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Akt as a victim, villain and potential hero in Parkinson's disease pathophysiology and treatment

Lloyd A. Greene¹, Oren Levy², and Cristina Malagelada³

¹Department of Pathology and Cell Biology, Columbia University, New York, NY 10032

²Department of Neurology, Columbia University, New York, NY 10032

³Department of Pharmacology, Faculty of Medicine, University of Barcelona, 08036, Catalonia, Spain

Summary

There are two major purposes of this essay. The first is to summarize existing evidence that irrespective of the initiating causes, neuron death and degeneration in Parkinson's disease (PD) are due to the common feature of failure of signaling by Akt, a kinase involved in neuron survival and maintenance of synaptic contacts. The second is to consider possible means by which such a failure of Akt signaling might be benignly prevented or reversed in neurons affected by PD, so as to treat PD symptoms, block disease progression, and potentially, promote recovery.

Keywords

Parkinson's disease; Akt; neurodegeneration; neuroprotection

Introduction

This essay is dedicated to the memory of Marshall Nirenberg, a "titan" of modern biological research. Although Marshall (as he wished to be called by his trainees, of which LAG was fortunate to be among) focused primarily on research issues of fundamental nature, he was keenly aware and interested in how new discoveries in biochemistry and genetics could be harnessed to treat human maladies, including Parkinsonism (Nirenberg, 2003). He also championed the notion of thinking about, and working on, new, though potentially risky, ideas and it is in this context that we present this essay.

Parkinson's disease (PD) is a progressive neurodegenerative disorder that affects movement as well as cognition and other functions (Fahn, 2003). While associated with degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc), it also affects a number of other neuronal populations (Dickson et al., 2009; Shulman et al., 2010). Present treatments largely deal with management of symptoms, but do not appear to block or reverse disease progression. Genetic studies have uncovered a number of genes that, when mutated, are associated with familial PD or increased risk of the disorder as well as polymorphisms that enhance disease susceptibility (Hardy, 2010; Shulman et al., 2010). In addition, there are numerous hypotheses regarding the causes of sporadic PD (Levy et al., 2009; Shulman et al., 2010).

The existence of many potential initiating causes of PD as well as the involvement of various distinct neuronal populations raises a major challenge for devising universal treatments for this disorder. An alternative strategy would be to identify a common mechanism on which all or most initiating causes of the disease converge to promote neuron degeneration and death. Such a shared mechanism might then be targeted to develop clinical treatments to reverse, stop or slow the progression of PD.

There are two related purposes of this paper. The first is to present the case that a common focal point on which many initiating causes converge in PD is the protein kinase Akt and that failure of Akt signaling is the “common core” event that underlies neuronal degeneration and cell death in this disorder. The second purpose is to consider means by which loss of Akt signaling might be prevented or reversed so as to effectively treat PD, and to block and potentially reverse its progression.

Akt signaling

The properties and physiological activities of Akt (also known as PKB) have been amply reviewed (Franke 2008; Methany and Adamo, 2009; Fayard et al., 2010) and so only a brief discussion will be given here. There are 3 highly homologous Akt isoforms in mammals (Akt1-3). Full activation of Akt requires successive phosphorylation at 2 sites. The first phosphorylation is within the catalytic domain (Thr308 in hAkt1) and is carried out by the protein kinase PDK1. This event is dependent on PI(3,4,5)P3 which recruits Akt and PDK1 to lipid-containing membranes. PIP3 is the product of class 1a PI3K, which is in turn activated by growth factor occupation of receptor tyrosine kinases. Akt phosphorylation at Thr308 permits phosphorylation at a second site (Ser473 in hAkt1) within a C-terminal hydrophobic domain. Although phosphorylation at Thr308 is sufficient for Akt activity, phosphorylation at both sites yields full catalytic activation of the enzyme. Phosphorylation of Akt at Ser473 appears to be mainly dependent on the mammalian target of rapamycin complex mTORC2. Activation of Akt by phosphorylation is reversed by protein phosphatases, of which protein phosphatase 2A appears to be a major player.

Once activated, Akt can phosphorylate a number of downstream protein substrates on serine and threonine residues, on the order of at least 50 of which have been characterized thus far. Akt in this way regulates a number of downstream signaling cascades that impact on a variety of cellular activities including survival, differentiation, proliferation, migration, polarity and metabolism.

Akt and neuron survival

A number of *in vitro* studies have shown that activation of Akt is both necessary and sufficient to maintain survival of a range of different neuron types as well as of other cell types and that Akt mediates the neuronal survival-promoting activities of a variety of neurotrophic factors (Dudek et al., 1997; Crowder and Freeman, 1998; Brunet et al., 2001; Orike et al., 2001; Downward, 2004; Duronio, 2008). Interference with activation or activity of Akt causes death of cultured neurons, while transfection with a constitutively active form of the kinase promotes their survival in the absence of other forms of support. Although there are relatively few studies regarding the role of Akt signaling in survival of non-stressed neurons *in vivo*, this issue has been addressed in the post-natal substantia nigra (SN), a brain area of high relevance to PD (Ries et al., 2009). Delivery of a dominant-negative form of Akt by adeno-associated virus reduced the numbers of dopaminergic neurons in the SN and doubled the incidence of apoptotic neurons. Conversely, transduction with a constitutively active form of Akt significantly reduced developmental neuron death in the SN. These findings are especially significant because they underscore the role of active Akt in maintaining the survival of nigral dopaminergic neurons under basal conditions.

Akt and neurites

A key feature of PD is degeneration of axons and loss of synaptic contacts preceding cell death (reviewed by Cheng et al., 2010). Such degeneration can lead to impaired synaptic transmission, loss of neuronal function and symptoms associated with PD. Moreover, degeneration of axons in PD is likely to interfere with normal retrograde transport of neurotrophic factors and signals from targets, thereby ultimately driving or contributing to degeneration and death. Accumulating data have established a role for Akt in promoting neurite outgrowth and in enhancing the diameter of processes (Markus et al., 2002; Kwon et al., 2006; Read and Gorman, 2009;). There is also evidence that Akt can increase axonal branching and regeneration (Namikawa et al., 2000; Grider et al., 2009). Significantly, in the Ries et al. (2009) study cited above, dominant-negative Akt also decreased the density of tyrosine hydroxylase (TH) positive fiber staining in the striatum and this correlated with a reduction in number of individual TH+ fibers. Conversely, expression of constitutively active Akt appeared to cause extensive sprouting of TH+ processes in the striatum.

Defective Akt signaling in Parkinson's disease and in models of familial and sporadic PD

Reduced Akt signaling in post-mortem PD brain

The involvement of Akt in neuron survival and in the growth, caliber and branching of processes raises the issue of whether it may play a direct role in PD, and in particular whether the neuron death and neurite degeneration that occurs in this disorder is associated with a failure of Akt signaling. Several types of data support this idea. For one, there is evidence regarding PD itself. Immunostaining of post-mortem brains indicates that Akt phosphorylation at Ser473 (Malagelada et al., 2008; Timmons et al., 2009) and Thr308 (Malagelada et al., 2008) is significantly diminished in dopaminergic substantia nigra neurons of PD patients compared with non-PD patients. One study also found a drop in total Akt staining in such neurons from PD patients (Timmons et al., 2009).

α -Synuclein

In addition to sporadic PD, inherited forms of PD have also been linked to compromised Akt signaling via cell and animal models. Mutations in α -synuclein were the first to be associated with a familial form of PD (reviewed by Hardy, 2010) and a variety of evidence implicates this protein in the sporadic disease as well (Venda et al., 2010). While both cellular and animal models have been generated in which over-expressed wt or mutant α -synuclein promote neuron death, there do not appear at this time to be any published studies that examined Akt activity in these cases. Nevertheless, an indirect association has been suggested from studies on the highly related protein β -synuclein. Neurodegenerative responses (including loss of synaptic contacts) in transgenic mice over-expressing human α -synuclein were reversed by virally-induced over-expression of β -synuclein (Hashimoto et al., 2004b). This was correlated with elevated phosphorylation of Akt at Ser473 and it was suggested that the enhanced Akt activity contributed to the protective actions of β -synuclein. In line with this, β -synuclein was also found to protect cultured neuroblastoma cells from rotenone and this was mediated by elevation of phosphorylated Akt levels (Hashimoto et al., 2004a). The latter effect was promoted by direct binding of β -synuclein with Akt. Finally, a recent publication examined β -synuclein and phospho-Akt levels in α -synuclein null mice (Thomas et al., 2011). Nigral DA neurons in the latter mice are resistant to MPTP as compared with wt mice. This was correlated with increased expression in ventral midbrain of β -synuclein as well as elevated levels of phospho-Akt.

DJ-1

Mutations that confer a loss-of-function to the gene DJ-1 are associated with a familial form of early-onset PD (Hardy, 2010). In drosophila, knockdown of the DJ-1 homologue DJ-1A reduced Akt phosphorylation and led to neurodegeneration (Yang et al., 2005). In another set of studies (Aleyasin et al., 2010), virally delivered wild-type Akt protected SN neurons against MPTP in control mice, but not in DJ-1 null mice. Similar observations were found in complementary *in vitro* experiments with hydrogen-peroxide treated wild type and DJ-1 null cortical neurons. In addition, a dominant-negative form of Akt diminished the capacity of over-expressed DJ-1 to protect cultured cortical neurons from hydrogen peroxide. Although the mechanism of the interaction between Akt and DJ-1 was not fully explored in these studies, evidence was presented that DJ-1 promotes translocation of Akt to membranes where it is activated. Taken together, these findings support the idea that mutations that affect DJ-1 function lead to diminished Akt signaling and consequently, to neurodegeneration.

Parkin

Another instance in which loss-of-function mutations are associated with familial PD is for the E3 ligase parkin (Hardy, 2010). Intriguingly, it was reported that there is impairment of Akt signaling in a Drosophila parkin model of PD (Yang et al., 2005). Another study found that Akt signaling mediated by EGF receptors was deficient in synaptosomes from parkin null mice (Fallon et al., 2006). This was due to accelerated EGF receptor internalization and degradation. Although it has not been reported whether parkin affects Akt signaling in organisms other than flies or whether it regulates signaling by neurotrophic factors other than EGF, these findings suggest that further study of the parkin-Akt link is merited.

PINK1

A third gene in which loss-of-function is associated with familial PD is the protein kinase PINK1 (Hardy, 2010). Although generally thought to be involved in mitochondrial function, a recent report links PINK1 to phosphorylation of Akt at Ser473 and provides evidence that this effect mediates the neuroprotective actions of over-expressed PINK1 in a cellular model of PD (Murata et al., 2010). Over-expressed PINK1 (but not a kinase-dead version) was found to phosphorylate rictor, a component of the mTOR complex mTORC2 and this in turn activated mTORC2 and enhanced its capacity to phosphorylate Akt at Ser473. In addition, down-regulation of endogenous PINK1 led to reduction of Akt phosphorylation and sensitized test cells (SH-SY5Y neuroblastoma cells) to oxidative and ER stress. Finally, interference with Akt activity abolished the capacity of over-expressed PINK1 to protect SH-SY5Y cells from the PD mimetic, rotenone. Overall, these findings are consistent with the model that PINK1 promotes neuronal survival by stimulating Akt phosphorylation at Ser473 and that inactivating mutations of PINK1 place neurons at risk by reducing Akt phosphorylation.

Toxin models of PD

A variety of *in vitro* studies also support a role for compromised Akt signaling in PD. Akt phosphorylation at both Ser473 and Thr308 (but not the level of total Akt) is substantially lowered by treatment of cultured neuronal cells with PD mimetic toxins (Malagelada et al., 2008; Rodriguez-Blanco et al., 2008; Tasaki et al., 2010). Conversely, treatments that restore or block loss of Akt phosphorylation are protective in such models (Malagelada et al. 2010; Tasaki et al., 2010).

Protective action of enhancing Akt activity in PD models

If Akt activity is deficient in PD neurons and PD models and this is responsible for neurodegeneration, then it follows that elevation of Akt activity should be protective. *In vitro* models employing oxidative injury or PD mimetics show impressive protection by over-expression of wild-type Akt or by a constitutively active form of Akt (Salinas et al.; 2001; Signore et al., 2006; Malagelada et al., 2008; Aleyasin et al., 2010). Similarly, the abilities of a large array of trophic substances and neuroprotective compounds to block death in cellular models of PD are dependent, at least in part, on Akt signaling (Shimoke and Chiba, 2001; Kihara et al., 2002; Hashimoto et al., 2004; Presgraves et al., 2004; Signore et al., 2006; Fernandez-Gomez et al., 2006; Nakaso et al., 2008; Kao, 2009; Tasaki et al., 2010; Malagelada et al., 2010; Steidinger et al., 2011). Collectively, these findings suggest that a common feature of many treatments that are neuroprotective in PD models is their capacity to promote Akt activation.

Several animal studies also point to the protective effects of Akt signaling in PD models. Activated Akt, delivered via an adeno-associated virus, produced near-complete protection of mouse SN dopaminergic neurons from death produced by 6-OHDA (Ries et al., 2006). There was also a substantial preservation of dopaminergic axons by this treatment. The protective effects of activated Akt from 6-OHDA were functionally significant. Mice receiving virus encoding this protein showed significantly diminished contraversive rotations in response to apomorphine, which is a sign that dopaminergic synapses in the striatum were intact (Ries et al., 2006). In another study, viral delivery of either wild-type or activated Akt protected SN dopaminergic neurons in a mouse MPTP model of PD (Aleyasin et al., 2010). In a rat 6-OHDA PD model, both estrogen and IGF-1 treatment protected SN dopaminergic neurons from death, preserved TH+ axons in the striatum and significantly reduced impairment of motor behavior (Quesada et al., 2008). As judged by western blotting, both treatments enhanced Akt phosphorylation in the SN of non-lesioned animals. Moreover, the protective effects of estrogen and IGF-1 on neuron survival, axonal preservation and behavior in 6-OHDA-treated animals were largely reversed by infusion with LY294002, an inhibitor PI3 kinase that reduces Akt activation.

Additional *in vivo* and *in vitro* evidence for Akt's role in PD comes from studies with G-substrate, an endogenous inhibitor of Ser/Thr protein phosphatases (Chung et al., 2007). A comparison of transcripts in PD-vulnerable SN dopaminergic neurons versus PD-resistant DA neurons in the ventral tegmental area revealed higher expression of the gene encoding G-substrate in those neurons spared in the disease. In line with its capacity to inhibit phosphatases, over-expression of G-substrate in cultured neuroblastoma cells or in dopaminergic SN neurons *in vivo* led to elevation of Akt phosphorylation. Over-expression of G-substrate in rat SN neurons or in cultured neuroblastoma cells also protected them from death caused by 6-OHDA. In addition, knockdown of Akt in neuroblastoma cells substantially reversed the protective effects of G-substrate from 6-OHDA. Such findings support the idea that G-substrate expression may be important in regulating the level of Akt activity in neurons and that the lower levels of G-substrate in SN dopaminergic neurons may account for their selective vulnerability in PD.

Why is Akt signaling compromised in PD?

In the above sections, we have argued that Akt signaling is compromised in PD. In this section, we briefly consider some (and by no means, all) of the potential causes for this loss of Akt activity.

Genetic influences

Above, we have reviewed evidence that several loss-of-function mutations associated with familial PD lead to impairment of Akt signaling. In the case of DJ-1, there is some indication that loss of this gene affects translocation to membranes, a necessary step in Akt activation (Aleyasin et al., 2010). Findings with parkin suggest that this gene may be required for Akt activation by upstream trophic factors (Fallon et al., 2006) while recent data implicate PINK1 as a regulator of Akt phosphorylation via activation of mTORC2 (Murata et al., 2010). While mutations in these genes are rare causes of PD, it is likely that the encoded proteins are affected in sporadic cases of PD as well, which may in turn lead to impaired Akt signaling. Interestingly, one study has reported that a specific haplotype of Akt1 is associated with a reduced risk of PD (Xiomerisiou et al., 2008).

Loss of trophic support or signaling

Neurons require support by trophic substances for their sustained survival and for maintenance of their synaptic interactions. Many such trophic agents including growth factors and hormones, lead to Akt activation and thereby maintain neurites and connectivity and prevent death. Conversely, loss of trophic support results in diminished Akt activation and an enhanced risk of degeneration and death. It therefore follows that PD-associated failure of Akt signaling may result from inadequate trophic support of affected neurons (Stewart and Appel, 1988). This could arise from various causes including lack of trophic factor synthesis or processing, faulty retrograde transport of trophic factors and signals from the nerve periphery, or failure of trophic-factor-activated signal transduction pathways leading to Akt phosphorylation. Evidence for defective retrograde transport of neurotrophins has been found in a clinical trial testing intrastratial injection of AAV encoding the growth factor neurturin (see below). In brains from patients who have come to autopsy, there is ample neurturin immunoreactivity in the striatum, but almost none in the SNpc, suggesting that the growth factor could not be transported from the distal processes to the neuronal cell bodies (Bartus et al., 2010).

The reliance of trophic factor signaling on retrograde transport from synapses, the activation of Akt by trophic signaling, and the roles of trophic factor signaling and Akt in maintenance of neurites and synaptic connections suggests a possible deadly spiral of linked events in PD. In this scenario, diminished Akt signaling would cause axon degeneration and loss of synapses, which would in turn impair retrograde trophic signaling, leading to further compromise of Akt activation and so forth. Conditions (genetic or environmental) that affect any point in this loop would be sufficient to lead to a lethal outcome.

Inhibition of Akt activation

Aside from its regulation by trophic signaling, Akt activity is subject to additional levels of potential influence that may be relevant in PD. Among these is induction of the stress protein RTP801/Redd1. RTP801 transcripts and protein are robustly induced in cell models of PD (Ryu et al., 2005; Malagelada et al., 2006). Over-expression of the protein is sufficient to promote neuron death while knockdown indicates that RTP801 is necessary for death of cultured neural cells induced by PD mimetics (Malagelada et al., 2006; 2008; 2010). The elevation of RTP801 seen in cellular models of PD appears to be relevant to the disease since it is also more highly expressed in SN dopaminergic neurons of PD patients as compared to controls (Malagelada et al., 2006). The mechanism by which elevated RTP801 causes neuron death appears to follow from its capacity to block activation of the kinase mTOR and in the consequent inhibition of Akt phosphorylation (Malagelada et al., 2006; 2008, 2010). Thus, the fall in Akt phosphorylation caused by 6-OHDA and MPP+ in cultured neurons is blocked by knockdown of RTP801 and is mimicked by inhibition of mTOR. Several additional regulators of Akt activation have been described (reviewed by

Franke, 2008; Liao and Hung, 2010) and it remains to be seen if any might be involved in PD.

Excessive Akt dephosphorylation

Because Akt is activated by phosphorylation, it is therefore subject to inactivation by phosphatase activity. Of relevance to this, the activity/level of protein phosphatase 2A (PP2A), for which phospho-Akt is a substrate, is elevated by alpha synuclein (Peng et al., 2005) and in response to 6-OHDA (Ryu and Greene, 2005; Chung et al., 2007) in cultured cells. In addition, as reviewed above, the constitutively low expression of the G-substrate PP2A-inhibitory protein in SN dopaminergic neurons may render them especially sensitive to Akt dephosphorylation (Chung et al., 2007). Furthermore, mTOR phosphorylates PP2A and by this means suppresses its activity (Peterson et al., 1999). Thus, decreased mTOR activity, which occurs at least in cellular models of PD (Malagelada et al., 2006), would promote PP2A activation. One might imagine additional events that might lead to elevation of phosphatase 2A activity in PD-vulnerable neurons.

ER stress and oxidative stress

ER stress and oxidative stress are two linked cellular responses that have been associated with neurodegeneration in PD models and in PD (Levy et al., 2009; Scheper and Hoozemans, 2009; Malkus et al., 2009). As reviewed above, PD mimetic toxins that cause oxidative stress also reduce Akt phosphorylation. Likewise, there are a number of models of ER stress that result in inactivation of Akt (Hyoda et al., 2006; Hosoi et al., 2007; Qin et al., 2010). The mechanism by which such stresses lead to diminished Akt signaling are unclear, but at least in one case appeared to be due to impaired mTOR signaling (Qin et al., 2010). Given the induction of RTP801 by ER stress and oxidative stress, this raises the possibility that this protein may at least in part mediate the effect of such stresses on Akt activity.

Taken together the above reviewed findings support the idea that multiple types of cellular stresses implicated in the pathophysiology of PD may converge on signaling pathways that compromise Akt activation, and that this in turn at least in part, mediates neuronal degeneration and death.

Can we treat PD by manipulating Akt activity?

If neurodegeneration and cell death in PD are indeed due to failure of Akt signaling, then this opens the door to possible Akt-directed treatments of the disease once it is diagnosed (Burke 2007). Approaches might range from maintaining Akt phosphorylation to actively promoting its activation. Such interventions would be attractive not only because they might prevent disease progression, but may also because they might also restore function and reverse symptoms. The latter possibility is suggested for instance by the observations discussed above that elevation of Akt activity in neurons promotes axon growth and sprouting both *in vitro* and *in vivo*. This raises the prospect of growth of new connections to replace those lost in the initial stages of the disease.

Despite its possible attractions for treating PD, stimulation of Akt activity is not without its potential perils. Elevated Akt activity has been associated with survival growth and metastasis of cancer cells (Qiao et al., 2008; Steelman et al., 2008; Franke, 2009) and indiscriminate effects on this kinase are likely to put patients at risk for malignancies. Additionally, it has been reported that elevated Akt phosphorylation is associated with L-Dopa-induced dyskinesias in MPTP-treated monkeys (Morissette et al., 2010). Thus, it is incumbent to seek approaches that limit manipulation of Akt activity to those neurons affected in PD. Another potential issue is that it would be preferable to be able to titrate the level of neuronal Akt activity in any clinical treatment. For instance, excess activity could

lead to exuberant axonal sprouting that may have undesirable side effects on behavior and motor function.

Viral delivery of Akt or Akt activity regulators

Advances in targeted viral delivery of DNA permits the possibility of directly transducing affected neurons in PD patients with genes or shRNAs whose products regulate Akt activity (Bjorklund and Kirik, 2009). This might include delivery of Akt or Myr-Akt, PI3K, mTOR activating proteins such as Rheb, protein phosphatase 2a inhibitory proteins such as G-substrate, or PDK1. Alternatively, activation might be achieved by knockdown of negative regulators of Akt signaling such as PTEN, protein phosphatase 2a or of proteins discussed above that may lead to Akt inactivation such as RTP801 and alpha-synuclein. Though the technology to achieve this approach is rapidly becoming available, there are the drawbacks that full treatment of PD would require transduction of multiple types of neurons (and therefore directed delivery to many parts of the nervous system) and that it is presently challenging to regulate the degree of transduction and activity regulation brought about by this approach.

Delivery of neurotrophic factors

In some ways, neurotrophic factors represent an excellent treatment for PD. They activate Akt as well as other signaling pathways that provide neuroprotection and enhance growth of processes and formation/maintenance of synaptic connections. They also have at least a degree of specificity, which can limit potential side effects. The best studied of these in the context of PD are GDNF and its related family member neurturin (see reviews by Yasuda and Mochizuki, 2010; Manfredsson et al., 2009; Ramaswamy et al., 2009; Rangasamy et al., 2010). Acting through the Ret receptor, GDNF activates Akt signaling to promote neuron survival and neurite outgrowth (Perrinjaquet et al., 2010). Preclinical trials with GDNF in animal PD models have shown both protection of cell bodies and apparent regeneration of nerve terminals as well as improved motor behavior (Manfredsson et al., 2009; Ramaswamy et al., 2009; Yasuda and Mochizuki, 2010). However, clinical trials with PD patients using direct administration of GDNF have to date shown at best questionable efficacy (see Rangasamy et al., 2010 for review). Targeted viral delivery of GDNF-expressing constructs appears to be a viable alternative and has shown good efficacy in animal models although no data on human trials has been published (Manfredsson et al., 2009; Ramaswamy et al., 2009; Yasuda and Mochizuki, 2010). While animal experiments with neurturin have shown similar promise, a recently reported trial in PD patients with virally-delivery of neurturin to the putamen did not show efficacy and caused adverse effects in a significant number of patients (Marks et al., 2010). In addition to GDNF and neurturin, several other neurotrophic factors have been found to provide protection in both *in vitro* and *in vivo* PD models (Yasuda and Mochizuki, 2010; Rangasamy et al., 2010) and at least some of these have been shown to lead to Akt activation. Thus, the door is open to further possibilities of using trophic factors for a PD therapy that includes Akt activation.

Despite the potential appeal of using trophic factors to treat PD, there remain a number of potential challenges to this approach such as delivery mode, place of delivery, and dosing. Moreover, while viral “gene therapy” can be effective, it is not readily reversible, especially in the case of undesirable side effects. In addition, treatment of the multiple neuron types affected in PD may require multiple neurotrophic factors as well as multiple sites of delivery. Furthermore, as mentioned above, axonal dysfunction may interfere with the retrograde signaling required for typical neurotrophin signaling. An alternative to delivery of the factors themselves would be treatments that lead to elevated synthesis of endogenous neurotrophic factors. An elegant recent approach has involved direct stimulation of endogenous GDNF synthesis in the SN by a virally-delivered engineered Zn finger protein

(Laganiere et al., 2010). This provided neuroprotection and behavioral recovery in a rat 6-OHDA model.

Akt activation by small molecules

The ideal magic bullet for treating PD via regulation of Akt would be a small molecule with the following properties: 1) selectively activates Akt in neurons affected by PD; 2) can be dosed to provide optimal protection and neurite growth; 3) has no major side effects. Although it may be difficult or impossible to entirely meet all of these requirements, there are several avenues that appear to be worth considering, and several of these are discussed below.

Rapamycin—Rapamycin is a bacterial product that inhibits some, but not all activities associated with mTOR in a dose-dependent manner (Foster and Toschi, 2009). It is used clinically as an immunosuppressant in certain types of transplant surgery. Several groups have reported significant protection by rapamycin in both *in vivo* and *in vitro* models of PD (Pan et al., 2009; Malagelada et al., 2010; Dehay et al., 2010). One suggestion has been that such protection is due to induction of autophagy (a consequence of interfering with mTOR function) (Webb et al., 2003; Pan et al., 2009; Dehay et al., 2010). An alternate interpretation has been offered. Aside from inducing autophagy, another action of rapamycin is partial inhibition of protein translation (also due to its actions on mTOR) (Foster and Toschi, 2009). Rapamycin was found to interfere with synthesis of the protein RTP801, which, as described above, is elevated in PD and PD models and which promotes neuron death by blocking Akt activation (Malagelada et al., 2010). Thus, in both *in vitro* and *in vivo* PD models, rapamycin blocked the increase in RTP801 protein levels and preserved Akt phosphorylation at Thr308. Evidence was presented that it was this action of rapamycin on Akt phosphorylation that accounted for its protective actions in PD models (Malagelada et al., 2010). These findings indicate that rapamycin or similar drugs (“rapalogs”) with better brain penetration, may provide treatment for PD by elevating or maintaining Akt activity. One potential drawback of rapamycin itself is that although it is tolerated by patients, it is an immunosuppressant. An alternative would be development of other small molecules targeted to mTOR or to the aspects of the protein translation machinery affected by rapamycin and that are involved in translation of RTP801.

GLP-1—GLP-1 (glucagon-like peptide 1) is a naturally occurring peptide with antihyperglycemic activity that can inhibit apoptosis of pancreatic beta cells and that has effects in both the central and peripheral nervous systems (Baggio and Drucker, 2007). Consequently, stable analogs of GLP-1 (such as exendin-4) and inhibitors of GLP-1 degradation are currently in clinical use for treating type 2 diabetes (Hare and Knop, 2010). Several reports have shown that exendin-4 can protect neurons in *in vitro* and *in vivo* models of PD (Harkavyi et al., 2008; Li et al., 2009; Kim et al., 2009). *In vivo*, both dopaminergic cell bodies and processes are preserved and there is enhanced recovery of function. The drug was effective even if given after the lesion (Harkavyi et al., 2008). GLP-1 receptors appear to be widely expressed in the nervous system and the protective actions of exendin-4 in at least one PD model were dependent on their presence (Li et al., 2009). Although GLP-1 receptors are G-proteins linked to stimulation of adenylate cyclase, there is evidence that their activation leads to Akt activation, and that this, at least in part mediates its protective effects in both non-neuronal and neuronal cells (Trumper et al., 2000; Li et al., 2009; Widenmaier et al., 2009; Kimura et al., 2009). Such a mechanism involving Akt stimulation would be consistent with the efficacy of exendin-4 in PD models, both with respect to prevention of neuron death and stimulation of recovery. The current clinical use of GLP-1 analogs, their apparent relative safety, the neuroprotective effects achieved by exendin-4 in

PD models and the capacity of GLP-1 and analogs to activate Akt all argue for further examination of its potential use for treatment of PD (see also Harkavyi and Whitton, 2010).

Rasagiline and epigallocatechin gallate—Rasagiline is a monoamine oxidase B inhibitor that is currently in use for treatment of PD, either alone or in combination with other drugs (Weinreb et al., 2010). It provides neuroprotection in both *in vivo* and *in vitro* models of PD, and clinical trials suggest a mild neuroprotective benefit in early PD. There is evidence that in addition to its MAOB inhibitory activity, rasagiline stimulates neurotrophic signaling including activation of Akt (Sagi et al., 2007; Weinreb et al., 2010). Epigallocatechin gallate is a component of green tea that has also proven to be protective in *in vitro* and animal PD models (Levites et al., 2001; Chao et al., 2010) and that was reported to block the dephosphorylation of Akt induced in neuroblastoma cells by 6-OHDA (Chao et al., 2010). A recent study reported that low doses of rasagiline and epigallocatechin gallate act synergistically in MPTP-treated mice to rescue dopaminergic neurons and to prevent loss of Akt phosphorylation (Reznichenko et al., 2010). Thus, these small molecules, are easily tolerated in patients, preserve Akt phosphorylation and, promote neuronal protection in PD models and therefore seem to hold promise for treatment and potentially, reversal, of PD and its associated symptoms.

Docosahexaenoic acid (DHA)—DHA is the most abundant polyunsaturated fatty acid in the brain and is acquired both by synthesis and diet (Kim et al., 2007). Several studies have shown that administration of DHA is neuroprotective in animal models (MPTP and 6-OHDA) of PD (Bousquet et al., 2008; Cansev et al., 2008). Cell culture studies have revealed that DHA promotes neuron survival by increasing membrane levels of phosphatidylserine, which in turn enhances translocation of Akt to membranes where it is activated (Akbar et al., 2005). Taken together, these findings suggest that DHA has the potential to be taken as a dietary supplement to elevate Akt signaling in brain and thereby to treat PD.

Closing comments

In this essay, we have presented the case that neuron degeneration and death in PD, irrespective of the initiating causes, are ultimately due, at least in part, to failure of Akt signaling. We have further argued that stimulation of Akt signaling in neurons affected by PD has the potential not only to arrest progression of the disease, but also to promote at least some degree of recovery. If these hypotheses are correct, then there remain ahead a number of challenges to exploit them for clinical use. Among these is identifying critical molecular targets that might be manipulated to elevate Akt activity in PD-affected neurons; identifying or synthesizing pharmaceuticals directed to these targets; delivering such potential Akt-activating therapeutics to neurons; and finding therapeutics without major side effects or that are selective for, or selectively delivered to, neurons that degenerate in PD. While these potential hurdles are significant, they are not in our view insurmountable. To this end, we have suggested here several possible therapeutic approaches to PD based on their capacities to stimulate or protect Akt activity in neurons and to do so in a relatively safe way. Given the very active status of current research efforts in PD and in Akt signaling, it seems highly likely that additional opportunities will arise in the future.

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