selective and strategic use of different descending signals during different phases of pursuit motor control (e.g., low-level signals may be more effective at driving the initial acceleration).

Perhaps the most striking finding in the study is that the catch-up saccade itself, rather than just the passage of time during the trial, appears to be critical for the emergence of the association between high-level speed judgments and the precision of post-saccadic pursuit. Moreover, a control experiment presented in the supplementary material shows that when the catch-up saccade is eliminated, the association disappears. These findings are puzzling, because other experiments have found that saccades are not necessary for smooth-pursuit of high-level motion. For example, when viewing a display containing bidirectional apparent motion, subjects experience reversals in perceived motion that can be smoothly followed with reversals in pursuit eye velocity without making any saccades (Madelain and Krauzlis, 2003).

One possibility is that saccades, pursuit, and high-level position tracking are all supported by common estimates of target position. Given that the time course of these estimates would likely vary from trial to trial, the occurrence of the targeting saccade would provide a temporal marker for when the estimate had reached a critical level, and pursuit would be expected to show changes at around the same time. This explanation also predicts that the effects observed by the authors should not be restricted to pursuit but apply to the saccades themselves. For example, subjects that were more precise in their judgments of high-level motion would be expected to show greater precision in the endpoints of their saccades. Presumably, estimates of target position remain available even when saccades are not executed, but without the temporal marker provided by saccades, the effects may become too diffuse to detect.

As these results illustrate, the sensory-motor corner provides a unique window into some of the core issues in systems neuroscience. Most likely, there are other surprising findings in store.

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Autophagy Induction Rescues Toxicity Mediated by Proteasome Inhibition

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The ubiquitin-proteasome and macroautophagy-lysosome pathways are major routes for intracytosolic protein degradation. In many systems, proteasome inhibition is toxic. A *Nature* article by Pandey et al. shows that this toxicity can be modulated by altering autophagic activity. Their tantalizing results suggest that overexpression of *HDAC6* may increase flux through the autophagy pathway, thereby attenuating the toxicity resulting from proteasome inhibition.

Intracytosolic proteins can be degraded either by the ubiquitin-proteasome system or by a range of lysosome-related pathways (reviewed in Rubinsztein, 2006). The ubiquitin-proteasome pathway typically regulates levels of short-lived proteins. These are usually initially tagged for degradation by linkage of a ladder of ubiquitin molecules to lysine residues. The ubiquitin chain constitutes a recognition sequence that allows them to be transported to the proteasome, a barrel-shaped, multiprotein, proteolytic complex. The proteasome degrades the proteins into peptides, which are further degraded to amino acids by cytosolic and nuclear peptidases.

The proteasome has a narrow pore, which precludes entrance of organelles, multiprotein complexes, and

oligomers or aggregated precursors of the intracellular inclusions that characterize many neurodegenerative diseases (like polyglutamine expansion diseases, including Huntington's disease and Kennedy's disease). Such structures can be degraded by macroautophagy (which I will call autophagy). In this pathway, cells form double-layered vesicles around a portion of cytosol. These autophagosomes, which are believed to engulf cytosolic contents in a largely unselective manner, then eventually fuse with lysosomes, where their contents are degraded. In addition to this form of autophagy, there are two other autophagic pathways that can deliver substrates to the lysosome. The first, called microautophagy, involves direct sequestration of cytosolic contents via lysosomal membrane invagination or septation and has only been studied in any depth in yeast. The second pathway, called chaperone-mediated autophagy, involves recognition of certain cytosolic proteins that contain a KFERQ (or similar) pentapeptide motif by hsc70. This then interacts with the lysosomal membrane protein *LAMP2a*, allowing direct translocation across the lysosomal membrane.

Pandey and colleagues have recently shown that proteasome inhibition is toxic to *Drosophila* eyes (Pandey et al., 2007). This initial result was not unexpected—proteasome inhibition is toxic in many settings (e.g., Chen et al., 2005), as it leads to the accumulation of many key molecules that need to be tightly regulated to prevent toxicity, like p53. Furthermore, global proteasome inhibition may lead to intracellular aggregate formation (Rideout et al., 2001). The striking result that these authors reported was that the toxicity resulting from the proteasome inhibition mediated by a dominant-negative proteasome subunit was largely rescued by overexpression of *HDAC6* (and was enhanced by *HDAC6* knockdown). *HDAC6* is a member of the histone deacetylase family. Unlike many of its relatives, which have nuclear functions regulating gene expression, *HDAC6* is mainly found in the cytosol and has a range of possible functions (reviewed by Boyault et al., 2006). *HDAC6* is a microtubule- and dynein-associated protein, and microtubule- and dynein-mediated transport of autophagosomes are required for delivery to lysosomes (Rubinsztein, 2006). Kopito and colleagues previously showed that HDAC6 was required for degradation of mutant huntingtin, an autophagy substrate (Iwata et al., 2005). This raised the possibility that *HDAC6* may be acting to enhance autophagy. Indeed, induction of autophagy with rapamycin also attenuated the toxicity induced by proteasome inhibition (Pandey et al., 2007).

Pandey et al. went on to show in *Drosophila* that overexpression of the mutant polyglutamine-expanded androgen receptor (modeling Kennedy's disease) in the presence of its ligand also resulted in toxicity associated with proteasome inhibition and that this toxicity could also be attenuated by overexpression of *HDAC6* (Pandey et al., 2007). This effect of *HDAC6* overexpression was associated with enhanced turnover of the mutant androgen receptor. This effect was likely due to autophagy, confirming previous studies that have shown that autophagy induction via rapamycin enhances clearance of a range of aggregate-prone, disease-associated intracytosolic proteins in cells, *Drosophila* and mice, thereby attenuating their toxicities (Ravikumar et al., 2002, 2004; Berger et al., 2006). We previously showed that these effects were autophagy dependent in *Drosophila*, as no effects of rapamycin were observed in flies with hemizygous mutations in the autophagy gene *Atg1* (Berger et al., 2006).

The Pandey et al. (2007) study raises a number of tantalizing possibilities. The first is that there is genuine cross-talk between the ubiquitin-proteasome and autophagy-lysosome pathways, as autophagy induction rescued toxicity caused by proteasome inhibition. It is tempting to speculate that autophagy upregulation rescued toxicity mediated by proteasome impairment by simply providing another route for the clearance of the substrates that ordinarily would have been removed by the proteasome. The simplistic expectation is that the proteasome substrates that would be most toxic in the presence of proteasome inhibition would be those with the shortest half-lives—the ubiquitin-proteasome system is characterized by its selectivity and the capacity to clear certain proteins rapidly. By contrast, the autophagy-lysosome pathway typically clears long half-life proteins. Does this mean that autophagy upregulation can provide enough flux to normalize the clearance of short-half-life proteins that would otherwise accumulate rapidly when the proteasome was impaired? This would be surprising given the classical literature suggesting (at least in liver) that the clearance of short-half-life proteins is not influenced by lysosomal inhibitors or by physiological perturbations like starvation that induce autophagy (Mortimore and Poso, 1987).

While autophagy upregulation may partially compensate short-lived protein degradation in the presence of proteasomal impairment, it is possible that the predominant protective effect of autophagy upregulation may be not at the level of protein clearance, but at the level of cell death. Autophagy inhibition has been shown to sensitize cells to apoptotic insults, while autophagy induction reduces cellular susceptibility to subsequent apoptotic stimuli mediated by the mitochondrial pathway, probably because autophagy reduces the mitochondrial load by removing mitochondria (Boya et al., 2005; Ravikumar et al., 2006). Furthermore, autophagy induction protects *Drosophila* from paraquat toxicity, possibly by the same mechanism (Ravikumar et al., 2006). Pandey et al. (2007) addressed this possibility in their proteasome toxicity scenario by showing that *HDAC6* overexpression did not rescue the rough eye phenotype mediated by the *Drosophila* cell death protein *reaper*. However, it is difficult to make conclusive inferences from this experiment, as *reaper* mediates much of its toxicity in the cytosol by antagonizing inhibitor of apoptosis proteins (Kornbluth and White, 2005), and recent data do implicate a role

for mitochondrial permeabilization in *Drosophila* cell death pathways (Abdelwahid et al., 2007). So, autophagy induction may still be protecting against proteasome inhibition-mediated toxicity by removing some of the mitochondria—cells can tolerate a significant reduction in mitochondrial load before showing effects on respiration.

Another intriguing possibility suggested by the paper is that proteasome induction leads to a compensatory increase in autophagy. This was suggested by data reporting an increased number of autophagosomes in flies with proteasome inhibition. These findings are consistent with previous reports showing similar phenomena in cell culture and in *C. elegans* (Chen et al., 2005; Iwata et al., 2005). While the idea that cells may induce autophagy to protect themselves in situations where the ubiquitin-proteasome pathway is inhibited is appealing, there are again other possibilities that could be considered. Autophagosomes accumulate if there is increased autophagosome synthesis (where there is generally an increase in autophagic protein clearance), but also if there is decreased autophagosome removal due to impaired autophagosome-lysosome fusion (which would result in decreased protein clearance from a block in the autophagic pathway). It will be important in future studies to discriminate between these possibilities.

This study also suggests that *HDAC6* overexpression enhances clearance of various substrates via autophagy. It is likely that this is how *HDAC6* is working, as it enhanced the clearance of ligand-bound mutant androgen receptor. Also, its overexpression protected against toxicity mediated by proteasome inhibition. In the future, it will be important to directly test whether *HDAC6* enhances autophagic protein clearance under both normal conditions and in the presence of proteasome inhibition. It will also be interesting to know how *HDAC6* modulates autophagy and at what stage of the process.

While the results reported by Pandey et al. (2007) are intriguing, *HDAC6* overexpression/hyperactivity may not be a straightforward therapeutic target for polyglutamine diseases or for autophagy upregulation. Recently, Boyault and colleagues showed that *HDAC6* negatively regulates proteasomal turnover of ubiquitinated proteins (Boyault et al., 2006). This suggests that *HDAC6* overexpression may be beneficial if the proteasome is significantly impaired, but may slow turnover of at least a subset of proteins in normal conditions. Although Pandey et al. (2007) show that the proteasome is inhibited in *Drosophila* by ligand-bound polyglutamine-expanded androgen receptor, this phenomenon has not been observed in mouse models of a number of other polyglutamine diseases (reviewed in Rubinsztein, 2006). *HDAC6* also regulates other processes relevant to at least some polyglutamine diseases. Saudou and colleagues reported that the Huntington's disease mutant protein impairs the intracellular microtubule-dependent transport of *BDNF*-containing vesicles, resulting in decreased trophic support to neurons and increased susceptibility to cell death. In contast to the autophagy scenario, *HDAC6* inhibition appears to be beneficial in this context by increasing tubulin acetylation, thereby increasing the flux of *BDNF*-containing vesicles, with consequent greater release of this neurotrophin (Dompierre et al., 2007).

The Pandey et al. (2007) study raises a number of important questions in the context of intracellular protein degradation. First, to what extent can autophagy upregulation normalize turnover of short-lived proteins in cells with compromised proteasome function? Second, is there an increased production of autophagosomes (as opposed to decreased clearance) in cells with proteasome impairment? Third, while their data suggest that *HDAC6* accelerates clearance of autophagy substrates, what is/are the underlying mechanisms involved in this process? Finding answers to these questions may have relevance for a range of neurodegenerative diseases caused by aggregate-prone intracytosolic proteins that are autophagy substrates.

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