Will it Ever Become Possible to Prevent Dopaminergic Neuronal Degeneration?

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Abstract: Parkinson's disease (PD) is the second leading age-related degenerative brain disease in the world affecting millions of people. This neurological disorder disrupts the quality of life of patients and their families, exerts an enormous emotional and physical strain on caregivers, and has a large cost for society. Moreover, the increasing numbers of elderly people in the population will result in a sharp increase in the prevalence of PD. The understanding of its pathophysiology and treatment has advanced at a very impressive rate during past decades. Nevertheless, PD is still fatal and there is at present no cure for it. Furthermore, there are no proven therapies for prevention of PD and although evidence exists of risk and protective factors, this is not strong enough to warrant specific measures in an attempt to diminish risk or enhance protection. Drug development programmes are engaged in finding neuroprotective and neurorestorative therapies or, even better, discovering drugs able to *rejuvenate* the dopaminergic neurons. The latest developments in this promising field will be discussed with reference to the current literature together with the advantages and pitfalls of suggested drugs. Finally, an analysis of the role of various dietary recommendations, lifestyle, environmental and other factors in reducing the risk of PD is carried out.

Keywords: Parkinson's disease, neurodegeneration, risk factors, neuroprotection, prevention.

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease in the elderly population with an inevitable *exitus*. The idiopathic form is a progressive disorder the impact of which reaches far beyond the clinical signs and symptoms exhibited by those afflicted. This neurodegenerative disorder not only places a severe burden on the patients but also on their family, friends and society.

It is estimated that close to 4 million people worldwide suffer from PD. The disease afflicts both sexes, and the initial symptoms typically appear when people are in their late 50's or early 60's. Indeed, nearly 1% of the population over the age of 65 is estimated to suffer from the disease. Moreover, the number of PD sufferers is expected to grow as the general population in the Western world ages. In fact, it has been estimated that this number will double to between 8.7 and 9.3 million by 2030 [1]. Accordingly, the costs of treatment (health and social care), estimated at between £560,000 and £1.6 million per 100,000 population, is expected to rise sharply [2-4].

Clinical features at presentation include the asymmetric onset of cardinal motor symptoms such as tremor at rest, bradykinesia, muscular rigidity, stooped posture and instability [5]. These are the result of the loss of dopaminergic (DAergic) neurons in the substantia nigra pars compacta (SNc), which causes a consequent reduction of dopamine (DA) levels in the striatum [6-8] and changes in the basal ganglia-thalamocortical network activity [9]. Regrettably, the symptoms of PD do not appear until up to 80% of the DAergic nerve cells have been lost [10-11]. In the early stages of the disease, DA replacement therapy, using the DA precursor levodopa, is effective but the dose response decreases with disease progression and motor complications (dyskinesias) and other side effects (e.g. mood disorders, sleep disturbances) arise after chronic treatment. These complications may be due either to the advanced stage of the disease when degenerating DAergic neurons cannot buffer the fluctuating plasma levels of levodopa, resulting in pulsatile stimulation of the DA receptors, or to the further degeneration in non-DAergic regions [12-13]. Since the underlying mechanisms of neuronal loss in patients are not known, current therapies work mainly to alleviate symptoms rather than to halt the progression of the disease [14].

There have been major advances in understanding the etiopathogenesis of PD, the modalities whereby the neurodegenerative process begins and progresses (Fig. **1**), therefore the development of drugs to slow and halt DAergic neuronal degeneration or even to prevent the disease, now seem realistic goals.

This new optimism that PD can be defeated is tempered by the realization that we have not yet cured any neurodegenerative disorder, and defeating PD will require new discoveries that cannot now be predicted with certainty. This is complicated by the large number of factors that seem to be involved in the onset of this disease, such as aging, genetic vulnerability, exogenous or endogenous toxins, hydroxyl radicals ($^{\cdot}OH$) production, neuronal metabolic disturbances, inflammation and apoptosis [5,15-21].

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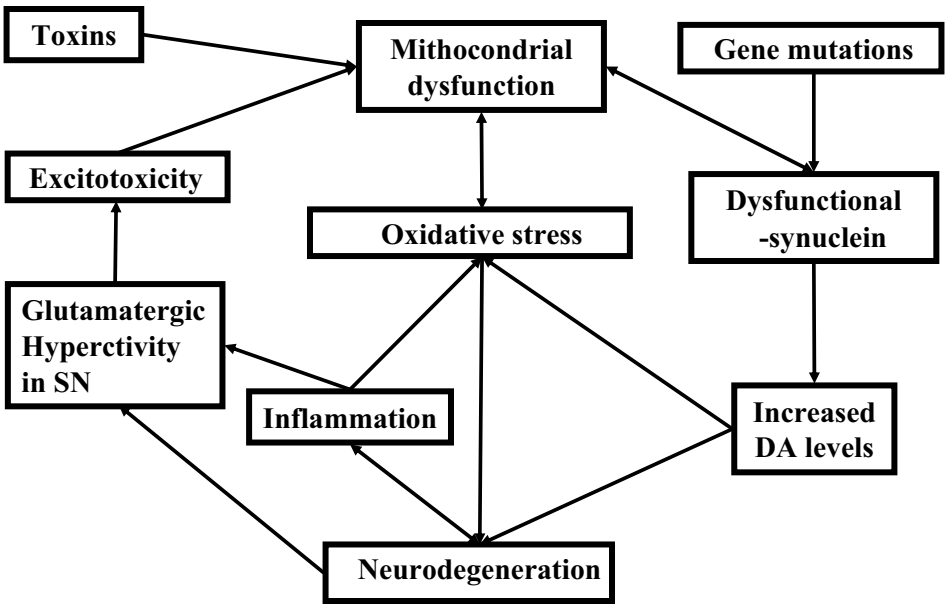


Fig. (1). A simplified diagram showing the interaction of different factors leading to nigral cell damage and death.

Nigral Dopaminergic Neurons

Dopamine is one of the most intensively studied neurotransmitters in the brain due to its involvement in several mental and neurological disorders, such as schizophrenia, depression and PD. The SNc resides in the ventral part of mesencephalon, laterally to the ventral tegmental area of Tsai (VTA), the other major DAergic nucleus in the central nervous system (CNS) [22-26]. The majority (>90%) of cells in the SNc are medium sized aspiny DAergic neurons with sparsely branching dendritic trees. These neurons' preferred pathway is to the caudate nucleus and the putamen, i.e. the dorsal part of the striatum, and therefore this pathway is often called the nigrostriatal DAergic system [27]. According to their neurotransmitter, nigral neurons are classified into DAergic and γ-aminobutyric acid (GABA)-ergic neurons [28-30].

From an electrophysiological point of view, DAergic neurons in the SNc can be further distinguished from other neuronal populations in the brain on the basis of intrinsic membrane properties that allow them to discharge *in vivo* spontaneously, in a spectrum of patterns ranging from pacemaker, to random and bursting modes [31-34]. These firing patterns, which are controlled by a complex interplay of ion or receptor channels [35,36], allow DA neurons to optimize the release of DA in their terminal fields [37]. However. the peculiarity of SNc DA neurons is that they are spontaneously active even *in vitro* without synaptic input. Such autonomous 'pacemaking' activity is seen in many types of neurons and requires ion channels that can open at membrane potentials lower than the threshold for firing action potentials. Pacemaker activity seems to be critical to the function of SNc DAergic neurons by maintaining DA levels in target structures like the striatum. Also, emerging evidence indicates that electrical activity might participate in the control of DAergic neuron survival, not only during development, but also in the adult brain, thus raising the possibility that alterations in ionic currents could contribute actively to the demise of these neurons in PD [38]. The electrical current entering the cell through these channels then depolarizes the membrane to the threshold for action potentials. Differently from other pacemaking neurons where sodium ions are involved, the driving pacemaking current in the DAergic neurons in adult animals is carried mainly by calcium ions (Ca^{2+}) through the low-voltage-activated neuronal L-type Ca^{2+} channels (VGCC) with the α subunit $Ca_v1.3$ [39-41]. Strikingly, in juvenile SNc DAergic neurons, pacemaking is driven by sodium channels in conjunction with hyperpolarization-activated cyclic nucleotide-gated cation (HCN) channels. Thereafter, there is a gradual switch as $Ca_v1.3$ current increases, during the second week following birth, perhaps as the voltage dependence of HCN channels is shifted toward more negative membrane potentials, essentially inactivating HCN channels [41]. The development of SNc Ca^{2+}-driven pacemaking occurs in tandem with an increased expression of slowly inactivating somatodendritic L-type Ca^{2+} channels that drive the neurons into oscillations, due to the presence of $Ca_v1.3$ α subunits, which open in a relatively hyperpolarized subthreshold range. In support of these new observations, knockout mice that do not express the $Ca_v1.3$ α subunit of L-type Ca^{2+} channels continue to show SNc pacemaking driven by the sodium/HCN currents throughout their lives. In this respect, SNc DAergic neurons of knockout mice also resembled juvenile SNc DAergic neurons. The mechanisms underlying the shift from juvenile and adult pacemaking are not known yet. Nevertheless, it seems plausible that cyclic adenosine monophosphate (cAMP) and Ca^{2+}-inhibited isoforms of the enzyme that produces cAMP are involved. When the Ca^{2+} cytoplasmic concentration drops due to the absence of expression of $Ca_v1.3$ channels the cAMP concentration increases inside the DA neuron. Consequently the HCN channels that are regulated by cAMP in a positive positive allosteric manner, drive the pacemaking activity [41].

Calcium Channel Blockers: Rejuvenating Agents?

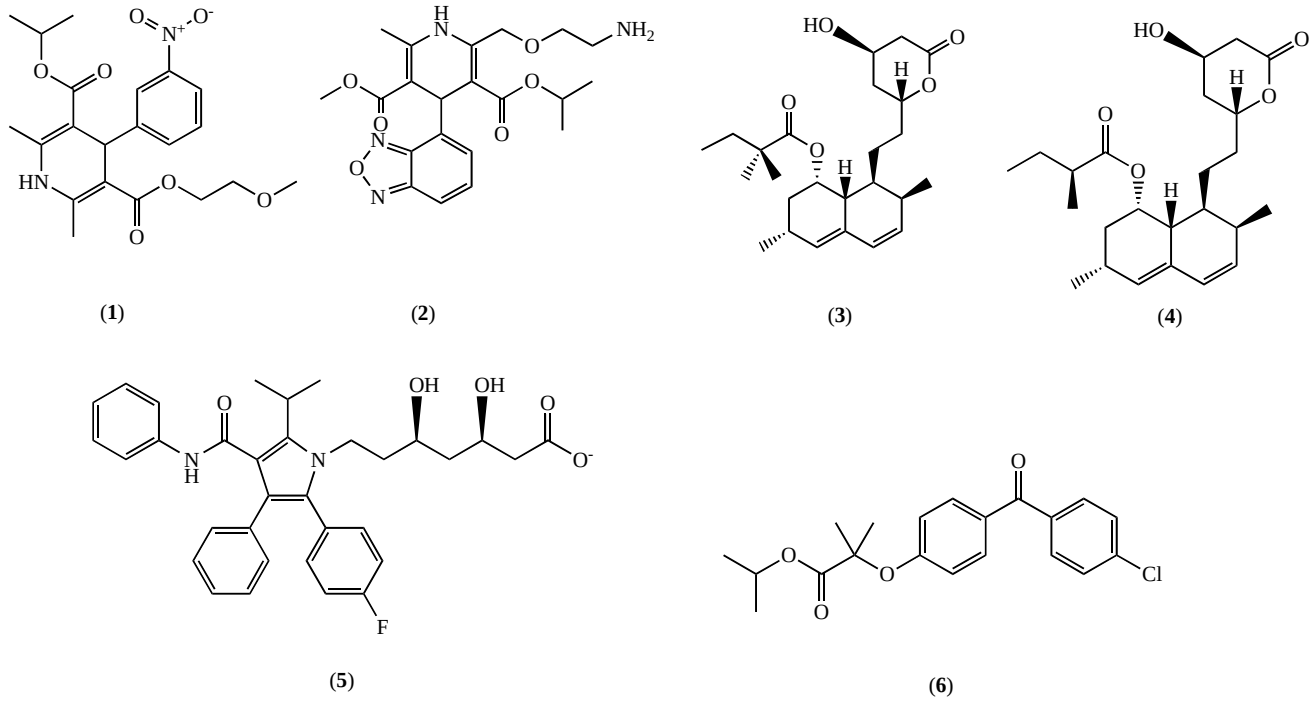
DAergic neurons seem to be particularly prone to dying owing to their peculiar characteristics such as high iron levels, low glutathione concentration and high presence of reactive glia [42]. These neurons are further stressed *via* their

pacemaking activity which leads to an intracellular Ca^{2+} accumulation and might unsettle the ion cellular homeostasis. This phenomenon, in predisposed individuals, can cause the death of DAergic neurons. Ca^{2+} can kill DA neurons by different mechanisms. Ca^{2+} activates cysteine proteases called calpains and caspases triggering apoptotic cascades. In addition, Ca^{2+} induces oxidative stress through several different mechanisms, including activation of oxygenases, perturbation of mitochondrial Ca^{2+} and energy metabolism, and induction of membrane associated oxidative stress (MAOS). In consequence, there is an intracellular accumulation of reactive oxygen species (ROS) such as superoxide anion radical, hydrogen peroxide, hydroxyl radical, nitric oxide (NO) and peroxynitrite [43,44]. In line with these findings, it has been suggested that Ca^{2+} channel blockers (CCBs), such as nimodipine and other dihydropyridine drugs (Fig. **2**), might be useful to heal neuronal death resulting from excessive Ca^{2+}entry [44]. This hypothesis is corroborated by the evidence that DAergic neurons expressing relatively high levels of the Ca^{2+}-binding proteins calbindin and calretinin appear to be resistant to degeneration in PD [45,46]. CCBs may inhibit the Ca^{2+}-dependent process of apoptosis [47] and be neuroprotective in PD and other conditions in which apoptosis contributes substantially to cell death [48]. Furthermore, some epidemiologic studies have revealed a significant decreased risk of PD associated with hypertension and blood pressure medication [49,50]. In animal models of PD, nimodipine prevented neurotoxicity induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in non-human primates [51], mice [52], and in cerebellar granule cells [53] but unexpectedly not in rats [54]. In common marmosets and mice, pretreatment with nimodipine completely prevented (in a dose-dependent manner) the MPTP-induced decrease of nigral tyrosine hydroxylase (TH) immunoreactive cells, but neither attenuated the behavioural impairments in MPTP-treated animals nor antagonized the striatal neurotoxin-induced DA depletion. These data suggest that nimodipine might protect at the cellular nigral level, but not at the synaptic striatal level, implicating differential mechanisms of the actions of MPTP-induced neurotoxicity at the nigral versus the striatal level [51,52]. Recently, it has been shown that isradipine (Fig. **2**), another CCB drug of the dihydropyridine class, may have potential uses for treating and preventing PD [41]. Its neuroprotective action is linked to the block of the Ca^{2+}current underlying pacemaking in SNc neurons, interrupting the ion accumulation. The treatment with isradipine switches the pacemaker activity of SNc neurons from $Ca_v1.3$ channels to the immature pacemaking driven by HCN channels. Theoretically, the drug rejuvenates aged SNc neurons into a state in which they are more resistant to oxidative stress. This hypothesis is confirmed by the evidence that the pesticide rotenone *in vitro* has a far less damaging effect on SNc DAergic neurons in $Ca_v1.3$-deficient mice than in wild mice, and that the damage can be reduced by isradipine. Moreover, in a mouse model of PD produced by MPTP injection, isradipine administered *in vivo* reduces both the loss of SNc neurons and the development of movement disorders. There is hope that the drug will protect DA neurons in humans as well, so that if taken early enough by those at high risk of PD, it will prevent the disease. Isradipine could be taken in much the same way as aspirin is taken to protect the heart and might also significantly benefit people who already have PD [41]. The fact that the 'rejuvenation' can be brought about by treatment with isradipine, a very well-tolerated drug that is widely used in the treatment of hypertension and stroke, points to a neuroprotective strategy that could be tried immediately. These are exciting results, because nimodipine is a well studied drug with relatively mild side effects. However, there are some caveats. It is uncertain whether the 'rejuvenated' pacemaking in nimodipine-treated SNc neurons leads to adequate DA release, especially from dendrites. Moreover, the nimodipine concentrations used in the *in vitro* studies by Chan *et al.* [41] were far higher than the plasma concentrations of this drug that occur in its clinical use for treating high blood pressure, and thus might produce more severe side effects than are so far known. A further note of caution is struck from the observation that mice that lack the $Ca_v1.3$ subunit are deaf [55], as might be expected from the abovementioned roles of L-type Ca^{2+} channels in cochlear hair cell activity. Finally, L-type channels further appear to underlie forms of synaptic plasticity, and CCBs may interfere with these normal synaptic functions. In line with these experimental findings, a retrospective study of hypertensive patients suggested that dihydropyridine use might lower the incidence of PD by 30-50% [48]. Diminishing the vulnerability of SNc DAergic neurons should not only decrease the incidence of PD but also slow its progression, broadening the therapeutic window for PD patients in the early stages of the disease. Preliminary population studies have been performed to date, suggesting that CCBs use may be less common in hypertensive PD patients than in non-PD hypertensive patients. However, the enthusiasm for a rationale for the use of CCBs in PD has been dampened by a recent population-based case-control study [56] in which the risk of PD associated with CCBs and beta-blockers was undertaken. No association with PD risk for either class of medication in terms of duration, dose, number of prescriptions or pattern of use was observed. The weakness of these associations and the absence of the additional influence of dose or duration of use argue against any causal interpretation [56]. More extensive investigations of this type and prospective studies of Ca^{2+} antagonist use in PD will be required to determine if these agents truly have a salutary effect on Parkinsonism. Nevertheless, CCBs neuroprotective therapy should begin well before the appearance of symptoms, at a stage where altering the rate of cell loss can have the greatest effect on the timing of the threshold crossing and the emergence of symptoms.

Lipid-Lowering Drugs in PD?

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors or statins are the most successful cardiovascular drugs of all time. By interrupting cholesterol synthesis in the liver, they activate hepatocyte low-density lipoprotein (LDL) receptors and produce consistent and predictable reductions in circulating LDL cholesterol (LDL-C) with resulting reproducible improvements in cardiovascular risk by retarding or even reversing the progression of atherosclerosis in all major arterial trees [57]. As such, statins are amongst the most extensively investigated pharmaceutical agents in current clinical use [57].

Interestingly, a number of recent studies indicate that apart from their lipid-lowering activities, statins and fibrates (Fig. **2**) (the latter activate instead the peroxisome proliferator-activated receptors (PPAR)), exhibit multiple functions



(**1**) (**2**) (**3**) (**4**)

(**5**) (**6**)

Fig. (2). (**1**) Nimopidine, O5-(2-methoxyethyl) O3-propan-2-yl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate. (**2**) Isradipine, O5-methyl O3-propan-2-yl 4-(2,1,3-benzoxadiazol-7-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate. (**3**) Simvastatin, [(1S,3R,7S,8S,8aR)-8-[2-[(2R,4R)-4-hydroxy-6-oxooxan-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl] 2,2-dimethylbutanoate. (**4**) Lovastatin, [(1S,3R,7S,8S,8aR)-8-[2-[(2R,4R)-4-hydroxy-6-oxooxan-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl] (2S)-2-methylbutanoate. (**5**) atorvastatin, (3R,5R)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-propan-2-ylpyrrol-1-yl]-3,5-dihydroxyheptanoic acid. (**6**) Fenofibrate, propan-2-yl 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoate.

and serve to modulate intracellular signalling pathways, inhibit inflammation, suppress the production of reactive oxygen species, and modulate T cell activity. Therefore, these drugs are now being considered as possible therapeutics for several forms of human disorders including PD and Alzheimer disease (AD) [58].

Strong evidence has supported a rationale for the use of statins in AD [59] since the polymorpholism of genes of apolipoprotein (APOE) ε4 consistently associated with higher plasma LDL-C is associated with the frequency of AD development [60,61]. A positive correlation between a high serum cholesterol level and risk factor for AD has been shown, and treatment with statins reduces the frequency of AD development [59].

Cholesterol and fat levels seem to be involved in PD pathophysiology as well. Nevertheless, the association between fat intakes and risk of PD is less clear than in AD and contradictory epidemiological findings have been reported [62,63]. Recent results do not support the importance of overall fat intake in the pathogenesis of PD, but a possible adverse effect of saturated fat for men could not be excluded. Conversely, high intake of unsaturated fatty acids might instead protect against PD [64,65]. However, a recent systematic review, demonstrated that APOE ε2 allele, associated with lower plasma LDL-C, is positively associated with higher prevalence of sporadic PD, suggesting that LDL-C levels are associated with PD [66]. In effect, Huang *et al.* [67] reported that lower serum concentrations of LDL-C were associated with a higher prevalence of PD, whereas use of cholesterol-lowering drugs was significantly associated with a decreased occurrence of PD. Therefore, either an etiologic role of LDL-C in PD pathogenesis or a neuroprotective effect of statins has been suggested [67]. This association was found in both men and women and persisted after further adjusting for LDL-C concentration. Although these observations were made in a relatively small, retrospective case-control study, they have been confirmed by a recent publication from the Rotterdam Study group [68]. In this study a significant association was revealed between higher levels of total serum cholesterol and a decreased risk of PD, with analyses in quintiles showing a clear linear relation. Surprisingly, the cholesterol protection was restricted to women and the association between statin use and risk of incident PD was not significant, although the trend was positive. The high serum cholesterol neuroprotective effect can be related to the consequent high levels of coenzyme Q10 (CoQ 10) transported by LDL-cholesterol. CoQ 10 is essentially a vitamin or vitamin-like substance with a powerful antioxidant activity and electron acceptor for mitochondrial complex I [69]. Given the hypothesis that oxidative stress and mitochondrial complex I dysfunction play a central role in the pathogenesis of PD, CoQ 10 is considered a candidate drug for treatment of PD and has already been investigated in small trials [70,71]. However, further research is needed to unravel the association between cholesterol, CoQ 10, and PD pathogenesis.

The neuroprotective effects of statins has not been confirmed by Kreisler and colleagues [72] but revealed in another larger study [73]. In this study, using a population of 4.5 million people, subjects taking simvastatin were associated with a 49% decrease in incidence of PD. Not all statins were equal;

indeed, lovastatin, and atorvastatin were not associated with a reduction in the number of cases of PD [73]. The different effect of statins might derive from their diverse biological actions, such as effectiveness at modifying lipid metabolism, ability to penetrate the blood-brain barrier and other independent effects from the hypolipidemic actions [74].

The importance of non hypocholesterolemic properties of statins in protecting DAergic neurons was suggested for the first time by Obata and Yamanaka [75]. In fact, it has been shown that fluvastatin decreased formation of $^{\cdot}OH$ induced by the MPP^+ probably blocking LDL oxidation [75], simvastatin inhibited the activated microglia thereby iinhibiting the production of tumor necrosis factor (TNF)-α, nitric oxide, and superoxide without affecting cholesterol concentrations in the plasma or in the striatum [76]. In addition, lovastatin reduced α-synuclein (α-syn) accumulation and aggregation [77].

Nevertheless, Kreisler *et al*. [72], showed that atorvastatin and simvastatin instead had a deleterious effect on the number of TH-positive cells in MPTP-lesioned mice. The evidence is not surprising considering that statin toxicity has been observed not only in myocytes but also in other cell types, due to some oncotic and apoptotic mechanisms [78] or proteasome inhibition [79].

Another member of the lipid-lowering drugs, fenofibrate, has shown to have a protective effect against the toxic effect of MPTP in animals *in vivo* [72]. Fibrates are synthetic ligands for PPAR-α. This receptor is expressed in various tissues, including CNS neurons and astrocytes in the rat SNc and striatum [72,80,81]. PPAR-α is activated by natural ligands (such as fatty acids and their derivatives), and modulates the transcription of a large number of target genes *via* formation of heterodimeric transcription factor complexes with the retinoid X receptor. PPAR-α probably modulates oxidative stress [82] activating the major antioxidant enzymes in the brain [83], reduces the production of inflammatory cytokines, such as the TNF-α, interleukin-6 (IL-6), and inhibits pro-inflammatory proteins such as nuclear factor-kappa B (NF-κB), inducible NO synthase (iNOS), cyclooxygenase-2 (COX-2), vascular cell adhesion molecule-1 and intracellular adhesion molecule-1 [84]. Hence, PPAR-α activation appears to be an interesting pharmacological target in preventing or slowing PD.

Noticeably, the synthetic activation of PPAR-α by fenofibrates increases the number of DAergic neurons in the control animals, likely inducing cell differentiation [84].

Overall, although not all consistent, these results indicate that lipid-lowering drugs might be useful in prevention of PD; particularly in secondary prevention once subjects at risk of developing PD have been identified. Indeed, after the disease onset their use may no longer be beneficial, as Lieberman and colleagues [85] have reported. They did not find any difference in the statin versus no statin group of PD patients for dementia, dyskinesia and wearing-off rates. Anecdotally, five patients reported a worsening of PD within 1-3 months of starting a statin [85].

Aspirin in PD Prevention?

Recently, the involvement of inflammation and microglial activation in the pathogenesis of PD has been emphasized [42,86]. The brain had been considered an immune privileged site, free from immune reactions, since it is protected by the blood-brain-barrier. However, accumulating findings have revealed that immune responses may occur in the brain, especially due to activation of the microglia. The inflammatory process is now thought to be fundamental to, if not at first the initiator of, the progression of PD pathogenesis. Results of neurotoxin models of PD, corroborating findings obtained in transgenic animal models and epidemiological studies, strongly support the hypothesis that this neurodegenerative disease is not purely neuronal, as has been previously considered [87,88]. Thus, DAergic neuronal degeneration is the likely result of multiple pathogenic factors occurring both within and outside the cell.

Moreover, neuroinflammation may aggravate the course of the disease and, as has recently been suggested, may be a primary factor in some cases of PD [86,88]. In fact, postmortem examinations have shown that neuronal degeneration in PD is associated with massive gliosis due to a subset of activated glial cells, the microglia [89], evidence that has been confirmed in MPTP-induced parkinsonism in monkeys [87]. Interestingly, healthy SNc exhibits the highest concentration of microglia in the brain especially in the ventral tier of the pars compacta [90]. Glial cells once activated become phagocytes and ingest degenerating DA neurons piece-by-piece [91]. In addition, activated glial cells release detrimental compounds such as, interleukin-1β (IL-1β), IL-6, TNF-α and interferon γ (IFN-γ), which may act by stimulating iNOS, or which may exert a more direct deleterious effect on DAergic neurons by activating receptors that contain intracytoplasmic death domains involved in apoptosis [92]. Inflammation has been rightly defined as a double-edged sword. It normally starts as a defence reaction, but the failure of its control mechanism can lead to an uncontrolled and continuous extremely damaging immune response. A brief pathogenic insult, furthermore, can induce an ongoing inflammatory response and the toxic substances released by the glial cells may be involved in the propagation and perpetuation of neuronal degeneration.

From this evidence it appears clear that inflammatory process and oxidative stress derived from DA metabolism, constitute a vicious cycle that lead to the final demise of nigral DA cells (Fig. **1**) [88]. Furthermore, it has been demonstrated that the COX-2 is up-regulated in SNc DAergic neurons in both PD patients and animal models of PD [42].

The above discussion makes it plausible that drugs with the capacity to rescue DA neurons from microglia toxicity and inflammatory processes may result in an amelioration of Parkinsonian symptoms by delaying the onset and slowing the progression of the disease and, strikingly, decreasing the risk of developing it. Therefore, aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) (Fig. **3**) may represent a possible new therapeutic approach for treating PD and maybe for its prevention [42].

NSAIDs are capable of halting eicosanoids synthesis and suspending inflammatory process progression. NSAIDs inhibit COX activity inducing a diminution of prostaglandins (PGs) levels, accompanied by a compensatory increase in levels of leucotrienes (LTs). Although some of the NSAIDs' pharmacological actions are related to the ability to inhibit PG biosynthesis (*classical effects*), more of their beneficial

therapeutic effects are not and are also not completely understood (*non classical effects*) [42]. Indeed, NSAIDs are able to inactivate the NF-κB, factor activator protein 1 (AP-1) [93,94], inhibit the expression of some genes such as COX-2, iNOS and IL-4 [95,96].

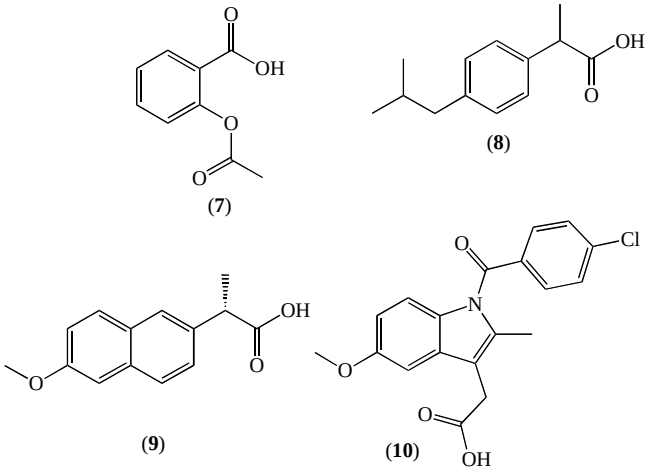


Fig. (3). (**7**) Aspirin, 2-acetyloxybenzoic acid. (**8**) Ibuprofen, 2-[4-(2-methylpropyl)phenyl]propanoic acid. (**9**) Naproxen, (2S)-2-(6-methoxynaphthalen-2-yl)propanoic acid. (**10**) Indomethacin, 2-[1-(4-chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]acetic acid.

In addition, it has been shown that NSAIDs in neuronal cells, might directly and dose-dependently scavenge ROS and reactive nitrogen species (RNS) blocking their detrimental effects [97]. Furthermore, some NSAIDs such as ibuprofen and indomethacin, show agonistic activity with the PPAR-γ [98]. Almost all the experimental findings in this field have consistently shown a neuroprotective effect of NSAIDs in different PD models both *in vivo* and *in vitro*. Differently, the mechanism whereby aspirin and the other NSAIDs act is still a matter of debate. Some experimental evidence suggests that their neuroprotective properties are essentially due to a *non-classical mechanism* such as inhibition of NF-κB [99], ROS scavenging activity [100,104], caspase activation [103] mitochondrial function restoration [105] or some COX-independent effects not yet identified [106].

On the other hand, numerous findings have instead emphasized the selective involvement of COX-2 inhibition in NSAIDs neuroprotective effects [107,111]. Pre-treatment with COX-2 inhibitors has constantly induced neuroprotection [111,112], supporting a possible role for them as prophylactic therapy for PD. Nevertheless, the selective COX-2 inhibitor indomethacin, did not show any neuroprotective effect when administered after toxin-induced nigral degeneration, revealing that the time of COX-2 inhibition is critical to achieve a protective effect [113]. Indeed, COX-2 activity, PGs production and oxygen species formation might not play a detrimental role in neuronal cells' death, at least when the injury process has started already. Furthermore, in later stages of injury, COX-2, through the formation of cyclopentenone PGs derived from PG D_2 (PGD_2), may participate in the resolution of inflammation and even in the regeneration process. Consequently, the inhibition of COX-2 activity could be harmful to neurons injured by toxins. This hypothesis is supported by the fact that neither pharmacological nor genetic abrogation of COX-2 activity mitigates inflammatory processes [107]. Differently to COX-2 inhibitors, aspirin appears to offer an adjuvant effect as well as the prophylactic one acting as a neuroprotectant even after the toxin-induced nigral degeneration [114].

Despite the evidence of inflammation in the brains of patients with PD, and in animal models of PD, NSAIDs have not yet been formally tested in PD.

The first epidemiological study in the subject showed a noteworthy evidence that regular users of aspirin have a significantly lower risk (-45%) of PD than non-users [115]. These findings were partially confirmed in a successive study from the same group [116], in which only ibuprofen and not aspirin among all the NSAIDs was associated with a lower risk of PD.

Recently, a case-control study on subjects with no history of PD or parkinsonism-related drug use at baseline reported a surprising finding: non-aspirin NSAIDs use reduces PD risk in men but not in women. Use of non-aspirin NSAIDs was associated with a 20% reduction in the incidence of PD among men, and a 20% increase in the incidence of PD among women [117]. Less promising insights have been provided by the last studies [56,118-120]. Bower and colleagues [118] found that cases of PD used NSAIDs (excluding aspirin) less frequently than controls; however, the difference did not reach significance. No significant association between PD and aspirin, ibuprofen and naproxen in reducing the risk of PD was also observed in other population-based case-control studies [56, 118,119]. Therefore, the indications for a rationale for the use of NSAIDs for the prevention and treatment of PD are unclear and must be clarified and corroborated by clinical trial before any firm conclusions can be drawn.

A Vaccine for Parkinson's Disease?

As we have described in the previous paragraph, inflammation increases the risk of PD and is now considered a hallmark of DAergic neuron demise [42,92]. Therefore, attenuating brain inflammation can affect the disease process. A possible strategy might be represented by adaptive immunity. Indeed, it has been shown that vaccination with CNS antigens expressed at the lesion site, can attenuate neuronal death [121]. Such self-antigen-stimulated T cells may retard neuronal injury by producing neurotrophins or by influencing their production by local glial cells [122]. Consistent with this evidence, a recent report by Gendelman's group [123] showed that therapeutic immunization protects DAergic neurons in a mouse model of PD. This is the first time that a vaccine strategy has been used to confer neuroprotection for DAergic neurons. The authors experimented with a drug called copolymer-1 (Copaxone). Previous studies have shown that Copaxone, which is commonly used to treat multiple sclerosis (MS), increases the number of immune T cells that secrete anti-inflammatory cytokines and growth factors. Injection of immune cells from mice that had received Copaxone immunization into MPTP-treated mice was capable of significantly decreasing the degeneration of DAergic neurons. These mice also lost fewer DA nerve fibres than control mice and showed only a small decrease in the amount of DA in the striatum. T cells in the treated mice migrated to the damaged area of the brain, reduced the harmful reactions of the microglia, and triggered a neuroprotective response. In addition, the vaccine dramatically increased the amount of glial-derived neurotrophic factor (GDNF), a growth factor that helps prevent neu-

rodegeneration [123]. In addition, in a successive study Gendelman's group further showed Copaxone immune cell protection of the nigrostriatal DAergic pathway in MPTP-intoxicated mice using quantitative proton magnetic resonance spectroscopic imaging (^{1}H MRSI) [124]. ^{1}H MRSI performed in MPTP-intoxicated animals showed that Copaxone immunization strategies counteract the decrease of N-acetylaspartate (NAA) levels seen in the control group, in the SNc and striatum. What makes this research noteworthy is the new evidence that DAergic degeneration can be evaluated by ^{1}H MRSI which can serve as a monitoring system to assess therapeutic outcomes for PD.

These studies offer proof of the concept that the vaccination might modify the behaviour of the glial cells so that their responses are beneficial to the nervous system rather than harmful. In these studies adoptive transfer of Copaxone - treated cells to MPTP recipient animals was necessary because the toxin immunotoxicity precluded active immunization. However, Copaxone could be given to humans directly. Follow-up studies to confirm these results and to identify the specific cytokines, nerve growth factors, and other proteins that play a role in the protective response are warranted. Other work is needed to determine how to translate the study results into a therapy for humans and to make sure the treatment is safe for patients with PD, who may not react to the drug in the same way as MS patients. While Copaxone is currently approved by the U.S. Food and Drug Administration for use in treating MS, the dose needed to treat PD will probably be quite different from the dose used in treating MS. The timing of treatment may also prove critical. It is likely that this therapy might eventually be able to slow the course of PD in humans.

A different immunotheraupetical approach to PD has been suggested by Masliah *et al*. [125]. The intended vaccine stimulates the immune system to target the abnormal form of the protein α-syn. Transgenic mice vaccinated with Human α-syn (hα-syn) presented a decreased accumulation of aggregated α-syn in neuronal cell bodies and synapses that was associated with reduced neurodegeneration. Furthermore, antibodies produced by immunized mice recognized abnormal α-syn associated with the neuronal membrane and promoted the degradation of α-syn aggregates, probably *via* lysosomal pathways. Similar effects were observed with an exogenously applied FITC-tagged α-syn antibody. The antibodies produced by the vaccinated mice recognized and reduced only the abnormal form of α-syn, since the protein's normal form is in a cellular compartment where antibodies are unable to reach it. Abnormal α-syn finds its way to the cell membrane, where antibodies can recognize it. Although this evidence is really promising, experimental active immunization, while effective in mice, may not be as useful in humans. Indeed, to immunize humans in this way by triggering antibody development could create harmful inflammation. However, it might be feasible to inject antibodies directly, as if the patients were creating their own.

WHO GETS PARKINSON'S DISEASE? REDUCING RISK FACTORS

PD develops much less frequently than AD, ranging from 0.1% to 0.5% annually. Depending on the study, the annual incidence rate for PD ranges from 110 to 300 per 100.000 individuals over age 50 [126]. After age 80 years, the incidence rate increases to 400 to 500 individuals per 100.000 annually. Incidence rates for PD increase with age both in men and women, but the rate in men exceeds that for women twofold [127]. Among persons over 65 years of age, the prevalence of PD has been estimated at 1.8%, increasing from 0.6% between ages to 2.6% for those 85-98 years [128]. From birth the lifetime risk of developing PD is about 2% for men and 1.3% for women. These risks increase with age [129]. Although idiopathic PD is usually sporadic, it is now well established that there is a genetic component to the disease [130]. Approximately 5-10% of PD patients have a familial form of parkinsonism with an autosomal-dominant pattern of inheritance [130]. Case control studies have typically indicated a 2-14-fold increase in incidence in close relatives of PD patients [131] and although concordance rates between identical twins are low for overt expression of the disease, they are much higher when subclinical decline in striatal DAergic dysfunction is measured by positron emission tomography (PET) imaging (53% in monozygotic twins of PD patients, compared with 13% in dizygotic cases [132]. The disease was once thought to affect primarily whites, but recent studies have demonstrated equal prevalence in African Americans and whites living in the same geographic area. To date, no studies have determined the prevalence or incidence of PD in Hispanics, and retrospective epidemiologic studies performed in various major cities have yielded contradictory information. Variations in the prevalence of the disease in individual racial groups in different geographic areas have suggested an increased risk associated with rural living. Pesticides and other toxins have been suspected, but none has been proved to be a definite causative factor [133]. It appears clear that in PD, the demise of DAergic neurons is induced by non-genetic factors such as environmental exposures to various toxins, diet and other lifestyle issues, and head injury, probably in interaction with susceptibility genes [134].

Premorbid Parkinsonian Personality

The hypothesis of a premorbid parkinsonian personality has been suggested since the beginning of the last century [135]. In view of the fact that the risk factors for PD are unclear, the possibility of this distinctive parkinsonian personality is intriguing and of clinical importance. Indeed, if there is a personality type in people predisposed to PD, relatively simple personality screenings could be used to evaluate individual risk for the disease. This assumption has been confirmed by successive studies that have shown the existence of some personality traits and behaviours that are found in those who go on to develop PD [136,137]. This premorbid personality consists of traits such as industriousness, punctuality, emotional and attitudinal inflexibility, cautiousness, lack of affect and a predisposition to depressive illness [136]. These personality characteristics may precede the onset of overt clinical symptoms in PD by several years. Thus, patients with PD show reduced scores on impulsive sensation seeking (ISS) inventories [138] and it seems likely that this non-engagement in novelty seeking behaviour precedes the development of motor abnormalities. Introspective, over-controlled, anhedonic personality traits together with suppressed aggressiveness are frequently found. In medicated and unmedicated PD patients, high harm avoidance has also been demonstrated in comparison with healthy controls

[139]. In addition, epidemiologic evidence [140] shows that there is a low incidence of cigarette smoking, coffee drinking, and alcohol consumption, in people who develop PD, again suggesting that there is a behaviour pattern that predates PD. Therefore, there is the possibility of a neurobiological link between low sensation seeking traits, which might underlie the parkinsonian personality, and the hypothetical protective effect of cigarette smoking and caffeine consumption on PD. Accordingly, the use of these substances might be an epiphenomenon rather than being causally linked. Low sensation seekers may also be more susceptible to environmental toxicants. Shyness is a low ISS trait that is found more frequently in first degree relatives of PD patients compared with controls and predicts higher reported illness rates in response to xenobiotics, such as pesticides [141]. In discordant PD monozygotic twins, shyness has been found to be more common in the affected sibling [142].

To confirm this evidence, further research is required. Even then, the term premorbid is difficult to define due to the unknown latent period before onset of PD. Additional research would involve correlating personality characteristics with activities or changes in the brain.

Premorbid Health Conditions of PD

Obesity

Dopamine plays important roles in the regulation of food intake [143]. Obese persons have lower DA D2 receptor availability in the striatum and a body mass index (BMI) correlated negatively with the measures of D2 receptors [144]. This potential association between obesity and the risk of PD has recently been the subject of investigation. Hu *et al*. [145] found in a Finnish population that excess weight, defined as a BMI $\geq$ 23, is associated with an elevated risk of PD among middle-aged men and women. The evidence that being overweight may increase the risk of PD has been confirmed in a Japanese population study [146]. Compared to the value before the onset of PD, BMI was significantly reduced at 2 years after the onset.

Even though the mechanism behind the association between obesity and the risk of PD is poorly understood, several factors associated with high BMI can be involved, such as lower level of physical activity, dietary factors, etc.

Conversely, once the disease is full-blown, PD patients exhibit lower body weight when compared to age-matched healthy subjects. Possible determinants of weight loss in PD patients include hyposmia, impaired hand-mouth coordination, difficulty chewing, dysphagia, intestinal hypomotility, depression, decreased reward processing of DAergic mesolimbic regions, nausea, and anorexia as the side effects of medication, and increased energy requirements due to muscular rigidity and involuntary movements. There is enough evidence for recommending monitoring the body weight of PD patients as the disease progresses [147**]**.

Hypertension, Hypercholesterolemia and Diabetes

Hypertension, hypercholesterolemia, and diabetes are important risk factors for atherosclerosis [148] and have been associated with an increased incidence of stroke, AD, and dementia [149,150]. Although the aetiology of PD is poorly understood, vascular factors may be influential in modulating disease risk. Recently, Ascherio's group analysed the association between a history of vascular conditions and risk of PD in two large prospective cohorts [151]. Risk of PD was not associated with the history of hypertension or diabetes. They also found no associations between history of use of antihypertensive drugs or cholesterol-lowering medication and risk of PD.

Differently, total cholesterol levels were associated with a decreased risk of PD. Analyses stratified by sex revealed a modest but significant trend of decreasing PD risk with increasing cholesterol in women but not in men. When analyzed as a continuous variable, every 50 mg/dL increase in total cholesterol was associated with an 18% lower risk of PD in women but only a 10% lower risk in men. Men with the highest total cholesterol (>270 mg/dL) had a significantly lower risk of PD when compared with men with the lowest total cholesterol (<159 mg/dL). This evidence should be interpreted with caution because the results are only marginally significant and could have occurred by chance. However, they are consistent with the lower levels of LDL cholesterol among patients with PD than controls [67] and the protective effect against PD of increasing cholesterol observed in women but not in men [68]. Further investigation of the potential protective effect of high cholesterol and PD is nevertheless warranted (see paragraph on statins). Nevertheless, a history of hypertension [49,50,152] or diabetes [152,153] has been associated with a decreased risk of PD. In a recent case-control study, a 40% lower risk of PD was estimated among subjects with diabetes, and a significant interaction between smoking status and diabetes was found among men but not women [153]. On the other hand, in a cohort study in Finland, risk of PD was 85% higher in men and women with type 2 diabetes [154].

Uric Acid

Uric acid (Fig. **4**) is an antioxidant and iron chelator in the human body. It has been shown to scavenge hydroxyl radicals and peroxynitrate, which are considered to be central mediators of oxidative damage in the pathogenesis of PD [155,156]. Uric acid can form complexes with iron ions [157] and its synthesis seems to be coupled to the production of ferritin through a yet unidentified mechanism [158], indicating that both these molecules are involved in sequestering free iron in the body. Both ferritin and uric acid levels in the SNc of PD brains have been reported to be decreased [159,160] and a low level of plasma uric acid and a high intake of iron are considered risk factors for the disease [161,162]. Plasma uric acid levels are significantly lower in PD patients when compared with controls [163]. Interestingly, two prospective population-based cohort studies showed that higher serum levels of uric acid were associated with a significantly decreased risk of Parkinson's disease (40-30% reduction in PD incidence), with evidence for a dose-effect relationship [161,164]. Although the possibility that these findings are due to residual confounding or confounding by unmeasured factors cannot be completely ruled out, these results support the hypothesis that oxidative stress is involved in the pathogenesis of PD and that uric acid might reduce the risk of PD *via* antioxidant and iron-chelating properties. These findings raise the possibility that interventions to increase plasma urate may reduce the risk and delay PD progression.

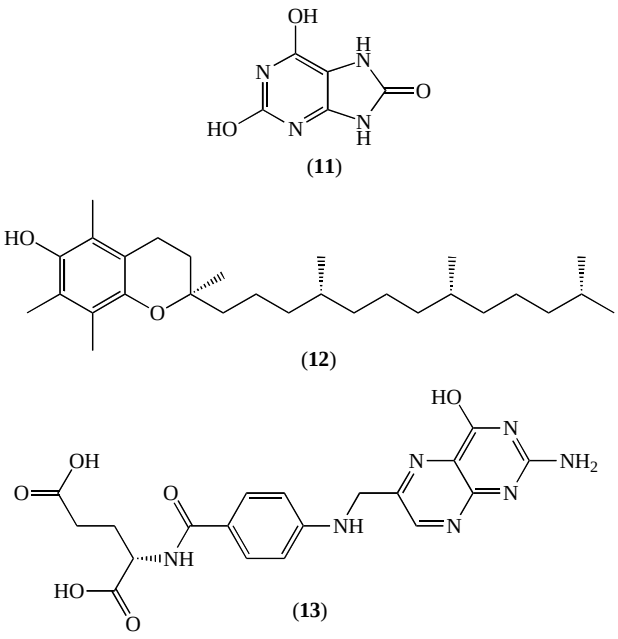


Fig. (4). (**11**) Uric acid, 7,9-dihydro-3H-purine-2,6,8-trione. (**12**) α-tocopherol 2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-ol. (**13**) Folate, (2S)-2-[[4-[(2-amino-4-oxo-1H-pteridin-6-yl)methylamino]benzoyl]amino]pentanedioic acid.

Coenzyme Q10

Coenzyme Q10 is used in the treatment of a variety of disorders primarily related to suboptimal cellular energy metabolism and oxidative injury. CoQ 10 is a component in the electron transport system, and operates between, on the one hand, two flavin proteins, succinyl dehydrogenase and NADH dehydrogenase, and on the other, cytochromes, and plays an important role in ATP production during cell respiration (Fig. **1**). Immunostaining examination of the autopsied brains of sporadic PD patients has shown decreases in mitochondrial electron transfer complex I and α-ketoglutarate dehydrogenase (KGDH) activity [165,166]. Mitochondrial respiratory dysfunction can cause oxidative stress, and this in turn may cause further mitochondrial respiratory dysfunction, consequently leading to a vicious cycle, resulting in neuronal damage. Beneficial effects of oral CoQ 10 administration have been found in animal models for PD [167,168] and in a multicenter, placebo-controlled, randomized phase II trial [70]. Surprisingly, a recent randomized, double-blind, placebo-controlled trial failed to show improvement of PD symptoms by nanoparticular CoQ 10 and did not meet its primary or secondary end points [169]. The levels of CoQ 10 in PD analyzed in blood samples, failed to find consensus between the findings; some studies have reported decreased plasma levels, whereas others found no significant changes [170,171]. Recently, the concentrations of oxidized CoQ 10 and reduced CoQ 10 in the cerebrospinal fluid (CSF) of patients with PD has been examined in order to determine whether the balance in oxidized and reduced CoQ 10 is related to the pathogenesis of PD [172]. The percentage of oxidized/total CoQ 10 (%CoQ 10) in the CSF was significantly higher in the untreated PD group compared to the normal control group. The %CoQ 10 in the CSF of PD patients showed significant negative correlation with the duration of illness. These findings in living patients provide *in vivo* evidence for a possible role for %CoQ 10 in the pathogenesis in the early stages of PD development [172].

DIET AND LIFESTYLE

Diet may play an important role in the aetiology of neurodegenerative disorders such as AD and PD, by affecting the neuronal membrane constitution, altering the oxidative balance in the brain or serving as a vehicle for environmental neurotoxins. Few epidemiologic studies have been able to examine potential associations between diet and PD because of the relatively low incidence of the disease and its insidious onset. Potential roles of foods and nutrients in determining PD risk have been investigated, although the results for more of them are still elusive. Elevated risks have been reported for higher intakes of total energy, dietary fats, carbohydrate, monosaccharide and disaccharide, chocolates and desserts, iron, and lutein, and reduced risk for higher intakes of potatoes, niacin, and foods containing niacin [173,174]. Most of these studies used a retrospective case-control design that is not well suited for such investigations because of the potential for recall and selection biases and because of the difficulty of controlling for the effects that the disease status may have on diet. Moreover, intakes of many nutrients are highly correlated and specific associations are therefore not always easily identified. Only a few population-based prospective cohort studies have been done so far.

It is well established that consumption of diets rich in antioxidant and anti-inflammatory agents, such as those found in fruit and vegetables, may lower the risk of PD. New evidence suggests that dietary supplementation with fruit or vegetable extracts can decrease the age-enhanced vulnerability to oxidative stress and inflammation. Thus, nutritional intervention may exert therapeutic protection against PD. Accordingly, it has been suggested that vegan diets may be notably protective with respect to PD [175]. Moreover, a caloric restriction diet, a reduction of food intake by 40-60% without malnutrition, has recently been shown to protect the central DAergic neurons from neurotoxins, at least in part by induction of heat-shock proteins [176]. Dietary restriction has remarkable benefits for health and lifespan, extending the survival of diverse species and can protect against PD [177], conceivably, the protection afforded by vegan diets reflects a similar mechanism [175]. It is well established that exposure of neurons to a mild metabolic stress, can protect them against excitotoxicity and other Ca^{2+}-mediated neurodegenerative processes. This type of metabolic hormesis seems mediated by transcription factors. Exposure of neurons to subtoxic levels of noxious chemicals is increasingly recognized as a means of inducing hormesis. This has been well established for mitochondrial toxins such as cyanide, but may also be a major mode of action of many of the health-promoting phytochemicals present in vegetables and fruit. Examples include sulforaphane (present at high levels in broccoli), curcumin from tumeric root, and resveratrol from red grapes [177]. The possibility that vegan diets could be therapeutically beneficial in PD, by slowing the loss of surviving DAergic neurons, thus retarding progression of the syndrome, may merit examination. Vegan diets could also be helpful to PD patients by promoting vascular health and aiding the blood-brain barrier transport of L-dopa [175]. The overall evidence from these studies appears to support a healthy unbalance of calorie intake and output, preferring a

reduction of food intake; this may be better interpreted as maintaining a healthy weight rather than severely restricting calories.

Macronutrients

Fat and Fatty Acids

Evidence from several research areas underlines the importance of unsaturated fatty acids for neuronal cell function. The relation between dietary fat and PD is unclear. Diets with high lipid content could theoretically increase the amount of oxygen radicals by lipid peroxidation and thus increase the risk of PD [178]. On the contrary, a significant inverse association between total fat intake and PD risk has been reported [64], emphasizing the selective role of unsaturated fatty acids in lowering the risk of PD. In this prospective population-based cohort study intakes of total fat, monounsaturated fatty acids (MUFAs), and polyunsaturated fatty acids (PUFAs) were significantly associated with a lower risk of PD. They observed an association for omega3-PUFA intake seemed to be driven by the subtype of α-linolenic acid, which makes up 88% of all omega3-PUFA intake. Linoleic acid accounts for 99% of all omega6-PUFA intake and drove the association for total omega6-PUFA. Intakes of other subtypes were very low and not related to the risk of PD. An inverse association of total fat intake with PD risk was found which was very similar to the one for cis-unsaturated fatty acids (MUFA and PUFA together). This association may have been partly driven by the association between cis-unsaturated fatty acids and PD, as more than half of total fat intake consists of cis-unsaturated fatty acids. Indeed, a trend for an inverse association between saturated fatty acids and cholesterol and the risk of PD has also been reported. There are several reasons why dietary intake of unsaturated fatty acids might influence the risk of neurodegenerative diseases and in particular PD. First, PUFAs have anti-inflammatory and neuroprotective properties [179] and MUFAs are thought to reduce oxidative stress [180]. Second, the fatty acid composition of cell membranes is affected by diet [181]. Third, PUFAs are precursors for endogenous cannabinoids, which play a role in the control of movement by modulating DAergic activity in the basal ganglia [182]. Finally, evidence is increasing that lipids may also regulate α-syn aggregation, the major component of the inclusion bodies found in the brains of patients with PD [183]. Few studies focused on unsaturated fat in relation to PD. Within the Honolulu-Asia Aging Study, a significantly reduced risk of PD observed with higher intake of PUFAs [184] was only partially confirmed in the Health Professionals Follow-Up Study and the Nurses' Health Study [68]. Of the several PUFA subtypes, only arachidonic acid was significantly associated with a lower PD risk. However, isocaloric replacement of polyunsaturated fat with saturated fat was associated with a significantly increased risk of PD in the men [68].

Dairy Food Consumption and Risk of Parkinson's Disease

Recently [185-187], the association between intake of dairy products and risk of PD has been investigated. Higher consumption of dairy products was associated with increased risk of PD. The association was stronger in men and was mostly explained by milk consumption [187]. Men in the highest quintile of intakes of dairy products had a 50 to 80% increase in PD risk compared with men in the lowest quintile [187]. Men who consumed more than 16 ounces (0.5 liters) of milk per day had a 130% higher risk of PD than men who did not drink milk [186]. The effect of milk consumption on PD seems also independent of the intake of Ca^{2+}. However, dairy intake was not associated with PD risk in women, and no other food groups were associated with PD risk in either men or women. Among men, PD risk increased significantly with greater intakes of cream cheese, other cheese, and sour cream, and marginally with skim or low fat milk intake. In addition, PD risk was not significantly associated with intake of dairy fat or animal fat, but rather with intakes of nonfat constituents of dairy foods in men. Moreover, there was a lack of association between PD risk and calcium, vitamin D, and protein from nondairy foods or supplements, suggesting that intake of these nutrients is not causally related to PD risk [187]. The exact cause of is not clear; however, the process may include oxidative stress and mitochondrial dysfunction. There is no apparent evidence linking intake of milk or its components to DAergic neuron death in PD. Repeated oral infusions of milk decreased extracellular DA concentrations in newborn rats [188] but no information on the effects of milk consumption in adult animals has been reported. Neither the presence of some unmeasured components nor contamination of dairy with pesticides or polychlorinated biphenyls can be excluded. The fact that a similar association was not present in women requires caution in interpreting the results. Future epidemiologic and experimental investigations are needed to further evaluate this association and to ascertain the underlying mechanisms.

Micronutrients

Vitamins

Antioxidants such as vitamin C (ascorbic acid), vitamin E (α-tocopherol) (Fig. **4**), and carotenoids such as β carotene are thought to protect cells from oxidative injury [189]. A recent meta-analysis [190] showed that a moderate intake of vitamin E seemed to decrease the risk of developing PD by 20%, suggesting that foods rich in vitamin E may be protective. This protective influence was seen with both moderate intake and high intake of vitamin E, although the possible benefit associated with high intake of vitamin E was not significant. The risk of PD, however, is significantly reduced among men and women with high intake of dietary vitamin E (from foods only) [91]. Consumption of nuts is also significantly associated with a reduced risk of PD. Neither vitamin C nor β carotene seems to have a neuroprotective effect. Given that these data are observational, confirmation from well-designed randomised controlled trials is necessary before suggesting changes in routine clinical practice.

Vitamin B complex has been studied as well. Vitamin B6 is required to convert homocysteine to cysteine, which in turn is the rate-limiting precursor in the synthesis of glutathione [191]. Reduced levels of glutathione, a major antioxidant, have been found in DAergic neurons of PD patients [192]. Consequently, higher intakes of folate (Fig. **4**) and vitamins B12 and B6 might decrease the risk of PD by decreasing homocysteine levels which might enhance DAergic cell death through neurotoxic effects. This hypothesis has been corroborated by a recent publication of the Rotterdam Study group showing that dietary vitamin B6 was associated with a lower risk of PD with evidence for a dose-effect rela-

tionship [193]. In addition, stratified analyses revealed that this association was restricted to smokers, probably accounted for by mutually reinforcing beneficial effects of smoking and vitamin B6 intake on the risk of PD. Conversely, no significant association with PD risk was observed for folate and vitamin B12, although their potential effect on PD risk is not completely ruled out [193]. Several lines of evidence suggest neuroprotective properties of vitamin B6 through antioxidant capacities, in addition to decreasing plasma homocysteine [194]. Because oxidative stress may be prominent in PD pathogenesis, higher vitamin B6 intake may thus reduce PD risk through antioxidant effects.

Minerals

Dietary Iron

Analysis of iron in the brain of PD patients has shown a selective and increased level of iron in the SNc [195]. If iron is freed from binding to neuromelanin or ferritin, hydroxyl radicals produced by Fenton reaction might induce DAergic neurons' death. Thus, it is plausible that selective increase of iron in the melanized SNc DAergic neurons, possibly due to excessive dietary intake and impaired iron metabolism, could lead to progressive degeneration of these neurons. Two case-control studies found a positive association between iron intake and PD [63,162]. Powers and colleagues [63] performed analyses of dietary iron intake stratified on intake of multivitamins or iron supplements, and observed a moderate association between iron intake from foods and PD. The added increase in risk from iron in food plus iron from multivitamins and iron supplements supports the hypothesis that total iron intake is a potential risk factor for PD. Moreover, these authors showed a consistent moderately elevated risk for high manganese intake as well. Of paramount importance is the evidence that an increased intake of iron plus manganese could accentuate (nearly twofold increase) the risk of PD by either metal alone. There are foods in common linking these two elements as potential risk factors, such as spinach, lima beans, peas, wheat bread, peanuts, and other nuts and seeds. Multivitamins also contain manganese; thus, the added risk may be partly due to the joint effect of iron and manganese. These findings are not in agreement with former evidence that failed to show any association between iron intake and risk of PD [196,173]. Further studies on the relation between dietary iron and the risk of PD are consequently warranted.

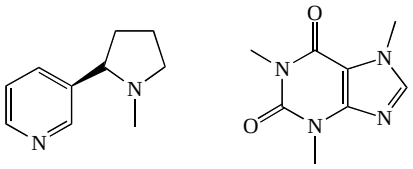
Selenium

Selenium is very important in the cellullar control of oxyradicals. The dietary significance of selenium was clarified by the demonstration that it was a component of the detoxifying enzyme seleno-glutathione peroxidase (GPx) [197]. Many DAergic neurons of the SNc express low levels of GPx antigen, in contrast to the VTA [198]. Nutritional deficiency in selenium is accompanied by a decrease in the activity of GPx [199]. Although selenium deficiency occurs rarely, it may be produced by a change in the diet during short periods of malnutrition which are not rare during aging due to a decrease in appetite and the loss of taste capacity. A selenium-deficient diet for a short period of time decreases brain protection, principally in the SNc, against oxidative damage [200]. Incongruously, selenium increases in CSF of PD patients [201]. Dietary selenium and risk of PD has not been studied so far.

Dietary Supply of Antioxidants

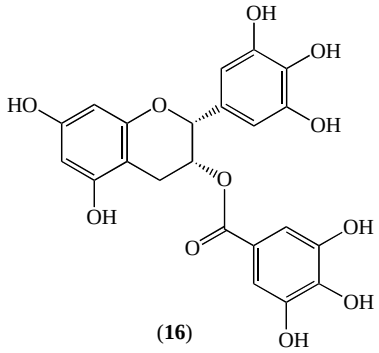
Although antioxidants and supplements theoretically could help in the treatment of PD, the clinical data supporting their role are marginal. It is possible that dietary intake of foods high in antioxidants may reduce risk of developing PD. Although the available data are still limited, epidemiological studies indicate that dietary antioxidants influence the incidence of neurodegenerative disorders such as dementia (including AD) and PD [201-205]. For example, incidence data from the so-called PAQUID (Personnes Agees Quid) study showed that people drinking 3-4 glasses of wine per day had an 80% decreased incidence of dementia and AD 3 years later, compared to those who drank less or did not drink at all [203-205]. These protective effects are most likely due to the presence of antioxidants in food and beverages inasmuch as it has been found that wine drinking and the consumption of other foods and drinks which are rich in polyphenols can increase the antioxidant activity in serum [204]. More recently, investigators in the Rotterdam Study [206] reported that any form of moderate alcohol would have the same beneficial effects. The risk reduction associated with alcohol is possibly related to its antioxidant properties or its effects on lipid metabolism. The clinical findings indicating a protective effect of dietary flavonoids against neurodegenerative diseases are supported by data obtained in laboratory animals showing that dietary supplementation containing fruit and vegetables rich in antioxidants (blueberries, strawberries and spinach) can have beneficial effects on age-related decline of neuronal and cognitive functions in old rats [207]. Several thousands molecules having a polyphenolic structure have been identified in higher plants and are generally involved in defence against ultraviolet radiation or aggression by pathogens [208]. More than 4000 varieties of flavonoids have been identified, many of which are responsible for the attractive colours of flowers, fruits, and leaves. Flavonoids represent the single, most widely occurring group of phenolic phytochemicals [209]. In recent years, there has been an increasing interest in investigating the many positive pharmacological properties of flavonoids. Much of this interest has been spurred by the dietary anomaly referred to as the "French paradox", the apparent compatibility of a high saturated fat diet with a low incidence of coronary atherosclerosis [210]. Epidemiological studies have shown that moderate wine consumption can be protective against neurological disorders such as age-related macular degeneration [211]. Moreover, *in vitro* and *in vivo* pre-clinical studies have shown the neuroprotective effect of lyophilized red wine [212], grape polyphenols [213], quercetin [214], *trans*-resveratrol [212,215,216], and (+)-catechin [217]. There is also increasing interest for the role of tea (*Camellia sinensis*) in maintaining health and in treating disease. Despite the high consumption of tobacco, Asia and Japan in particular have among the lowest incidences of arteriosclerosis and lung cancer per capita. It has been postulated that this paradox, this time referred to as the "Asian Paradox", exists as a result of the high consumption of green tea in this region, and most benefits occur when approximately 1.2 L of green tea are consumed every day. Although tea consists of several components, research has focused on polyphenols, especially

those found in the unfermented tea leaves, known as green tea. The green tea polyphenols include (-)-epicatechin (EC), (-)-epigallocatechin (EGC), (-)-epicatechin-3-gallate (ECG), (-)-epigallocatechin-3-gallate (EGCG) (Fig. **5**). Of these, EGCG generally accounts for greater than 40% of the total [218]. Green tea polyphenols are potent antioxidants [219]. EGCG usually has the greatest antioxidant activity, and is the most widely studied polyphenol for disease prevention [218,210]. Many of the putative health benefits of tea are presumed to be a result of its antioxidant effects.



(**14**)

(**15**)



(**16**)

Fig. (5). (**14**) (-)-epigallocatechin-3-gallate (EGCG), [(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl] 3,4,5-trihydroxybenzoate. (**15**) Nicotine, 3-(1-methylpyrrolidin-2-yl)pyridine. (**16**) Caffeine, 1,3,7-trimethylpurine-2,6-dione.

The epidemiological evidence indicating the putative role of nutritional antioxidants in the prevention and attenuation of neurodegenerative disorders is receiving experimental confirmation in a number of laboratory studies [218,220, 221].

Moreover, recent reports have revealed that flavonoids may be neuroprotective in neuronal primary cell cultures. For example, the Ginkgo biloba extract, known to be enriched with flavonoids, has been shown to protect hippocampal neurons from NO or β-amyloid derived peptide-induced neurotoxicity [222,223]. In addition, the extract of Ginkgo biloba referrred to as Egb 761 is one of the most popular plant extracts used in Europe to alleviate symptoms associated with a range of cognitive disorders [224]. The mechanism of action of Egb 761 in the CNS is only partially understood, but the main effects seem to be related to its antioxidant properties, which require the synergistic action of the flavonoids, the terpenoids (ginkgolides, bilobalide), and the organic acids, principal constituents of Egb [225]. These compounds to varying degrees act as scavengers of ROS, which have been considered the mediators of the excessive lipid peroxidation and cell damage observed in PD [226].

In summary, the bulk of recently published data illustrated the emerging and promising role of polyphenolic compounds as therapeutic tools in PD. Many studies highlighted that polyphenols could protect neurons against various toxic compounds. The emerging view is that polyphenolic compounds could exert beneficial effects on cells not only through their antioxidant potential but also through the modulation of different pathways such as signalling cascades, anti-apoptotic processes. Moreover, different pathways could be activated by different polyphenols present in the same extracts with benefical interactions or synergistic effects. Elucidation of their mechanism of action should provide new insight for new targets for neuroprotective drugs. The studies described above demonstrate that the concentrations of polyphenols from diet are high enough *in vivo* to display pharmacological activity in the brain. Furthermore, polyphenol supplements such as green tea polyphenols or catechins, ginseng, ginkgo biloba and EGb 761, polygonum, triptolide, might have potential clinical benefit in prevention of PD in humans [226].

Tobacco, Coffee, and Alcohol

Smoking

An inverse association between cigarette smoking and PD has been consistently confirmed by different epidemiological studies [227-229]. It seems clear that a protective, dose-dependent role for cigarette smoking and potentially other types of tobacco use on PD risk exists. Importantly, estimated effects seem unaltered by sex or education but are stronger among those with younger age of disease onset [227]. Nevertheless, only randomized intervention trials can confirm that some components in tobacco are truly neuroprotective, negating the possibility that a premorbid personality influences smoking behaviour among those who later develop PD. The biological basis that might underlie smoking effects is still poorly understood. Several mechanisms have been proposed to explain the potential neuroprotective effect of cigarette smoking. The most likely explanation for this effect is due to the nicotine in tobacco (Fig. **5**). Nicotine interacts with multiple nicotinic receptor (nAChR) subtypes in the peripheral and central nervous system, as well as in skeletal muscle. Recent results show that striatal α6β2-containing nAChRs are particularly susceptible to nigrostriatal damage, with a decline in receptor levels that closely parallels losses in striatal DA. These observations suggest that development of nAChR agonists or antagonists targeted to α6β2-containing nAChRs may represent a particularly relevant target for PD therapeutics [230,231]. Although a major focus is on receptor-mediated protection, nicotine might play also a more direct role bypassing nACh receptors. Indeed, new evidence shows that nicotine can act as a neuroprotectant *via* an anti-inflammatory mechanism mediated by the modulation of microglial activation [232]. Along with various nicotine effects, this anti-inflammatory mechanism could have a major therapeutic implication in the preventive treatment of PD. It is evident that the observation of a reduced PD risk in smokers needs cautious interpretation as it might result from bias due to selective mortality of smokers among people without PD, inaccurate recording of PD diagnoses in smokers, and confounding by unknown factors.

Coffee and Tea Consumption

The adverse effects of cigarette smoking on health and the difficulty in determining whether nicotine or other tobacco chemicals may be potentially beneficial in preventing PD have tempered the enthusiasm for pursuing the investiga-

tion of the potential neuroprotective effects of tobacco. In contrast, the identification of caffeine (Fig. **5**) as the explanatory molecule for the reduced risk of PD in coffee drinkers appears more promising. Indeed, numerous studies have described associations for caffeine consumption in relation to PD risk indicating that caffeine consumers are significantly less likely to develop PD than those never exposed [229]. Caffeine is generally thought to be the active component, given that total caffeine intake and intake of caffeine from non-coffee sources were found to be inversely related to PD risk, whereas no association was seen between other components in coffee and the risk of PD [233]. Experimental evidence suggests that caffeine has potential antiparkinsonian properties, as demonstrated by its protective effects against toxins [234,235]. Caffeine is an antagonist at the A_1 and A_{2A} subtypes of adenosine receptors, and selective drugs for these receptors have been proposed for PD therapy [236]. The epidemiological studies have shown that the inverse association between coffee and PD is strong and significant only in men, whereas in women it is weaker and only marginally significant [233,237]. The explanation for this contrasting gender differences might depend on oestrogen effect on caffeine metabolism. In fact, oestrogen, which can serve as a neuroprotectant in its own right, interferes with neuroprotection by caffeine against nigral DAergic degeneration [238]. Furthermore, this gender difference disappears when men are compared to those women who had never used oestrogen replacement therapy but not those who had used it [239,240]. This evidence suggests that oestrogen replacement therapy may prevent the beneficial effect of caffeine in reducing the risk of developing PD. A better understanding of the interplay between environmental factors like caffeine and oestrogen may suggest effective preventative as well as therapeutic strategies for this neurodegenerative disorder. Recently, green tea has attracted great attention particularly with respect to its potential for preventing and treating cancer, cardiovascular or inflammatory diseases [241]. Consumption of tea seems to have beneficial role in reducing risk of PD as well [242,243]. The consumption of the number of cup-years of tea is inversely correlated with risk of PD. One unit of tea (3 cups/day for 10 years) would lead to 28% risk reduction of PD [243]. The tea beneficial role is likely depending on flavonoids (30% of the dry weight of a leaf) including catechins and their derivatives rather than caffeine that is also present in tea. Hence, the polyphenol epicatechin was shown to attenuate neurotoxicity induced by oxidized low-density lipoprotein in mouse-derived striatal neurons [220]. Thus a pretreatment of mice with either green tea or EGCG prevented DAergic neurons in the nigro-striatal pathway induced by MPTP [218]. Tea extracts and EGCG attenuated the neurotoxic action of 6-hydroxydopamine (6-OHDA) in rat PC12 cells and human neuroblastoma SH-SY5Y cells [221]. EGCG exerts potent DAergic neuroprotective activity by means of microglial inhibition [244]. In addition, the neuroprotective effect of EGCG may involve its catechol structure, its free radical scavenging and metal chelator (especially iron) properties [245]. Although a negative association between cigarette smoking, tea or coffee drinking with the occurrence of PD is well documented, unfortunately these factors do not have a disease modifying effect in already diagnosed PD [246].

Alcohol Consumption

It has been reported that the risk of PD is significantly lower in drinkers of 2+ alcoholic drinks/day compared to abstainers; this applied to both wine and liquor drinkers [50,247,248]. However, this protective effect has not been confirmed in other studies [249,250]. There is enough experimental evidence [212-217] that red wine consumption may be beneficial in the prevention of age-related neurodegenerative disorders such as PD.

CONCLUDING REMARKS

Based on the epidemiological evidence reviewed so far, numerous factors seem to predispose certain individuals to develop PD. Furthermore, a variety of acquired factors, such as exposure to well water, herbicides, industrial chemicals, wood pulp mills, farming, and living in a rural environment may contribute to disease pathogenesis. A number of exogenous toxins have been associated with the development of parkinsonism, including trace metals, cyanide, lacquer thinner, organic solvents, carbon monoxide, and carbon disulfide [130].

Prevention strategies can be developed only if the risk and protective factors for PD are known. Older age and smoking habits are the only risk factors for PD that have consistently been found across studies so far. For most of the factors, evidence remains uncertain and not fully understood. For example in the recent positive association found between fatherhood and PD [251], where surprisingly the risk seems to increase with increasing number of children.

We are far away from knowing with clarity all the risk factors of PD. Epidemiology will help and some methods will become more sophisticated, but the basic principles of minimizing the role of chance, bias, and confounding will remain. Indeed, initial studies were too small or had methodological limitations that hampered the interpretability of their findings. Large, well-designed, prospective population-based cohort studies are the only studies suited to examine the effects of multiple potential risk factors and their interactions, as well as effects that develop over a longer period. In the coming years, and possibly through pooling of studies to further increase statistical power, we will gain a better insight into the role of environmental factors in the pathogenesis of this devastating disease. Based on current knowledge of risk and protective factors, prevention strategies for those who have no clinical symptoms of PD, and those who are at high risk of developing these neurological disorders can be proposed. Collectively, the available data suggest that a brain-healthy diet is very similar to a heart-healthy diet. This involves a balanced low-calorie diet that contains unsaturated fat and plenty of fruit and vegetables rich in antioxidants. Although antioxidants should derive essentially from fresh food, vitamin E supplementation is recommended. Moreover, regular consumption of a variety of juices (200 ml per day), namely, purple grape juice, which contains the highest levels of flavan-3-ols and procyanidins, anthocyanins, and hydroxycinnamates, a flavonol-rich cranberry juice drink, grapefruit juice, which contains flavanones in high levels, and cloudy apple juice, which is a good source of hydroxychalcones and flavan-3-ols should be part of the meal [252]. Overall, it is of paramount importance to maintain brain antioxidants at levels that are higher than normally

provided by nature and a high dietary intake may be indicated from childhood.

Moreover, life modifications should begin early and should include daily moderate exercise, reduced stress and no tobacco smoking (nicotine's neuroprotective effect should be obtained by other drug preparations), drinking coffee, green tea and moderate intake of alcohol especially red wine, avoiding exposure to pesticides and intake of iron and Mn through supplements.

Unfortunately, a strong rationale does not exist instead for the use of statins, CCBs or NSAIDs in primary prevention of PD. On the other hand, the vaccine development and other immunotherapies against PD that would provide benefits to people who are not diagnosed with PD seem far away.

In conclusion, we do not know if PD will be prevented, without doubt we can reduce the risk so far known.

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ABBREVIATIONS

%CoQ 10 = Oxidized/total CoQ 10

$^{\cdot}OH$ = Hydroxyl radicals

6-OHDA = 6-Hydroxydopamine

AD = Alzheimer disease

AP-1 = Activator protein 1

APOE = Apolipoprotein

BMI = Body mass index

Ca^{2+} = Calcium ions

cAMP = Cyclic adenosine monophosphate

CCBs = Ca^{2+} channel blockers

CNS = Central nervous system

CoQ 10 = Coenzyme Q10

COX-2 = Cyclooxygenase-2

CSF = Cerebrospinal fluid

DA = Dopamine

DAergic = Dopaminergic

EC = (-)-Epicatechin

ECG = (-)-Epicatechin-3-gallate

EGC = (-)-Epigallocatechin ()

EGCG = (-)-Epigallocatechin-3-gallate

GDNF = Glial-derived neurotrophic factor

HCN = Hyperpolarization-activated cyclic nucleotide-gated cation

HMG-CoA = 3-Hydroxy-3-methylglutaryl coenzyme A

hα-syn = Human α-syn

IFN-γ = Interferon γ

IL-1β = Interleukin-1β

IL-6 = Interleukin-6

iNOS = Inducible NO synthase

ISS = Impulsive sensation seeking

LDL = Low-density lipoprotein

LDL-C = LDL cholesterol

LTs = Leucotriens

MAOS = Membrane associated oxidative stress

MPTP = 1,2,3,6-Tetrahydropyridine

MS = Multiple sclerosis

MUFAs = Monounsaturated fatty acids

NAA = N-acetylaspartate

nAChR = Nicotinic receptor

NF-κB = Nuclear factor-kappa B

NO = Nitric oxide

NSAIDs = Nonsteroidal anti-inflammatory drugs

VGCC = Voltage-Gated Calcium Channel

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