Prion 7:1, 85–91; January/February 2013; © 2013 Landes Bioscience

The pathology roadmap in Parkinson disease

D. James Surmeier[1,*] and David Sulzer[2]

[1]Department of Physiology; Feinberg School of Medicine; Northwestern University; Chicago, IL USA; [2]Departments of Psychiatry, Neurology & Pharmacology; Columbia University; New York, NY USA

Keywords: Parkinson disease, calcium, mitochondria, oxidant stress, neuroprotection, ion channel

An under-appreciated clue about pathogenesis in Parkinson disease (PD) is the distribution of pathology in the early and middle stages of the disease. This pathological "roadmap" shows that in addition to dopaminergic neurons in the substantia nigra pars compacta (SNc), a significant number of other central and peripheral neuronal populations exhibit Lewy pathology, phenotypic dysregulation or frank degeneration in PD patients. This spatially distributed, at-risk population of neurons shares a number of features, including autonomously generated activity, broad action potentials, low intrinsic calcium buffering capacity and long, poorly myelinated, and highly branched axons. Many, and perhaps all, of these traits add to the metabolic burden in these neurons, suggesting that mitochondrial deficits could drive pathogenesis in PD—in agreement with a large segment of the literature. What is less clear is how this neuronal phenotype might shape the susceptibility to proteostatic dysfunction or to the spread of α-synuclein fibrils deposited in the extracellular space. The review explores the literature on these issues and their translational implications.

Introduction

The loss of mesencephalic substantia nigra (SN) dopaminergic neurons in PD is responsible for its core motor symptoms.[1] However, a variety of other neurons exhibit signs of pathology in post-mortem analysis of PD patients. For example, intracellular protein aggregates in the dorsal motor nucleus of the vagus (DMV), a region within the medulla oblongata, are a consistent feature of the pathology in the brains of PD patients.[2,3] These aggregates are known as Lewy bodies and Lewy neurites or Lewy pathology. Alpha-synuclein is a major component of Lewy pathology, enabling pathologists to use immunocytochemical approaches to map Lewy pathology in postmortem samples from PD patients.[4] Although they have caveats, these studies have given us a "roadmap" of the PD trajectory that should inform our theories about pathogenesis. This review attempts to summarize this literature and to determine if there is a connection to mitochondrial dysfunction, which has long been thought to be a causative factor in PD.[99]

*Correspondence to: D. James Surmeier;
Email: j-surmeier@northwestern.edu
Submitted: 10/27/12; Revised: 12/26/12; Accepted: 01/11/13
http://dx.doi.org/10.4161/pri.23582

Vulnerable Neuronal Populations in PD

Both central and peripheral nervous systems are affected in PD. The peripheral nervous system can be divided into three parts: sensory, motor and autonomic. Generally, peripheral sensory and motor neurons do not display Lewy pathology or signs of degeneration in PD patients. In contrast, there are clear signs of pathology in the autonomic nervous system. The autonomic nervous system has three major divisions: sympathetic, parasympathetic and enteric. All three have been reported to exhibit Lewy pathology and dysfunction in PD patients. For example, orthostatic hypotension occurs in a significant fraction of late stage PD patients. This symptom has been attributed to a sympathetic denervation of the heart or vasculature.[5-9] In some PD and dementia with Lewy bodies patients, Lewy pathology is present in the peripheral vagal nerve and ganglia.[10,11] These axons originate in the DMV. There are reports of strong Lewy pathology in the DMV preganglionic parasympathetic neurons of nearly all PD patients studied (see below). A subset of parasympathetic neurons in the intrinsic cardiac ganglia also appear to be at risk in PD.[8] The parasympathetic inferior salivatory nucleus (ninth cranial nerve), which innervates the parotid gland, also features Lewy pathology in PD,[11,12] but it is unclear whether there is neuronal loss. In PD patients, Lewy pathology has been seen in both in the submandibular gland and the superior cervical ganglion.[11] Djaldetti and colleagues have reported a marked denervation of all autonomic neurites in skin,[13] work supported by analyses of skin biopsies from PD patients.[5,14]

Lewy pathology and dopaminergic neuron loss also has been found in the enteric nervous system of many PD patients, particularly the lower gastrointestinal tract, which might be responsible for decreased gastric motility and constipation.[15,16] The inevitability of enteric nervous system pathology in PD has been challenged, however.[17-19] These studies show that enteric nervous system Lewy pathology is a frequent, but not necessary concomitant of PD. Conversely, although gastrointestinal dysfunction is frequently found in PD patients,[5] it is also common among aged individuals without any sign of PD.[20] Making matters worse, enteric nervous system neurons are very heterogeneous and attempts to identify the phenotype of those exhibiting Lewy pathology have not reached a consensus.[21,22]

In summary, Lewy pathology is found in several types of peripheral neuron in PD. The only neurons that are well established to be lost in PD are noradrenergic neurons innervating the heart and skin. Lower intestine enteric nervous system neurons commonly display Lewy pathology in PD patients and this might be responsible for constipation that commonly accompanies PD.

In the central nervous system, the vast majority of the neurons lost or displaying signs of pathology in early and mid-state PD patients are found in the brainstem. In the brainstem, Lewy pathology and cell loss has been reported in the region of the DMV, the medullary reticular formation, the raphe nuclei, the locus coeruleus, the pedunculopontine nuclei, the substantia nigra pars compacta (SNc) and, to a lesser extent, the ventral tegmental area and retrorubral area. The evidence for the involvement of these nuclei will be discussed in turn.

James Parkinson theorized that damage to the medulla caused PD. Axons entering the vagus nerve from the DMV can have strong Lewy pathology;[23] Lewy pathology within the DMV has been reported in most,[12] but not all PD patients.[24,25] Additional neurons in this region have some variable degree of Lewy pathology.[12] Neuronal counts demonstrate that DMV neurons are lost in PD,[26] but there are differences in the literature regarding which neurons are lost, probably due to differences in stages of the disease. Classical studies report neuromelanin containing neurons in the DMV region were lost in PD brains, including the original report,[27] which states that "The pigmented cells of the dorsal vagal nucleus also degenerated, often with vacuolation, by contrast with the non-pigmented cells in this nucleus which remained healthy." Eadie did not confirm this and reported that cholinergic motoneurons were lost, consistent with a later study.[26] Braak and collaborators suggest that the preganglionic parasympathetic projection neurons are first to degenerate, and neuromelanin neurons might be lost later.[28] These might not be distinct neuronal populations, however. New work suggests that some cholinergic DMV neurons also express tyrosine hydroxylase and aromatic acid decarboxylase, the enzymes that produce dopamine; while these neurons might synthesize catecholamines, they lack detectable vesicular monoamine transporter, making it unlikely they release it.[29]

The loss of dopaminergic neurons in the SNc is the best-documented sequela of PD. The loss of neuromelanin in the SNc of PD patients was reported early in the 20th century[30] and confirmed by many subsequent studies.[27,31-33] The loss of neuromelanin is seen in all PD patients,[34] but not all patients with parkinsonism.[35] Parkinsonism is a bradykinetic syndrome that can include rigidity, tremor and postural instability. PD is the most common cause of parkinsonism, but progressive supranuclear palsy and multiple system atrophy also fall into this category. Lewy pathology is nearly always found in the neuromelanin-positive neurons in the SNc of PD patients, particularly in the posterolateral regions.[12] Some Lewy pathology has been reported in the neighboring ventral tegmental area and retrorubral field neurons as well,[53] but neuronal loss in these two regions is variable.[36,37] Profound neuronal loss in the SNc appears to be specific to parkinsonian etiologies[119] and not Alzheimer disease.[38] The most heavily neuromelanin pigmented neurons that are lost in the SNc of PD patients appear to be those with lower levels of vesicular monoamine transporter type 2 and with decreased vesicular accumulation of dopamine as well as low levels of calbindin.[39-41]

Locus coeruleus neurons have long been known to be lost in PD.[27,33] Lewy pathology is observed in neuromelanin pigmented locus coeruleus neurons and is absent from non-neuromelanin cells in the complex,[34] confirming selective damage to noradrenergic neurons. Virtually all PD patients appear to have a substantial loss of locus coeruleus neurons, with a mean neuronal loss of 83% in later stages of the disease.[38] There is also an average 68% loss of these neurons in Alzheimer disease, but the extent of locus coeruleus loss is more variable in Alzheimer disease patients than PD patients.[38]

Neurons in the raphe nuclei are responsible for serotoninergic innervation of the CNS. In incidental Lewy body disease and PD, Lewy pathology is most apparent in medium-sized neurons of the caudal raphe nucleus.[12] The ventrorostral raphe region around the medial lemniscus also exhibits Lewy pathology in PD.[34] Raphe nuclei neurons not only display Lewy pathology, but are lost in PD, with a reduction of over half these neurons in the median raphe and a somewhat smaller fractional loss reported in the raphe obscurus.[34,42]

The pedunculopontine nucleus is rostral to the locus coeruleus and includes a mixture of cholinergic, glutamatergic and GABAergic neurons with an array of targets in the mesencephalon and diencephalon.[43] The pedunculopontine nucleus was reported to exhibit Lewy pathology by Braak's group.[4,28] Lewy pathology and neuronal loss also were reported.[44,45] Although prominent in PD, pedunculopontine nucleus loss is not specific to PD and is also seen in progressive supranuclear palsy and Alzheimer disease.[42,44,45]

There is also substantial pathology in regions rostral to the brainstem relatively early in PD. One of these is the olfactory system. In the olfactory bulb, mitral cells exhibit Lewy pathology, but this is also seen in Alzheimer disease.[46,47] The anterior olfactory nucleus also shows Lewy pathology in incidental Lewy body disease.[12] The existence and targeting of neuronal loss in the olfactory system is controversial.[48,49] This issue is complicated by the neurogenesis in this region.[50]

There are several other regions that have been reported to have either neuronal loss or Lewy pathology in PD, many in single studies. These include the lateral hypothalamus[51] and the intralaminar nuclei of the thalamus.[52] The specificity of these changes is unclear. In the case of the thalamic nuclei, the loss is also seen in progressive supranuclear palsy.[52] In apparent later stages of PD, Lewy pathology is also scattered throughout the cerebral cortex, amygdala and hippocampus.[53,54] Retinal dopaminergic also has been reported to decline, but Lewy pathology was not identified.[55]

The nucleus basalis of Meynert is a prominent site of Lewy pathology and cell loss in PD patients. The specificity of the pathology is less clear as the nucleus basalis of Meynert also figures prominently in Alzheimer disease.[56] This issue was addressed by a comparative study that found a loss of about half of the nucleus basalis of Meynert neurons measured by cresyl violet label in 11 PD patients, which was significantly greater than age-matched control subjects.[57] Not all of these subjects displayed Alzheimer disease-like symptoms, suggesting that there was a symptomatic threshold. There was no correlation between PD symptom severity and nucleus basalis of Meynert loss in this study. The most extensive comparative study of PD and Alzheimer disease brains in this region found similar neuronal losses, also as labeled

by cresyl violet, on average (~40%), but there was a great deal of variability.[38] Thus, Lewy pathology and neuronal loss in the nucleus basalis of Meynert appears to be a common feature of PD and Alzheimer disease.

Determinants of vulnerability. The obvious question is what links this seemingly diverse set of neurons. There are several possible phenotypic traits that have been proposed to underlie vulnerability.

A common reactive neurotransmitter. SNc, locus coeruleus, raphe nuclei, enteric dopaminergic neurons and sympathetic postganglionic neurons each synthesize a monoamine neurotransmitter and high levels of cytosolic monoamines are reactive and hypothesized to underlie selective neuronal death under several conditions.[58-62] Although pre-ganglionic DMV neurons are nominally cholinergic, some of these neurons appear to possess and/or secrete monoamines. SNc and locus coeruleus are the most similar in this regard and both have neuromelanin deposition in humans. These two nuclei exhibit the greatest loss in PD. Nevertheless, some highly pigmented A2 catecholaminergic, neuromelanin-positive neurons in the caudal medulla do not appear to be lost in PD,[32] and so neuromelanin synthesis per se, which may be a neuroprotective response,[63,64] is not sufficient for neuronal death. In the periphery, the loss of NE neurons is variable, with some sympathetic neurons appearing to be vulnerable and others not. Moreover, their loss is not specific to PD, as is also the case for locus coeruleus neurons.

However, there are two arguments against the reactive monoamine transmitter hypothesis of PD. One is that there clearly is pathology and loss of neurons that do not use monoamines. Vulnerable neurons in the DMV, pedunculopontine nucleus, LH, nucleus basalis of Meynert and enteric nervous system do not use a monoamine transmitter. It is true that neuronal loss in at least some of these regions is known not to be specific to PD. But the same is true of neuronal loss in locus coeruleus. It has been recently suggested that loss of cholinergic neurons is a consequence of the preceding loss of monoamine neurons,[120] but this conjecture awaits compelling support. The other key argument is that use of L-DOPA—the precursor for dopamine—to treat PD does not accelerate the progression of the disease as one would expect if dopamine or noradrenaline was the toxic agent in the disease.[1]

A long, highly branched axon with multiple release sites. SNc, locus coeruleus, raphe nuclei, pedunculopontine nucleus, DMV and nucleus basalis of Meynert neurons all have unusually long highly branched axons that are unmyelinated or thinly myelinated.[7,65] This feature is particularly well documented for SNc dopaminergic neurons. Single SNc axons terminating in the striatum are highly branched and possess as many as several hundred thousand synaptic release sites.[66] This is an order of magnitude greater than most neurons that have been carefully studied. Interestingly, these terminals do not appear to have an elevated mitochondrial oxidant stress.[67] However, maintaining a massive terminal field is very likely to create a metabolic and proteostatic burden on the cell body. Mitochondrial trafficking could prove particularly problematic; in fact, mitochondrial density in the somatodendritic region of SNc dopaminergic neurons is low[68] possibly reflecting the need to traffic mitochondria to axons. It is worth noting that α-synuclein is a presynaptic regulator of synaptic vesicle exocytosis;[69-71] the proteostatic burden it creates could scale with the number of synaptic release sites and may contribute to mishandling of presynaptic mitochondria.[72] It is unclear whether ventral tegmental area and retrorubral field dopaminergic neurons have as extensive an axonal field as do SNc dopaminergic neurons. Matsuda et al. did not report profound differences in dorsal and ventral striatal terminal fields, which should correspond to SNc and ventral tegmental area; as a consequence, the differences in vulnerability between these regions would have to be explained by other factors. Neurons of the locus coeruleus also have very long and complex projections. Based upon the distance traveled and terminal field, the axons of DMV neurons are also long and highly branched, and many enteric nervous system neurons are also highly branched.

A common physiological phenotype. An extended discussion of this hypothesis has recently been published.[73] PD is a disease of neurons, not of the liver, kidney or heart. An implication of this fact is that one or more of the features distinguishing neurons from these other cell types must contribute in a seminal way to pathogenesis. A cardinal feature of neurons that separates them from nearly all other cell types is excitability. Neurons use steep electrochemical gradients across their plasma membrane to perform computations on incoming chemical signals from other neurons and to pass the outcome of this computation to other cells. Each step in this process expends energy. Action potentials (or spikes) and synaptic transmission dissipate the ionic gradients for sodium, potassium, calcium and chloride that are maintained by adenosine triphosphate dependent pumps and exchangers. Although all neurons share this basic set of properties, the parameters of spikes and synaptic transmission vary dramatically. The physiological phenotype of neurons ranges from what might be called a "wallflower" or quiescent phenotype to a "chatter box" phenotype that never stops spiking. SNc, locus coeruleus, raphe nuclei, nucleus basalis of Meynert, pedunculopontine nucleus and DMV neurons all fall into the chatterbox phenotype. That is, all of them spike continuously in vivo during the waking state.[74-81] SNc, locus coeruleus, DMV and pedunculopontine nucleus neurons are autonomous pacemakers (they spike on their own in the absence of synaptic input).

One particularly expensive ion that enters neurons during spiking is calcium. It is metabolically expensive because it must be pumped out of the cell against a much steeper (~2,000-fold) electrochemical gradient than sodium, potassium or chloride ions. Most neurons keep this burden to a minimum by restricting calcium entry to the brief period during spikes, keeping these spikes short in duration and by expressing specialized calcium binding proteins that effectively buffer calcium—"grabbing" it after it enters and keeping it in place for plasma membrane pumps and transporters. This is not true of vulnerable neurons; they seem to do all the wrong things. For example, typically vulnerable neurons are continually spiking and have broad, slow spikes; this is certainly true of SNc, locus coeruleus, raphe nuclei, pedunculopontine nucleus and nucleus basalis of Meynert neurons (see references above). Although less well studied, many of

the neurons in the autonomic nervous system, particularly those in the enteric nervous system, also are spontaneously active and have broad spikes.[82-84] The expression of calcium binding proteins is low in those vulnerable neurons that have been studied carefully. SNc, locus coeruleus and DMV neurons express relatively little of these calcium binding proteins[77,85] (raphe nuclei, pedunculopontine nucleus and nucleus basalis of Meynert have not been rigorously characterized in this regard to our knowledge). In contrast, most other relatively PD-resistant autonomous pacemakers in the brain express a high level of calcium binding proteins (e.g., ventral tegmental area neurons, Purkinje neurons, globus pallidus neurons, striatal cholinergic interneurons).[86,87] The expression of known calcium binding proteins in the autonomic nervous system and enteric nervous system varies from cell type to cell type.[88-90] In addition, SNc and locus coeruleus neurons allow significant amounts of calcium to enter during the period between spikes.[91-93]

The pacemaking phenotype characteristic of vulnerable neurons opens the door to another potential source of stress. Pacemaking neurons reside at relatively depolarized membrane potentials where NMDA receptors are relieved of their magnesium block, creating another point of sodium and calcium entry during excitatory synaptic transmission; excitotoxicity is one of the earliest theories of pathogenesis in PD.[94,95]

In addition to creating a metabolic stress, activity-dependent elevation in cytosolic calcium levels increases cytosolic dopamine in SNc neurons, possibly due to an effect on synthesis.[60] Enhanced dopamine levels in the cytosol can lead to α-synuclein-dependent neuronal death.[60]

In most neurons, the metabolic burden associated with activity and synaptic transmission is thought to significantly diminish the respiratory reserve of mitochondria.[96] In SNc dopaminergic neurons, and others of its kind, this reserve should be even smaller. In fact, there is a measurable increase in the oxidation of mitochondrial thiol proteins in SNc and DMV neurons that are simply pacemaking.[97,98] Unpublished work by our group (DJS) has revealed that locus coeruleus neurons have a similar mitochondrial oxidant stress. Mitochondrial dysfunction is widely viewed as a pivotal step in PD pathogenesis.[99] A sustained mitochondrial oxidant stress should in principle lead to the accumulation of mitochondrial DNA (mtDNA) mutations and impaired complex I function seen in the SNc with aging and PD.[100-102] Genetic mutations affecting mitochondria and environmental toxins that compromise mitochondrial respiration could synergize with this cell type specific stress, hastening bioenergetic failure and degeneration.

An interaction between neuronal phenotype and proteostatic dysfunction. The data summarized thus far is consistent with the hypothesis that vulnerable neurons have a distinctive physiology, leading to increased mitochondrial oxidant stress and susceptibility to insults that compromise mitochondrial function. Does this model provide an explanation of Lewy pathology and proteostatic dysfunction in these neurons? The answer is clearly no. However, it is self-evident that bioenergetic deficits could impair proteostatic function simply by diminishing the availability of adenosine triphosphate. Elevated cytosolic calcium levels seen in many vulnerable neurons could also play a direct role. For example, increasing calcium concentration, even transiently, increases the aggregation of α-synuclein.[103] Lysosomes and autophagic vacuoles that deliver intracellular components to lysosomes, key elements in the catabolic machinery, are dependent upon calcium signaling for their regulation[104] and are potential sites of ROS generation.[64] A number of genes linked to PD have effects on lysosomal function as well.[105] These observations raise the possibility that proteostatic challenges that increase lysosomal activity could exacerbate basal oxidant stress in vulnerable neurons, promoting degeneration.

Another hypothesis of pathogenesis that has received a great deal of attention lately is the so-called prion hypothesis.[106] In this model, α-synuclein fibrils in the extracellular space are taken up by neurons and these fibrils seed Lewy pathology; some subset of these fibrils are then released, spreading the pathology. Thus, α-synuclein fibrils behave in a prion-like way. The most compelling support for this hypothesis comes from (1) the observation that dopaminergic neurons grafted into the brains of PD patients rapidly developed Lewy pathology[107] and (2) the demonstration that inoculation of brains with α-synuclein fibrils leads to a spreading Lewy-like pathology.[108,118] On the face of it, this model is very difficult to reconcile with the pattern of PD pathology. In the brain of a PD patient, Lewy pathology does not follow a nearest neighbor rule. For example in the caudal brainstem, neurons in the nucleus tractus solitarius never show Lewy pathology or degeneration in PD, but are near neighbors of DMV neurons and project axons to them. Synaptic connectivity per se also does not predict the pattern of Lewy pathology in PD. The spread of pathology reported by Lee's group following injection of α-synuclein fibrils into the brain appears to be more like a wave than spread based upon the strength of synaptic connectivity.[108] Thus, if α-synuclein fibrils spread the pathology in PD, then there has to be a modifier of susceptibility that accounts for its non-uniform distribution. Could susceptibility to α-synuclein fibril "infection" be determined by physiological phenotype? One of the key features of these neurons is that they have robust elevations in cytosolic calcium concentration. Calcium regulates exocytosis and exosome-mediated protein release.[109-111] These are the presumptive mechanisms by which α-synuclein fibrils will be delivered and taken up. Neuronal exosomal release is increased by depolarization[112] and exosome-mediated release of α-synuclein in particular is calcium-dependent.[113] Endocytosis, at least at nerve terminals, is also increased by calcium.[114] The vast axonal arbor of vulnerable neurons could also serve as a potent conduit for the propagation of pathology. If activity-dependent elevation in cytosolic calcium is required for the spread of α-synuclein pathology, then the pattern of pathology becomes understandable. It also would mean that vulnerable neurons are assaulted from two directions: metabolic and proteostatic.

Therapeutic implications. The translational question is how to devise a therapeutic strategy to stop or slow the progression of PD. Although there are not clear strategies for altering the risk factors associated with transmitter choice or axonal arbor, there is a way in which the consequences of the chatterbox phenotype on mitochondrial stress could be diminished. One of the

ion channels contributing to the basal metabolic stress in SNc, DMV and locus coeruleus neurons is the L-type calcium channel with a Cav1.3 pore-forming subunit. As mentioned above, antagonizing these channels diminishes mitochondrial oxidant stress in these neurons and lowers potentially damaging levels of cytosolic dopamine. Diminishing intracellular calcium levels could also lower the risk of α-synuclein aggregation and of taking up and passing on α-synuclein fibrils. There are FDA approved antagonists (dihydropyridines) of these channels that have an excellent safety record in humans. Moreover, there is epidemiological evidence that sustained use of dihydropyridines reduces the observed risk of PD.[115-117]

Summary

The pathological "roadmap" created by Lewy pathology and neuronal loss shows that PD is far from just a disease of dopaminergic neurons in the SNc. The spatially distributed, at-risk population of neurons share a number of features, including autonomously generated activity, broad action potentials, low intrinsic calcium buffering capacity and long, poorly myelinated, highly branched axons. These features might render them more vulnerable to infection by prion-like α-synuclein fibrils and more likely to propagate it. Although this constellation of features is likely to drive pathogenesis through a number of parallel pathways, mechanisms driven by the opening of L-type calcium channels appear to be the most therapeutically accessible.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

This work was supported by grants from the JPB Foundation (D.S. and D.J.S.), NIH (P50NS047085) (D.J.S.), NIH (P50NS38370) (D.S.) and Parkinson Disease Foundation (D.S.). We thank Drs Jaime Guzman, Javier Sanchez Paul Schumacker, Robert Burke, Luigi Zecca, Oren Levy, Michael Gershon, Kelly Del Tredici and Lloyd Greene for helpful discussion.

References

1. Fahn S, Sulzer D. Neurodegeneration and neuroprotection in Parkinson disease. NeuroRx 2004; 1:139-54; PMID:15717014; http://dx.doi.org/10.1602/neurorx.1.1.139.
2. Del Tredici K, Braak H. Lewy pathology and neurodegeneration in premotor Parkinson's disease. Mov Disord 2012; 27:597-607; PMID:22508278; http://dx.doi.org/10.1002/mds.24921.
3. Jellinger KA. Neuropathology of sporadic Parkinson's disease: evaluation and changes of concepts. Mov Disord 2012; 27:8-30; PMID:22081500; http://dx.doi.org/10.1002/mds.23795.
4. Braak H, Del Tredici K. Neuroanatomy and pathology of sporadic Parkinson's disease. Adv Anat Embryol Cell Biol 2009; 201:1-119; PMID:19230552.
5. Cersosimo MG, Benarroch EE. Autonomic involvement in Parkinson's disease: Pathology, pathophysiology, clinical features and possible peripheral biomarkers. J Neurol Sci 2011;313: 57-63; PMID:22001247; http://dx.doi.org/10.1016/j.jns.2011.09.030.
6. Goldstein DS, Holmes CS, Dendi R, Bruce SR, Li ST. Orthostatic hypotension from sympathetic denervation in Parkinson's disease. Neurology 2002; 58:1247-55; PMID:11971094; http://dx.doi.org/10.1212/WNL.58.8.1247.
7. Orimo S, Uchihara T, Kanazawa T, Itoh Y, Wakabayashi K, Kakita A, et al. Unmyelinated axons are more vulnerable to degeneration than myelinated axons of the cardiac nerve in Parkinson's disease. Neuropathol Appl Neurobiol 2011; 37:791-802; PMID:21696416; http://dx.doi.org/10.1111/j.1365-2990.2011.01194.x.
8. Ghebremedhin E, Del Tredici K, Langston JW, Braak H. Diminished tyrosine hydroxylase immunoreactivity in the cardiac conduction system and myocardium in Parkinson's disease: an anatomical study. Acta Neuropathol 2009; 118:777-84; PMID:19802627; http://dx.doi.org/10.1007/s00401-009-0596-y.
9. Amino T, Orimo S, Itoh Y, Takahashi A, Uchihara T, Mizusawa H. Profound cardiac sympathetic denervation occurs in Parkinson disease. Brain Pathol 2005; 15:29-34; PMID:15779234; http://dx.doi.org/10.1111/j.1750-3639.2005.tb00097.x.
10. Takeda S, Yamazaki K, Miyakawa T, Arai H. Parkinson's disease with involvement of the parasympathetic ganglia. Acta Neuropathol 1993; 86:397-8; PMID:8256591; http://dx.doi.org/10.1007/BF00369454.
11. Del Tredici K, Hawkes CH, Ghebremedhin E, Braak H. Lewy pathology in the submandibular gland of individuals with incidental Lewy body disease and sporadic Parkinson's disease. Acta Neuropathol 2010; 119:703-13; PMID:20229352; http://dx.doi.org/10.1007/s00401-010-0665-2.
12. Del Tredici K, Rüb U, De Vos RA, Bohl JR, Braak H. Where does parkinson disease pathology begin in the brain? J Neuropathol Exp Neurol 2002; 61:413-26; PMID:12030260.
13. Djaldetti R, Lev N, Melamed E. Lesions outside the CNS in Parkinson's disease. Mov Disord 2009; 24:793-800; PMID:19224610; http://dx.doi.org/10.1002/mds.22172.
14. Miki Y, Tomiyama M, Ueno T, Haga R, Nishijima H, Suzuki C, et al. Clinical availability of skin biopsy in the diagnosis of Parkinson's disease. Neurosci Lett 2010; 469:357-9; PMID:20026177; http://dx.doi.org/10.1016/j.neulet.2009.12.027.
15. Li Z, Chalazonitis A, Huang YY, Mann JJ, Margolis KG, Yang QM, et al. Essential roles of enteric neuronal serotonin in gastrointestinal motility and the development/survival of enteric dopaminergic neurons. J Neurosci 2011; 31:8998-9009; PMID:21677183; http://dx.doi.org/10.1523/JNEUROSCI.6684-10.2011.
16. Wakabayashi K, Takahashi H, Takeda S, Ohama E, Ikuta F. Parkinson's disease: the presence of Lewy bodies in Auerbach's and Meissner's plexuses. Acta Neuropathol 1988; 76:217-21; PMID:2850698; http://dx.doi.org/10.1007/BF00687767.
17. Anlauf M, Schäfer MK, Eiden L, Weihe E. Chemical coding of the human gastrointestinal nervous system: cholinergic, VIPergic, and catecholaminergic phenotypes. J Comp Neurol 2003; 459:90-111; PMID:12629668; http://dx.doi.org/10.1002/cne.10599.
18. Singaram C, Ashraf W, Gaumnitz EA, Torbey C, Sengupta A, Pfeiffer R, et al. Dopaminergic defect of enteric nervous system in Parkinson's disease patients with chronic constipation. Lancet 1995; 346:861-4; PMID:7564669; http://dx.doi.org/10.1016/S0140-6736(95)92707-7.
19. Lebouvier T, Chaumette T, Paillusson S, Duyckaerts C, Bruley des Varannes S, Neunlist M, et al. The second brain and Parkinson's disease. Eur J Neurosci 2009; 30:735-41; PMID:19712093; http://dx.doi.org/10.1111/j.1460-9568.2009.06873.x.
20. Gallegos-Orozco JF, Foxx-Orenstein AE, Sterler SM, Stoa JM. Chronic constipation in the elderly. Am J Gastroenterol 2012; 107:18-25, quiz 26; PMID:21989145; http://dx.doi.org/10.1038/ajg.2011.349.
21. Wakabayashi K, Takahashi H, Ohama E, Ikuta F. Parkinson's disease: an immunohistochemical study of Lewy body-containing neurons in the enteric nervous system. Acta Neuropathol 1990; 79:581-3; PMID:1972853; http://dx.doi.org/10.1007/BF00294234.
22. Lebouvier T, Neunlist M, Bruley des Varannes S, Coron E, Drouard A, N'Guyen JM, et al. Colonic biopsies to assess the neuropathology of Parkinson's disease and its relationship with symptoms. PLoS One 2010; 5:e12728; PMID:20856865; http://dx.doi.org/10.1371/journal.pone.0012728.
23. Del Tredici K, Braak H. A not entirely benign procedure: progression of Parkinson's disease. Acta Neuropathol 2008; 115:379-84; PMID:18320198; http://dx.doi.org/10.1007/s00401-008-0355-5.
24. Kalaitzakis ME, Graeber MB, Gentleman SM, Pearce RKB. Controversies over the staging of alpha-synuclein pathology in Parkinson's disease. Acta Neuropathol 2008; 116:125-8, author reply 129-31; PMID:18446352; http://dx.doi.org/10.1007/s00401-008-0381-3.
25. Jellinger KA. A critical evaluation of current staging of alpha-synuclein pathology in Lewy body disorders. Biochim Biophys Acta 2009; 1792:730-40; PMID:18718530; http://dx.doi.org/10.1016/j.bbadis.2008.07.006.
26. Gai WP, Blumbergs PC, Geffen LB, Blessing WW. Age-related loss of dorsal vagal neurons in Parkinson's disease. Neurology 1992; 42:2106-11; PMID:1436519; http://dx.doi.org/10.1212/WNL.42.11.2106.
27. Foix C, Nicolesco J. *Cérébrale: Les Noyauz Gris Centraux Et La Région Mésencephalo-Soue-Optique. SuiviD'Un Appendice Sur L'Anatomic Pathologique De La Maladie De Parkinson*. (Masson et Cie.: Paris, 1925).
28. Braak H, Del Tredici K, Rüb U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 2003; 24:197-211; PMID:12498954; http://dx.doi.org/10.1016/S0197-4580(02)00065-9.
29. Weihe E, Depboylu C, Schütz B, Schäfer MKH, Eiden LE. Three types of tyrosine hydroxylase-positive CNS neurons distinguished by dopa decarboxylase and VMAT2 co-expression. Cell Mol Neurobiol 2006; 26:659-78; PMID:16741673; http://dx.doi.org/10.1007/s10571-006-9053-9.

30. Tretiakoff C. Contribution a l'etude de l'anatomie pathologique du locus niger de Soemmering avec quelques dedutions relatives a la pathogenie des troubles du tonus musculaire et de la maladie de Parkinson. These de Paris 1919.
31. Eadie MJ. The pathology certain medullary nuceli in Parkinsonism. Brain 1963; 86:781-92; PMID:14090529; http://dx.doi.org/10.1093/brain/86.4.781.
32. Saper CB, Sorrentino DM, German DC, de Lacalle S. Medullary catecholaminergic neurons in the normal human brain and in Parkinson's disease. Ann Neurol 1991; 29:577-84; PMID:1892359; http://dx.doi.org/10.1002/ana.410290602.
33. Greenfield JG, Bosanquet FD. The brain-stem lesions in Parkinsonism. J Neurol Neurosurg Psychiatry 1953; 16:213-26; PMID:13109537; http://dx.doi.org/10.1136/jnnp.16.4.213.
34. Halliday GM, Li YW, Blumbergs PC, Joh TH, Cotton RG, Howe PR, et al. Neuropathology of immunohistochemically identified brainstem neurons in Parkinson's disease. Ann Neurol 1990; 27:373-85; PMID:1972319; http://dx.doi.org/10.1002/ana.410270405.
35. Fahn S. Description of Parkinson's disease as a clinical syndrome. Ann N Y Acad Sci 2003; 991:1-14; PMID:12846969; http://dx.doi.org/10.1111/j.1749-6632.2003.tb07458.x.
36. McRitchie DA, Cartwright HR, Halliday GM. Specific A10 dopaminergic nuclei in the midbrain degenerate in Parkinson's disease. Exp Neurol 1997; 144:202-13; PMID:9126172; http://dx.doi.org/10.1006/exnr.1997.6418.
37. Hirsch E, Graybiel AM, Agid YA. Melanized dopaminergic neurons are differentially susceptible to degeneration in Parkinson's disease. Nature 1988; 334:345-8; PMID:2899295; http://dx.doi.org/10.1038/334345a0.
38. Zarow C, Lyness SA, Mortimer JA, Chui HC. Neuronal loss is greater in the locus coeruleus than nucleus basalis and substantia nigra in Alzheimer and Parkinson diseases. Arch Neurol 2003; 60:337-41; PMID:12633144; http://dx.doi.org/10.1001/archneur.60.3.337.
39. Liang CL, Sinton CM, Sonsalla PK, German DC. Midbrain dopaminergic neurons in the mouse that contain calbindin-D28k exhibit reduced vulnerability to MPTP-induced neurodegeneration. Neurodegeneration 1996; 5:313-8; PMID:9117542; http://dx.doi.org/10.1006/neur.1996.0042.
40. Liang CL, Nelson O, Yazdani U, Pasbakhsh P, German DC. Inverse relationship between the contents of neuromelanin pigment and the vesicular monoamine transporter-2: human midbrain dopamine neurons. J Comp Neurol 2004; 473:97-106; PMID:15067721; http://dx.doi.org/10.1002/cne.20098.
41. Damier P, Hirsch EC, Agid Y, Graybiel AM. The substantia nigra of the human brain. II. Patterns of loss of dopamine-containing neurons in Parkinson's disease. Brain 1999; 122:1437-48; PMID:10430830; http://dx.doi.org/10.1093/brain/122.8.1437.
42. Gai WP, Halliday GM, Blumbergs PC, Geffen LB, Blessing WW. Substance P-containing neurons in the mesopontine tegmentum are severely affected in Parkinson's disease. Brain 1991; 114:2253-67; PMID:1718530; http://dx.doi.org/10.1093/brain/114.5.2253.
43. Jenkinson N, Nandi D, Muthusamy K, Ray NJ, Gregory R, Stein JF, et al. Anatomy, physiology, and pathophysiology of the pedunculopontine nucleus. Mov Disord 2009; 24:319-28; PMID:19097193; http://dx.doi.org/10.1002/mds.22189.
44. Jellinger K. The pedunculopontine nucleus in Parkinson's disease, progressive supranuclear palsy and Alzheimer's disease. J Neurol Neurosurg Psychiatry 1988; 51:540-3; PMID:3379428; http://dx.doi.org/10.1136/jnnp.51.4.540.
45. Hirsch EC, Graybiel AM, Duyckaerts C, Javoy-Agid F. Neuronal loss in the pedunculopontine tegmental nucleus in Parkinson disease and in progressive supranuclear palsy. Proc Natl Acad Sci U S A 1987; 84:5976-80; PMID:3475716; http://dx.doi.org/10.1073/pnas.84.16.5976.
46. Ubeda-Bañon I, Saiz-Sanchez D, de la Rosa-Prieto C, Argandoña-Palacios L, Garcia-Muñozguren S, Martinez-Marcos A. alpha-Synucleinopathy in the human olfactory system in Parkinson's disease: involvement of calcium-binding protein- and substance P-positive cells. Acta Neuropathol 2010; 119:723-35; PMID:20383714; http://dx.doi.org/10.1007/s00401-010-0687-9.
47. Wilson RS, Yu L, Schneider JA, Arnold SE, Buchman AS, Bennett DA. Lewy bodies and olfactory dysfunction in old age. Chem Senses 2011; 36:367-73; PMID:21257733; http://dx.doi.org/10.1093/chemse/bjq139.
48. Pearce RK, Hawkes CH, Daniel SE. The anterior olfactory nucleus in Parkinson's disease. Mov Disord 1995; 10:283-7; PMID:7651444; http://dx.doi.org/10.1002/mds.870100309.
49. Huisman E, Uylings HBM, Hoogland PV. Gender-related changes in increase of dopaminergic neurons in the olfactory bulb of Parkinson's disease patients. Mov Disord 2008; 23:1407-13; PMID:18581481; http://dx.doi.org/10.1002/mds.22009.
50. Baker H, Liu N, Chun HS, Saino S, Berlin R, Volpe B, et al. Phenotypic differentiation during migration of dopaminergic progenitor cells to the olfactory bulb. J Neurosci 2001; 21:8505-13; PMID:11606639.
51. Thannickal TC, Lai YY, Siegel JM. Hypocretin (orexin) cell loss in Parkinson's disease. Brain 2007; 130:1586-95; PMID:17491094; http://dx.doi.org/10.1093/brain/awm097.
52. Henderson JM, Carpenter K, Cartwright H, Halliday GM. Loss of thalamic intralaminar nuclei in progressive supranuclear palsy and Parkinson's disease: clinical and therapeutic implications. Brain 2000; 123:1410-21; PMID:10869053; http://dx.doi.org/10.1093/brain/123.7.1410.
53. Jellinger KA. Lewy body-related alpha-synucleinopathy in the aged human brain. J Neural Transm 2004; 111:1219-35; PMID:15480835; http://dx.doi.org/10.1007/s00702-004-0138-7.
54. Dickson DW, Braak H, Duda JE, Duyckaerts C, Gasser T, Halliday GM, et al. Neuropathological assessment of Parkinson's disease: refining the diagnostic criteria. Lancet Neurol 2009; 8:1150-7; PMID:19909913; http://dx.doi.org/10.1016/S1474-4422(09)70238-8.
55. Harnois C, Marcotte G, Daigle M, Di Paolo T. Retinal dopamine sensitivity to MPP+ toxicity: electrophysiological and biochemical evaluation. Neurosci Lett 1989; 107:19-25; PMID:2616030; http://dx.doi.org/10.1016/0304-3940(89)90784-2.
56. Cullen KM, Halliday GM. Neurofibrillary degeneration and cell loss in the nucleus basalis in comparison to cortical Alzheimer pathology. Neurobiol Aging 1998; 19:297-306; PMID:9733161; http://dx.doi.org/10.1016/S0197-4580(98)00066-9.
57. Nakano I, Hirano A. Parkinson's disease: neuron loss in the nucleus basalis without concomitant Alzheimer's disease. Ann Neurol 1984; 15:415-8; PMID:6732189; http://dx.doi.org/10.1002/ana.410150503.
58. Larsen KE, Fon EA, Hastings TG, Edwards RH, Sulzer D. Methamphetamine-induced degeneration of dopaminergic neurons involves autophagy and upregulation of dopamine synthesis. J Neurosci 2002; 22:8951-60; PMID:12388602.
59. Cubells JF, Rayport S, Rajendran G, Sulzer D. Methamphetamine neurotoxicity involves vacuolation of endocytic organelles and dopamine-dependent intracellular oxidative stress. J Neurosci 1994; 14:2260-71; PMID:8158268.
60. Mosharov EV, Larsen KE, Kanter E, Phillips KA, Wilson K, Schmitz Y, et al. Interplay between cytosolic dopamine, calcium, and alpha-synuclein causes selective death of substantia nigra neurons. Neuron 2009; 62:218-29; PMID:19409267; http://dx.doi.org/10.1016/j.neuron.2009.01.033.
61. Martinez-Vicente M, Talloczy Z, Kaushik S, Massey AC, Mazzulli J, Mosharov EV, et al. Dopamine-modified alpha-synuclein blocks chaperone-mediated autophagy. J Clin Invest 2008; 118:777-88; PMID:18172548.
62. Chen L, Ding Y, Cagniard B, Van Laar AD, Mortimer A, Chi W, et al. Unregulated cytosolic dopamine causes neurodegeneration associated with oxidative stress in mice. J Neurosci 2008; 28:425-33; PMID:18184785; http://dx.doi.org/10.1523/JNEUROSCI.3602-07.2008.
63. Sulzer D, Bogulavsky J, Larsen KE, Behr G, Karatekin E, Kleinman MH, et al. Neuromelanin biosynthesis is driven by excess cytosolic catecholamines not accumulated by synaptic vesicles. Proc Natl Acad Sci U S A 2000; 97:11869-74; PMID:11050221; http://dx.doi.org/10.1073/pnas.97.22.11869.
64. Sulzer D, Mosharov E, Talloczy Z, Zucca FA, Simon JD, Zecca L. Neuronal pigmented autophagic vacuoles: lipofuscin, neuromelanin, and ceroid as macroautophagic responses during aging and disease. J Neurochem 2008; 106:24-36; PMID:18384642; http://dx.doi.org/10.1111/j.1471-4159.2008.05385.x.
65. Braak H, Ghebremedhin E, Rüb U, Bratzke H, Del Tredici K. Stages in the development of Parkinson's disease-related pathology. Cell Tissue Res 2004; 318:121-34; PMID:15338272; http://dx.doi.org/10.1007/s00441-004-0956-9.
66. Matsuda W, Furuta T, Nakamura KC, Hioki H, Fujiyama F, Arai R, et al. Single nigrostriatal dopaminergic neurons form widely spread and highly dense axonal arborizations in the neostriatum. J Neurosci 2009; 29:444-53; PMID:19144844; http://dx.doi.org/10.1523/JNEUROSCI.4029-08.2009.
67. Choi SW, Gerencser AA, Lee DW, Rajagopalan S, Nicholls DG, Andersen JK, et al. Intrinsic bioenergetic properties and stress sensitivity of dopaminergic synaptosomes. J Neurosci 2011; 31:4524-34; PMID:21430153; http://dx.doi.org/10.1523/JNEUROSCI.5817-10.2011.
68. Liang CL, Wang TT, Luby-Phelps K, German DC. Mitochondria mass is low in mouse substantia nigra dopamine neurons: implications for Parkinson's disease. Exp Neurol 2007; 203:370-80; PMID:17010972; http://dx.doi.org/10.1016/j.expneurol.2006.08.015.
69. Abeliovich A, Schmitz Y, Fariñas I, Choi-Lundberg D, Ho WH, Castillo PE, et al. Mice lacking alpha-synuclein display functional deficits in the nigrostriatal dopamine system. Neuron 2000; 25:239-52; PMID:10707987; http://dx.doi.org/10.1016/S0896-6273(00)80886-7.
70. Larsen KE, Schmitz Y, Troyer MD, Mosharov E, Dietrich P, Quazi AZ, et al. Alpha-synuclein overexpression in PC12 and chromaffin cells impairs catecholamine release by interfering with a late step in exocytosis. J Neurosci 2006; 26:11915-22; PMID:17108165; http://dx.doi.org/10.1523/JNEUROSCI.3821-06.2006.
71. Nemani VM, Lu W, Berge V, Nakamura K, Onoa B, Lee MK, et al. Increased expression of alpha-synuclein reduces neurotransmitter release by inhibiting synaptic vesicle reclustering after endocytosis. Neuron 2010; 65:66-79; PMID:20152114; http://dx.doi.org/10.1016/j.neuron.2009.12.023.
72. Nakamura K, Nemani VM, Azarbal F, Skibinski G, Levy JM, Egami K, et al. Direct membrane association drives mitochondrial fission by the Parkinson disease-associated protein alpha-synuclein. J Biol Chem 2011; 286:20710-26; PMID:21489994; http://dx.doi.org/10.1074/jbc.M110.213538.

73. Surmeier DJ, Guzman JN, Sanchez J, Schumacker PT. Physiological phenotype and vulnerability in Parkinson's disease. Cold Spring Harb Perspect Med 2012; 2:a009290; PMID:22762023.
74. Williams JT, North RA, Shefner SA, Nishi S, Egan TM. Membrane properties of rat locus coeruleus neurones. Neuroscience 1984; 13:137-56; PMID:6493483; http://dx.doi.org/10.1016/0306-4522(84)90265-3.
75. Aston-Jones G, Cohen JD. An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. Annu Rev Neurosci 2005; 28:403-50; PMID:16022602; http://dx.doi.org/10.1146/annurev.neuro.28.061604.135709.
76. Travagli RA, Gillis RA, Rossiter CD, Vicini S. Glutamate and GABA-mediated synaptic currents in neurons of the rat dorsal motor nucleus of the vagus. Am J Physiol 1991; 260:G531-6; PMID:1672243.
77. Goldberg JA, Guzman JN, Estep CM, Ilijic E, Kondapalli J, Sanchez-Padilla J, et al. Calcium entry induces mitochondrial oxidant stress in vagal neurons at risk in Parkinson's disease. Nat Neurosci 2012; 15:1414-21; PMID:22941107; http://dx.doi.org/10.1038/nn.3209.
78. McCann MJ, Rogers RC. Oxytocin excites gastric-related neurones in rat dorsal vagal complex. J Physiol 1990; 428:95-108; PMID:2231433.
79. Chan JY, Chan SH. Passive electrical properties of spontaneously active neurons in the nucleus reticularis gigantocellularis of the cat. Neurosci Lett 1989; 97:169-74; PMID:2919002; http://dx.doi.org/10.1016/0304-3940(89)90158-4.
80. Serafin M, Khateb A, Mühlethaler M. Electrophysiology and lucifer yellow injection of nucleus gigantocellularis neurones in an isolated and perfused guinea pig brain in vitro. Neurosci Lett 1990; 120:5-8; PMID:2293091; http://dx.doi.org/10.1016/0304-3940(90)90154-2.
81. Kang Y, Kitai ST. Electrophysiological properties of pedunculopontine neurons and their postsynaptic responses following stimulation of substantia nigra reticulata. Brain Res 1990; 535:79-95; PMID:2292031; http://dx.doi.org/10.1016/0006-8993(90)91826-3.
82. Mao Y, Wang B, Kunze W. Characterization of myenteric sensory neurons in the mouse small intestine. J Neurophysiol 2006; 96:998-1010; PMID:16899648; http://dx.doi.org/10.1152/jn.00204.2006.
83. Rugiero F, Gola M, Kunze WA, Reynaud JC, Furness JB, Clerc N. Analysis of whole-cell currents by patch clamp of guinea-pig myenteric neurones in intact ganglia. J Physiol 2002; 538:447-63; PMID:11790812; http://dx.doi.org/10.1113/jphysiol.2001.013051.
84. Clerc N, Furness JB, Bornstein JC, Kunze WA. Correlation of electrophysiological and morphological characteristics of myenteric neurons of the duodenum in the guinea-pig. Neuroscience 1998; 82:899-914; PMID:9483544; http://dx.doi.org/10.1016/S0306-4522(97)00318-7.
85. Foehring RC, Zhang XF, Lee JCF, Callaway JC. Endogenous calcium buffering capacity of substantia nigral dopamine neurons. J Neurophysiol 2009; 102:2326-33; PMID:19675297; http://dx.doi.org/10.1152/jn.00038.2009.
86. Schmidt H, Arendt O, Brown EB, Schwaller B, Eilers J. Parvalbumin is freely mobile in axons, somata and nuclei of cerebellar Purkinje neurones. J Neurochem 2007; 100:727-35; PMID:17263794; http://dx.doi.org/10.1111/j.1471-4159.2006.04231.x.
87. Goldberg JA, Teagarden MA, Foehring RC, Wilson CJ. Nonequilibrium calcium dynamics regulate the autonomous firing pattern of rat striatal cholinergic interneurons. J Neurosci 2009; 29:8396-407; PMID:19571130; http://dx.doi.org/10.1523/JNEUROSCI.5582-08.2009.
88. Clerc N, Furness JB, Li ZS, Bornstein JC, Kunze WA. Morphological and immunohistochemical identification of neurons and their targets in the guinea-pig duodenum. Neuroscience 1998; 86:679-94; PMID:9881879; http://dx.doi.org/10.1016/S0306-4522(98)00025-6.
89. Tamura K, Ito H, Wade PR. Morphology, electrophysiology, and calbindin immunoreactivity of myenteric neurons in the guinea pig distal colon. J Comp Neurol 2001; 437:423-37; PMID:11503144; http://dx.doi.org/10.1002/cne.1293.
90. Gibb WRG. Melanin, tyrosine hydroxylase, calbindin and substance P in the human midbrain and substantia nigra in relation to nigrostriatal projections and differential neuronal susceptibility in Parkinson's disease. Brain Res 1992; 581:283-91; PMID:1382801; http://dx.doi.org/10.1016/0006-8993(92)90719-P.
91. Puopolo M, Raviola E, Bean BP. Roles of subthreshold calcium current and sodium current in spontaneous firing of mouse midbrain dopamine neurons. J Neurosci 2007; 27:645-56; PMID:17234596; http://dx.doi.org/10.1523/JNEUROSCI.4341-06.2007.
92. Guzman JN, Sánchez-Padilla J, Chan CS, Surmeier DJ. Robust pacemaking in substantia nigra dopaminergic neurons. J Neurosci 2009; 29:11011-9; PMID:19726659; http://dx.doi.org/10.1523/JNEUROSCI.2519-09.2009.
93. Putzier I, Kullmann PHM, Horn JP, Levitan ES. Cav1.3 channel voltage dependence, not Ca2+ selectivity, drives pacemaker activity and amplifies bursts in nigral dopamine neurons. J Neurosci 2009; 29:15414-9; PMID:20007466; http://dx.doi.org/10.1523/JNEUROSCI.4742-09.2009.
94. Beal MF. Excitotoxicity and nitric oxide in Parkinson's disease pathogenesis. Ann Neurol 1998; 44(Suppl 1):S110-4; PMID:9749581.
95. Slivka A, Cohen G. Hydroxyl radical attack on dopamine. J Biol Chem 1985; 260:15466-72; PMID:2999117.
96. Nicholls DG. Spare respiratory capacity, oxidative stress and excitotoxicity. Biochem Soc Trans 2009; 37:1385-8; PMID:19909281; http://dx.doi.org/10.1042/BST0371385.
97. Guzman JN, Sanchez-Padilla J, Wokosin D, Kondapalli J, Ilijic E, Schumacker PT, et al. Oxidant stress evoked by pacemaking in dopaminergic neurons is attenuated by DJ-1. Nature 2010; 468:696-700; PMID:21068725; http://dx.doi.org/10.1038/nature09536.
98. Goldberg JA, Guzman JN, Estep CM, Ilijic E, Kondapalli J, Sanchez-Padilla J, et al. Calcium entry induces mitochondrial oxidant stress in vagal neurons at risk in Parkinson's disease. Nat Neurosci 2012; 15:1414-21; PMID:22941107; http://dx.doi.org/10.1038/nn.3209.
99. Schapira AH. Mitochondria in the aetiology and pathogenesis of Parkinson's disease. Lancet Neurol 2008; 7:97-109; PMID:18093566; http://dx.doi.org/10.1016/S1474-4422(07)70327-7.
100. Bender A, Schwarzkopf RM, McMillan A, Krishnan KJ, Rieder G, Neumann M, et al. Dopaminergic midbrain neurons are the prime target for mitochondrial DNA deletions. J Neurol 2008; 255:1231-5; PMID:18604467; http://dx.doi.org/10.1007/s00415-008-0892-9.
101. Bender A, Krishnan KJ, Morris CM, Taylor GA, Reeve AK, Perry RH, et al. High levels of mitochondrial DNA deletions in substantia nigra neurons in aging and Parkinson disease. Nat Genet 2006; 38:515-7; PMID:16604074; http://dx.doi.org/10.1038/ng1769.
102. Kraytsberg Y, Simon DK, Turnbull DM, Khrapko K. Do mtDNA deletions drive premature aging in mtDNA mutator mice? Aging Cell 2009; 8:502-6; PMID:19416127; http://dx.doi.org/10.1111/j.1474-9726.2009.00484.x.
103. Nath S, Goodwin J, Engelborghs Y, Pountney DL. Raised calcium promotes α-synuclein aggregate formation. Mol Cell Neurosci 2011; 46:516-26; PMID:21145971; http://dx.doi.org/10.1016/j.mcn.2010.12.004.
104. Lloyd-Evans E, Platt FM. Lysosomal Ca(2+) homeostasis: role in pathogenesis of lysosomal storage diseases. Cell Calcium 2011; 50:200-5; PMID:21724254; http://dx.doi.org/10.1016/j.ceca.2011.03.010.
105. Pan T, Kondo S, Le W, Jankovic J. The role of autophagy-lysosome pathway in neurodegeneration associated with Parkinson's disease. Brain 2008; 131:1969-78; PMID:18187492; http://dx.doi.org/10.1093/brain/awm318.
106. Angot E, Steiner JA, Lema Tomé CM, Ekström P, Mattsson B, Björklund A, et al. Alpha-synuclein cell-to-cell transfer and seeding in grafted dopaminergic neurons in vivo. PLoS One 2012; 7:e39465; PMID:22737239; http://dx.doi.org/10.1371/journal.pone.0039465.
107. Kordower JH, Chu Y, Hauser RA, Freeman TB, Olanow CW. Lewy body-like pathology in long-term embryonic nigral transplants in Parkinson's disease. Nat Med 2008; 14:504-6; PMID:18391962; http://dx.doi.org/10.1038/nm1747.
108. Volpicelli-Daley LA, Luk KC, Patel TP, Tanik SA, Riddle DM, Stieber A, et al. Exogenous α-synuclein fibrils induce Lewy body pathology leading to synaptic dysfunction and neuron death. Neuron 2011; 72:57-71; PMID:21982369; http://dx.doi.org/10.1016/j.neuron.2011.08.033.
109. Mills IG, Urbé S, Clague MJ. Relationships between EEA1 binding partners and their role in endosome fusion. J Cell Sci 2001; 114:1959-65; PMID:11329382.
110. Savina A, Furlán M, Vidal M, Colombo MI. Exosome release is regulated by a calcium-dependent mechanism in K562 cells. J Biol Chem 2003; 278:20083-90; PMID:12639953; http://dx.doi.org/10.1074/jbc.M301642200.
111. Barclay JW, Morgan A, Burgoyne RD. Calcium-dependent regulation of exocytosis. Cell Calcium 2005; 38:343-53; PMID:16099500; http://dx.doi.org/10.1016/j.ceca.2005.06.012.
112. Fauré J, Lachenal G, Court M, Hirrlinger J, Chatellard-Causse C, Blot B, et al. Exosomes are released by cultured cortical neurones. Mol Cell Neurosci 2006; 31:642-8; PMID:16446100; http://dx.doi.org/10.1016/j.mcn.2005.12.003.
113. Emmanouilidou E, Melachroinou K, Roumeliotis T, Garbis SD, Ntzouni M, Margaritis LH, et al. Cell-produced alpha-synuclein is secreted in a calcium-dependent manner by exosomes and impacts neuronal survival. J Neurosci 2010; 30:6838-51; PMID:20484626; http://dx.doi.org/10.1523/JNEUROSCI.5699-09.2010.
114. Dittman J, Ryan TA. Molecular circuitry of endocytosis at nerve terminals. Annu Rev Cell Dev Biol 2009; 25:133-60; PMID:19575674; http://dx.doi.org/10.1146/annurev.cellbio.042308.113302.
115. Becker C, Jick SS, Meier CR. Use of antihypertensives and the risk of Parkinson disease. Neurology 2008; 70:1438-44; PMID:18256367; http://dx.doi.org/10.1212/01.wnl.0000303818.38960.44.
116. Ritz B, Rhodes SL, Qian L, Schernhammer E, Olsen JH, Friis S. L-type calcium channel blockers and Parkinson disease in Denmark. Ann Neurol 2010; 67:600-6; PMID:20437557.
117. Pasternak B, Svanström H, Nielsen NM, Fugger L, Melbye M, Hviid A. Use of calcium channel blockers and Parkinson's disease. Am J Epidemiol 2012; 175:627-35; PMID:22387374; http://dx.doi.org/10.1093/aje/kwr362.
118. Luk KC, Kehm V, Carroll J, Zhang B, O'Brien P, Trojanowski JQ, et al. Pathological α-synuclein transmission initiates Parkinson-like neurodegeneration in nontransgenic mice. Science 2012; 338:949-53; PMID:23161999; http://dx.doi.org/10.1126/science.1227157.
119. Song YJ, Huang Y, Halliday GM. Clinical correlates of similar pathologies in parkinsonian syndromes. Mov Disord 2011; 26:499-506; PMID:21259341; http://dx.doi.org/10.1002/mds.23336.
120. Szego ÉM, Gerhardt E, Outeiro TF, Kermer P. Dopamine-depletion and increased α-synuclein load induce degeneration of cortical cholinergic fibers in mice. J Neurol Sci 2011; 310:90-55; PMID:21774947; http://dx.doi.org/10.1016/j.jns.2011.06.048