Neurotox Res (2018) 33:515–522
DOI 10.1007/s12640-017-9804-z

REVIEW

Neuromelanin in Parkinson's Disease: from Fenton Reaction to Calcium Signaling

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Received: 10 May 2017 / Revised: 14 August 2017 / Accepted: 23 August 2017 / Published online: 6 September 2017

Abstract Neuromelanin is supposed to play a key role in the pathogenesis of Parkinson's disease. A common theory is the formation of reactive oxygen species through the Fenton reaction catalyzed by neuromelanin-bound iron ions and subsequent death of the dopaminergic cells in the substantia nigra. From a physicochemical point of view, this pathway is rather implausible: a highly reactive radical built within a powerful radical scavenger would more promptly be inactivated before it might diffuse within the cell to reach a target to exert its deleterious potential. This review of the literature provides evidence for an interaction of neuromelanin with the calcium signaling pathway in Parkinson's disease and expands the view of the pathophysiological contribution of neuromelanin towards a cytoprotective involvement of this macromolecule in the calcium signaling system. More probably than being directly involved in the production of reactive oxygen species, neuromelanin may act as a calcium reservoir and thus protect dopaminergic cells from cell death. A loss of neuromelanin, as observed in the substantia nigra of Parkinson patients, would lead to enhanced calcium messaging through the loss of an important calcium reservoir and thus finally via the formation of reactive oxygen species to cell death within the substantia nigra.

Keywords Parkinson's disease · Neuromelanin · Calcium · Iron

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Parkinson's disease (PD) is one of the most frequent human neurodegenerative diseases. The prevalence of this neurological disorder rises with the age of the population. The main clinical features of the disease include slowness of movement (bradykinesia), disturbances in balance, rigidity of muscles, and rest tremor. These symptoms are due to a progressive degeneration of dopamine neurons in the substantia nigra (SN), a small structure of about 500 mg located deep in the brain mesencephalon. The first clinical symptoms of PD appear after the death of about 50% of the neurons in SN (Cacabelos 2017; Poewe et al. 2017). Dopamine neurons containing neuromelanin (NM) are preferentially lost in PD, but the reason is still unclear.

Several studies suggest that mitochondrial dysfunction is involved in PD (Abou-Sleiman et al. 2006; Moore et al. 2005). The most widely held theory suggests a role of dopamine itself. There is evidence that oxidation of cytosolic dopamine (and its metabolites) leads to the production of damaging free radicals (Segura-Aguilar et al. 2014; Sulzer and Zecca 2000). Neuronal damage due to excessive release of glutamate or dysfunction of glutamate transporters (glutamate excitotoxicity) has been regarded as a mechanism contributing to degeneration of SN neurons in PD and PD models. Genetic studies have identified several potential determinants in PD (Moore et al. 2005; Sulzer 2007). The recently formulated calcium-dysregulation hypothesis proposes that an uncontrolled rise in cytosolic Ca^{2+} level leads to stimulation of Ca^{2+}-dependent enzymes (calpains, phospholipases, endonucleases, NO synthase, etc.) and excessive Ca^{2+} entry into mitochondria (Zaichick et al. 2017; Zündorf and Reiser 2011). This results not only in increased reactive oxygen species (ROS) production but also increased susceptibility to toxins and other factors causing mitochondrial dysfunction.

All these hypotheses overlap in some regard; the excitotoxic hypothesis overlaps with the calcium dysregulation

hypothesis, since intracellular Ca^{2+} overload is also an essential element of glutamate toxicity. Similarly, the oxidative and proteolytic stress hypotheses overlap with the mitochondrial dysfunction hypothesis, since oxidative stress can lead to mitochondrial dysfunction and vice versa. In this context, NM could serve as a common element in all these hypotheses, since the SN dopaminergic neurons of the nigrostriatal system that are lost during PD contain NM (Hirsch et al. 1989).

This review of the literature provides evidence for an interaction of NM with the calcium signaling pathway in Parkinson's disease which leads to a completely new point of view on the role of NM and the melanin-containing cells in the pathogenesis of PD. A lower density of NM was observed in pigmented SN neurons in PD compared with controls, which may reflect a reduced NM synthesis in PD (Kastner et al. 1992). A loss of NM, as observed in the SN of Parkinson patients, leads to enhanced calcium messaging through the loss of an important calcium reservoir and thus finally to cell death within the SN.

Neuromelanin

Biosynthetic pathways leading to NM and the structure of NM are complex and only partly understood. Study of NM is mostly limited to chemical analysis of human NM derived from autopsy. The presence of pigmented SN is mostly restricted to humans and primates, the intensity of pigmentation being dependent on age. There are conflicting reports of pigmentation in other non-primate species, due to different staining techniques and differing definitions of NM, but some pigmented nigral neurons have been reported in species as varied as the horse, the giraffe, and the frog, while in the dog, melanic pigments have been reported not only in the substantia nigra but also in the hypothalamus (Fedorow et al. 2005). In contrast to humans, rodents have a very low number of melanic granules in the SN (DeMattei et al. 1986). Greater than 95% of the cells in the human SN pars compacta contain NM (Gibb 1992). Interestingly, there is a progressive increase in the intensity of pigmentation within the primates as the relationship to man becomes closer (Marsden 1961).

The pigment first appears within the cytoplasm of the dopaminergic nigral neurons at around the age of 3 years as small, pale granules. Size and number of the granules increase with age until adulthood when NM fills on average 47% of the cytoplasm. After the age of 20, the proportion of the cell occupied by NM remains stable, but measurements indicate that the amount of pigment progressively increases with age (Double et al. 2008; Zecca et al. 2002). After an age of 55–60 years, some histological studies report either an age-dependent loss of NM or no variations, dependent on the counting methods. In patients suffering from PD, less than 50% NM is found in SN compared to healthy age-matched control groups (Mann and Yates 1983; Zecca et al. 2002).

The structure of NM is very complex; it is composed of melanic, lipidic, and peptidic moieties that appear to be covalently linked to each other. The melanic portion has properties of both pheomelanins and eumelanins (Wakamatsu et al. 2003). The eumelanin residues are derived from the oxidative polymerization of dopamine (Ferrari et al. 2013; Zecca et al. 2001; Zucca et al. 2015). Whether the synthesis of NM is enzymatically mediated like the biosynthesis of cutaneous melanin or whether it is a pure autoxidation process of dopamine derivatives is still debated.

Tyrosinase, the key enzyme in melanin biosynthesis, or tyrosinase-like activity has been found in human brains by several investigators (Miranda et al. 1984; Xu et al. 1997). In other studies, however, no tyrosinase activity has been detected in the human SN (Ikemoto et al. 1998; Tribl et al. 2007). It was suggested that NM is synthesized from excess cytosolic dopamine and its oxidized metabolites not accumulated by synaptic vesicles. By permanent accumulation of excess catechols, quinones, and catechol adducts, NM may thus provide an antioxidant and neuroprotective mechanism for catecholamine neurons (Sulzer et al. 2000). However, this hypothesis as the major pathway of NM biosynthesis has several shortcomings. The main objection against the autoxidation hypothesis consists in the fact that clearly measureable amounts of such a polymerization product of dopamine should be found in every animal with dopaminergic neurotransmission. Considering the life span and supposing that the rate of accumulation of NM in aging is similar in different animal species and man, the autoxidation hypothesis would explain the quasi selective presence of NM in humans and primates.

Although the question of NM biosynthesis remains unanswered until now, it seems that some enzymatic steps must be involved in the formation of NM. During formation of the pigment, copolymerization with proteins and fatty acids occurs, resulting in a complex macromolecule with an aromatic backbone and peptide and aliphatic substructures (Engelen et al. 2012). The aromatic backbone is made up of a complex of dihydroxyindole and benzothiazine units believed to arise primarily from the products of dopamine metabolism (Wakamatsu et al. 2003). The amino acid content of the peptide component was reproducible and corresponded to about 15% of the NM weight. Recently, the binding of the melanic component with the peptide component has been modeled in vitro employing a protein with cross β-sheet structure like that found in NM from human brain (Ferrari et al. 2017). NM also showed the ability to absorb specifically lipid molecules, about 20% of its weight, and among these lipids cholesterol was identified, constituting about 5% of the total lipid mixture (Zecca et al. 2000).

A characteristic feature of NM is the ability to bind a number of ions and molecules which may also contribute to its

structure. Like other melanins, NM interacts with numerous organic molecules, including drugs, pesticides, and toxic compounds (Ings 1984; Karlsson and Lindquist 2016; Larsson 1993; Zecca et al. 2001), thereby contributing to the control of the intraneuronal concentration of these molecules.

Neuromelanin, Iron, and PD

NM can interact with many heavy metal ions such as zinc, copper, manganese, chromium, cobalt, mercury, lead, and cadmium (Zecca et al. 1994). NM also strongly binds alkaline metal and alkaline earth metal ions with a high capacity (Liu et al. 2004). In addition, it provides binding sites for iron ions (Bridelli et al. 1999; Liu et al. 2004). The metals bound to NM have attracted great attention due to the potential link between iron-NM-induced oxidative stress and selective degeneration of neurons in the SN of the brains of patients with PD (Fasano et al. 2006).

NM has a high binding capacity for iron; the postmortem iron concentrations in SN of PD patients were found significantly higher than in control SN (Dexter et al. 1989; Sian-Hülsmann et al. 2011; Sofic et al. 1988). Thus, an increased intraneuronal accumulation of iron catalyzing the formation of hydroxyl radicals via the Fenton reaction has been suggested as a mechanism by which intraneuronal NM would render melanized neurons vulnerable (Faucheux et al. 2003; Jellinger et al. 1992).

Neuromelanin, being considered an effective radical scavenger in normal conditions, can potentiate the formation of oxygen radicals in the presence of excess Fe^{3+}, but this occurs only when most of the iron-binding sites are saturated (Ben-Shachar et al. 1991; Pilas et al. 1988). This indicates that the ion-exchange and electron-exchange properties of melanin may be independent from each other, which means that different functional groups are involved in reducing and in binding Fe^{3+} ions. H_2O_2 generated by the deamination and autoxidation of dopamine participates with free Fe^{3+} and iron-saturated melanin to drive the Fenton reaction, thereby liberating cytotoxic hydroxyl radicals. This may lead to a selective degeneration of pigmented neurons in SN. Such a selective vulnerability of the NM-pigmented subpopulation of dopaminergic neurons in PD has been shown histochemically (Hirsch et al. 1988). Recent studies using Mössbauer spectroscopy did not confirm the increase in the overall concentration of iron in parkinsonian SN compared to the control observed in earlier studies, but showed a significant increase in the labile, non-bound iron in PD (Galazka-Friedman and Friedman 2011). Mössbauer spectroscopy is widely used in bioanorganic chemistry, especially for the study of iron-containing biopolymers. This technique is often applied to determine the oxidation state of iron. Although Mössbauer spectroscopy is good for structure studies, it is poor for iron quantification. Therefore, this conclusion on the absence of increase of iron in PD is not reliable. Excess free iron may elicit oxidative or nitrative stress via production of reactive free radicals and trigger the cascades of cell destruction (Sian-Hülsmann et al. 2011). Magnetic resonance studies with early-stage PD patients showed a clear reduction of NM within the SN, but there was no significant correlation with the iron content (Reimao et al. 2016).

The main event in the iron hypothesis is the formation of cytotoxic hydroxyl free radicals from elevated levels of H_2O_2 in the SN in the presence of iron ions bound to NM (Fenton reaction). This generation of a maximal rate of free radicals creates oxidative stress and finally leads to cell death (Ben-Shachar et al. 1991). Although the hypothesis that ROS created by iron bound to NM may be an important factor in the pathogenesis of PD is widely accepted, there are several shortcomings in this theory.

Currently, we know that the efficiency of the Fenton reaction depends on several parameters, mainly H_2O_2 concentration, pH, Fe^{2+}/H_2O_2 ratio, complexation chemistry of the iron ions, and reaction time. Based on merely mechanistical considerations, Saran et al. (2000) concluded that the H_2O_2 concentration required for the Fenton reaction in buffered solutions is close to 1 M with free Fe^{2+} ions; complexation of the iron ions may reduce the required H_2O_2 concentrations into the millimolar range. This still unreasonably high concentration would result in manifold overkill of any cell by this toxic agent. Additionally, in the presence of elevated H_2O_2 concentrations, catecholamines are oxidized by several enzymes like cytochrome c (Rosei et al. 1998), lipoxygenase (Rosei et al. 1994), or xanthine oxidase (Foppoli et al. 1997) to yield melanin.

A well-established physiological function of both, eumelanins and pheomelanins, is the scavenging of free radicals (Bustamante et al. 1993; Dunford et al. 1995; Rozanowska et al. 1999; Tada et al. 2010). Like all melanins, NM also is an excellent radical scavenger, directly interacting with and inactivating free radical species (Double et al. 2008). In addition, the antioxidant action of neuromelanin is also due to its ability to sequester redox-active metal ions such as iron (Zecca et al. 2008). Only under the extreme condition that all iron-binding sites within the melanin were saturated with ferric ions; melanin enhanced the formation of free radicals (Korytowski et al. 1995). It was shown that higher amounts of iron bound to NM increase the degradation rate of NM itself in the presence of H_2O_2 (Zecca et al. 2008). This process of NM degradation by H_2O_2 occurs in PD where the extraneuronal NM left by dead neurons is phagocytosed by microglia and degraded by H_2O_2 produced by microglia (Zhang et al. 2011).

Another argument against this hypothesis is merely physical: the hydroxyl radical produced in the Fenton reaction has

a very short in vivo half-life of approximately 10^{-9} s and a high reactivity (Sies 1993). In a study on the reactivity of radicals with melanin in vitro, the hydroxyl radical showed with an apparent rate constant of 1.1–1.5 × 10^9 M^{-1} s^{-1}, the strongest reactivity with melanin of all radicals investigated (Sarna et al. 1986). Together with the fact, that the Fenton reaction proceeds within or at best on the surface of the excellent radical scavenger NM, it is implausible that the radical might diffuse through the cytosol to reach its putative site of action. Therefore, it is most probable that the nascent radicals formed by the Fenton reaction are in situ inactivated by surrounding NM.

A correlation between the grade of cell pigmentation and the cell loss in PD in six control brains and six PD brains revealed that the lightly melanized cells in the ventrolateral group were completely lost in patients suffering from PD. In the deeply pigmented rostral, intermediate, and dorsal group, a moderate number of preserved cells were found (Gibb and Lees 1991). Another study (four controls, four PD) came to similar results. Very heavy melanized neurons seemed to be relatively resistant to the pathological process; in a region that contains a relatively low proportion of heavily to lightly pigmented neurons, there seemed to be a dramatic neuronal loss in PD (Kastner et al. 1992). These observations do not fit into a hypothesis of oxidative stress generated in some way by NM as a pathophysiological cause for PD.

Melanins are formed in all pigmented tissues as cytoprotectives (Breathnach 1988; Nicolaus 2005). Why should just the role of NM in such a central organ like the brain be another than cytoprotection? A recent review on the role of iron and NM in the pathogenesis of PD pointed out that NM synthesis may provide a hitherto ignored neuroprotective pathway. NM interferes with the dysregulation of cytosolic DA and reactive metals, most prominently iron. It blocks reactive iron by forming stable complexes which prevents iron toxicity. Under conditions in which these steps are no longer sufficient or are disturbed, iron and NM may initiate a series of toxic and neuroinflammatory steps that builds up a vicious circle which sustains the progression of disease (Zucca et al. 2015).

Neuromelanin, Calcium, and PD

Over the past three decades, focus in the research into the role of metal ion binding to NM in the pathogenesis of PD was put on the interaction between NM and iron. Other physiologically active ions like the second messenger calcium often were neglected.

A study into the metal content of Sepia eumelanin showed that the most abundant metal ions bound were Mg^{2+} (23.600 ppm) and Ca^{2+} (17.200 ppm), followed by the alkali ions Na^+ (3.500 ppm) and K^+ (2.300 ppm); other metal ions were only found in traces (Liu et al. 2004). This is a surprising finding, since the composition of seawater is significantly different. Sepia melanin seems to selectively accumulate the alkaline earth metal ions Ca^{2+} and Mg^{2+}. Recent studies have shown that Sepia melanin is the most appropriate study model for the binding characteristics of neuromelanin (Schroeder et al. 2015).

A study on $^{45}Ca^{2+}$ binding to pigmented and albino eyes showed the strongest labeling in pigmented tissues due to the high concentration of melanin. This binding of Ca^{2+} to the retinal pigment epithelium of mice was pH dependent. No structure in the eye (and probably the whole organism) bound Ca^{2+} as effectively as pigmented tissue. Because under normal physiological conditions, Ca^{2+} and Mg^{2+} are the only metal ions with melanin affinity that are present in more than trace amounts; the Ca^{2+} binding to melanin must be strong enough to account for the very high concentrations found in pigmented tissues (Dräger 1985).

The metal ion content in SN and NM was investigated in autoptic material of human subjects without neurological disorders (Zecca et al. 1994). The most abundant metal ions in NM were iron, calcium, and zinc. The metal ion concentrations in NM were higher than the corresponding values in SN. In particular, it was observed that the lower the concentration of metal ions in the SN, the higher was the relative distribution in NM. Ca^{2+} was below the detection limit of the assay in SN, whereas Ca^{2+} concentrations in NM amounted up to 8 mg g^{-1} dry weight.

Through its Ca^{2+}-binding property, NM may act as a Ca^{2+} reservoir in SN and may be involved in Ca^{2+} homeostasis. As Ca^{2+} is a key signaling messenger in the cascade of apoptosis, the Ca^{2+} sequestration by NM may play a crucial role in neuroprotection. The role Ca^{2+} plays within the human body are numerous, essential and highly regulated by a wide array of Ca^{2+}-binding proteins responsible for trafficking, signaling, and buffering Ca^{2+} levels in both the intracellular and extracellular environments. Within this context, the ability of melanin to bind Ca^{2+} should be regarded in more detail.

The biological importance of Ca^{2+} as a second messenger requires strict regulation of Ca^{2+} homeostasis for a cell to function normally. The basal concentration of free cytosolic Ca^{2+} in most resting cells is around 100 nM. This concentration is maintained primarily by Ca^{2+} ion channels and pumps, cytosolic Ca^{2+} buffers, and intracellular Ca^{2+} stores. Intracellular Ca^{2+} concentrations ≥ 10 μM will lead to the activation of Ca^{2+}-dependent proteases, resulting in a cell death cascade. The uptake, storage, and regulated release of Ca^{2+} are therefore highly controlled by specialized proteins, such as calmodulin, calbindin, annexins, parvalbumin, and S-100 (Bush and Simon 2007).

A strong correlation exists between the specific function of each Ca^{2+}-binding protein and its respective binding constant for Ca^{2+}. Proteins with high binding affinity (> 10^6 M^{-1}) have

specialized roles in specific calcium transport and signaling, whereas proteins with low binding affinity (< 10^4 M^{-1}) have roles in sequestering, buffering, and storing Ca^{2+}. The association constant for Ca^{2+} to Sepia melanin was determined by isothermal titration calorimetry to be in the range of 3.3×10^3 M^{-1}, a value comparable with the well-established intracellular Ca^{2+}-binding proteins that serve to buffer Ca^{2+} concentrations (Bush and Simon 2007).

The important role of melanins in Ca^{2+} homeostasis is established for peripheral melanin-containing organs. Studies involving skin, retinal, and inner ear melanocytes showed that melanin acts as a biological reservoir for Ca^{2+} and influences the regulation of multiple Ca^{2+} dependent cellular processes (Dräger 1985; Gill and Salt 1997; Hoogduijn et al. 2004; Panessa and Zadunaisky 1981).

Cutaneous melanin has been postulated to play a role in the Ca^{2+}-mediated pathway of regulating keratinocyte proliferation and differentiation. It has been shown that the ability of human epidermal melanocytes to buffer against transient exposure to high levels of Ca^{2+} is dependent upon the melanin present in the cell. The difference in maintaining Ca^{2+} homeostasis between poorly and well-melanized melanocytes may be the result of the clearance of cytoplasmic Ca^{2+} into melanosomes and the greater capacity for this in the more pigmented melanocytes (Hoogduijn et al. 2003).

High Ca^{2+} levels have been reported in retinal pigment epithelium (RPE), suggesting that the Ca^{2+} buffering capacity of the cells is very high. As in other cells, these high concentrations of Ca^{2+} can be achieved by sequestration in intracellular organelles which in RPE have been identified as melanin granules (Panessa and Zadunaisky 1981; Salceda and Sanchez-Chavez 2000). Retinal melanin has been shown to bind Ca^{2+} effectively and in a pH-dependent fashion. Ca^{2+} concentrations in the RPE are seven- to tenfold lower in albino than in pigmented animals (Dräger 1985).

Melanin-containing pigmented cells in the inner ear are mainly present in the cochlea, the vestibular organ, and in the endolymphatic sac. This pigmentation is essential for the perfect inner ear function. A study with inner ear melanocytes has shown that melanin acts as a biological reservoir for Ca^{2+} and influences the regulation of various Ca^{2+}-dependent cellular processes. A reduction in melanization of the inner ear is associated with defects in the auditory system (Meyer zum Gottesberge 1988).

A common feature of SN dopamine neurons and the other brainstem nuclei that degenerate in Parkinson's disease is that they are autonomously active, with prominent transmembrane calcium currents that generate regular, slow, broad action potentials (2–4 Hz) in the absence of synaptic input (Surmeier et al. 2011). This pacemaking activity maintains basal neurotransmitter levels in regions that are innervated by these neurons. While most neurons rely exclusively on monovalent cation channels to drive pacemaking, studies in animals indicate that neurons vulnerable to neurodegeneration in SN preferentially use voltage-gated calcium channels for pacemaking. The use of Ca^{2+} rather than monovalent cation ions for pacemaking uses more energy to maintain a non-toxic intracellular Ca^{2+} concentration, which may make the SN neurons more susceptible to Ca^{2+}-mediated excitotoxicity (Hurley et al. 2013; Surmeier et al. 2011). However, within regions that have pacemaking neurons, there is still variation in the susceptibility of neurons to degenerate and this has been postulated to coincide with the level of Ca^{2+}-binding proteins that can buffer potentially toxic fluctuations in intracellular Ca^{2+} concentrations (Damier et al. 1999; Yamada et al. 1990).

As early as in 1983, Mann and Yates (1983) concluded that the primary step in SN neuronal cell loss must be the reduction of the average amount of NM per cell after which the neurons die at random. Recent studies using magnetic resonance verified that the pathophysiology of PD starts with a reduction of NM within the SN (Reimao et al. 2016). In any case, PD patients have a severe decrease of NM concentration in SN of about 60% compared to the age matched controls (Zecca et al. 2002). Pigmented SN neurons in later stages of degeneration showed a significant reduction of intracellular NM, whereas surviving SN neurons of normal morphological appearance and no characteristic pathology in PD exhibited significantly increased NM density (Halliday et al. 2005).

This decreased NM concentration in SN makes the neurons through the loss of Ca^{2+} buffering capacity more susceptible for cell destructive mechanisms. Disturbance of the Ca^{2+} homeostasis leads to the initiation of Ca^{2+}-induced damages within the cells with the consequences already described by the Ca^{2+} hypothesis of PD (Surmeier 2007; Zündorf and Reiser 2011).

In contrast to the hitherto existing theories for the loss of NM by the death of dopaminergic neurons through enhanced ROS production, the hypothesis presented in the present paper assumes the loss of NM within the dopaminergic neurons as a first step in the degeneration of these cells. The loss of NM and thereby the reduction of protection from free cytosolic Ca^{2+} may be seen as the cause for the loss of dopaminergic neurons in PD.

There are several hints that skin pigmentation may be related to the prevalence of PD, black races being partially protected against this disease (Marttila and Rinne 1981). The crude prevalence for PD in Sub-Saharan African states (Ethiopia, Nigeria, Togo, and Tanzania) varies from 7 to 20 per 100.000, considerably less than in the developed world, although it is difficult to compare crude prevalence rates between developing and developed countries (Blanckenberg et al. 2013). Lower life expectancies and less access to medical care may be factors for the apparent low prevalence of PD among blacks, but the factor pigmentation cannot be totally excluded.

A central issue is to identify possible causes responsible for the degeneration of dopaminergic neurons in the nigrostriatal system during PD. Besides a reduced biosynthesis of NM, a degradation of the pigment in SN of patients suffering from PD is imaginable. Contributions of the immune system (Curtin et al. 2006; Depboylu et al. 2011; Double et al. 2009; Oberländer et al. 2011; Orr et al. 2005; Zhang et al. 2011) or interactions of NM with proteins like α-synuclein (Pan et al. 2012; Xu and Chan 2015) will have to be considered. A loss of melanin seems to be a general phenomenon associated with aging as the loss of NM in the SN, the graying of hairs, or the reduction of melanin in RPE with age (Schmidt and Peisch 1986).

Conclusions

Although PD is a multifactorial disease, a participation of NM in the pathogenesis of this neurodegenerative disorder is beyond dispute. The interaction of NM with excess cytosolic iron is well established. This review expands the view of the pathophysiological contribution of NM towards a cytoprotective involvement of this macromolecule in the Ca^{2+} signaling system. More probably than being directly involved in ROS production, NM may act as a Ca^{2+} reservoir and thus protect dopaminergic cells from cell death. A loss of NM will therefore result in a loss of cytoprotection and finally to the death of the pigmented dopaminergic neurons. With this background, further studies on the role of NM in PD may be initiated or pursued.

Compliance with Ethical Standards

Conflict of Interest The author declares that he has no conflict of interest.

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