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CELL TYPE-SPECIFIC LOCALIZATION OF OPTINEURIN IN THE STRIATAL NEURONS OF MICE: IMPLICATIONS FOR NEURONAL VULNERABILITY IN HUNTINGTON'S DISEASE

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Abstract—Striatal neuropathology of Huntington's disease (HD) involves primary and progressive degeneration of the medium-sized projection neurons, with relative sparing of the local circuit interneurons. The mechanism for such a patterned cell loss in the HD striatum continues to remain unclear. Optineurin (OPTN) is one of the proteins interacting with huntingtin and plays a protective role in several neurodegenerative disorders. To determine the cellular localization pattern of OPTN in the mouse striatum, we employed a highly sensitive immunohistochemistry with the tyramide signal amplification system. In this study, we show that OPTN appeared as a cytoplasmic protein within the subsets of the striatal neurons. Of particular interest was that OPTN was abundantly expressed in the interneurons, whereas low levels of OPTN were observed in the medium projection neurons. This cell type-specific distribution of OPTN in the striatum is strikingly complementary to the pattern of neuronal loss typically observed in the striatum of patients with HD. We suggest that OPTN abundance is an important cellular factor in considering the cell type-specific vulnerability of striatal neurons in HD.

Key words: Huntington's disease, optineurin, huntingtin, striatum, interneurons, neurodegeneration.

Huntington's disease [HD (MIM 143100)] is an autosomal dominant neurodegenerative disorder that causes late-onset motor, cognitive, and psychiatric disturbances (Albin and Tagle, 1995). HD is the result of disrupted regulation of transcriptional machinery due to the expansion of a CAG trinucleotide repeat in the *huntingtin* (*Htt*) gene, which translates into an abnormally long polyglutamine (polyQ) tract in the huntingtin (Htt) protein (The Huntington's Disease Collaborative Research Group, 1993). The neuropathology of HD is characterized by primary and progressive degeneration of the medium spiny neurons (MSNs) in the striatum, with relative sparing of striatal interneurons (Ferrante et al., 1985, 1987; Kowall et al., 1987; Reiner et al., 1988; Albin et al., 1990; Cicchetti et al., 2000). However, the precise mechanism by which such cell type-specific loss of striatal neurons occurs in HD is yet to be elucidated.

Optineurin (OPTN) is a ubiquitous protein with high expression levels in the central nervous system (Li et al., 1998; Rezaie et al., 2005). It is a negative regulator of the nuclear factor-κB (NF-κB) signaling (Zhu et al., 2007; Mrowka et al., 2008; Sudhakar et al., 2009; Nagabhushana et al., 2011) and a multifunctional protein involved in protein and vesicular trafficking (Sahlender et al., 2005; Park et al., 2010), glutamate receptor signaling (Anborgh et al., 2005), and transcription activation (Moreland et al., 2000). OPTN has been identified as a gene mutated in some cases of hereditary glaucoma that causes retinal degeneration leading to visual loss (Rezaie et al., 2002), and our recent study has shown that loss of OPTN can induce degenerative loss of motor neurons in familial amyotrophic lateral sclerosis (Maruyama et al., 2010). These findings suggest that OPTN could be a common factor involved in protection against cell death in neurodegeneration. Of particular interest is that OPTN is one of the Htt-interacting proteins (Hattula and Peränen, 2000), which exerts a protective effect on glutamate-induced neurotoxicity associated with mutant Htt (Anborgh et al., 2005). To seek an association between expression of OPTN and specific patterns of neuropathology in HD, we here examined the cellular localization patterns of OPTN in the mouse striatum.

EXPERIMENTAL PROCEDURES

All procedures involving the use of animals and analysis of brain anatomy were approved by the Institutional Care and Use Committees of the University of Tokushima.

Animals and tissue preparation

Male C57BL/6 mice (Nihon SLC Co., Shizuoka, Japan), 8–10 weeks of age, were used (n=5). Mice were intraperitoneally injected with a lethal dose of pentobarbital (Sigma, St Louis, MO, USA) and were transcardially perfused with 0.01 M phosphate-buffered saline (PBS) at pH 7.4, followed by cold 4% paraformaldehyde in 0.1 M phosphate buffer (PB) at pH 7.4. The brains were

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Abbreviations: ChAT, choline acetyltransferase; CR, calretinin; DARPP-32, dopamine and cAMP-regulated phosphoprotein of 32 kDa; HD, Huntington's disease; Htt, huntingtin; MSNs, medium spiny neurons; NPY, neuropeptide Y; OPTN, optineurin; PB, phosphate buffer; PBS, phosphate-buffered saline; PV, parvalbumin; SDS-PAGE, sodium dodecyl sulfate-polyacrylamide gel electrophoresis; TSA, tyramide signal amplification.

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removed, post-fixed overnight in the same fixative at 4 °C, and stored in a 10%–30% sucrose gradient in 0.1 M PB at 4 °C for cryoprotection. Sections were cut on a cryostat at 10- or 15-μm thickness, and they were stored in PBS containing 0.05% NaN_3 until use.

Western blot assay

Brains obtained from deeply anesthetized C57BL/6 mice (Nihon SLC Co., Shizuoka, Japan; n=2), 9–10 weeks of age, were homogenized in 0.05 M Tris–HCl at pH 7.2 containing 0.025 M KCl, 0.005 M $MgCl_2$, and 0.32 M sucrose. The protein lysates (20 μg of protein) were subjected to 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), and separated proteins were then transferred onto a polyvinylidene difluoride membrane. The membranes were incubated with rabbit polyclonal antibody against OPTN (1:1000; Cayman Chemical, Ann Arbor, MI, USA) (Table 1), and were then incubated with horseradish peroxidase-conjugated anti-rabbit IgG. The bound antibodies were detected by chemiluminescence staining (ECL plus kit, GE Healthcare, Buckingham, UK).

Single-label immunohistochemistry

Immunostaining was performed on free-floating sections by using the tyramide signal amplification (TSA) method (Sako et al., 2011; Morigaki et al., 2011). Rabbit polyclonal antibody against OPTN (1:10,000; Cayman Chemical) was used as a primary antibody (Table 1). The bound primary antibodies were detected by the Histofine Simple Stain Kit (Nichirei, Tokyo, Japan) and the TSA system with Cyanine 3 (Perkin Elmer, Shelton, CT, USA).

Double-label immunohistochemistry

For double immunostaining, the striatal sections were first stained for OPTN with the TSA-Cyanine 3 system according to the previously described protocols. To remove the bound antibodies, the stained sections were incubated in 0.1 M glycine-HCl at pH 2.2 at room temperature for 30 min. After incubation with PBS for 1 h, they were labeled with rabbit polyclonal antibodies against choline acetyltransferase (ChAT) (1:20,000; Millipore, St. Louis, MO, USA), parvalbumin (PV) (1:100,000; Abcam, Cambridge, UK), neuropeptide Y (NPY) (1:20,000; Affiniti, Nottingham, UK), calretinin (CR) (1:100,000; Chemicon, Temecula, CA, USA), or dopamine and cAMP-regulated phosphoprotein of 32 kDa (DARPP-32) (1:20,000; Cell Signaling, Denver, MA, USA) (Table 1). Goat polyclonal antibody against Htt (1:20,000; Santa Cruz Biotechnology, Santa Cruz, MA, USA) was also used (Table 1). The bound antibodies were detected by the Histofine Simple Stain Kit (Nichirei, Tokyo, Japan) and the TSA system with fluorescein (Perkin Elmer, Shelton, CT, USA).

Digital imaging and densitometric analyses

Digital microscopy images were captured using an Olympus BX51 microscope (Olympus, Tokyo, Japan), imported into Adobe Photoshop CS4, and processed digitally. Cell density analyses were made at a level of the striatum in the anterior-to-posterior coordinate (AP: +0.5 to +1.0 mm) (Hof et al., 2000) for each mouse (n=5). We counted the number of cells labeled for each marker within a 0.5×0.5-mm^2 field in the striatum, according to the methods that we previously reported (Sato et al., 2008; Sako et al., 2010). Among the striatal cells strongly labeled for OPTN, the percent population of those cells co-localized with ChAT, PV, NPY, or CR was also calculated. To estimate the cytoplasmic density of OPTN labeling in the striatal neurons labeled for ChAT, PV, NPY, CR, or DARPP-32, double-immunostaining of the striatal sections with these antibodies was simultaneously performed with the same protocols. High-power photomicrographs of labeled neurons were obtained using a 100× oil-immersion objective, and they were digitally changed to the non-colored images in a gray scale. We measured the optical density of OPTN labeling within the cytoplasm of striatal neurons (n=20) doubly labeled for ChAT, PV, NPY, CR, or DARPP-32 from each mouse (n=5). The mean cytoplasmic density of OPTN labeling was then calculated in each striatal neuron subclass.

Statistical analysis

All quantitative data were expressed as means±SEM values. The Student's t-test (two-tailed, paired) was used for two group comparisons. P-values less than 0.05 were considered statistically significant.

Table 1. Antibodies used for immunohistochemistry with tyramide signal amplification (TSA) system

Antibody to	Immunogen (C) carboxy terminal (N) amino terminal	Source	Dilution
Optineurin	Synthetic peptide Amino acids: 575–591 (C)	Cayman (Ann Arbor, MI, USA) Rabbit polyclonal antibody No. 0420152-1	1:10,000
Choline acetyltransferase	Human placental enzyme	Millipore (St. Louis, MO, USA) Rabbit polyclonal antibody No. AB143	1:20,000
Parvalbumin	Purified parvalbumin	Abcam (Cambridge, UK) Rabbit polyclonal antibody No. ab11427	1:100,000
Neuropeptide Y	Synthetic porcine NPY	Affiniti (Nottingham, UK) Rabbit polyclonal antibody No. NA 1233	1:20,000
Calretinin	Recombinant rat calretinin	Chemicon (Temecula, CA, USA) Rabbit polyclonal antibody No. AB149	1:100,000
DARPP-32	Synthetic peptide for the residues around Thr34 of human DARPP-32	Cell Signaling (Denver, MA, USA) Rabbit polyclonal antibody No. 19A3	1:20,000
Huntingtin	Synthetic peptide (N)	Santa Cruz (Santa Cruz, CA, USA) Goat polyclonal antibody No. SC-8767	1:20,000

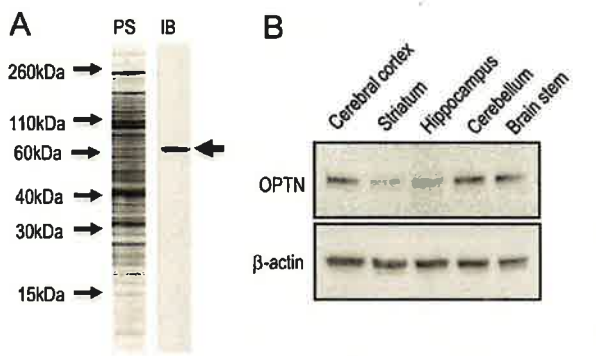

Fig. 1. Western blot analysis of OPTN expression in the brain. (A) Crude homogenates of protein (20 μg) from mouse brain were loaded onto 10% gel for SDS-PAGE and then processed for the transimmunoblot technique using an anti-OPTN antibody. Note that a protein band (arrow) with an approximate molecular mass corresponding to the predicted size (67 kDa) of OPTN native protein was selectively detected. PS, protein staining; IB, immunoblot. (B) Crude homogenates of protein (20 μg) extracted from the cerebral corex, striatum, hippocampus, cerebellum, and brain stem were processed for the Western blot. Note that the OPTN protein was expressed at the lowest levels in the striatal extract compared to the other extracts.

RESULTS

Western blot analysis with anti-OPTN antibody

To identify OPTN expression by Western blot and histological analyses, we used a polyclonal antibody against a synthetic peptide at the C-terminus of OPTN (Table 1). On the immunoblots of mouse brain extracts (Fig. 1A), a protein band with an approximate molecular mass of 67 kDa, corresponding to the predicted size of the native OPTN protein, was selectively detected. Of the brain regions examined (Fig. 1B), the extracts from the striatal region expressed relatively low levels of OPTN.

Distribution of OPTN immunoreactivity in the brain

Single-label immunohistochemistry on the sagittal brain sections revealed a wide distribution of OPTN labeling throughout the brain (Fig. 2A). However, OPTN-staining densities were differential across the brain regions, and the striatum exhibited weak OPTN labeling (Fig. 2A). The frontal sections from the anterior to the posterior of the forebrain (Fig. 2B) showed low OPTN labeling in the striatum, consistent with the pattern of immunoreactivity observed in the sagittal sections. A scattered distribution of tiny cells labeled for OPTN was also found in the striatum, which consists of the caudoputamen, accumbens, and olfactory tubercle (Fig. 2B).

Cellular localization of OPTN in the striatum

A striking pattern of localization of OPTN was found in the striatum. There was a distinct subset of striatal cells with strong OPTN labeling in their neuronal cytoplasms and processes (Fig. 2C–E). These OPTN-enriched cells comprised 9.2%±1.8% of the total number of striatal neurons examined (n=500) and were large or medium sized. High power microscopy images also showed that the vast majority of striatal neurons were poor in OPTN labeling and that all of them were medium sized (Fig. 2C–E).

Double-label immunohistochemistry indicated a cell type-specific difference in OPTN abundance in these striatal neurons (Figs. 3 and 4). All neurons positive for ChAT, a marker of the large cholinergic interneurons (Pisani et al., 2007), were also strongly labeled for OPTN (Fig. 3A, B). Like cholinergic cells, all neurons positive for NPY, a marker of the medium-sized interneurons co-containing somatostatin and neuronal nitric oxide synthase (Figueredo-Cardenas et al., 1996), exhibited strong OPTN immunoreactivity (Fig. 3C, D). Strong OPTN labeling was also found in 91% of the total number of cells positive for PV, a marker of medium and large aspiny interneurons (Cicchetti et al., 2000) (Fig. 3E, F), and in 65% of that for PV, a marker of the medium-sized interneurons in rodents (Cicchetti et al., 2000) (Fig. 3G, H). By contrast, the OPTN-rich cells were all devoid of immunoreactivity for DARPP-32, a protein phosphatase inhibitor highly expressed in striatal MSNs (Langley et al., 1997) (Fig. 4A, B). As the vast majority of striatal neurons contain Htt protein (Fusco et al., 1999), the cells enriched in OPTN were all co-labeled with Htt (Fig. 4C).

The percent population study (Fig. 5A) revealed that $ChAT^+$, PV^+, NPY^+, and CR^+ neurons comprised 35%± 8%, 22%±6%, 30%±5%, and 9%±3%, respectively, of all striatal neurons that were strongly positive for OPTN (n=100). This finding indicates that striatal cells enriched in OPTN largely consist of the interneurons. Quantitative cytoplasmic density analyses (Fig. 5B) showed that OPTN labeling was high in the striatal interneurons positive for ChAT, PV, NPY, and CR, but it was particularly low in the striatal projection neurons positive for DARPP-32.

DISCUSSION

In this study, using the TSA protocol as a highly sensitive immunohistochemical method, we examined the regional and cellular localization patterns of OPTN in the mouse brain. Our findings showed that OPTN is a cytoplasmic protein found in the neurons and that it is differentially concentrated among the brain regions. Of particular interest is that OPTN expression was found to be relatively low in the striatum, the brain region that is most affected in HD. Moreover, a cell type-specific pattern of OPTN abundance was highly apparent in the striatal neurons.

HD is a transcriptional dysregulation syndrome that shows the occurrence of polyQ repeat in the Htt protein (Vermeulen et al., 1994). These expansions interfere with RNA polymerase II-dependent gene transcription, resulting in an increased neuronal susceptibility to certain genotoxic insults (Freiman and Tjian, 2002). In HD, the most striking neuropathology so far observed is the primary and progressive degeneration of striatal neurons in a cell type-specific pattern (Ferrante et al., 1985, 1987; Kowall et al., 1987; Reiner et al., 1988; Albin et al., 1990). However, the cellular mechanisms by which mutations in the *Htt* gene contribute to the histopathology of HD remain unclear. Inconsistent with the hypothesis that in neurodegenerative disorders, selectivity of neuronal death is because of the high concentration of the affected protein in the targeted

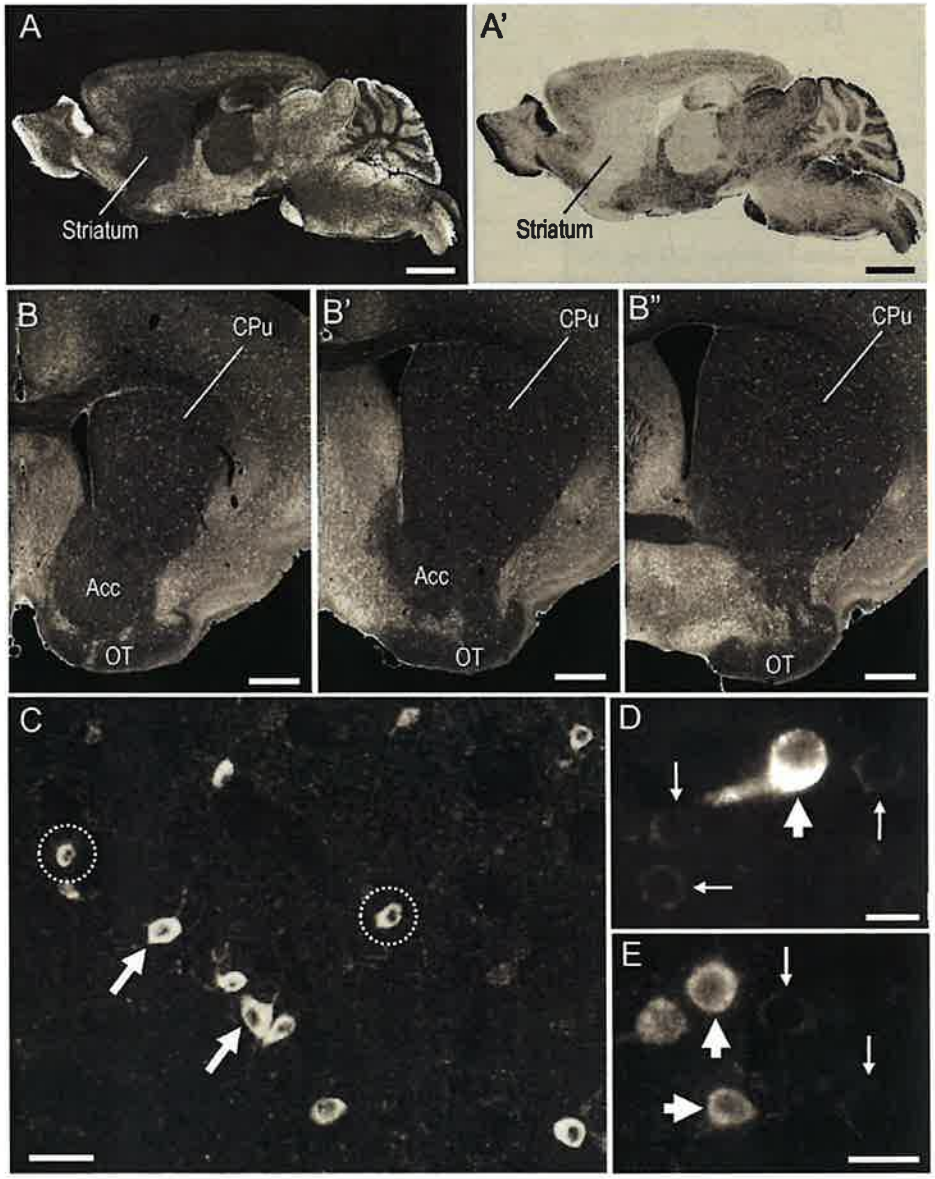

Fig. 2. Regional and cellular localization of OPTN in the brain. (A) Photomontage of a parasagittal brain section stained for OPTN. The inversed image is shown in (A'). (B) Frontal sections stained for OPTN in the anterior (B), middle (B'), and posterior (B") levels of the striatum. Note that there is a scattered distribution of tiny dots (cells) labeled for OPTN in the striatum. CPu, caudoputamen; Acc, accumbens; OT, olfactory tubercle. (C) Low-power image of a striatal section stained for OPTN. Examples of large-sized (arrows) and medium-sized (dashed open circles) cells labeled for OPTN are shown. (D, E) High-power images of the striatal areas stained for OPTN show large-sized (thick arrow in D) and medium-sized (thick arrows in E) cells that are strongly positive for OPTN. Medium-sized neurons that are weakly (or faintly) labeled for OPTN are indicated by thin arrows in (D) and (E).Scale bars: (A), 1 mm; (B), 500 μm; (C), 50 μm; (D) and (E), 20 μm.

cells (Trottier et al., 1995), both Htt protein and mRNA are widely distributed in the brain, whereas their expressions are less abundant in the striatum compared with many other brain regions (Li et al., 1993; DiFiglia et al., 1995; Sharp et al., 1995; Bhide et al., 1996; Gourfinkel-An et al., 1997). Moreover, studies of postmortem HD-affected tissue indicate that the abundance of Htt protein and mRNA in the surviving striatal neurons is not obviously altered by the mutation or the disease progression (Landwehrmeyer et al., 1995; Schilling et al., 1995; Trottier et al., 1995; Gourfinkel-An et al., 1997; Sapp et al., 1997). Although extensive studies have examined the correlation between cellular localization of Htt protein in the striatal neurons and cell type-specific loss in the HD-affected striatum (Gutekunst et al., 1995; Landwehrmeyer et al., 1995; Ferrante et al., 1997; Kosinski et al., 1997; Sapp et al., 1997; Fusco et al., 1999), their results are conflicting. In this study, we investigated whether a cellular factor that could exert protective effects against Htt neurotoxicity might contribute to HD-specific histopathology.

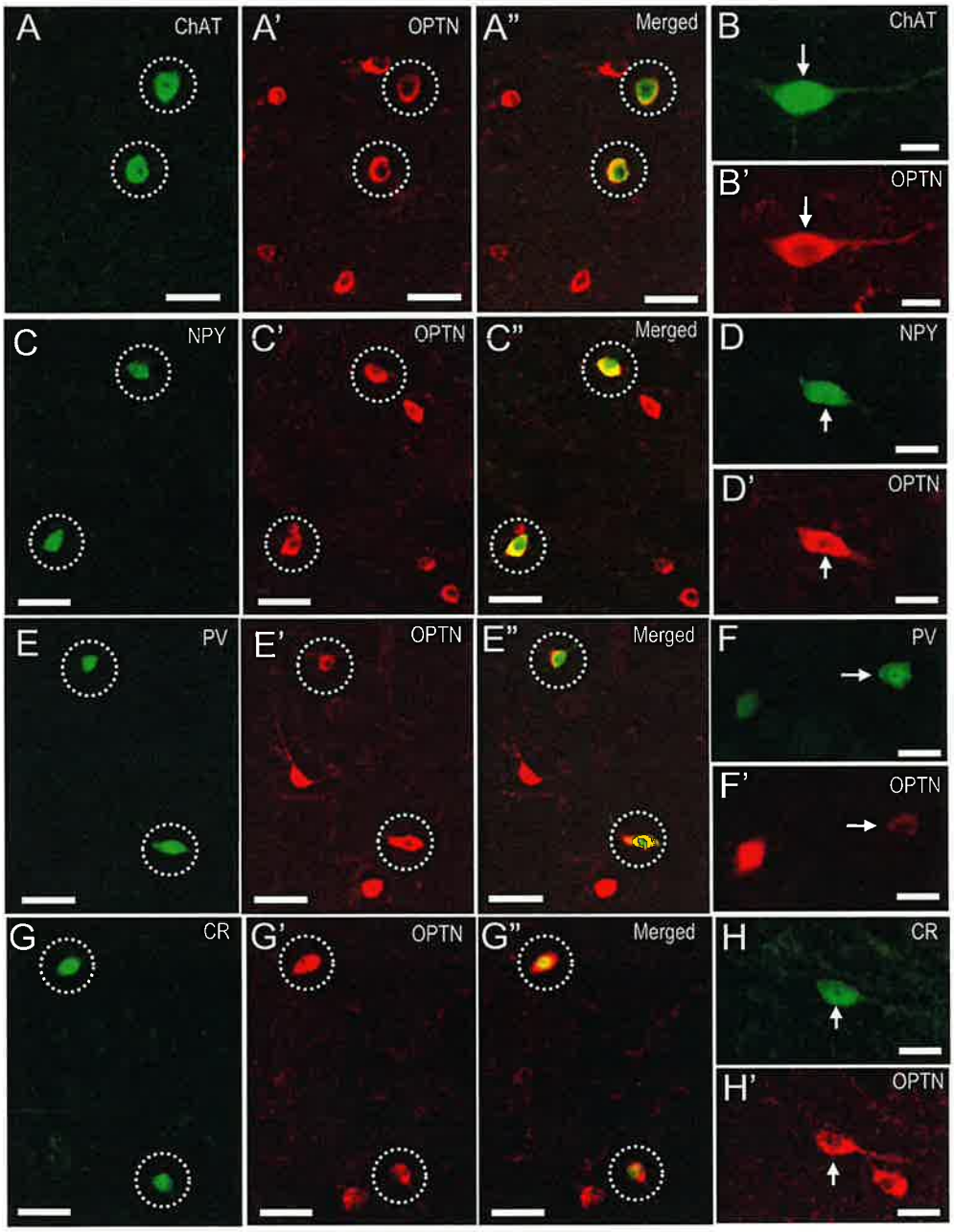

Fig. 3. Striatal interneuron subsets enriched in OPTN labeling. (A, B) Double labeling for ChAT (A) and OPTN (A'). Merged image is shown in (A"). ChAT$^+$ cells rich in OPTN are indicated by dashed open circles in (A, A', and A"). High-power images of a ChAT$^+$ cell rich in OPTN (arrows in B and B') are also shown. (C, D) Double labeling for NPY (C) and OPTN (C'). Merged image is shown in (C"). NPY$^+$ cells rich in OPTN are indicated by dashed open circles in (C, C', and C"). High-power image of an NPY$^+$ cell rich in OPTN (arrows in D and D') is also shown. (E, F) Double labeling for PV (E) and OPTN (E'). Merged image is shown in (E"). PV$^+$ cells rich in OPTN are indicated by dashed open circles in (E, E', and E"). High-power image of a PV$^+$ cell expressing only a weak OPTN labeling (arrows in F and F') is also shown.(G, H) Double labeling for CR (G) and OPTN (G'). Merged image is shown in (G"). CR$^+$ cells rich in OPTN are indicated by dashed open circles in (G, G', and G"). High-power image of a CR$^+$ cell rich in OPTN (arrows in H and H') is also shown. Scale bars: (A), (C), (E), and (G), 50 μm; (B), (D), (F), and (H), 20 μm.

Our present findings demonstrate a striking correlation between cellular distribution of OPTN and pattern of neuron loss observed in HD. Among brain regions, the striatum exhibited relatively low levels of OPTN expression, as determined by Western blotting and immunohistochemical analyses. In the striatum of HD patients, the MSNs are most vulnerable to loss, but the large- and medium-sized interneurons marked by ChAT, PV, NPY, and CR are relatively spared (Ferrante et al., 1985, 1987; Kowall et al., 1987; Reiner et al., 1988; Albin et al., 1990; Harrington and Kowall, 1991; Cicchetti et al., 2000). Using double-labeling techniques, we here showed that in mice, OPTN expres-

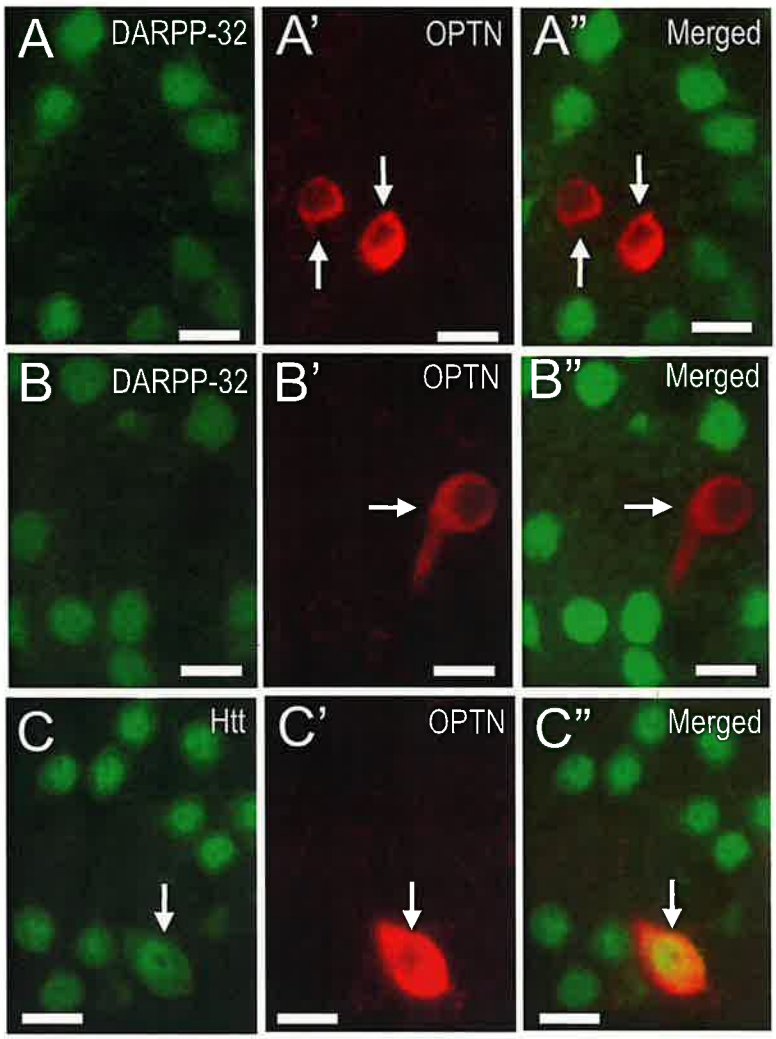

Fig. 4. Striatal medium-sized neurons poor in OPTN labeling. (A, B) Double labeling for DARPP-32 (A, B) and OPTN (A', B'). Merged images are shown in (A") and (B"). Note that medium-sized (arrows in A') and large-sized (arrow in B') cells strongly labeled for OPTN were devoid of DARPP-32 labeling. (C) Double labeling for Htt (C) and OPTN (C'). A merged image is shown in (C"). A large-sized cell rich in OPTN was co-labeled with Htt (arrows); however, the other Htt^+ cells of medium size were all poor in OPTN labeling. Scale bars: (A–C), 20 μm.

sion was poor in the striatal MSNs and was largely enriched in the striatal interneurons positive for ChAT, PV, NPY, and CR. Taken together, these findings suggest that at the regional and cellular levels, the distribution of OPTN protein shows an inverse relationship to the pattern of neuronal loss in HD. Given the potential role of OPTN in protection against neurotoxicity caused by mutations in the *Htt* gene, we suggest that in HD, the cell type-specific difference in neuronal vulnerability may depend on the differential levels of OPTN abundance in the individual neuronal subtypes and that profound loss of MSNs may be due to their paucity of OPTN protein.

CONCLUSION

In conclusion, we propose that elucidation of certain cellular factors having protective effects against harmful insults is important in identifying the pathomechanism by which patterned neuronal loss occurs in the striatum. In this study, we showed that OPTN protein is abundant in the striatal interneurons, but not in the striatal MSNs. This cell type-specific abundance of OPTN is quite complementary to the patterned cell loss observed in the HD-affected striatum. Collectively, the accumulating data suggest that OPTN could represent a common factor involved in protection against cell death in neurodegeneration. Our findings may also be applicable to the striatal pathology of other striatal disorders such as DYT3 dystonia, also named X-linked dystonia-parkinsonism (XDP/*DYT3*, MIM314250) (Goto et al., 2005), and cerebral ischemia (Chesselet et al., 1990; Uemura et al., 1990; Gubellini et al., 2004), in which the preferential loss of striatal projection neurons with relative sparing of striatal (cholinergic) interneurons has been documented. Further examination of the specific role of

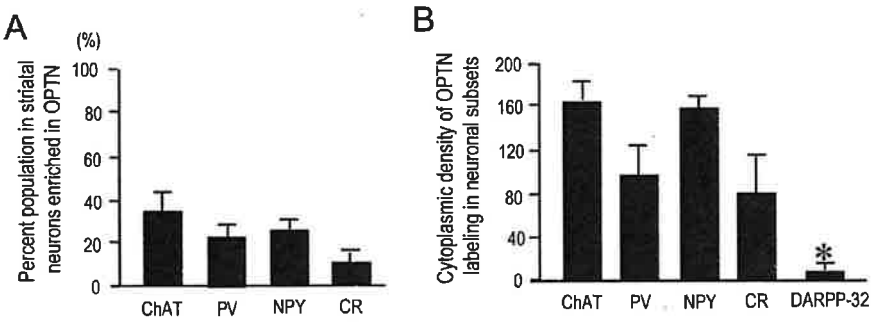

Fig. 5. Quantitative study on cellular localization of OPTN in the striatum. (A) Percent population of ChAT$^+$ cells, PV$^+$ cells, NPY$^+$ cells, and CR$^+$ cells from the total number of cells that were strongly positive for OPTN in a striatal area of 500×500 μm^2. Data are shown as mean±SEM (bars) values (n=100). (B) Measurements of cytoplasmic OPTN densities of ChAT$^+$, PV$^+$, NPY$^+$, CR$^+$, and DARPP-32$^+$ cells. Data are shown as means±SEM (bars) values (n=50). * indicates P<0.005, DARPP-32 vs. ChAT, PV, NPY, or CR.

OPTN in neuroprotection could be critical in understanding the pathomechanism that underlies the patterned loss of neurons in HD and in other striatal disorders.

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