the nucleus or cytoplasm suggesting that inclusion formation is unrelated to cell death. These data indicate that truncation of atrophin-1 may alter its ability to shuttle between the nucleus and cytoplasm, leading to abnormal nuclear interactions and cell toxicity.

Dentatorubral and pallidolysian atrophy (DRPLA)1 is a progressive neurodegenerative disorder, characterized by movement, cognitive, and emotional abnormalities (1–3), and caused by an expansion beyond 49 consecutive CAGs in the atrophin-1 gene on chromosome 12p (4–8). DRPLA is one of at least eight disorders, including Huntington’s disease and several forms of spinocerebellar ataxia (SCA), involving a polyglutamine expansion. These disorders are thought to occur through a genetic “gain of adverse function” mechanism (9–11). Of these diseases, DRPLA is most similar to Huntington’s disease.

Atrophin-1, the DRPLA gene product, encodes a hydrophilic 1184-amino acid protein (12, 13) with several simple repetitive motifs, including a serine-rich region, a variable length polyglutamine tract, a polyproline tract, and a region of alternating acidic and basic residues. The sequence of atrophin-1 contains a putative NLS in its N terminus and a putative NES in its C terminus. The atrophin-1 protein normally localizes to both the nucleus and cytoplasm of cells and its function is unknown (12, 14, 15). Atrophin-1 is expressed widely in brains of normal and affected individuals (8, 13, 14). Degeneration and cell death in DRPLA occurs mainly in the dentate nucleus of the cerebellum, red nucleus, globus pallidus, and subthalamic nucleus. Neurons in these regions show atrophin-1 containing inclusions and diffuse nuclear labeling. Therefore atrophin-1 expression levels alone do not explain the pathogenesis.

1 The abbreviations used are: DRPLA, dentatorubral and pallidolysian atrophy; PIPES, 1,4-piperazinediethanesulfonic acid; CHAPS, 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonic acid; GFP, green fluorescent protein; CBP, cAMP-response element-binding protein (CREB)-binding protein; SCA, spinocerebellar ataxia.

THE JOURNAL OF BIOLOGICAL CHEMISTRY Vol. 278, No. 15, Issue of April 11, pp. 13047–13055, 2003

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This paper is available online at http://www.jbc.org

10.1074/jbc.M211224200

Received for publication, November 4, 2002
Published, JBC Papers in Press, December 2, 2002

1 The work was supported in part by the Huntington’s Disease Society of America “Coalition for the Cure,” Hereditary Disease Foundation “Cure HD Initiative,” and National Institutes of Health Grants NS16375, NS4172, and NS38144 (to C. A. R.) and NS37090 (to T. M. D.). The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

2 Supported by National Institutes of Health Grant NS40251, the Huntington’s Disease Society of America, and the Hereditary Disease Foundation.

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Localization of a Non-caspase Truncation Product of Atrophin-1

The cellular site of toxicity in HD and DRPLA is controversial. Inclusions are predominantly nuclear in DRPLA (17, 18), and both nuclear and cytoplasmic in HD (19–21), but the presence of inclusions does not correlate well with toxicity. In some cell model studies of HD, an exogenous NLS or an exogenous NES was fused to the huntingtin protein, and cellular toxicity was correlated with nuclear localization (22, 23), although not all studies have come to similar conclusions (24).

Cleavage of atrophin-1 may also be relevant to pathogenesis, although the nature of the relevant cleavage product is uncertain. Igarashi et al. (25) generated several atrophin-1 constructs with varying lengths for all model studies. In transient transfection of COS-7 cells, small truncated constructs of atrophin-1 with expanded repeats caused cellular toxicity, whereas full-length or long fragments of atrophin-1 with normal or expanded repeats did not (25). These data suggest that generation of a short truncation fragment (which could diffuse into the nucleus) can lead to the formation of nuclear inclusions and cellular toxicity. Studies in HD have also indicated that short truncations of huntingtin are toxic (23, 26, 27). However, the DRPLA disease model mice and DRPLA patient tissue show a relatively large cleavage fragment of mutant atrophin-1, running in a gel at about 120 kDa (28, 29). This fragment would be too large to enter the nucleus via passive diffusion. It is not known whether a fragment of this length could be toxic. Caspase cleavage of atrophin-1 at Asp109 can generate a large C-terminal fragment (30–32); however, whether this is present in vivo is uncertain.

We have made several constructs to study the role of nuclear targeting and truncation of atrophin-1 in toxicity related to DRPLA. Our goal was to determine whether the putative endogenous NLS and NES sequences in atrophin-1 are functional, and whether a truncation fragment of the approximate size and site of cleavage seen in patients and transgenic mice enhances nuclear transport and cellular toxicity.

EXPERIMENTAL PROCEDURES

Atrophin-1 Constructs—Full-length constructs were prepared previously (13) and are in pcDNA-3 (Invitrogen). At-N917–65Q and At-N917–65Q were generated by restriction digest at unique BsrGI and XbaI sites blunt-ending, recircularizing, and deleting the region from BsrGI to XbaI. The NLS (amino acids 16–32) in atrophin-1 was mutated using PCR-based mutagenesis and designated At-N917–65Q–mNLS and the NES (amino acids 1033–1041) was mutated using PCR-based mutagenesis (33) and designated At-FL-65Q-mNES and At-FL-65Q-mNLS.

Immunofluorescence—Mouse Neuro-2a (N2a) cells were cultured in 1:1 Dulbecco’s modified Eagle’s medium:Opti-MEM 1 supplemented with 5% fetal bovine serum and antibiotics, plated at a density of 1.5 × 10^5 per well of one-well chamber slides (Nunc), cultured overnight, and transfected with 0.5 μg of DNA (At-FL-6Q, At-FL-65Q, At-N917–65Q, At-N917–65Q–mNLS, At-N917–65Q–mNES) in the presence of [35S]methionine. Translations were incubated with 10 μCi of each of the caspases for 20 s, and microcentrifuged for 1 min prior to loading. Proteins were resolved by SDS-PAGE in a 6% polyacrylamide–SDS gel and then transferred to a nitrocellulose membrane (Schleicher and Schuell). Transfer buffer was 25 mM Tris, 192 mM glycine, 0.1% SDS, and 10% methanol; and the blots were probed with anti-atrophin-1 antibody AP142, AP142, or APG840 (34). Bound antibodies were visualized with horseradish peroxidase-conjugated secondary antibodies and enhanced chemiluminescence (Renaissance; PerkinElmer Life Sciences).

Quantitation of Atrophin-1 Distribution—N2a cells were cultured and transfected and immunofluorescence was performed as described above. N2a cells transfected with each of the atrophin-1 constructs were assessed by randomly selected fields and at least 100 cells per condition were counted. Cells were scored based on nuclear, nuclear and cytoplasmic, or cytoplasmic staining using standard epifluorescence on a Zeiss microscope. Each condition was assessed at least three times.

Cell Toxicity Assay—N2a cells were seeded in six-well plates at a density of 1.5 × 10^5 and cotransfected with 0.5 μg of DNA of EGF and 0.5 μg of DNA for LacZ or atrophin-1 constructs (At-FL-6Q, At-FL-65Q, At-N917–65Q, At-N917–65Q–mNLS, At-N917–65Q–mNES, At-FL-6Q–mNES). GFP positive fluorescent cells were counted 48 h later by capture on a Zeiss Axiovert 135 inverted microscope via IP Spectrum Labs image analysis software. Each experiment contains cells from 10 randomly selected fields from each of three wells. Mean ± standard deviations are taken from at least three different experiments. As a measure of cell loss, GFP positive cells were counted in each condition and standardized to the LacZ condition (22, 35). We have previously shown that this measure of cell loss correlates with cell death as measured by propidium iodide to label dead cells and Hoechst 33342 to label total cells (22) or Hoeschst for shrunk and dead nuclei (35). Plasmids purified in separate preparations gave similar results.

RESULTS

The atrophin-1 protein with sequences relevant to this study is shown at the top of Fig. 1. Atrophin-1 is a 1184-amino acid protein with a glutamine repeat near the middle of the protein. It contains a putative NLS in its N terminus, a polymorphic polyglutamine tract near the middle of the protein, and a putative NES in its C terminus. The antibody AP302 binds to amino acids 1–15 and the antibodies AP142 and APG840 bind to amino acids 425–439. Four constructs were generated spanning the entire protein. The midportion could have either normal or mutant polyglutamine.

**FIG. 1.** Schematic diagram of atrophin-1 protein, antibody binding sites, and initial set of constructs. Atrophin-1 encodes a hydrophilic 1184-amino acid protein. It contains a putative NLS in its N terminus, a polymorphic polyglutamine tract near the middle of the protein, and a putative NES in its C terminus. The antibody AP302 binds to amino acids 1–15 and the antibodies AP142 and APG840 bind to amino acids 425–439. Four constructs were generated spanning the entire protein.
formed 48 h later. The N-terminal construct localized to the nucleus, whereas the other three constructs were cytoplasmic (Fig. 2), suggesting the existence of a functional NLS in the N terminus of the protein, and consistent with an NES in the C terminus of the protein.

Because DRPLA forms nuclear aggregates and the putative NLS is in the N terminus, we performed a Western blot analysis on nuclear extracts from transgenic mice to confirm that the truncation product contains the N terminus, using an antibody to the N terminus (AP302) and an antibody to an epitope near the glutamine repeat (AP840). Fig. 3 demonstrates the full-length protein of both alleles in the transgenic mice migrating at 190–200 kDa, and a band representing the truncation product, running at about 120 kDa (28) seen only in the transgenic mice with expanded atrophin-1. The truncation band is broader than the full-length bands, consistent with our previous observations that this band runs as doublet, and that there is an accumulation of this cleavage product over time (28). An antibody to the N terminus (AP302) recognizes this fragment in mice, but a C-terminal antibody does not (not shown), indicating that this truncation lacks the C terminus.

Next we generated constructs to determine whether the putative NES and putative NLS are functional, and to determine the effect of a truncation similar in size and location of truncation seen in the transgenic mice, indicating that the cleavage product does not arise from any of the caspases known to cleave atrophin-1.

We then compared the fragment in the DRPLA mouse model with the caspase fragments. When 293T extracts expressing full-length atrophin-1 with 65 glutamines were subjected to caspase-3, -6, or -7 treatment, the Western blot showed a band corresponding to full-length atrophin-1 in the absence of any caspase enzymes and a band migrating faster in the presence of these caspase enzymes, representing a cleavage product (Fig. 5). However, the product in each caspase condition is larger than the truncation seen in the transgenic mice, indicating that the cleavage product does not arise from any of the caspases known to cleave atrophin-1.

Two full-length constructs with 26 or 65 repeats (At-FL-26Q and At-FL-65Q, respectively) (Fig. 7) were generated to determine whether the putative localization signals functioned in the context of atrophin-1 and to determine whether the localization of the protein influenced toxicity.

We generated two constructs truncated at amino acid 917 with 26 or 65 repeats (At-N917–26Q and At-N917–65Q, respec-
This length was chosen because it removed the NES and should produce a product at least as large as, or slightly larger than, the 120-kDa fragment of mutant atrophin-1 seen in mice and DRPLA patients (Fig. 8). Fig. 8 shows At-N917–65Q running at /H11011120 kDa, demonstrating that At-N917–65Q is slightly larger than the truncation product seen in the mice and human patient tissue, and thus also too large to diffuse passively into the nucleus. Therefore, At-N917–65Q is reasonable to study in cell model experiments.

Two constructs truncated at amino acid 917, and with the NLS mutated (At-N917–26Q-mNLS and At-N917–65Q-mNLS), were generated, to determine whether the NLS is functional and if nuclear localization is related to toxicity (Fig. 7). Finally, two full-length constructs with the NES mutated were generated (At-FL-26Q mNES and At-FL-65Q mNES), to determine whether the NES is functional and whether eliminating it would enhance nuclear localization and cellular toxicity (Fig. 7).

Immunofluorescence and subcellular localization of these constructs in N2a cells transfected with full-length atrophin-1, At-FL-26Q or At-FL-65Q was quantified to determine the effect of altering the endogenous targeting signals (Figs. 9 and 10). Staining in most cells was in both the nucleus and cytoplasm. When atrophin-1 was truncated, removing the NES, At-N917–26Q, and At-N917–65Q showed predominately nuclear staining. Similar to the results from the truncation products, when the NES was mutated, At-FL-26Q-mNES or At-Fl-65Q-mNES showed predominately nuclear staining. When the NLS was mutated in the truncated product (At-N917–26Q-mNLS or At-N917–65Q-mNLS) most cells showed cytoplasmic staining (Figs. 9 and 10). In none of these experiments were there inclusion bodies or other large aggregates of atrophin-1, either in the nucleus or cytoplasm. These data suggest that both the putative NLS and NES are functional in the context of atrophin-1.

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Cell toxicity assays were performed using each of the constructs described above to determine the relationship between subcellular localization and cell death. Western blots using

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**Fig. 4. In vitro translation of atrophin-1 treated with recombinant caspase-1 through caspase-10.** Radiolabeled At-FL-65Q and At-FL-65Q (D109N) were incubated with the indicated recombinant caspases (10–100 nM) or in cleavage buffer (dash). We and others have previously shown that recombinant caspases cleaves atrophin-1 in the N-terminal region of atrophin-1 at Asp109 (32). Caspase-2, -3, -7, and -8 cleave atrophin-1 at the Asp109 site. Caspase-6 cleaves At-FL-65Q (D109N) and can recognize an additional site in atrophin-1.

**Fig. 5. Caspase-3 or caspase-6 cleavage of atrophin-1 generate fragments different from the fragment present in the transgenic mouse.** 293T cells or N2a cells were transfected with At-FL-65Q and analyzed by Western blot. Cellular extracts were treated with recombinant caspase-3, -6, or -7. Brain nuclei suspended in the same buffer were run in an adjacent lane for comparison. The Western blot demonstrates that the cleavage product seen in the DRPLA transgenic mice (with 65 glutamines) migrates faster than the cleavage products of At-FL-65Q treated with recombinant caspases, suggesting the cleavage product is not derived from any of the caspases. AP 142 directed at epitope 425–439 near the glutamine repeat in the middle of the protein was used to detect the atrophin-1 protein.

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**Fig. 6. Consensus and endogenous nuclear localization signals and nuclear export signals.** A consensus bipartite NLS is 2 basic amino acids, a 10-amino acid spacer, and 3–5 basic amino acids, and a consensus NES is a hydrophobic amino acid, 2–4 amino acids, a hydrophobic amino acid, 2 amino acids, a leucine, an amino acid, and a hydrophobic amino acid. Atrophin-1 contains a putative NLS in its N terminus and a putative NES in its C terminus. Highlighted residues were mutated to determine whether these signals function in atrophin-1.
antibody AP 142 showed that each of these constructs yields expression at approximately the same levels (Fig. 8 and data not shown) and therefore, we can directly compare each construct for cellular toxicity. We did not detect any aggregation at the top of the Western blot, consistent with the lack of nuclear inclusions or other visible aggregates in our transient cell transfection assay. Cell viability was determined by co-transfecting an atrophin-1 construct with GFP as a marker for transfected cells (22, 35). GFP positive cells were counted 48 h later. Baseline toxicity in this transfection assay is 10–18%.

Cells transfected with At-FL-26Q, At-FL-65Q, or At-N917–26Q showed essentially no difference in cell viability. However, At-N917–65Q caused a 2-fold increase in cell loss (Fig. 11). Because truncation removes a functional NES and increases nuclear localization, we performed the cell loss assay for At-FL-65Q-mNES, and cell loss was comparable with that seen with the truncation. Because truncation and mutation of the NES changed the localization of the protein from both nuclear and cytoplasmic to mostly nuclear, this suggests that nuclear localization enhances toxicity. To further test if nuclear localization is a factor in this enhanced toxicity we mutated the NLS in At-N917–65Q (which shifted the protein mostly to the cytoplasm), and this decreased toxicity to control levels. These data suggest that an effect of the truncation is to relieve atrophin-1 of its NES, concentrating atrophin-1 into the nucleus through its functional NLS, and leading to enhanced cellular toxicity.

**DISCUSSION**

Our data indicate that endogenous localization signals are functional in atrophin-1, and that nuclear localization and proteolytic cleavage to an N-terminal fragment containing an NLS contribute to atrophin-1 cell toxicity. Transfection of At-FL-65Q had no increased toxicity compared with At-FL-26Q. By contrast, both At-N917–65Q (which removes the NES) and At-FL-65Q-mNES showed increased nuclear labeling and an increase in cellular toxicity, compared with similar constructs with 26 glutamines or full-length atrophin-1. These data suggest that truncation and nuclear localization enhance cellular toxicity of the mutant protein, and that the C terminus with its NES is a relevant region deleted during truncation. Mutating the NLS in the truncated product shifted atrophin-1 to the cytoplasm and eliminated the increased toxicity, confirming that nuclear localization is relevant to enhanced toxicity. By contrast, there were no inclusions or other visible aggregation in the transfected cells, indicating that inclusion formation is not necessary for toxicity.

Most N2a cells transiently transfected with full-length atrophin-1 (either normal or expanded) showed both nuclear and cytoplasmic staining. Truncation (which removes the NES) or mutation of the NES increased the number of cells with nuclear localization of the protein. By contrast, mutating the NLS in the truncated protein shifted atrophin-1 to the cytoplasm and eliminated the increased toxicity, confirming that nuclear localization is relevant to enhanced toxicity. By contrast, there were no inclusions or other visible aggregation in the transfected cells, indicating that inclusion formation is not necessary for toxicity.
endogenous NES in its C terminus, and can shuttle between nucleus and cytoplasm.

Other regions of the protein may also influence localization, as the mutation in the NLS did not abolish nuclear localization in every cell, and neither truncation (which removes the NES) nor the mutation of the NES yielded complete nuclear localization in every cell. Comparable data have been reported for ataxin-1, the SCA1 gene product (38). Ataxin-1 can also translocate from the cytoplasm to the nucleus. Nuclear localization of ataxin-1 is mediated by a C-terminal NLS. When the NLS in ataxin-1 was mutated and that construct transfected into COS-7 cells, some of the protein still entered the nucleus, but in transgenic mice made with this construct the protein was concentrated in the nucleus, interfering with its shuttling between the nucleus and cytoplasm. The truncation product may accumulate to a higher concentration in the nucleus (28), or may localize to a different nuclear compartment and interact with different proteins within the nucleus compared with the full-length mutant protein (see below).

Previous studies have shown that DRPLA transgenic mice and patient brain tissue show accumulation of a 120-kDa cleavage fragment specific to mutant atrophin-1 (28). Immunoblotting experiments in the present study indicate that the 120-kDa fragment seen in DRPLA transgenic mice contains the N terminus of the protein, but lacks the C terminus. We thus have generated a construct comparable in cleavage site and length to the product identified in transgenic mice and DRPLA patient tissue. The protein product of the At-N917-65Q construct migrates similarly to the human and mouse truncation product or slightly slower; thus it is at least the same length, and no shorter.

Several studies have shown that caspases can cleave atrophin-1 at Asp109 (30-32) in the N terminus of the protein. Our current data indicate that it is unlikely that any of the caspases-1-10 generate the cleavage product seen in human patient or mouse tissue. The in vitro translation and Western analysis data presented here show that the caspase cleavage products are different from the cleavage product seen in the DRPLA transgenic mice. Our antibody data indicate that the cleavage product in patient and transgenic mice retains the N terminus and the NLS and deletes the C terminus of the protein. By contrast the caspase-3 cleavage product does not contain the N terminus or the NLS (and is a different size). Based on our in vitro translation data and Western blots from brain nuclei, the cleavage product is not generated from any of the other known caspase enzymes studied here.

It was not previously known whether a fragment as large as studied in the current experiments could cause toxicity. Igarashi et al. (24) found that the addition of exogenous NLS or NES sequences did shift huntingtin aggregates to either the nucleus or cytoplasm but did not alter toxicity. However, their model focused on shifts in aggregate location and not diffuse appearing nuclear staining, which may be more relevant to cellular toxicity. Furthermore, that study used 93T cells and induced toxicity with tamoxifen plus huntingtin. SCA1 transgenic mice with a mutation in the endogenous nuclear localization signal did not develop the disease (38), indicating a critical role for nuclear location in ataxin-1 toxicity.

For atrophin-1, we find that modifications that enhance nuclear localization enhance cellular toxicity. These data add to the growing evidence that nuclear localization is relevant to toxicity for polyglutamine disorders. However, nuclear localization alone is not likely to be the only determinant of toxicity. There is partial nuclear localization with the expanded full-length constructs, which are not toxic. It is possible that truncation may disrupt the normal regulated pattern of shuttling of atrophin between the nucleus and cytoplasm. The truncation product may accumulate to a higher concentration in the nucleus (28), or may localize to a different nuclear compartment and interact with different proteins within the nucleus compared with the full-length mutant protein (see below).

Fig. 9. Immunofluorescent localization of atrophin-1 full-length and truncated with or without altered localization signals demonstrates that the NLS and NES are functional. N2a cells transfected with full-length atrophin-1, At-FL-26Q, or At-FL-65Q showed that label in most cells localized to both the nucleus and cytoplasm. When atrophin-1 was truncated removing the NES, At-N917-26Q and At-N917-65Q showed predominately nuclear label. Similarly to the truncation products, when the NES was mutated, At-FL-26Q-mNES or At-FL-65Q-mNES showed predominately nuclear staining. When the NLS was mutated in the truncated product, At-N917–26Q-mNLS or At-N917–65Q-mNLS, most cells showed cytoplasmic localization. Affinity purified antibody AP 142 was used to detect atrophin-1 protein and ToTo-3 was used as a nuclear marker. The merged images show the localization of atrophin-1 relative to the nucleus. These data suggest that both the NLS and NES function in the context of atrophin-1.
the cytoplasm and toxicity was decreased to baseline. –
cated construct (At-N917 increase in cellular toxicity. When the NLS was mutated in the trun-
full-length construct with 26 or 65 repeats. When the putative NES was mutated –
– significant increase in toxicity. By contrast, At-N917 18%. Full-length atrophin-1 protein with 65 repeats does not cause a
function in the context of atrophin-1. One-
hundred cells were counted for each con-
three experiments is shown.

Our results are consistent with emerging data that polyglu-
tamine pathogenesis relates to abnormal interactions between
polyglutamine proteins and other proteins within cells, espe-
cially in the cell nucleus (45, 58). Several polyglutamine pro-
teins normally interact with nuclear constituents. Huntingtin
binds to the nuclear co-repressor protein N-CoR (60), and the
strength of this interaction is dependent on polyglutamine
repeat length. Atrophin-1 binds to even-skipped in
Drosophila, and both human and Drosophila atrophin-1 represses tran-
scription in vivo (61). Atrophin-1 binds to the ETO protein,
which is also a member of nuclear co-repressor complexes (57).
Huntington and atrophin-1 and other polyglutamine proteins
associate with TAFII130 (62) and Sp1 (63) and interactions
between DRPLA inclusions and promyelocytic leukemia pro-
tein have been identified (64, 65). Ataxin-1 alters nuclear ma-
trix domains containing promyelocytic leukemia protein (66)
and p53 (67). HD and DRPLA transgenic mice have altered
gene expression compared with control mice (68, 69).
We have demonstrated that atrophin-1 and huntingtin with expanded repeats, but not with normal repeats, can interact with cAMP-response element-binding protein (CREB)-binding protein (CBP) and interfere with CBP-mediated transcription, yielding toxicity. Full-length atrophin-1 with a normal or expanded repeat did not alter CBP-mediated transcription or cause cellular toxicity. By contrast, the At-N917 yielding toxicity. Full-length atrophin-1 with a normal or expanded repeat, but not with normal repeats, can interact with TAF II130 and Sp1 may also be important for pathogenesis (62, 63) related to Psychiatry for support.

acknowledgements—We thank David Borchelt and Gabriele Schilling for helpful discussions. We thank Mike Delano for expertise with the confocal microscope. We thank Paul McHugh and the Department of Psychiatry for support.

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Nuclear Localization of a Non-caspase Truncation Product of Atrophin-1, with an Expanded Polyglutamine Repeat, Increases Cellular Toxicity

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*J. Biol. Chem.* 2003, 278:13047-13055.
doi: 10.1074/jbc.M211224200 originally published online December 2, 2002

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