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Review

Selective Neuronal Vulnerability in Neurodegenerative Diseases: from Stressor Thresholds to Degeneration

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Neurodegenerative diseases selectively target subpopulations of neurons, leading to the progressive failure of defined brain systems, but the basis of such selective neuronal vulnerability has remained elusive. Here, we discuss how a stressor-threshold model of how particular neurons and circuits are selectively vulnerable to disease may underly the etiology of familial and sporadic forms of diseases such as Alzheimer's, Parkinson's, Huntington's, and ALS. According to this model, the intrinsic vulnerabilities of neuronal subpopulations to stressors and specific disease-related misfolding proteins determine neuronal morbidity. Neurodegenerative diseases then involve specific combinations of genetic predispositions and environmental stressors, triggering increasing age-related stress and proteostasis dysfunction in affected vulnerable neurons. Damage to vasculature, immune system, and local glial cells mediates environmental stress, which could drive disease at all stages.

Introduction

Neurodegenerative diseases (NDDs) such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotropic lateral sclerosis (ALS) each primarily affect defined subsets of neurons and involve characteristic ranges of pathological and molecular features. The main risk factor for NDDs is advancing age.

The accumulation of distinct protein-based macroscopic deposits is a hallmark of NDDs. Although phenotypic variations and comorbidities are frequent, the composition and distribution of the deposits is a defining property of each NDD, and some of the mutations associated with familial cases of the diseases affect folding of the major protein components of the deposits. Accordingly, NDDs are currently viewed as cerebral proteopathies, in which the accumulation of particular misfolded proteins is a key causative factor (e.g., Haass and Selkoe, 2007; Golde and Miller, 2009; Frost and Diamond, 2010). Since the misfolding proteins implicated in the etiology of NDDs are expressed ubiquitously, a major unresolved question is how deposit formation and pathology nevertheless selectively target specific subpopulations of neurons.

In addition to specific misfolding proteins, NDDs exhibit comparable patterns of proteostasis, signaling pathway, and organelle dysfunction (Wallace, 2005; Lin and Beal, 2006; Knott et al., 2008; Morimoto, 2008; Matus et al., 2011) and consistently involve pathways that regulate energy metabolism and cell repair, which have been implicated in the control of life span and aging (Hsu et al., 2003; Cui et al., 2006; Cohen and Dillin, 2008; Gan and Mucke, 2008; Cohen et al., 2009). Accordingly, selective neuronal vulnerability may involve neuron specific combinations of dysfunctions in cellular stress and proteostasis pathways, aggravated by advancing age.

This review focuses on the roles of specific neuronal vulnerabilities in the etiology of NDDs, i.e., on how intrinsic and environment-induced cellular stress and homeostasis pathways may intersect with the accumulation of misfolding proteins in particular vulnerable neurons to promote disease. More detailed treatments of each NDD, and of the key roles of local microenvironment factors such as glial dysfunction, immune system engagement, and vascular dysfunction in disease can be found in recent reviews (e.g., Zlokovic, 2005; Boillée et al., 2006b; Maragakis and Rothstein, 2006; Ballatore et al., 2007; Cepeda et al., 2007; Hawkes et al., 2007; Balch et al., 2008; Zacchigna et al., 2008; Golde and Miller, 2009; Ron-Harel and Schwartz, 2009; Glass et al., 2010).

A Stressor-Threshold Model of Selective Neuronal Vulnerability

As will be discussed below, a survey of disease mechanisms in AD, PD, HD, and ALS suggests that the neurons selectively vulnerable to NDDs are particularly sensitive to particular stressors, and subject to high physiological levels of excitation and intracellular Ca loads (e.g., Lin and Beal, 2006; Palop et al., 2006; Gleichmann and Mattson, 2010; Prahlad and Morimoto, 2009). Further sources of intrinsic stressor load relevant to disease include genetic background, preexisting conditions (e.g., diabetes), and advancing age. In addition to such predisposing factors, disease-relevant environmental stressors can include chronic consequences of physical and ischemic lesions (Vermeer et al., 2003; Blasko et al., 2004; Szczygielski et al., 2005), lesions left behind by previous infections, and chronic consequences of stress and environmental toxins. For example, repeated head trauma in football players is highly correlated with subsequent tauopathy with dementia (McKee et al., 2009).

Based on these considerations, we discuss a stressor-load model to account for how specific neuronal subpopulations contribute to the etiology of NDDs and how familial and sporadic forms of the diseases produce comparable disease

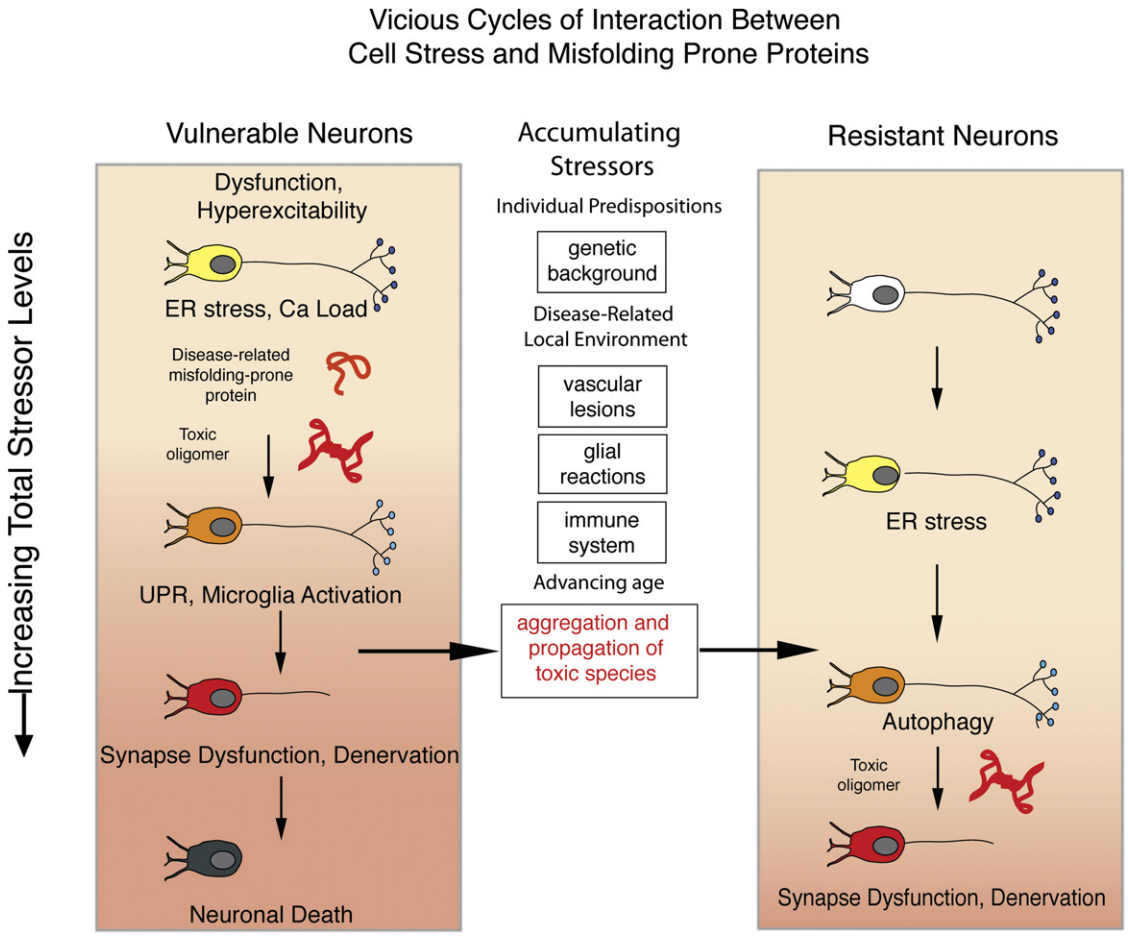

Figure 1. Schematic of How Gradually Increasing Stress in Affected and Selectively Vulnerable Neurons May Underlie the Etiology and Progression of NDDs

Specific NDDs may be defined by successive restrictions in the range of neurons affected by individual predispositions, local environmental factors, stress susceptibility, and sensitivity to misfolding-prone proteins. The connectivity and excitability properties of neuronal subpopulations may have a major role in determining their intrinsic sensitivity to stress. Intrinsic distinctions in the susceptibility of neurons to individual misfolding-prone proteins may account for similar disease patterns and pathology in sporadic and familial cases of the NDDs. Cascades of mutually reinforcing stress and proteostasis imbalance responses may escalate in an age-sensitive manner in affected, stress-sensitive, and misfolding-protein-sensitive neurons, causing their dysfunction and death. The accumulation of the toxic protein species may subsequently spread to other less vulnerable cells and increase their stressor load as well. Environmental factors may affect several brain systems through systemic involvement, e.g., involving the vasculature, inflammatory responses and the immune system, as well as spreading of toxic protein species.

manifestations and pathology. The model hypothesizes that against a background of environmental injuries related to individual ontogeny and genetic background, intrinsic stressors in vulnerable neurons and those associated with specific cellular protein, energy, and organelle homeostasis processes combine to produce vicious cycles of increasing stressor load and misfolding protein accumulation, eventually causing age-retaled degeneration in selectively vulnerable neurons (Figure 1). A tenet of the proposal is that particular misfolding-prone proteins may accumulate upon cell stress in or near the vulnerable neurons (first vulnerability), to then selectively interfere with neuronal function and cause more neuronal stress due to vulnerability to misfolding protein targets in those neurons (second vulnerability). The presence of such specific vulnerability combinations in particular neurons would thus favor proteostasis instability through vicious cycles involving cell stress and misfolding protein targets. In suggesting that stressor levels have a critical role throughout disease, the model differs from views that alterations in cellular stress pathways in neurons are just late consequences of disease.

The model implies the following:

- NDDs may be initiated by chronic perturbations acting at any of several critical components of cellular homeostasis pathways in vulnerable cells.
- Multiple stressors may converge and reinforce each other in vicious cycles to drive dysfunction and eventually degeneration in vulnerable neurons and their local microenvironment.
- Chronic disturbances that may lead to a NDD could initiate at any age, producing gradually increasing neuronal dysfunction, but suprathreshold dysfunction and progressive

degeneration would be triggered when age-related stressor tolerance fails to match the current load of disease-related stressors.
- Systemic involvement may initiate and aggravate disease, e.g., through vascular lesions, inflammation, and compromised immune responses.
- Above suprathreshold stressor levels, disease-related processes may include growing resident and systemic immune system recruitment, neuronal degeneration and death, and spreading of the pathology to less affected parts of the nervous system.

We first provide a general overview of cellular stress and homeostasis regulatory pathways and then review main features of NDDs and how they may be accounted for by a stressor-threshold model of selective neuronal vulnerabilities.

Cellular Stress and Homeostasis Pathways

All cells are endowed with homeostatic regulatory mechanisms to cope with altered physiological demands, survive periods of intense stress, adapt to milder but chronic stress, or self-destroy. Cells can experience different types of stress, including protein misfolding, high biosynthetic or secretory demands, alterations in redox balance (e.g., oxydative stress), alterations in organellar calcium, inflammatory reactions, caloric restriction, and aging (Mattson and Magnus, 2006; Lin et al., 2008; Hotamisligil, 2010; Rutkowski and Hegde, 2010; Roth and Balch, 2011). The cellular homeostasis processes that respond to cell stress include combinations of specific pathways that deal with particular stressors (Rutkowski and Hegde, 2010; Roth and Balch, 2011). Not surprisingly, these pathways are highly interconnected, leading to extensive crosstalk and comorbidities among them. Notably, however, in spite of the great variety of specific cellular homeostasis responses, the stress sensors associated with the endoplasmic reticulum (ER) membrane system seem to have central roles in orchestrating cell adaptions to altered physiological demands and in response to stressors (Bernales et al., 2006; Lin et al., 2008; Rutkowski and Hegde, 2010). Such uniquely central roles likely relate to the fact that the ER has major biosynthetic and secretory roles, is distributed throughout the internal volume of cells, and exhibits specialized interfaces with other membrane organelles such as the nucleus, mitochondria, the Golgi apparatus, lysosomes, phagosomes, and the plasma membrane, where stress signals can be exchanged. In keeping with the fact that the accumulation of misfolded proteins within its lumen is a major source of stress to the ER, triggering of the full spectrum of stress responses by the ER is designated the unfolded protein response (UPR).

From yeast to mammalian cells, the ER deals with the accumulation of misfolding proteins inside its lumen by the activation of transmembrane ER stress sensors (Bernales et al., 2006; Ron and Walter, 2007). In mammalian cells, these are IRE1, PERK, and ATF6. *IRE1* is the most conserved among the ER sensor pathways. Upon activation, IRE1 exhibits kinase and endoribonuclease activity, which leads to the nonconventional cytosolic splicing of Xbp-1 mRNA, disinhibiting translation of the corresponding transcription factor, which in turn promotes the expression of UPR genes. In addition, IRE1 activation leads to activation of the JNK and NFkB pathways. IRE1 is activated upon stress signals from the ER lumen, but also by signals not directly related to ER stress, including BAX, BAK, and ASK1-interacting protein 1. Upon activation, PERK directly phosphorylates its main substrate eIF2α (a translation factor), leading to its inactivation, inhibition of most translation, and enhanced translation of a few selected transcripts including *ATF-4*. The latter then activates transcription of UPR genes. These include the proapoptotic transcription factor *CHOP* (a.k.a. GADD153) and the major ER chaperon *BiP*. PERK further activates *Nrf2*, which acts against oxydative stress, and *NFkB*. Finally, activation of *ATF6* leads to its translocation from the ER to the Golgi, where it is cleaved to produce a fragment that translocates to the nucleus and promotes the transcription of UPR genes. In addition, ATF6 also activates the NFkB pathway. At first approximation, the activation of ER stress sensors thus leads to reduced protein synthesis, and to the transcription of UPR genes. In addition, ER stress sensors activate autophagy and inflammatory responses (Hotamisligil, 2010; Kimata and Kohno, 2011). Although ER chaperon proteins such as BiP, GRP94, Calnexin, Calretinin, and PDI are certainly involved, the precise mechanisms of how ER sensors are activated have remained poorly understood (Kimata and Kohno, 2011). Several models include a role for the relatively long-lived chaperons in preventing activation of the ER sensors by unfolded proteins. In addition to reduced translation, and in order to prevent overt activation of the UPR, the accumulation of misfolded proteins is counteracted by ER-activated protein degradation (ERAD) processes. These involve yet elusive channels to translocate misfolded proteins from the ER lumen to the cytosol, where they are degraded via polyuniquitination and the proteasome. To ensure homeostasis, ERAD is modulated by regulators such as EDEM1 and ERManI, proteins that are short lived in nonstressed cells.

Importantly, recruitment of ER stress pathways is not restricted to stressed cells (Rutkowski and Hegde, 2010). Thus, when cells initiate physiological processes that put higher demands on homeostasis systems they activate ER stress pathways to pro-actively and specifically cope with those higher demands. This is for example the case in differentiating B cells, in cells preparing to fight infections upon Toll-like receptor activation, in cells undergoing large morphologically changes (including neurons), and in professional secretory cells such as pancreatic β-cells. ER stress pathway recruitment in the basence of extra stress has been firmly established in studies that have used GFP reporters to visualize *Xbp-1* activation and that revealed physiological activation e.g., in liver or skeletal muscle (Rutkowski and Hegde, 2010). There is thus extensive potential for crosstalk and interference between cell homeostasis pathways upon stress or physiological conditions. Indeed, in addition to protein misfolding, eIF2α phosphorylation is enhanced upon hypoxia, changed nutritional status, hormonal activation, infection, or synaptic plasticity. Furthermore, ATF6 can interfere with CREB mediated transcription due to recruitment of the CREB coactivator CRTC2 upon *ATF6* activation. Given that physiological needs vary dramatically among different types of cells, overlaps between stress and physiological responses at ER stress pathways exhibit cell type specific features. The mechanisms that ensure that specific physiological demands

in particular types of cells are met by appropriate and limited activation of ER stress pathways are still poorly understood. These mechanisms appear to be specifically linked to conditions in vivo because cultured cells seem to recruit the fullblown UPR repertoire upon stressors (Rutkowski and Hegde, 2010). With respect to neurons, enhanced physiological demands likely include phases of axonal and dendritic growth, synaptogenesis, and synaptic plasticity, as well as major alterations in excitability and calcium fluxes. Accordingly, cell type-specific intersections between physiological demands, the misfolding of specific proteins, and age may assign central roles to ER stress pathways in defining selective neuronal vulnerabilities and driving progressive dysfunctions in NDDs (Matus et al., 2011).

Mechanisms that Target Neurons in NDDs

Accumulation of Misfolded Proteins

The majority of proteins comprise structured domains joined by potentially flexible linkers. By contrast, Aβ, tau, α-synuclein, and polyglutamine proteins involved in NDDs belong to the intrinsically disordered proteome, i.e., they are proteins with little stable three-dimensional structure in physiological solutions, which tend to assume stable folds upon interactions with other proteins. The corresponding misfolded species expose comparable beta sheet stretches particularly prone to protein interactions. These interactions are thought to involve regulatory protein complexes, possibly accounting for a "dominant" misregulation of multiple interconnected pathways in affected cells (e.g., Gidalevitz et al., 2006; Haass and Selkoe, 2007; Winklhofer et al., 2008; Williams and Paulson, 2008; Roth and Balch, 2011). For example, such interactions can saturate binding sites of scaffold proteins important for cell regulation or can sequester heat-shock proteins such as Hsc/p70 and Hsp40 important to maintain proteostasis and prevent disease (e.g., Roth and Balch, 2011). It seems likely that for each misfolding-prone protein certain types of neurons are more affected by how that protein disrupts cellular protein networks, and this may contribute to their selective vulnerability to a particular NDD (Figure 1). Indeed, consistent with dominant interference in subsets of neurons, genetic studies in *C. elegans* have provided evidence that disease-related human proteins such as α-synuclein preferentially form aggregates in certain worm neurons, where they enhance the vulnerability of the same neurons to misfolding-prone protein species such as constructs with subthreshold polyglutamine stretches (Brignull et al., 2006; Lim et al., 2008). Furthermore, mutant misfolding proteins associated with familial forms of NDDs can, at least to some extent, model the same diseases when expressed ubiquitously in evolutionarily distant model organisms such as zebrafish or *Drosophila* (e.g., Lessing and Bonini, 2009; Sheng et al., 2010; Xia, 2010). These studies are consistent with the notion that disease-associated misfolding proteins each interfere with cellular signaling and proteostasis networks in their own specific manners, thereby affecting preferentially particular subtypes of neurons whose properties are evolutionarily conserved.

Notably, the accumulation of misfolding proteins is often not sufficient to cause disease, and studies of human populations suggest how additional factors have to combine with the age-related accumulation of misfolding proteins for disease to develop. Thus, the same types of characteristic macroscopic deposits can accumulate in the same neurons or the same brain regions in some but not all aging brains in the absence of major disease manifestations (Jellinger, 2004; Brignull et al., 2006; Kern and Behl, 2009; but see Sperling et al., 2009; Hedden et al., 2009). Recent studies have provided intriguing insights into how deposit accumulation may relate to dysfunction in the absence or presence of disease. The studies combined amyloid and functional brain imaging and revealed that aged persons with deposits, but without noticeable AD, exhibit cognitive deficits involving cortical "default networks," i.e., cortical areas that are active even when the brain is not engaged and which may be involved in off-line processing. Comparable impairments were detected in patients with mild cognitive deficits, which frequently progress to develop full-blown AD, suggesting that the amyloid deposits may be associated with very early stages of AD (Sperling et al., 2009; Hedden et al., 2009). Such early stages may not necessarily progress to AD, and the mechanisms underlying disease conversion remain to be determined. Interestingly, however, early-onset AD patients with more rapid disease progression readily exhibit deposits paired with signs of local hypoactivity (reduced glucose utilization), whereas late-onset patients initially exhibit deposits paired with only very subtle signs of cognitive dysfunction (e.g., Rabinovici and Jagust, 2009). One possible interpretation of these findings is that neuronal responses linked to hypoactivation may synergize with deposit toxicity to precipitate disease. By extension, large fractions of the human population may develop amyloid deposits and mild cognitive impairments late in life without progressing to AD. These findings are consistent with the notion that toxic Aβ is critically important to AD but suggest that additional dysfunction processes that aggravate Aβ -dependent toxicity and promote misfolded tau accumulation are required to cause disease; the additional dysfunctions may develop more readily in the more aggressive early-onset forms of AD. Aging but only partially compromised neurons may be more resistant to the misfolded species and may more effectively neutralize toxic oligomeric species to form nontoxic macroscopic aggregates (Arrasate et al., 2004). By the same reasoning, familial cases of the diseases may augment the likelihood of disease conversion due to mutant protein versions more prone to cellular toxicity and misfolding.

A further important aspect relating misfolding proteins to particular NDDs is that several disease-associated misfolding proteins, e.g., tau, α-synuclein, and TDP-43, are implicated causally in NDDs with different pathological and clinical manifestations and affecting different parts of the nervous system. The mechanisms that underlie this striking feature of NDDs are currently not clear. However, one possibility consistent with current findings and with a stressor-threshold model of NDD etiology is that genetic predisposition and environmental factors may influence the initiation of NDDs with distinct manifestations and involving different neuronal systems (first level of specificity) and that the misfolding proteins may be critical cofactors that can promote neurodegeneration within a few specific potential neuronal settings (second level of specificity) (Figure 1).

Stress- and Age-Related Pathways

Given the critical involvement of protein misfolding processes, and the *trans*-effects involved in their toxicity, it is not surprising

that protein homeostasis and ER stress pathways are associated with NDDs. Indeed, ER stress and unfolded protein response (UPR) markers are consistently upregulated in CNS samples from patients suffering from familial or sporadic NDDs, and the same pathways are already activated at preclinical phases in animal models of the diseases (Malhotra and Kaufman, 2007; Rutkowski and Kaufman, 2007; Matus et al., 2011). Likewise, UPS and autophagy pathways have also been implicated in most NDDs (Komatsu et al., 2006; Finkbeiner et al., 2006; Morimoto, 2008). Notably, studies in genetic model organisms have provided evidence that ER stress, UPS and autophagy pathways do not just correlate with pathology and neurodegeneration, but are causally related to their progression. Thus, mice deficient in the autophagy protein Atg5 exhibited cytoplasmic inclusions and signs of neurodegeneration (Hara et al., 2006), absence of Atg7 in mice caused massive neurodegeneration and premature death (Komatsu et al., 2006), and deletion of the BH3-only protein Puma, an ER stress protein, had protective effects on motoneurons in a mouse model of ALS (Kieran et al., 2007). These findings have led to the notion that NDDs may involve cell-specific interplays between protein misfolding and cellular stress pathways (Figure 1). Because the effectiveness of the cell homeostasis pathways is known to diminish with advancing age, their involvement in NDDs ties in well with the age dependence of the neurodegenerative processes.

In further support of a close mechanistic relationship between cell homeostasis and protein misfolding pathways in NDDs, the signaling pathways that relate life span and aging to organelle and energy homeostasis powerfully influence the accumulation of misfolded proteins and the effectiveness of cell stress pathways (Gan and Mucke, 2008; Prahlad and Morimoto, 2009; Cohen et al., 2009). Groundbreaking studies in *C. elegans* have established that the effector of the Insulin/IGF1 pathway Daf16, which regulates longevity, also regulates the expression of *HSF1* (heat shock factor 1) chaperons that control protein homeostasis in response to misfolding-induced stress (Morley et al., 2002; Hsu et al., 2003). Furthermore, starvation and inhibition of the Insulin/IGF1 pathway promote autophagy pathways thought to directly promote longevity (Hsu et al., 2003). Perhaps most interestingly in the context of NDDs, inhibiting IGF1 signaling diminishes age-related proteotoxicity in mice (Cohen et al., 2009), and activation of the Insulin/IGF1 pathway promotes the accumulation of human Aβ aggregates in *C. elegans*, thus linking universal aging-related pathways with the accumulation of misfolded proteins implicated in AD in humans (Hsu et al., 2003; Prahlad and Morimoto, 2009). Along similar lines, an age-related decline in the PGC1α (peroxisome proliferator-activated receptor gamma coactivator 1-α) pathway that promotes cell plasticity, mitochondrial biogenesis, and energy production is causally related to increasing ER stress, increasing accumulation of misfolding proteins, and accelerated disease progression in animal models of NDDs (St-Pierre et al., 2006; Weydt et al., 2006; Cui et al., 2006).

Taken together, these findings delineate a rich set of interconnected signaling pathways potentially linking advancing age, impaired protein homeostasis, ER stress, and mitochondrial dysfunction to the accumulation of particular misfolded proteins and neurodegeneration. Since these pathways have all been related through genetic studies to neurodegeneration in animal models, dissecting the actual sequences of causal events that promote the initiation and progression of neurodegenerative processes in any specific NDD is critically important to elucidate mechanisms of disease.

Dissection of Disease Processes In Vivo

Earliest DiseaseRelevant Processes in FALS Mice

To investigate causal relationships in NDD models, it is useful to determine which are the earliest disease-related processes and whether their progression can be linked to the onset of clinical symptoms. This logic has been pursued extensively in mouse models of ALS, where the ages at which dysfunctions become detectable and the rates at which they progress can be predicted within 2–4 days. That allows a near to longitudinal approach to investigating disease mechanisms, which is of great help to elucidate issues of causality.

In transgenic mutant *SOD1* mice, point mutants of human SOD1 responsible for familial ALS (FALS) are overexpressed using human minigenes (Gurney et al., 1994; Wong et al., 1995). Although the transgene is expressed at comparable levels throughout the CNS, mice develop motoneuron disease with features closely comparable to late-onset ALS in humans. In one line of transgenic mice (G93A-fast), mice exhibit first clinical signs of muscle weakness at postnatal day (P) 80–90, and die at P135 (Gurney et al., 1994). A second line of mice overexpressing the same G93A mutant, but at lower levels (G93A-slow) exhibit clinical signs of weakness at P170–200 and die at P250–270, whereas transgenic mice overexpressing yet lower levels of the same mutant do not get motoneuron disease (Boillée et al., 2006b). Therefore, mice can cope with some levels of the mutant protein without developing disease, and varying the levels of the same misfolding-prone species is sufficient to determine the onset time of motoneuron disease.

Spinal cord preparations from early postnatal mutant *SOD1* transgenic mice exhibit a persistent pronounced hyperexcitability of motoneurons and a transient deficit to produce alternating ventral root activity (Bories et al., 2007). Hyperexcitability was also found in several types of neurons in neonatal mutant *SOD1* transgenics and in dissociated motoneuron cultures from transgenic embryos (Bories et al., 2007; van Zundert et al., 2008). To date, these findings document the earliest known deficits in these ALS mice, suggesting that imbalances in the excitation of motoneurons are very early abnormalities in a disease background. Hyperexcitability of upper and lower motoneurons figures prominently in sporadic and familial cases of ALS, suggesting that it may be a major feature of motoneuron dysfunction in ALS (e.g., Vucic et al., 2008). Enhanced excitability has also been related to susceptibility to disease in HD (Zeron et al., 2002; Garcia et al., 2007), PD (Chan et al., 2007), and AD (Palop et al., 2007; Busche et al., 2008) models, suggesting that it may be a major and currently understudied factor influencing the development of NDDs.

Systematic studies of hindlimb muscle innervation in mutant *SOD1* mice have revealed how the muscle fibers innervated by the most phasic functional subtypes of motoneurons (fast-fatiguable [FF] motoneurons) all become abruptly denervated

long before clinical symptoms (P48–50 in G93A-fast mice) (Frey et al., 2000; Pun et al., 2006). The other subtype of phasic motoneurons (fast fatigue-resistant (FR) motoneurons) disconnect from their muscle fibers in late presymptomatic mice (P80–90 in G93A-fast mice), and tonic motoneurons (slow [S] motoneurons) only disconnect around endstage (Pun et al., 2006). Notably, mutant SOD1 mouse strains developing clinical signs and death later in life exhibit the same temporal patterns of selective denervations, except for a corresponding shift in the time of the early FF denervations (Pun et al., 2006). A detailed longitudinal investigation of the transcriptome of these motoneuron subtypes in mutant *SOD1* mice revealed that the most vulnerable FF motoneurons exhibit signs of ER stress and upregulate ER chaperons already at the end of the third postnatal week, when no signs of glial or vascular alterations have yet been reported in these mice (Saxena et al., 2009). Depending on the particular mutant *SOD1* strain and mutant protein levels, signs of compensated ER stress augment at different rates, to reach a comparable level 20 days before FF denervation, when a UPR is initiated in these motoneurons. This is also the time when first signs of microglial activation were detected in these mice. Lesions to the vasculature were also detected early on in the FALS mice (Zhong et al., 2008). Interestingly, FR motoneurons only exhibit increasing ER chaperons levels around this transition time, and then go on to develop a UPR 20–30 days before disconnection of their peripheral synapses to muscle (Saxena et al., 2009).

Peripheral nerve crush experiments in wild-type and mutant mice established that FF motoneurons are selectively vulnerable to ER stress, suggesting that their selective vulnerability in ALS may reflect an intrinsic vulnerability of these highly phasic motoneurons to stressors (David et al., 2007; Saxena et al., 2009). Interestingly, a premature crush-induced UPR in vulnerable motoneurons of mutant SOD1 mice subsided upon sucessful regeneration, suggesting that when they are induced at a premature age elevated stressor levels in motoneurons do not accelerate disease (Saxena et al., 2009).

The combined findings from longitudinal studies in FALS mice suggest a model whereby sustained and growing ER stress in vulnerable neurons has a role in increasing net stressor levels, thus promoting disease progression from its earliest stages (Figure 1). This might imply the existence of at least two disease-related processes in these FALS mice: first, the presence of mutant SOD1 in neurons and nonneuronal cells may produce an age-related increase in stressor levels (e.g., an imbalance in protein networks and/or in synaptic functions) in motoneurons and possibly further vulnerable cells in the mutant mice; second, in the most stress-sensitive motoneurons this produces an increasing ER stress load, which eventually augments disease-related vicious cycles that promote disease progression. In sporadic cases of ALS, instead of being provided by mutant protein overexpression, the increased stressor levels may for example involve lesions leading to hyperexcitation of motoneurons, followed by comparable mechanisms of disease progression related to ER stress. Surprisingly, in spite of the very early ER stress processes within vulnerable motoneurons in the FALS mice, overexpression of mutant *SOD1* only in neurons did not cause signs of disease in transgenic mice (e.g., Lino et al., 2002; Clement et al., 2003). These results suggest the existence of yet unidentified additional effects of mutant *SOD1* on nonneuronal cells that must have an early impact on spinal motoneurons before the onset of known disease-related pathology.

Transitions and Accelerated Disease Progression

Although most NDDs manifest in middle or old age, they can progress rapidly from the first appearance of clinical signs. Cases with a familial component often manifest several years earlier and progress more rapidly than the sporadic cases. In addition, early-onset sporadic cases tend to progress more rapidly than the late-onset ones. Furthermore, and perhaps not unlike cancer, there may be early lesions in NDDs that can, but not necessarily do progress to full-blown disease. Consistent with this notion, in individuals carrying the *Epo-E4* allele amyloid pathology was detected decades before the expected clinical onset of AD, and with frequencies of >40% in individuals aged 50 to 59 years, i.e., substantially higher than the expected frequencies to develop AD (Kok et al., 2009). One way to account for these observations would be to hypothesize that there may be distinct transitions during the course of NDDs, possibly reflecting the existence of ''disease onset times,'' which would be followed by disease progression. More aggressive prodromal forms, including all the familial forms, may have a higher conversion rate to disease onset and progression. However, although the concept has appealing features, and may be important to understand and treat these diseases, the nature and indeed existence of such qualitative transitions in the disease process are poorly understood.

One line of evidence supporting the notion of disease transitions involves the studies in mutant *SOD1* models of ALS, where an abrupt transition to a UPR in FF motoneurons coincides in time with the local activation of CD11-positive microglia, and with signs of increasing ER stress in less vulnerable FR motoneurons (Saxena et al., 2009). A plausible scenario may be that the resident activated microglia (and/or additional local cell types) may eventually have a role in promoting disease accentuation and spreading. Such a possibility would be consistent with results implicating mutant microglia in disease progression in the ALS mice (Clement et al., 2003; Boillée et al., 2006a; Lobsiger and Cleveland, 2007; Harraz et al., 2008; Gowing et al., 2009; Appel et al., 2010). Microglia have also been implicated in presymptomatic HD (Björkqvist et al., 2008), PD (Tansey et al., 2007), AD (Simard et al., 2006; Bolmont et al., 2007; but see also Grathwohl et al., 2009), and tauopathies (Yoshiyama et al., 2007). Disease-related vasculature lesions (Zlokovic, 2005; Vermeer et al., 2003; Bell et al., 2009; Zhong et al., 2008) may also worsen at this time. Furthermore, the onset of a UPR in vivo has been generally linked to the initiation of inflammatory processes (Zhang and Kaufman, 2008). Although resident inflammatory cells are thought to have beneficial effects as a first line of defense in diseases of the nervous system (Ron-Harel and Schwartz, 2009; Appel et al., 2010; Björkqvist et al., 2009), inflammatory cell recruitment in a NDD background may have immediate adverse effects in promoting disease progression (e.g., Kang and Rivest, 2007; Zhao et al., 2010; Glass et al., 2010). In an example for beneficial effects, FALS mice with bone marrow cells lacking the myeloid differentiation factor *Myd88* and thus reduced inflammatory response exhibited

earlier disease onset and death (Kang and Rivest, 2007). Likewise, functional circulating monocytes can delay the onset of cognitive deficits and Aβ accumulation in AD model mice (Naert and Rivest, 2011). However, initially restorative processes may evolve into adverse ones either due to chronic inflammation paired to reduced systemic immune involvement or due to accelerated spreading of the disease through vascular routes (Ron-Harel and Schwartz, 2009). Taken together, the evidence from NDDs patients and from NDD models suggests that a pathological involvement of the local environment in the CNS, e.g., through inflammation or vascular lesions, may be an important mechanism through which prodromal lesions in vulnerable neurons may convert to full-blown NDD.

Spreading of Misfolded Proteins

NDDs can involve local initiation processes followed by spreading to yet unaffected parts of the nervous system. This can involve inflammation, the immune system, and the vasculature, but also spreading of the misfolded proteins themselves (e.g., Mackic et al., 2002; Decarli, 2004; Cole and Vassar, 2009). For example, recent studies have provided dramatic evidence for spreading of extracellular misfolded Aβ species, suggesting that AD may involve the seed-like dissemination of toxic protein species through the vasculature and/or neuronal processes (Mackic et al., 2002; Meyer-Luehmann et al., 2003; Meyer-Luehmann et al., 2006; Bolmont et al., 2007; Meyer-Luehmann et al., 2008; Eisele et al., 2010). Spreading has also been reported for misfolded tau in vitro (Frost et al., 2009) and in vivo (Clavaguera et al., 2009), for misfolding mutant SOD1 (Urushitani et al., 2008), and for Lewy bodies and misfolding α-synuclein (Brundin et al., 2008; Lee et al., 2005; Desplats et al., 2009).

In addition to spreading through extracellular space and systemically, NDDs can spread through axonal projections, leading to specific patterns of dissemination through interconnected systems. For example, prions and some amyloid species can spread through axons, whereas other amyloid species target the vasculature (Aguzzi and Calella, 2009; Frost and Diamond, 2010). Furthermore, synuclein-based deposits have been suggested to accumulate according to a complex pattern, involving intestinal, olfactory, and medullar circuits before targeting midbrain nigral neurons, and this could in principle involve an axonal spreading mechanism (Hawkes et al., 2007).

With respect to stressor-threshold models of disease, the likely implication of systemic factors and spreading mechanisms in the progression of NDDs may provide a key mechanistic element to account for the fact that most NDDs gradually spread across brain systems and that familial and sporadic forms of NDDs manifest with closely comparable progressions of dysfunctions and pathology. Disease-promoting reciprocal interactions between pathological processes in selectively vulnerable neurons and in the microenvironment in the CNS may provide a basis for the establishment and spreading of degenerative processes to non-affected parts of the nervous system and to less vulnerable neurons in the absence of disease-causing mutations (Figure 1).

Selective Vulnerabilities of Affected Neurons in NDDs

We finally discuss the evidence that the neurons most affected by a particular NDD are selectively vulnerable to specific stressors, which may influence the accumulation of disease-associated misfolding proteins, thus underlying the onset and progression of that disease.

Parkinson's Disease

Dopaminergic (DA) substantia nigra pars compacta (SNc) neurons, whose dysfunction and loss account for the major clinical manifestations of PD, appear to be particularly vulnerable to mitochondrial dysfunction (e.g., Biskup and Moore, 2006). This has prompted investigations trying to relate aging, mitochondrial respiratory chain dysfunction, and ROS levels to PD. Sporadic PD patients were found to exhibit specific complex 1 deficits in SNc DA neurons (Gu et al., 1997), and rats treated subcutaneously with the mitochondrial complex 1 inhibitor Rotenone exhibited enhanced reactive oxygen species levels in the SNc (Keeney et al., 2006), as well as signs of parkinsonism, with loss of DA SNc neurons, and accumulation of Lewy bodies, the protein deposits characteristic of PD (Sherer et al., 2003). This is in principle an important result as it suggests that enhancing mitochondrial stress systemically not only selectively affects DA SNc neurons but also leads to the accumulation of disease-related deposits. However, defining the actual causal relationships involving mitochondria and relevant to disease turned out to be more challenging. Thus, experiments directly testing mitochondrial function in hybrid cell lines provided evidence against a direct role for complex 1 dysfunction in PD (Choi et al., 2008; Fukui and Moraes, 2008). Further investigations suggested that disease-related mitochondrial dysfunction may involve disruptions in mitochondrial dynamics processes (Vives-Bauza et al., 2010; for similar conclusions on mitochondrial dysfunction in AD, see Cho et al., 2009; for a critical review, see Fukui and Moraes, 2008). The upshot of these studies is that elevated ROS levels and mitochondrial dysfunction in DA SNc neurons are clearly associated with PD. Mitochondrial vulnerability might be a first hit target, predisposing DA SNc neurons for vulnerability to PD, but the mitochondrial respiratory chain dysfunctions may be an aggravating consequence rather than a cause of disease.

Further supporting the notion that a selective vulnerability of DA SNc neurons to PD is linked to mitochondrial dysfunction, genes whose mutations are causally related to PD code for proteins that either accumulate at mitochondria (*Pink1*, *DJ-1*, *Htra2*, *LRRK2*), are implicated in mitochondrial functionality (Parkin), or influence each other's role in disease (*Parkin* and *α-synuclein*, *Parkin* and *Pink1*; e.g., Bogaerts et al., 2008; Banerjee et al., 2009). However, like for the pharmacological evidence, it is not clear whether the genes cause PD by specifically impairing mitochondrial functions. For example, studies of α-synuclein function have provided evidence that this protein has a critical role as a chaperone for SNARE assembly, and in regulating synaptic vesicle cycling (e.g., Nemani et al., 2010; Burré et al., 2010). The mechanistic relationship between *α-synuclein* mutations and PD may thus involve synaptic transmission and excitability. Likewise, DJ-1 has a role as oxidative stress sensor, and Parkin also has a role in stress protection (e.g., Banerjee et al., 2009; Guzman et al., 2010), suggesting that the relationship between these genes and PD may involve cellular stress pathways. The etiology of PD may thus involve overburdening of stress pathways involving mitochondria, which are particularly sensitive in DA SNc neurons.

How might DA SNc neurons be more vulnerable to mitochondrial dysfunction than other neurons? Studies addressing the excitability properties of PD-vulnerable neurons have provided exciting evidence as to how this vulnerability may come about. The studies show that adult DA SNc neurons are Ca-dependent pacemakers whose intrinsic activity is driven by Cav1.3 low voltage-dependent L-type Ca-channels (Chan et al., 2007). These particular channels open at relatively hyperpolarized membrane potentials, leading to high Ca flux loads in DA SNc neurons. Notably, reducing Ca load with L-type Ca channel antagonists reduced the susceptibility of the SNc neurons to parkinsonism-inducing drugs (Chan et al., 2007). A recent study provided evidence that the pacemaking produces oxydative stress selectively in SNc dopaminergic neurons (Guzman et al., 2010). The oxydative stress is compensated by partial uncoupling of mitochondria, which is impaired in the absence of DJ-1 (Guzman et al., 2010). Consistent with the notion that Ca overload has an important role in disease, a mtDNA polymorphism that compromises the ability of mitochondria to accumulate Ca is a risk factor in PD (Autere et al., 2004). Furthermore, and consistent with a critical role of Ca influx in the etiology of PD, a recent study provided evidence that L-DOPA-induced Ca influx through dihydropyridine-sensitive Ca channels led to enhanced cytosolic levels of dopamine in DA SNc neurons, which causes α-synuclein-dependent death of these neurons (Mosharov et al., 2009). In addition to mitochondria, ER compartments also have a major role in regulating Ca fluxes and sequestering Ca from the cytosol, providing for extensive potential crosstalk between Ca overload, mitochondrial dysfunction and ER stress in PD (e.g., Sulzer, 2007). Oxydative stress related to pacemaking and mitochondrial Ca load may thus be a causal factor in PD, specifically in DA SNc neurons.

Alzheimer's Disease

The neurons at higher risk in AD, including entorhinal cortex and hippocampal CA1 projection neurons are particularly vulnerable to decreased glucose and oxygen delivery through the vasculature and thus to energy deprivation (Hof and Morrison, 2004). Indeed, in early-onset cases, mild cognitive deficit conditions, which frequently progress to AD, correlate with reduced glucose utilization in the brain (Reiman et al., 2004; Mosconi et al., 2008; Rabinovici and Jagust, 2009). In addition, synaptic transmission, ER stress, and Ca homeostasis have been implicated as major targets of disease in AD (Bezprozvanny and Mattson, 2008; Dreses-Werringloer et al., 2008).

How may energy deprivation specifically relate to the molecular processes that have been causally associated to AD? Energy deprivation is a stress factor that can induce Pi-eIF2α, which in turn produces elevated levels of *BACE1* translation, the beta-secretase whose levels are enhanced in AD and in animal models of aging, and which is necessary to generate Aβ (Yang et al., 2003; Lammich et al., 2004; Velliquette et al., 2005; O'Connor et al., 2008; Vassar et al., 2009). Along similar lines, neuronal BACE1 levels are elevated by several cellular stress pathways, and by inflammation, again relating cellular stress to Aβ production. In turn, several studies have provided compelling experimental evidence that extracellular Aβ is toxic to synapses (e.g., Selkoe, 2008). Furthermore, Alzheimer precursor protein (APP) processing leading to Aβ production can also lead to the production of an extracellular amino-terminal fragment of APP, which can induce axon degeneration upon growth factor deprivation by activating the death receptor DR6 (Nikolaev et al., 2009). In possibly related findings, neurons exposed to Aβ exhibit enhanced cytosolic Ca levels and enhanced vulnerability to excitotoxicity (e.g., Meyer-Luehmann et al., 2008), and mouse models of AD exhibit enhanced excitability in cortex and hippocampus (Palop et al., 2006). The pathways leading to full-blown AD may thus involve hyperexcitation and Ca overload. Further relating AD to cellular Ca loads, AD-related mutations in presenilin (the gamma-secretase that produces Aβ) enhance Ca release from the ER, which can lead to higher Aβ processing (Tu et al., 2006; Cheung et al., 2008). In addition, BACE1 regulates Nav ion channel levels, a major factor in neuronal excitability (Kim et al., 2007). Finally, further relating cell stress to AD, the stress-related second messenger ceramide can promote Cdk5-mediated phosphorylation of tau, which promotes clustering of mitochondria with the ER, enhancing mitochondrial uptake of Ca (Darios et al., 2005; Wen et al., 2008). Taken together, these observations delineate possible disease pathways relating energy deficits and neuronal stress to enhanced BACE1 and Aβ, and on to synapse loss, network dysregulation, hyperexcitability, further neuronal stress, and the accumulation of tau-based tangles in the neurons most vulnerable to AD.

Huntington's Disease

With respect to corticostriatal involvement in HD, one selective vulnerability appears to involve the connectivity properties of striatial medium-sized spiny neurons, which again express Cav1.3 channels, and whose excitation is controlled by a combination of glutamatergic inputs from neocortex and dopaminergic inputs from SNc (Bamford et al., 2004; Cepeda et al., 2007). The cortical projections exhibit early hyperexcitation in HD, apparently leading to a toxic convergence of glutamate and dopamine signals onto the medium-sized spiny neurons, further enhancing their vulnerability to mutant Huntingtin (Surmeier et al., 2007). This scenario highlights the potential importance of non-cell-autonomous and circuit-based mechanisms to account for selective vulnerability in NDDs (for a conceptually related study in *C. elegans*, see Garcia et al., 2007). Mutant Huntingtin may have similar disrupting effects on several types of neurons and nonneuronal cells, e.g., by selectively interfering with the expression of important genes such as *BDNF* (Zuccato et al., 2001) and *PGC1α* (Chaturvedi et al., 2009). Reduced BDNF may impair adaptive plasticity, whereas a deficit in inducing PGC1α expression upon stress load compromises cellular adaptation to stress protection and to enhanced mitochondrial demand. Indeed, PGC1α levels are selectively reduced in striatal medium spiny neurons, and energy deficits are a prominent and early manifestation of disease in HD. The combination of these dysregulations in afferent and target neurons may aggravate excitotoxicity selectively in striatal medium-sized spiny neurons.

Amyotropic Lateral Sclerosis

Specific combinations of high intrinsic neuronal vulnerabilities to stress, and stress-generating connectivity properties also seem to account for the selective vulnerability of motoneurons in ALS. Thus, spinal motoneurons vulnerable to ALS are particularly prone to hyperexcitation due to their low expression of $GABA_A$

and glycine receptors (Lorenzo et al., 2006) and differ from motoneurons consistently not affected by this disease (e.g., oculomotor neurons) by their very low levels of cytosolic Ca buffering proteins, and their adaptation for rapid Ca signaling in order to produce high-frequency spiking (Siklós et al., 1998; Vanselow and Keller, 2000; von Lewinski and Keller, 2005). In addition, motoneurons depend on neuromodulatory activity acting via the activation of low voltage-gated ion channels such as Cav1.3, further enhancing Ca loads in order to produce spiking activity. The absence of intracellular Ca buffers renders these neurons particularly dependent on mitochondria for regulating cytosolic Ca transients, which predisposes them for excitotoxic vulnerability upon mitochondrial impairments (Rothstein, 1995–1996; Verkhratsky, 2005; von Lewinski and Keller, 2005; Browne et al., 2006; Spät et al., 2008; Teuling et al., 2007; Atkin et al., 2008; Urushitani et al., 2008). Taken together, motoneurons affected in ALS are particularly prone to excitotoxicity, cellular damage due to Ca overload, and cell stress.

Consistent with a role for these selective vulnerabilities in ALS, elevated persistent inward currents were detected early in corticospinal and in spinal motoneurons in ALS models and in aging motoneurons, supporting the notion that these are involved in the disease process (Kuo et al., 2005). Mutant *SOD1* specifically associates with motoneuron ER and mitochondria and interferes with their function in ALS; accordingly, ER stress and mitochondrial pathology have been detected early in ALS model mice (Kong and Xu, 1998; Liu et al., 2004; Pasinelli et al., 2004; Ferri et al., 2006; Vande Velde et al., 2008). Furthermore, VAPB has a role in the ER stress response, and *VAPB* mutations associated with familial ALS predispose to ER stress (Teuling et al., 2007; Kanekura et al., 2009). Cell stress pathways may also account for how mutations in the RNA-binding proteins TDP-43, FUS and VCP lead to sporadic and familial ALS (Sreedharan et al., 2008; Kwiatkowski et al., 2009; Gitcho et al., 2009; Johnson et al., 2010). Thus, the three proteins interact functionally, and VCP is involved in ubiquitin-dependent protein degradation and cell stress. In sum, mutations associated with familial ALS appear to enhance the sensitivity of motoneurons to stressors, supporting the notion that cellular stress has an important role in the etiology of ALS. Interestingly, the most vulnerable, highly phasic, motoneurons exhibit lowest membrane excitability properties, thus rendering them particularly inefficient to produce spiking activity under a regime of reduced synaptic and/or mitochondrial function (Siklós et al., 1998). This may account for compensatory hyperexcitability, which in a disease setting is particularly prominent in these motoneurons, setting them up for greater cytosolic Ca overloads upon recruitment, and thus enhanced vulnerability to stressors.

Summary

Although generalizations should be considered with caution at this point, selective neuronal vulnerability in PD, AD, HD, and ALS seems to share two main features. First, selectively vulnerable neurons exhibit unusual excitability properties coupled to high calcium fluxes under physiological conditions, and exhibit hyperexcitability in disease. Second, several of the genes that have been linked to familial forms of the diseases have roles in stress regulatory pathways and/or in the regulation of synaptic function and transmitter release. Considering how the regulation of synaptic plasticity and excitability in neurons may interface with ER stress pathways, these early indications suggest that NDDs may involve competitive crosstalk between pathways that maintain synaptic functions, excitability, and energy balance, and those that counteract protein misfolding in aging neurons.

Outlook

The current evidence regarding the neurons most affected in NDDs suggests that disturbances leading to persistent shifts in excitation may represent a major class of first hits along a path to neurodegeneration. In combination with chronic inflammation and/or vascular lesions, this may raise stressor levels in and around vulnerable neurons. This, in turn, may augment the levels of disease-related misfolded proteins, and at the same time impair pathways important to maintain proteostasis balances in vulnerable neurons. Vicious cycles between neuronal stressors and disease-related misfolding-prone proteins may then drive age-related dysfunction in vulnerable neurons. Elucidating how individual disease-related misfolding proteins are associated with particular NDDs will require further studies, but the current evidence is consistent with the existence of specific mechanistic associations between subsets of stressors, subsets of misfolding-prone proteins, and subsets of vulnerable neurons (Figure 1).

A stressor-threshold model of selective neuronal vulnerability and of the role of neuronal vulnerability in disease is consistent with a large body of observations in patients and in animal models. However, important causality issues remain to be addressed. These include the roles of increasing ER stress in triggering disease, the role of alterations in neuronal excitability in disease, whether and to what extent alterations in neuronal excitability influence ER stress, and the role of misfolding protein acumulation in triggering disease. Furthermore, disease process scenarios in which processes in selectively vulnerable neurons are mainly considered as consequences rather than causes in the etiology of disease have also been discussed. Ultimately, testing the role of selective neuronal vulnerabilities for the etiology of NDDs will require cell specific and conditional models of these diseases, possibly in combination with environmental factors that may be needed to trigger disease.

Critical issues to address in future experiments include the following:

- Selective vulnerability and neuronal excitability: do specific connectivity and excitability properties of neuronal subpopulations have a key role in their selective vulnerability to NDDs?
- Misfolding proteins and selective vulnerability: are subpopulations of neurons affected in disease particularly sensitive to the toxicity of relevant misfolding proteins, and what are the underlying mechanisms; does this sensitivity lead to vicious cycles of increasing stressor load and increasing misfolding protein accumulation in the vulnerable neurons?
- Misfolding protein accumulation in sporadic forms of the diseases: do environmental stressors targeting vulnerable neurons lead to the accumulation of disease-related misfolding proteins in those neurons?

- Implications for sporadic forms of NDDs: the model predicts that it should be possible to produce animal models of the sporadic forms of the diseases, e.g., through combinations of environmental stressors and sensitizing genetic backgrounds.
- Conversion to degenerative disease: what factors determine whether mild dysfunctions associated with disease-related deposits progress to neurodegeneration, and are cell specific stressor-load thresholds critically involved; does conversion depend on disease-related processes in the local CNS environment?
- Role of vascular lesions, inflammation, and immune system involvement: are systemic factors necessary, and may they even be sufficient to cause disease?

A stressor-threshold model of NDDs has potential implications for therapeutic strategies. Since advancing age gradually increases stressor load as long as underlying causes are present, strategies targeting cellular stressor pathways should aim at processes that are critical to drive vicious circles of increasing cellular stress and misfolding protein acumulation. Such critically important stressors may be identified through modifier screens in genetic model organisms and patient-derived stem cells, as well as through sequencing strategies in selected groups of patients. Potential targets may include specific regulators of neuronal excitability, and reagents to reduce the accumulation of specific misfolding species, such as chaperon-like molecules or specific antibodies. Key disease-relevant processes may differ among NDDs, and possibly also among NDD subtypes, suggesting that it may be important to establish and apply sensitive biomarkers of disease subtypes.

Should conversion processes indeed be critical to progress from prodromic dysfunction to advancing degeneration, then these would be potentially valuable targets for treatments, as they may prevent, and possibly even reverse conversion to disease. Candidate targets may involve local interactions within the neuronal environment in the CNS, e.g., inflammatory processes and/or vascular lesions.

Finally, at least in sporadic forms of the diseases, effective treatments may target disease spreading, thereby restricting degeneration to CNS regions initially affected by disease. Again, potential targets include vascular integrity, inflammation, and the immune system, and interventions aimed at reducing extracellular misfolding protein levels, e.g., through specific antibodies.

An evaluation of the potential value of such treatment strategies in well characterized animal models of NDDs should at the same time represent a valuable strategy to test and revise postulated causality relations in these diseases, which, in turn, should lead to further improvement of candidate treatment strategies. It seems reasonable to hope that such an iterative testing process in improved disease models will provide a rational path to develop treatments that will at last show efficacy in the clinics.

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