Perspective: Low Risk of Parkinson's Disease in Quasi-Vegan Cultures May Reflect GCN2-Mediated Upregulation of Parkin

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ABSTRACT

Mitochondrial dysfunction in dopaminergic neurons of the substantia nigra (SN) appears to be a key mediating feature of Parkinson's disease (PD), a complex neurodegenerative disorder of still unknown etiology. Parkin is an E3 ubiquitin ligase that promotes mitophagy of damaged depolarized mitochondria while also boosting mitochondrial biogenesis—thereby helping to maintain efficient mitochondrial function. Boosting Parkin expression in the SN with viral vectors is protective in multiple rodent models of PD. Conversely, homozygosity for inactivating mutations of Parkin results in early-onset PD. Moderate protein plant-based diets relatively low in certain essential amino acids have the potential to boost Parkin expression by activating the kinase GCN2, which in turn boosts the expression of ATF4, a factor that drives transcription of the Parkin gene. Protein-restricted diets also upregulate the expression of PINK1, a protein that binds to the outer membrane of depolarized mitochondria and then recruits and activates Parkin. This effect of protein restriction is mediated by the downregulation of the kinase activity of mammalian target of rapamycin complex 1; the latter suppresses PINK1 expression at the transcriptional level. During the 20th century, cultures in East Asia and sub-Sahara Africa consuming quasi-vegan diets were found to be at notably decreased risk of PD compared with the USA or Europe. It is proposed that such diets may provide protection from PD by boosting Parkin and PINK1 expression in the SN. Other measures that might be expected to upregulate protective mitophagy include supplemental *N*-acetylcysteine (precursor for hydrogen sulfide) and a diet rich in spermidine—a polyamine notably high in corn. *Adv Nutr* 2021;12:355–362.

Keywords: Parkinson's disease, quasi-vegan, nutritional therapy, GCN2, parkin, mitophagy, mitochondrial dysfunction, PINK1, nutraceuticals

Introduction

Parkinson's disease in a nutshell

The second most common neurodegenerative disorder following Alzheimer's disease, Parkinson's disease (PD), affects 1–2 per 1000 of the population; its prevalence increases with age, affecting ∼1% of the population aged above 60 y (1). Males are more often affected than females, with a ratio of ∼3:2, and it is less prevalent in those of African or Asian ancestry. PD is classified as a movement disorder in which the most prominent signs are bradykinesia, tremor, rigidity, and postural instability. However, nonmotor symptoms such as depression, anxiety, hyposmia, sleep disorders, cognitive impairments, and constipation are increasingly gaining attention, and are now included among the clinical diagnostic supportive criteria (2). They can typically precede the motoric dysfunctions, sometimes by several years, but the neuroanatomical pathways responsible for these symptoms remain to be elucidated (3).

Pathophysiologically, PD is characterized by disruptions to protein folding attributable to various factors such as mutations, errors in transcription/translation, yet-unidentified environmental factors, or age-related decline, which leads to failures in protein quality control (proteostasis) in susceptible dopaminergic neurons (4). This results in aggregation of misfolded proteins and their organization into larger deposited structures—a hallmark process in neurodegenerative

conditions in general and in PD in particular. PD is characterized by the presence in the substantia nigra (SN) of Lewy bodies (LBs), protein aggregates whose primary constituent is misfolded α-synuclein (ASN), a protein of 140 amino acids. The accumulation of these protease-resistant ASN-rich LBs is associated with a marked loss in dopaminergic neurons of the SN, leading to reduced facilitation of voluntary movements, manifested as movement abnormality.

Several susceptibility genes and environmental factors are associated with increased risk of PD. In an umbrella review of meta-analyses examining environmental influences on PD risk, the only clearly established associations were with constipation and physical activity (5). Notably, many other factors showed suggestive links, including microbial or viral infections (6–8) and nutritional deficiencies (9). Recently, food-based strategies for preventing or controlling PD have been suggested, such as ingestion of phospholipid membrane precursors and microbiota-directed therapy (10). Vegetarian or vegan diets have been linked to decreased risk of numerous chronic conditions, including ischemic heart disease, cardiovascular disease, obesity, hyperlipidemia, diabetes, metabolic syndrome, diverticular disease, cancer, and eye cataract (11–14). However, the possible impact of such diets on PD risk has so far received minimal attention.

Quasi-vegan diet
Quasi-vegan diets have also been referred to as flexitarian, meat-reduced, semi- or demi- or partial vegetarian and reducetarian diets (15, 16). These terms are often used interchangeably in the nutritional, clinical, or scientific literature. Quasi-vegan diets refer to diets that, although primarily plant-based, may include the occasional consumption of poultry, fish, eggs, and dairy products—but typically avoid red meat. The main menu of quasi-vegans includes vegetables, fruits, whole grains, legumes, seeds, nuts, eggs, and dairy foods, with occasional poultry and fish (17). The people who avoid animal products other than fish are called pesco-vegetarians or pescatarians. Lacto-ovo-vegetarian diets allow the consumption of dairy products and eggs but avoid flesh foods. The reasons that people adopt a quasi-vegan diet include purported health benefits, religious convictions (Hinduism, Buddhism, and Jainism), animal welfare concerns prompted by inhumane housing and slaughtering of animals, ecological concerns owing to the high carbon footprint and extravagant use of limited resources associated with meat production, and household budgetary concerns reflecting the relatively high cost of meat. Traditional diets in some less-wealthy societies have been quasi-vegan simply owing to the relatively high cost of animal rearing.

Since meat is a rich source of proteins, quasi-vegan consumers need to take into consideration their daily protein intake, to ensure that they fulfill the RDA of 0.8 g of protein per kilogram of weight (18). For those quasi-vegetarians who avoid meat or fish, adequate protein intakes (10–35% of total daily calories) can be achieved from numerous sources: green peas, chickpeas, nuts, beans, quinoa, grains, tempeh and tofu, leafy greens, sunflower, sesame and poppy seeds, eggs, milk, and dairy products. Fruits, alcoholic beverages, added oils, and refined sugars and starches are very low in protein, and should not be the predominant components of a quasi-vegan diet. Those eating wholly or primarily plant-based diets need to supplement with vitamin B-12 and might also be well advised to supplement with the long-chain ω-3 fatty acids found in marine fish.

In 2001, McCarty, making note of pertinent ecologic epidemiology, suggested that the consumption of a quasi-vegan diet might help to prevent or control PD by slowing the loss of dopaminergic neurons, and might aid the efficacy of L-dopa therapy by minimizing the impact of variations of plasma amino acid concentrations on the blood-brain barrier transport of L-dopa (19). Notably, the impacts of quasi-vegan diets on neurodegenerative disease in general, and PD in particular, have received minimal consideration. As summarized below, some geoepidemiological data points to a notably lower age-adjusted risk of PD in societies in East Asia and sub-Sahara Africa whose traditional diets are quasi-vegan (20, 21). In the present communication, we are proposing a mechanism whereby the long-term consumption of quasi-vegan diets might indeed lessen PD risk.

Mitochondrial dysfunction in PD
Despite the unidentified etiology of sporadic PD, the crucial pathophysiological place of mitochondrial dysfunction in this disorder is well established and was recently summarized (22). This is 1 of 3 major cellular pathways that are affected in PD, the other 2 being proteostasis and oxidative/nitroxidative stress; but all 3 are interconnected, reinforcing each other in multiple ways (23). Several endogenous and exogenous factors can inhibit mitochondrial functional integrity: heavy metals, agricultural pesticides and herbicides, paraquat, rotenone, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, high concentrations of nitric oxide, the dopamine metabolite aminochrome, and others have also been reported. With respect to familial PD, this has been linked to genetic polymorphisms of a number of genes coding for proteins that influence mitochondrial structure and function. These genes include *ATP13A2*, *PINK1*, *CHCHD2*, *LRRK2*, *SNCA*, *GBA* and also *Parkin*, a key focus of this review (24).

Polymerized ASN, the hallmark of PD, induces mitochondrial dysfunction. By binding to mitochondrial outer membrane proteins such as voltage-dependent anion-selective channel 1 (VDAC1), translocase of outer membrane (TOM) 40 and TOM20, it mediates mitochondrial dysfunction (25). Oxidative stress is tightly related to PD mitochondrial dysfunction. The accumulation of unfolded ASN in mitochondria inhibits complex I activity, thereby driving mitochondrial reactive oxygen species production (26). The accumulation of iron within the SN enhances oxidative stress and promotes local ASN aggregation, thereby exacerbating mitochondrial dysfunction (27).

The mitochondria are extremely dynamic intracellular organelles; a proper balance between mitochondrial biogenesis and mitophagy ensures that cells have adequate

numbers of functionally efficient mitochondria. The failure of mitochondrial quality control mechanisms is an important contribution to PD development. Dysfunction of the mitochondrial electron transport chain plays a central role in the pathogenesis of PD and is associated with oxidative stress and alterations to the mitochondrial genome (22).

The role of impaired mitophagy in the genesis of PD deserves some emphasis. Malfunctions of Parkin that are inherited (in some familial PD), or acquired, result in excessive expression of Drp1, which when phosphorylated and translocated to mitochondria, catalyzes mitochondrial fission (28). Excessive concentrations of nitric oxide can cause nitrosylation of Parkin, which suppresses its ubiquitin ligase activity, boosting Drp1 concentrations, and resulting in mitochondrial hyperfragmentation (29). It seems that all of the above PD-associated mitochondrial abnormalities interact and are crossconnected, hence, establishing the pathogenic basis of PD synucleinopathy.

Parkin Protects against PD by Preserving Efficient Mitochondrial Function

Individuals who are homozygous for loss of function of the E3 ubiquitin ligase Parkin develop early-onset PD (30, 31). This may reflect a key role for Parkin in promoting mitophagy of depolarized mitochondria, and in stimulating mitochondrial biogenesis (32, 33). PINK1 binds to the outer membrane of depolarized mitochondria and recruits Parkin, which promotes proteasomal degradation of outer membrane proteins that tether mitochondria to other structures, and mark the outer membrane with polyubiquitin chains that promote incorporation of mitochondria into developing autophagosomes (32). Concurrently, Parkin promotes mitochondrial biogenesis by inducing proteasomal degradation of PARIS, a protein that represses the transcription of $PGC1\alpha$, a key driver of mitochondrial biogenesis (34). Nitrosylation of Parkin suppresses its activity, whereas persulfidation boosts it—phenomena thought to contribute to the pathogenic role of excess nitric oxide, and the protective role of hydrogen sulfide (H_2S), respectively, in PD (35, 36). The maintenance of efficient mitochondrial bioenergetics is highly important to dopaminergic neurons in the SN, as their long, highly arborized axons make over a million synaptic connections; maintaining the proper function of these connections imposes a heavy energy burden that can only be met by rapid mitochondrial ATP generation (37). It is notable that mutations of other proteins required for efficient mitophagy—such as PINK1 and LRRK2—have likewise been linked to early-onset PD (33).

The overexpression of Parkin in the SN via lentiviral vectors protects mice from PD induced with 6-hydroxydopamine, MTPT, or mutant ASN (38–40). This suggests that more clinically practical measures for enhancing striatal Parkin expression might aid prevention or control of PD. The ATF4 transcription factor has been shown to promote transcription of the *Parkin* gene (41, 42). The protein expression of ATF4 is increased when, under certain stress conditions, eIF2α kinase is activated, leading to phosphorylation of

eIF2α that selectively boosts translation of ATF4 mRNA (43). Intriguingly, drugs that amplify the activation of this kinase—salubrinal and guanabenz—have been shown to be protective in rodent models of PD (44, 45).

Parkin Expression Can be Boosted by Dietary Restriction of Essential Amino Acids

GCN2 is a kinase that very selectively phosphorylates and thereby activates eIF2α kinase (46). GCN2, in turn, functions as a detector of essential amino acid deficiency; uncharged tRNAs that accumulate when cellular concentrations of 1 or more essential amino acids are low can bind to and directly activate GCN2 (46–48). Protein-restricted diets in mice lead to an increase in hepatic eIF2α phosphorylation and a marked increase in hepatic production of fibroblast growth factor-21 (FGF21), whose transcription is driven by ATF4; this effect is absent in GCN2 knockout mice (49). Upregulation of FGF21, by reducing the responsiveness of hepatocytes to growth hormone, may be responsible for the decrease in hepatic IGF-I production associated with low-protein diets (50, 51). Protein-restricted diets in humans have likewise been shown to increase plasma FGF21 and decrease plasma insulin-like growth factor (IGF-I) (49, 51). A recent cross-sectional study found that plasma concentrations of FGF21 tend to be about 3-fold higher in vegans than in omnivores ($P < 0.01$) (52). Vegan diets of modest protein content tend to be relatively low in certain essential amino acids, notably methionine and lysine (53, 54). Furthermore, vegans are known to have relatively low plasma IGF-I concentrations (54, 55).

Low-Protein Diets Also Promote Efficient Mitophagy by Downregulating Mammalian Target of Rapamycin Complex 1 Activity

Amino acid status regulates not only GCN2 activity, but also that of the crucial regulatory kinase mammalian target of rapamycin complex 1 (mTORC1). Increased cellular concentrations of leucine, arginine, and of the methionine metabolite S-adenosylmethionine boost mTORC1 activity by suppressing mechanisms that turn off this activity (56–62). Crucially, mTORC1 acts to inhibit the expression of PINK1 at the transcriptional level; this effect might be mediated, in part, by transcriptional repression of FOXO1a, which binds to the promoter of the *PINK1* gene and promotes its transcription (63–65). Since PINK1 is required for the recruitment of Parkin to damaged depolarized mitochondria, mTORC1 functions to suppress mitophagy (63–65). Conversely, low-protein diets can be expected to boost mitophagy by the concurrent activation of GCN2 and deactivation of mTORC1. As might be expected, certain genetic variants of *PINK1* have been linked to autosomal recessive early-onset PD (66).

Quasi-Vegan Diets Have Been Associated with Lower Parkinson's Risk

During the 20th century, epidemiological analyses found that age-adjusted PD rates in Europe and the Americas tended

to relatively uniform, whereas those in sub-Sahara Africa, rural China, and Japan tended to be notably lower (18, 20, 21). Investigations conducted by Schoenberg and colleagues comparing the age-adjusted prevalence of PD in the USA, rural China, and Nigeria found that this prevalence was notably lower in the latter 2 (67). Although more recent studies suggest that the prevalence of PD in black Americans is lower than that of whites or Asians, Schoenberg's door-to-door community-based studies, using identical assessment methods, found that age-adjusted PD prevalence was 5 times higher among blacks in Mississippi than those in Nigeria (67–70). These observations suggest that environmental factors may be largely responsible for the observed discrepancies in risk. Although black Americans often carry genes of non-African origin, it seems unlikely that this alone could account for disparities in PD risk of this magnitude. It is notable that the traditional diets of the low-risk areas tend to be relatively low in protein and are quasi-vegan. We, therefore, suggest that the relatively low risk of PD observed in sub-Saharan Africanand East Asian cultures may reflect, in part, a modest intake of protein and essential amino acids. This could be expected to decrease PD risk by upregulating the striatal production of Parkin via increased GCN2 and ATF4 activity, and by upregulating PINK1 synthesis via the downregulation of mTORC1 activity—thereby boosting mitophagy. We do not rule out the possibility that a lower daily calorie intake, increased physical activity, or other factors might also contribute to lower PD risk in these cultures.

Conceivably, vegan diets might also confer protection from PD owing to a decreased content of fat-soluble chemical contaminants that tend to accumulate in animal fat—some of which are potentially toxic to dopaminergic neurons (71–73). Moreover, whole-food plant-based diets tend to be rich in phytochemicals, many of which have phase 2-inductive activity, increasing the expression of various antioxidant enzymes and boosting glutathione synthesis (71, 74, 75). Prospective epidemiology has linked increased dietary flavonoid intakes to a lower risk of PD (75).

The impact of protein restriction on animal models of PD appears to have received little study. Protein-restricted or plant-based diets have been studied clinically in short-term studies as a strategy for improving the response to levodopa therapy – as postprandial increases in plasma branched-chain amino acids competitively inhibit the transport of levodopa through the blood-brain barrier—but not as a measure for preventing or slowing the progression of PD (76–78). A handful of anecdotal reports in journals or the internet are consistent with the possibility that plant-based diets might slow PD progression (19, 79). It would be of interest to determine how low-protein diets or diets restricted in single essential amino acids influence Parkin and PINK1 expression in the striatum of rodents, and whether such diets might be protective in rodent PD models.

Adjunctive Measures for Upregulating Mitophagy—Spermidine and Dietary Corn

Upregulation of mitophagy may be viewed as a key strategy for the prevention of PD. Both autophagy and mitophagy can be promoted by various measures, which prevent the lysine acetylation of certain proteins that are key mediators of autophagy. In particular, agents that prevent or reverse the activity of the histone acetylase EP300—dubbed "caloric restriction mimetics"—have been shown to have this effect (80–85). Of particular interest in this regard is the polyamine spermidine, which competitively inhibits the binding of EP300 to its substrate acetyl-CoA (85). Dietary spermidine is well absorbed, and spermidine-enriched diets have been shown to promote both autophagy and mitophagy in rats and other organisms (86–89). Moreover, the administration of spermidine has been shown to protect rats from rotenone-induced PD, and nematodes and fruit flies from a Parkinsonian syndrome induced by ASN overexpression (90, 91). The cerebrospinal fluid concentrations of spermidine in PD patients were found to be lower than those of controls (92). Commercial spermidine nutraceuticals are not yet available, but certain foods are relatively rich in this compound. The food which stands out most in this regard is corn; a cup (250 g) of canned corn contains about 60 mg of spermidine (whereas the median daily intake of spermidine in American postmenopausal women has been estimated to be ~10 mg) (93, 94). A search for correlations between corn consumption and PD risk revealed a Japanese study in which corn-raising regions in Japan were found to be at decreased risk of PD (95, 96). Perhaps a vegan diet high in corn might be of particular merit for PD protection; the notably low tryptophan and lysine content of the chief corn protein, zein, may aid GCN2 activation in such diets (97). Consistent with a role for autophagy/mitophagy in the promotion of lifespan/health span, dietary spermidine intake has been found to correlate inversely with total mortality in a prospective epidemiological investigation (98, 99).

Although it is an amino acid, cysteine may upregulate mitophagy by serving as a substrate for the production of H_2S (100). Via persulfidation, this boosts the activity of USP8, a deubiquitinase that aids mitophagy by removing K6-linked polyubiquitin chains from Parkin; for reasons that remain unclear, the self-induced polyubiquitination of Parkin hinders mitophagy (101, 102). Furthermore, as noted above, persulfidation of Parkin itself boosts its catalytic activity (36). H_2S can also promote both autophagy and mitophagy by activating AMP-activated kinase (AMPK) via calmodulin-activated kinase kinase-β; how H_2S activates the latter has not been determined (103, 104). AMPK promotes macroautophagy by conferring inhibitory phosphorylation on mTORC1 as well as activating phosphorylation on ULK1, a key initial mediator in the initial formation of autophagosomes (105, 106). Not surprisingly, supplemental N-acetylcysteine has been found to be protective in rodent models of PD (107, 108).

However, increased dietary cysteine also has the potential to decrease mitophagy by diminishing the *need* for mitophagy. Cysteine is the rate-limiting substrate for glutathione synthesis; intramitochondrial glutathione provides antioxidant protection for the mitochondrial respiratory chain, and hence may tend to prevent the decline in mitochondrial potential that triggers mitophagy (109). Glutathione concentrations in the SN of PD patients have been found to be low relative to control concentrations (110, 111). Especially in the elderly, in whom tissue concentrations of both cysteine and glutathione tend to decline, supplementation of low-protein diets with *N*-acetylcysteine may be advisable, for the promotion of both glutathione and H_2S synthesis (112, 113).

Broader Health Ramifications of Mitophagy Upregulation

A more general thesis that might be derived from these considerations is that vegan diets of modest protein content may help to minimize oxidative stress of mitochondrial origin by upregulating mitophagy. Hence, such diets may be protective in the range of disorders in which mitochondrial oxidative stress plays a pathogenic role—PD being a notable case in point. Intriguingly, Parkin can protect the heart from ischemia-reperfusion damage by promoting ubiquitination and degradation of cyclophilin-D; the latter is required for the formation of mitochondrial permeability transition pores, which precipitates cardiomyocyte necrosis during cardiac ischemia-reperfusion injury (114). Moreover, studies employing the phosphatase inhibitor salubrinal, which upregulates the phosphorylation of eIF2α, find that this drug provides protection in cardiac and cerebral ischemia-reperfusion, cardiac hypertrophy, hypoxic pulmonary hypertension, and brain trauma (115–123); the extent to which ATF4 and/or Parkin contribute to these benefits remains to be evaluated. In any case, these results suggest that moderately protein vegan diets, via activation of GCN2 and consequent phosphorylation of eIF2α, may be protective in these syndromes.

ATF4 also promotes transcription of the gene coding for nrf2, the mediator of phase 2 induction of cytoprotective/antioxidant enzymes—suggesting an additional mechanism whereby low-protein vegan diets may aid control of oxidative stress (124, 125). Indeed, a low-protein diet has been shown to increase the expression of nrf2 mRNA in the monocytes of patients with chronic renal disease (126). This effect could be expected to interact synergistically with the administration of clinically effective phase 2-inductive nutraceuticals, such as lipoic or ferulic acids (127, 128).

Conclusions

Efficient mitochondrial function is of great importance for the proper function and survival of dopaminergic neurons of the SN, which, owing to their vastly ramified neural connections, have an extremely high requirement for mitochondrially generated ATP. A failure of well-coordinated mitophagy and compensatory mitochondrial biogenesis in these neurons during the evolution of PD results in the accumulation of mitochondria that are dysfunctional, hyperfragmented, and a major source of oxidative stress. The proteins Parkin and PINK1 are key mediators of mitophagy and mitochondrial biogenesis, and upregulation of their expression is notably protective in rodent models of PD. Diets relatively low in protein and certain essential amino acids tend to boost the activity of GCN2—leading to an ATF4-dependent transcriptional upregulation of Parkin expression—and a decline in mTORC1 activity, resulting in enhanced transcription of the gene coding for PINK1. These phenomena may rationalize, at least in part, epidemiology pointing to relatively low age-adjusted risk of PD in African and East Asian populations whose traditional diets have been quasi-vegan. The influence of quantity and quality of dietary protein on SN expression of Parkin/PINK1 in rodents, and on PD risk in rodent models of PD, should be examined. Other dietary measures that upregulate mitophagy/autophagy, such as increased dietary spermidine, may also have potential for PD prevention; further epidemiology should evaluate a possible correlation between dietary spermidine content—or corn consumption—and PD risk.

Acknowledgments

References

1. Tysnes OB, Storstein A. Epidemiology of Parkinson's disease. J Neural Transm 2017;124:901–5.
2. Klingelhoefer L, Reichmann H. The gut and nonmotor symptoms in Parkinson's disease. Int Rev Neurobiol 2017;134:787–809.
3. Schapira AHV, Chaudhuri KR, Jenner P. Non-motor features of Parkinson disease. Nat Rev Neurosci 2017;18:435–50.
4. Shrestha A, Megeney LA. Yeast proteinopathy models: a robust tool for deciphering the basis of neurodegeneration. Microb Cell 2015;2:458–65.
5. Bellou V, Belbasis L, Tzoulaki I, Evangelou E, Ioannidis JP. Environmental risk factors and Parkinson's disease: an umbrella review of meta-analyses. Parkinsonism Relat Disord 2016;23:1–9.
6. Limphaibool N, Iwanowski P, Holstad MJV, Kobylarek D, Kozubski W. Infectious etiologies of Parkinsonism: pathomechanisms and clinical implications. Front Neurol 2019;10:652.
7. Jang H, Boltz DA, Webster RG, Smeyne RJ. Viral Parkinsonism. Biochim Biophys Acta 2009;1792:714–21.
8. Perez-Pardo P, Hartog M, Garssen J, Kraneveld AD. Microbes tickling your tummy: the importance of the gut-brain axis in Parkinson's disease. Curr Behav Neurosci Rep 2017;4:361–8.
9. Barichella M, Cereda E, Pezzoli G. Major nutritional issues in the management of Parkinson's disease. Mov Disord 2009;24: 1881–92.
10. Perez-Pardo P, Kliest T, Dodiya HB, Broersen LM, Garssen J, Keshavarzian A, Kraneveld AD. The gut-brain axis in Parkinson's disease: possibilities for food-based therapies. Eur J Pharmacol 2017;817:86–95.
11. Dinu M, Abbate R, Gensini GF, Casini A, Sofi F. Vegetarian, vegan diets and multiple health outcomes: a systematic review with

meta-analysis of observational studies. Crit Rev Food Sci Nutr 2017;57:3640–9.

12. Appleby PN, Key TJ. The long-term health of vegetarians and vegans. Proc Nutr Soc 2016;75:287–93.

13. Chiu YF, Hsu CC, Chiu TH, Lee CY, Liu TT, Tsao CK, Chuang SC, Hsiung CA. Cross-sectional and longitudinal comparisons of metabolic profiles between vegetarian and non-vegetarian subjects: a matched cohort study. Br J Nutr 2015;114:1313–20.

14. Kahleova H, Levin S, Barnard N. Cardio-metabolic benefits of plant-based diets. Nutrients 2017;9(8):848.

15. Forestell CA. Flexitarian diet and weight control: healthy or risky eating behavior? Front Nutr 2018;5:59.

16. Derbyshire EJ. Flexitarian diets and health: a review of the evidence-based literature. Front Nutr 2016;3:55.

17. Wozniak H, Larpin C, de MC, Guessous I, Reny JL, Stringhini S. Vegetarian, pescatarian and flexitarian diets: sociodemographic determinants and association with cardiovascular risk factors in a Swiss urban population. Br J Nutr 2020;1–9.

18. Committee on Dietary Allowances FaNB. Recommended Dietary Allowances. Washington (DC): National Academy Press: 1989.

19. McCarty MF. Does a vegan diet reduce risk for Parkinson's disease? Med Hypotheses 2001;57:318–23.

20. Williams U, Bandmann O, Walker R. Parkinson's disease in sub-Saharan Africa: a review of epidemiology, genetics and access to care. JMD 2018;11:53–64.

21. Ma CL, Su L, Xie JJ, Long JX, Wu P, Gu L. The prevalence and incidence of Parkinson's disease in China: a systematic review and meta-analysis. J Neural Transm 2014;121:123–34.

22. Park JS, Davis RL, Sue CM. Mitochondrial dysfunction in Parkinson's disease: new mechanistic insights and therapeutic perspectives. Curr Neurol Neurosci Rep 2018;18:21.

23. Ganguly G, Chakrabarti S, Chatterjee U, Saso L. Proteinopathy, oxidative stress and mitochondrial dysfunction: cross talk in Alzheimer's disease and Parkinson's disease. Drug Des Devel Ther 2017;11:797–810.

24. Lesage S, Brice A. Role of mendelian genes in "sporadic" Parkinson's disease. Parkinsonism Relat Disord 2012;18(Suppl 1):S66–70.

25. Pozo Devoto VM, Falzone TL. Mitochondrial dynamics in Parkinson's disease: a role for alpha-synuclein? Dis Model Mech 2017;10:1075–87.

26. Mullin S, Schapira A. alpha-Synuclein and mitochondrial dysfunction in Parkinson's disease. Mol Neurobiol 2013;47:587–97.

27. Munoz Y, Carrasco CM, Campos JD, Aguirre P, Nunez MT. Parkinson's disease: the mitochondria-iron link. Parkinsons Dis 2016;2016:7049108.

28. Santos D, Esteves AR, Silva DF, Januario C, Cardoso SM. The impact of mitochondrial fusion and fission modulation in sporadic Parkinson's disease. Mol Neurobiol 2015;52:573–86.

29. Zhang Z, Liu L, Jiang X, Zhai S, Xing D. The essential role of Drp1 and its regulation by S-nitrosylation of Parkin in dopaminergic neurodegeneration: implications for Parkinson's disease. Antioxid Redox Signal 2016;25:609–22.

30. Kitada T, Asakawa S, Hattori N, Matsumine H, Yamamura Y, Minoshima S, Yokochi M, Mizuno Y, Shimizu N. Mutations in the Parkin gene cause autosomal recessive juvenile Parkinsonism. Nature 1998;392:605–8.

31. Abbas N, Lucking CB, Ricard S, Dürr A, Bonifati V, De Michele G, Bouley S, Vaughan JR, Gasser T, Marconi R, et al. A wide variety of mutations in the Parkin gene are responsible for autosomal recessive Parkinsonism in Europe. French Parkinson's Disease Genetics Study Group and the European Consortium on Genetic Susceptibility in Parkinson's Disease. Hum Mol Genet 1999;8:567–74.

32. Mouton-Liger F, Jacoupy M, Corvol JC, Corti O. PINK1/Parkin-dependent mitochondrial surveillance: from pleiotropy to Parkinson's disease. Front Mol Neurosci 2017;10:120.

33. Wang X. Destructive cellular paths underlying familial and sporadic Parkinson disease converge on mitophagy. Autophagy 2017;13:1998–9.

34. Castillo-Quan JI. Parkin' control: regulation of PGC-1alpha through PARIS in Parkinson's disease. Dis Model Mech 2011;4:427–9.

35. Chung KK, Thomas B, Li X, Pletnikova O, Troncoso JC, Marsh L, Dawson VL, Dawson TM. S-nitrosylation of Parkin regulates ubiquitination and compromises Parkin's protective function. Science 2004;304:1328–31.

36. Vandiver MS, Paul BD, Xu R, Karuppagounder S, Rao F, Snowman AM, Ko HS, Lee YI, Dawson VL, Dawson TM, et al. Sulfhydration mediates neuroprotective actions of Parkin. Nat Commun 2013;4:1626.

37. Pissadaki EK, Bolam JP. The energy cost of action potential propagation in dopamine neurons: clues to susceptibility in Parkinson's disease. Front Comput Neurosci 2013;7:13.

38. Vercammen L, Van der Perren A, Vaudano E, Gijsbers R, Debyser Z, Van den Haute C, Baekelandt V. Parkin protects against neurotoxicity in the 6-hydroxydopamine rat model for Parkinson's disease. Mol Ther 2006;14:716–23.

39. Lo BC, Schneider BL, Bauer M, Sajadi A, Brice A, Iwatsubo T, Aebischer P. Lentiviral vector delivery of Parkin prevents dopaminergic degeneration in an alpha-synuclein rat model of Parkinson's disease. Proc Natl Acad Sci USA 2004;101:17510–5.

40. Yasuda T, Hayakawa H, Nihira T, Ren YR, Nakata Y, Nagai M, Hattori N, Miyake K, Takada M, Shimada T, et al. Parkin-mediated protection of dopaminergic neurons in a chronic MPTP-minipump mouse model of Parkinson disease. J Neuropathol Exp Neurol 2011;70:686–97.

41. Bouman L, Schlierf A, Lutz AK, Shan J, Deinlein A, Kast J, Galehdar Z, Palmisano V, Patenge N, Berg D, et al. Parkin is transcriptionally regulated by ATF4: evidence for an interconnection between mitochondrial stress and ER stress. Cell Death Differ 2011;18:769–82.

42. Sun X, Liu J, Crary JF, Malagelada C, Sulzer D, Greene LA, Levy OA. ATF4 protects against neuronal death in cellular Parkinson's disease models by maintaining levels of Parkin. J Neurosci 2013;33:2398–407.

43. Rutkowski DT, Kaufman RJ. All roads lead to ATF4. Dev Cell 2003;4:442–4.

44. Wu L, Luo N, Zhao HR, Gao Q, Lu J, Pan Y, Shi JP, Tian YY, Zhang YD. Salubrinal protects against rotenone-induced SH-SY5Y cell death via ATF4-parkin pathway. Brain Res 2014;1549:52–62.

45. Sun X, Aime P, Dai D, Ramalingam N, Crary JF, Burke RE, Greene LA, Levy OA. Guanabenz promotes neuronal survival via enhancement of ATF4 and Parkin expression in models of Parkinson disease. Exp Neurol 2018;303:95–107.

46. Berlanga JJ, Santoyo J, De HC. Characterization of a mammalian homolog of the GCN2 eukaryotic initiation factor 2alpha kinase. Eur J Biochem 1999;265:754–62.

47. Sood R, Porter AC, Olsen DA, Cavener DR, Wek RC. A mammalian homologue of GCN2 protein kinase important for translational control by phosphorylation of eukaryotic initiation factor-2alpha. Genetics 2000;154:787–801.

48. Ravishankar B, Liu H, Shinde R, Chaudhary K, Xiao W, Bradley J, Koritzinsky M, Madaio MP, McGaha TL. The amino acid sensor GCN2 inhibits inflammatory responses to apoptotic cells promoting tolerance and suppressing systemic autoimmunity. Proc Natl Acad Sci USA 2015;112:10774–9.

49. Laeger T, Henagan TM, Albarado DC, Redman LM, Bray GA, Noland RC, Münzberg H, Hutson SM, Gettys TW, Schwartz MW, et al. FGF21 is an endocrine signal of protein restriction. J Clin Invest 2014;124:3913–22.

50. Maiter D, Fliesen T, Underwood LE, Maes M, Gerard G, Davenport ML, Ketelslegers JM. Dietary protein restriction decreases insulin-like growth factor I independent of insulin and liver growth hormone binding. Endocrinology 1989;124:2604–11.

51. Fontana L, Cummings NE, Arriola Apelo SI, Neuman JC, Kasza I, Schmidt BA, Cava E, Spelta F, Tosti V, Syed FA, et al. Decreased consumption of branched-chain amino acids improves metabolic health. Cell Rep 2016;16:520–30.

52. Castano-Martinez T, Schumacher F, Schumacher S, Kochlik B, Weber D, Grune T, Biemann R, McCann A, Abraham K, Weikert C, et al.

Methionine restriction prevents onset of type 2 diabetes in NZO mice. FASEB J 2019;33:7092–102.

53. McCarty MF, Barroso-Aranda J, Contreras F. The low-methionine content of vegan diets may make methionine restriction feasible as a life extension strategy. Med Hypotheses 2009;72:125–8.

54. McCarty MF. GCN2 and FGF21 are likely mediators of the protection from cancer, autoimmunity, obesity, and diabetes afforded by vegan diets. Med Hypotheses 2014;83:365–71.

55. McCarty MF. Insulin and IGF-I as determinants of low "Western" cancer rates in the rural third world. Int J Epidemiol 2004;33:908–10.

56. Lee JH, Cho US, Karin M. Sestrin regulation of TORC1: is Sestrin a leucine sensor? Sci Signal 2016;9:re5.

57. Xu D, Shimkus KL, Lacko HA, Kutzler L, Jefferson LS, Kimball SR. Evidence for a role for Sestrin1 in mediating leucine-induced activation of mTORC1 in skeletal muscle. Am J Physiol Endocrinol Metab 2019;316:E817–28.

58. Chantranupong L, Scaria SM, Saxton RA, Gygi MP, Shen K, Wyant GA, Wang T, Harper JW, Gygi SP, Sabatini DM. The CASTOR proteins are arginine sensors for the mTORC1 pathway. Cell 2016;165: 153–64.

59. Saxton RA, Chantranupong L, Knockenhauer KE, Schwartz TU, Sabatini DM. Mechanism of arginine sensing by CASTOR1 upstream of mTORC1. Nature 2016;536:229–33.

60. Gu X, Orozco JM, Saxton RA, Condon KJ, Liu GY, Krawczyk PA, Scaria SM, Harper JW, Gygi SP, Sabatini DM. SAMTOR is an S-adenosylmethionine sensor for the mTORC1 pathway. Science 2017;358:813–8.

61. Kitada M, Ogura Y, Monno I, Xu J, Koya D. Methionine abrogates the renoprotective effect of a low-protein diet against diabetic kidney disease in obese rats with type 2 diabetes. Aging 2020;12: 4489–505.

62. Li XZ, Yan XH. Sensors for the mTORC1 pathway regulated by amino acids. J Zhejiang Univ Sci B 2019;20:699–712.

63. Bartolome A, Garcia-Aguilar A, Asahara SI, Kido Y, Guillén C, Pajvani UB, Benito M. mTORC1 regulates both general autophagy and mitophagy induction after oxidative phosphorylation uncoupling. Mol Cell Biol 2017;37(23):eoo441–17.

64. Bordi M, Darji S, Sato Y, Mellén M, Berg MJ, Kumar A, Jiang Y, Nixon RA. mTOR hyperactivation in Down Syndrome underlies deficits in autophagy induction, autophagosome formation, and mitophagy. Cell Death Dis 2019;10:563.

65. Zhang X, Sergin I, Evans TD, Jeong SJ, Rodriguez-Velez A, Kapoor D, Chen S, Song E, Holloway KB, Crowley JR, et al. High-protein diets increase cardiovascular risk by activating macrophage mTOR to suppress mitophagy. Nat Metab 2020;2:110–25.

66. Krohn L, Grenn FP, Makarious MB, Kim JJ, Bandres-Ciga S, Roosen DA, Gan-Or Z, Nalls MA, Singleton AB, Blauwendraat C, et al. Comprehensive assessment of PINK1 variants in Parkinson's disease. Neurobiol Aging 2020, doi: 10.1016/j.neurobiolaging.2020.03.003.

67. Schoenberg BS. Environmental risk factors for Parkinson's disease: the epidemiologic evidence. Can J Neurol Sci 1987;14(3 Suppl):407–13.

68. Kurtzke JF, Goldberg ID. Parkinsonism death rates by race, sex, and geography. Neurology 1988;38:1558–61.

69. Dahodwala N, Siderowf A, Xie M, Noll E, Stern M, Mandell DS. Racial differences in the diagnosis of Parkinson's disease. Mov Disord 2009;24:1200–5.

70. Schoenberg BS, Osuntokun BO, Adeuja AO, Bademosi O, Nottidge V, Anderson DW, Haerer AF. Comparison of the prevalence of Parkinson's disease in black populations in the rural United States and in rural Nigeria: door-to-door community studies. Neurology 1988;38:645–6.

71. Shah SP, Duda JE. Dietary modifications in Parkinson's disease: a neuroprotective intervention? Med Hypotheses 2015;85:1002–5.

72. Nandipati S, Litvan I. Environmental exposures and Parkinson's disease. Int J Environ Res Public Health 2016;13(9):881.

73. Summermann W, Rohleder H, Korte F. [Polychlorinated biphenyls (PCB) in food. The situation in the Federal Republic of Germany (author's transl)]. Z Lebensm Unters Forsch 1978;166:137–44.

74. Jung UJ, Kim SR. Beneficial effects of flavonoids against Parkinson's disease. J Med Food 2018;21:421–32.

75. Gao X, Cassidy A, Schwarzschild MA, Rimm EB, Ascherio A. Habitual intake of dietary flavonoids and risk of Parkinson disease. Neurology 2012;78:1138–45.

76. Wang L, Xiong N, Huang J, Guo S, Liu L, Han C, Zhang G, Jiang H, Ma K, Xia Y, et al. Protein-restricted diets for ameliorating motor fluctuations in Parkinson's disease. Front Aging Neurosci 2017;9: 206.

77. Cereda E, Barichella M, Pedrolli C, Pezzoli G. Low-protein and protein-redistribution diets for Parkinson's disease patients with motor fluctuations: a systematic review. Mov Disord 2010;25:2021–34.

78. Baroni L, Bonetto C, Tessan F, Goldin D, Cenci L, Magnanini P, Zuliani G. Pilot dietary study with normoproteic protein-redistributed plant-food diet and motor performance in patients with Parkinson's disease. Nutr Neurosci 2011;14:1–9.

79. Kurlan R, Kumari R, Ganihong I. Dramatic response of Parkinsonism to a vegan diet: case report. J Parkinsons Dis Alzeimer Dis 2016;3(1):2.

80. Madeo F, Pietrocola F, Eisenberg T, Kroemer G. Caloric restriction mimetics: towards a molecular definition. Nat Rev Drug Discov 2014;13:727–40.

81. Marino G, Pietrocola F, Madeo F, Kroemer G. Caloric restriction mimetics: natural/physiological pharmacological autophagy inducers. Autophagy 2014;10:1879–82.

82. Madeo F, Carmona-Gutierrez D, Hofer SJ, Kroemer G. Caloric restriction mimetics against age-associated disease: targets, mechanisms, and therapeutic potential. Cell Metab 2019;29:592–610.

83. Marino G, Pietrocola F, Eisenberg T, Kong Y, Malik SA, Andryushkova A, Schroeder S, Pendl T, Harger A, Niso-Santano M, et al. Regulation of autophagy by cytosolic acetyl-coenzyme A. Mol Cell 2014;53:710–25.

84. Pietrocola F, Lachkar S, Enot DP, Niso-Santano M, Bravo-San Pedro JM, Sica V, Izzo V, Maiuri MC, Madeo F, Mariño G, et al. Spermidine induces autophagy by inhibiting the acetyltransferase EP300. Cell Death Differ 2015;22:509–16.

85. Castoldi F, Pietrocola F, Maiuri MC, Kroemer G. Aspirin induces autophagy via inhibition of the acetyltransferase EP300. Oncotarget 2018;9:24574–5.

86. Uda K, Tsujikawa T, Fujiyama Y, Bamba T. Rapid absorption of luminal polyamines in a rat small intestine ex vivo model. J Gastroenterol Hepatol 2003;18:554–9.

87. Qi Y, Qiu Q, Gu X, Tian Y, Zhang Y. ATM mediates spermidine-induced mitophagy via PINK1 and Parkin regulation in human fibroblasts. Sci Rep 2016;6:24700.

88. Eisenberg T, Abdellatif M, Schroeder S, Primessnig U, Stekovic S, Pendl T, Harger A, Schipke J, Zimmermann A, Schmidt A, et al. Cardioprotection and lifespan extension by the natural polyamine spermidine. Nat Med 2016;22:1428–38.

89. Nilsson BO, Persson L. Beneficial effects of spermidine on cardiovascular health and longevity suggest a cell type-specific import of polyamines by cardiomyocytes. Biochem Soc Trans 2019;47:265–72.

90. Sharma S, Kumar P, Deshmukh R. Neuroprotective potential of spermidine against rotenone induced Parkinson's disease in rats. Neurochem Int 2018;116:104–11.

91. Buttner S, Broeskamp F, Sommer C, Markaki M, Habernig L, Alavian-Ghavanini A, Carmona-Gutierrez D, Eisenberg T, Michael E, Kroemer G, et al. Spermidine protects against alpha-synuclein neurotoxicity. Cell Cycle 2014;13:3903–8.

92. Paik MJ, Ahn YH, Lee PH, Kang H, Park CB, Choi S, Lee G. Polyamine patterns in the cerebrospinal fluid of patients with Parkinson's disease and multiple system atrophy. Clin Chim Acta 2010;411:1532–5.

93. Zoumas-Morse C, Rock CL, Quintana EL, Neuhouser ML, Gerner EW, Meyskens FL, Jr. Development of a polyamine database for assessing dietary intake. J Am Diet Assoc 2007;107:1024–7.

94. Vargas AJ, Ashbeck EL, Wertheim BC, Wallace RB, Neuhouser ML, Thomson CA, Thompson PA. Dietary polyamine intake and colorectal

cancer risk in postmenopausal women. Am J Clin Nutr 2015;102:411–9.

95. Moriyama TF. Corn might prevent Parkinson's disease. Clin Nutr 2001;20:559.

96. Fukushima T, Tanaka K, Ushijima K, Moriyama M. Retrospective study of preventive effect of maize on mortality from Parkinson's disease in Japan. Asia Pac J Clin Nutr 2003;12:447–50.

97. Li C, Song R. The regulation of zein biosynthesis in maize endosperm. Theor Appl Genet 2020;133:1443–53.

98. Kiechl S, Pechlaner R, Willeit P, Notdurfter M, Paulweber B, Willeit K, Werner P, Ruckenstuhl C, Iglseder B, Weger S, et al. Higher spermidine intake is linked to lower mortality: a prospective population-based study. Am J Clin Nutr 2018;108:371–80.

99. Pietrocola F, Castoldi F, Kepp O, Carmona-Gutierrez D, Madeo F, Kroemer G. Spermidine reduces cancer-related mortality in humans. Autophagy 2019;15:362–5.

100. DiNicolantonio JJ, OKeefe JH, McCarty MF. Boosting endogenous production of vasoprotective hydrogen sulfide via supplementation with taurine and *N*-acetylcysteine: a novel way to promote cardiovascular health. Open Heart 2017;4:e000600.

101. Sun Y, Lu F, Yu X, Wang B, Chen J, Lu F, Peng S, Sun X, Yu M, Chen H, et al. Exogenous H_2S promoted USP8 sulfhydration to regulate mitophagy in the hearts of db/db mice. Aging Dis 2020;11:269–85.

102. Durcan TM, Tang MY, Perusse JR, Dashti EA, Aguileta MA, McLelland GL, Gros P, Shaler TA, Faubert D, Coulombe B, et al. USP8 regulates mitophagy by removing K6-linked ubiquitin conjugates from Parkin. EMBO J 2014;33:2473–91.

103. Zhou X, Cao Y, Ao G, Hu L, Liu H, Wu J, Wang X, Jin M, Zheng S, Zhen X, et al. CaMKKbeta-dependent activation of AMP-activated protein kinase is critical to suppressive effects of hydrogen sulfide on neuroinflammation. Antioxid Redox Signal 2014;21:1741–58.

104. Chen X, Zhao X, Lan F, Zhou T, Cai H, Sun H, Kong W, Kong W. Hydrogen sulphide treatment increases insulin sensitivity and improves oxidant metabolism through the CaMKKbeta-AMPK pathway in PA-induced IR C2C12 cells. Sci Rep 2017;7:13248.

105. Hardie DG. AMPK and autophagy get connected. EMBO J 2011;30:634–5.

106. Zhang CS, Lin SC. AMPK promotes autophagy by facilitating mitochondrial fission. Cell Metab 2016;23:399–401.

107. Park SW, Kim SH, Park KH, Kim SD, Kim JY, Baek SY, Chung BS, Kang CD. Preventive effect of antioxidants in MPTP-induced mouse model of Parkinson's disease. Neurosci Lett 2004;363:243–6.

108. Sharma A, Kaur P, Kumar V, Gill KD. Attenuation of 1-methyl-4-phenyl-1, 2,3,6-tetrahydropyridine induced nigrostriatal toxicity in mice by N-acetyl cysteine. Cell Mol Biol 2007;53:48–55.

109. Aparicio-Trejo OE, Reyes-Fermin LM, Briones-Herrera A, Tapia E, León-Contreras JC, Hernández-Pando R, Sánchez-Lozada LG, Pedraza-Chaverri J. Protective effects of N-acetyl-cysteine in mitochondria bioenergetics, oxidative stress, dynamics and S-glutathionylation alterations in acute kidney damage induced by folic acid. Free Radic Biol Med 2019;130:379–96.

110. Sian J, Dexter DT, Lees AJ, Daniel S, Agid Y, Javoy-Agid F, Jenner P, Marsden CD. Alterations in glutathione levels in Parkinson's disease and other neurodegenerative disorders affecting basal ganglia. Ann Neurol 1994;36:34–55.

111. Perry TL, Godin DV, Hansen S. Parkinson's disease: a disorder due to nigral glutathione deficiency? Neurosci Lett 1982;33:305–10.

112. Droge W, Kinscherf R, Hildebrandt W, Schmitt T. The deficit in low molecular weight thiols as a target for antiageing therapy. Curr Drug Targets 2006;7:1505–12.

113. Droge W. Oxidative stress and ageing: is ageing a cysteine deficiency syndrome? Philos Trans R Soc Lond B Biol Sci 2005;360:2355–72.

114. Sun T, Ding W, Xu T, Ao X, Yu T, Li M, Liu Y, Zhang X, Hou L, Wang J. Parkin regulates programmed necrosis and myocardial ischemia/reperfusion injury by targeting cyclophilin-D. Antioxid Redox Signal 2019;31:1177–93.

115. Anuncibay-Soto B, Perez-Rodriguez D, Santos-Galdiano M, Font E, Regueiro-Purrinos M, Fernandez-Lopez A. Post-ischemic salubrinal treatment results in a neuroprotective role in global cerebral ischemia. J Neurochem 2016;138:295–306.

116. Font-Belmonte E, Ugidos IF, Santos-Galdiano M, González-Rodríguez P, Anuncibay-Soto B, Pérez-Rodríguez D, Gonzalo-Orden JM, Fernández-López A. Post-ischemic salubrinal administration reduces necroptosis in a rat model of global cerebral ischemia. J Neurochem 2019;151:777–94.

117. Liu Y, Qi SY, Ru LS, Ding C, Wang HJ, Li AY, Xu BY, Zhang GH, Wang DM. Salubrinal improves cardiac function in rats with heart failure post myocardial infarction through reducing endoplasmic reticulum stress-associated apoptosis. Zhonghua Xin Xue Guan Bing Za Zhi 2016;44:494–500.

118. Li RJ, He KL, Li X, Wang LL, Liu CL, He YY. Salubrinal protects cardiomyocytes against apoptosis in a rat myocardial infarction model via suppressing the dephosphorylation of eukaryotic translation initiation factor 2alpha. Mol Med Rep 2015;12:1043–9.

119. Wang ZF, Gao C, Chen W, Gao Y, Wang H-C, Meng Y, Luo C-L, Zhang M-Y, Chen G, Chen X-P, et al. Salubrinal offers neuroprotection through suppressing endoplasmic reticulum stress, autophagy and apoptosis in a mouse traumatic brain injury model. Neurobiol Learn Mem 2019;161:12–25.

120. Logsdon AF, Lucke-Wold BP, Nguyen L, Matsumoto RR, Turner RC, Rosen CL, Huber JD. Salubrinal reduces oxidative stress, neuroinflammation and impulsive-like behavior in a rodent model of traumatic brain injury. Brain Res 2016;1643:140–51.

121. Rubovitch V, Barak S, Rachmany L, Goldstein RB, Zilberstein Y, Pick CG. The neuroprotective effect of salubrinal in a mouse model of traumatic brain injury. NeuroMol Med 2015;17:58–70.

122. Rani S, Sreenivasaiah PK, Cho C, Kim DH. Salubrinal alleviates pressure overload-induced cardiac hypertrophy by inhibiting endoplasmic reticulum stress pathway. Mol Cells 2017;40:66–72.

123. He YY, Liu CL, Li X, Li RJ, Wang LL, He KL. Salubrinal attenuates right ventricular hypertrophy and dysfunction in hypoxic pulmonary hypertension of rats. Vasc Pharmacol 2016;87:190–8.

124. Sarcinelli C, Dragic H, Piecyk M, Barbet V, Duret C, Barthelaix A, Ferraro-Peyret C, Fauvre J, Renno T, Chaveroux C, et al. ATF4-dependent NRF2 transcriptional regulation promotes antioxidant protection during endoplasmic reticulum stress. Cancers 2020;12(3):569.

125. Suzuki T, Motohashi H, Yamamoto M. Toward clinical application of the Keap1-Nrf2 pathway. Trends Pharmacol Sci 2013;34:340–6.

126. Anjos JSD, Cardozo L, Black AP, Santos da Silva G, Vargas Reis DCM, Salarolli R, Carraro-Eduardo JC, Mafra D. Effects of low protein diet on nuclear factor erythroid 2-related factor 2 gene expression in nondialysis chronic kidney disease patients. J Ren Nutr 2020;30:46–52.

127. Koriyama Y, Nakayama Y, Matsugo S, Kato S. Protective effect of lipoic acid against oxidative stress is mediated by Keap1/Nrf2-dependent heme oxygenase-1 induction in the RGC-5 cellline. Brain Res 2013;1499:145–57.

128. Ma ZC, Hong Q, Wang YG, Liang QD, Tan HL, Xiao CR, Tang XL, Shao S, Zhou SS, Gao Y. Ferulic acid induces heme oxygenase-1 via activation of ERK and Nrf2. Drug Discov Ther 2011;5:299–305.