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REVIEW ARTICLE

Melanin and neuromelanin binding of drugs and chemicals: toxicological implications

Oskar Karlsson[1,2] · **Nils Gunnar Lindquist**[2]

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Abstract Melanin is a polyanionic pigment that colors, e.g., the hair, skin and eyes. The pigment neuromelanin is closely related to melanin and is mainly produced in specific neurons of the substantia nigra. Certain drugs and chemicals bind to melanin/neuromelanin and are retained in pigment cells for long periods. This specific retention is thought to protect the cells but also to serve as a depot that slowly releases accumulated compounds and may cause toxicity in the eye and skin. Moreover, neuromelanin and compounds with high neuromelanin affinity have been suggested to be implicated in the development of adverse drug reactions in the central nervous system (CNS) as well as in the etiology of Parkinson's disease (PD). Epidemiologic studies implicate the exposure to pesticides, metals, solvents and other chemicals as risk factors for PD. Neuromelanin interacts with several of these toxicants which may play a significant part in both the initiation and the progression of neurodegeneration. MPTP/MPP^+ that has been casually linked with parkinsonism has high affinity for neuromelanin, and the induced dopaminergic denervation correlates with the neuromelanin content in the cells. Recent studies have also reported that neuromelanin may interact with α-synuclein as well as activate microglia and dendritic cells. This review aims to provide an overview of melanin binding of drugs and other compounds, and possible toxicological implications, with particular focus on the CNS and its potential involvement in neurodegenerative disorders.

Keywords ALS/PDC · BMAA · Pesticides · MPTP · Neuromelanin · Parkinson's disease · Retinopathy

Introduction

Melanin is polyanionic pigment that colors, e.g., the hair, skin and eyes. The retinal pigment epithelium (RPE) of the eye and epithelial cells in the inner ear also contain melanin. An important biological function of melanin is to attenuate UV-light penetration of the skin and protect from UV-induced DNA damage. The melanin in the RPE, located between the choriocapillaris and the light-sensitive photoreceptors, plays an important photoprotective role by absorbing radiation and scavenging free radicals and reactive oxygen species (ROS) (Boulton et al. 2001; Rozanowska et al. 1999). In the inner ear, melanin is found in, e.g., the stria vascularis in the cochlea and planum semilunatum in the ampullae. Similar to the eye, this location of the melanin-containing cells suggests that melanin has a role to protect the receptor cells by filtering the endolymph in the inner ear. Chemically, there are two distinct groups of melanin: brown to black eumelanin and yellow to reddish pheomelanin. Neuromelanin is a pigment closely related to other melanins and mainly produced in specific neurons of the *substantia nigra*.

Certain drugs and chemicals bind to melanin and are retained in pigment cells for long periods. This specific retention in pigmented tissues is thought to protect the cells but may also serve as a depot that slowly releases accumulated toxicants and may cause adverse effects (Larsson 1993; Lindquist et al. 1987). Melanin affinity is also

✉ Oskar Karlsson
Oskar.Karlsson@ki.se

[1] Department of Clinical Neuroscience, Center for Molecular Medicine, Karolinska Institute, 171 76 Stockholm, Sweden

[2] Department of Pharmaceutical Biosciences, Uppsala University, Box 591, 751 24 Uppsala, Sweden

important in fields such as ocular drug efficacy and toxicity (Salminen and Urtti 1984; Manzanares et al. 2016; Salazar-Bookaman et al. 1994; Reilly et al. 2015), melanoma imaging and imaging-guided chemotherapy (Zhang et al. 2015; Liu et al. 2013; Larsson 1993), and forensic science where hair analysis for drugs of abuse is in practice (Potsch et al. 1997; Kintz 2012).

The function of neuromelanin in the brain is not well understood. Several compounds can be retained in pigmented parts of the brain (D'Amato et al. 1986; Double et al. 2003; Karlsson et al. 2009; Ostergren et al. 2004; Lyden et al. 1983). For instance, incubation of human brain sections in ^{35}S-chlorpromazine revealed a distinct and highly specific uptake in the neuromelanin-containing neurons in *substantia nigra* and *locus coeruleus* (Lindquist 1972). Neuromelanin and compounds with high neuromelanin affinity have been suggested to be implicated in the development of adverse drug reactions in the central nervous system (CNS) as well as in the etiology of Parkinson's disease (PD). The aim of the present review is to provide an overview of melanin/neuromelanin binding of drugs and other compounds, and possible toxicological implications, with particular focus on the CNS and its potential involvement in neurodegenerative disorders.

Melanin and neuromelanin synthesis

The biosynthesis of melanin mainly takes place in melanocytes (Prota 1992). These cells originate from the neural crest and migrate during embryogenesis, primarily to the basal layer of the epidermis, but also to the choroid, ciliary body, iris of the eye, inner ear and leptomeninges of the brain (Sanes et al. 2006; Prota 1992). The RPE has neuroectodermal origin and is derived from the optic vesicle (Sanes et al. 2006; Prota 1992).

Both eumelanin and pheomelanin are derived from the precursor dopaquinone formed by oxidation of the amino acid L-tyrosine by tyrosinase (Ito 2003; Jimbow 1995). Dopaquinone undergoes a series of spontaneous reactions, leading to the production of eumelanin (Fig. 1). In addition to tyrosine, the amino acid cysteine participates in melanin synthesis. Cysteine reacts with melanin precursor dopaquinone and forms the intermediates 5-S- and 2-S-cysteinyldopa which also can be incorporated into the melanin polymer, leading to the formation of pheomelanin (Ito 2003; Jimbow 1995). Most mammalian melanin consists of a mixture of eumelanin and pheomelanin (Wakamatsu et al. 2003, 2008). Pheomelanin appears to be restricted to the core of the pigment granule, while the surface may be covered with eumelanin (Ito and Wakamatsu 2008).

Neuromelanin is produced in the *substantia nigra* but also in catecholaminergic neurons in other brain areas such as the *locus coeruleus* (Zecca et al. 2008a). A significant number of dopaminergic midbrain cells do not synthesize the pigment (Gaspar et al. 1983; Prota 1992). The dopamine neurons of the *substantia nigra pars compacta* (A9 neurons) are in humans the most heavily pigmented neuronal cells (Halliday et al. 2005). Studies revealing different phases in neuromelanin production indicate that the synthesis is regulated, possibly through enzymatic processes (Fedorow et al. 2006). However, the mechanism for neuromelanin synthesis is not fully understood and the role of the melanin producing enzyme tyrosinase is debated (Greggio et al. 2005; Tribl et al. 2007). The main precursor of neuromelanin is dopamine and cysteine appears to be partially incorporated. In *locus coeruleus*, norepinephrine and its metabolites are involved in the neuromelanin synthesis (Wakamatsu et al. 2015; Solano 2014). Neuromelanin synthesis appears to be driven by an excess of cytosolic catecholamines not accumulated in synaptic vesicles (Sulzer et al. 2000; Liang et al. 2004). Neuromelanin is a complex polymeric multilayer system, and each layer consists of a polymer of melanic groups bound to aliphatic and peptide chains (Zecca et al. 2003). It has also been reported to consist of β-sheet proteins and dolichols (Zecca et al. 2008a; Engelen et al. 2012). Neuromelanin is located in organelles that often are surrounded by a double membrane and also includes lipid bodies (Duffy and Tennyson 1965; Zecca et al. 2008a). The initiation of pigmentation in human brain starts at approximately 3 years of age after which neuromelanin continues to accumulate in the *substantia nigra* during aging (Fenichel and Bazelon 1968; Zecca et al. 2002; Halliday et al. 2006).

Melanin and neuromelanin function

A major biological function of melanin is to attenuate UV-light penetration of the eye and skin to protect for UV-induced DNA damage (Hu et al. 2008). Eumelanin acts as a photoprotective antioxidant, while pheomelanin exhibits phototoxic pro-oxidant behavior that rather increases the risk of UV-induced skin damage (Simon et al. 2009). Furthermore, melanin scavenges ROS, toxic free radicals, redox active metal ions and various xenobiotics (Sarna 1992; Lindquist 1973; Lindquist et al. 1987; Larsson 1993).

The heterogeneity of compounds that bind to melanin is large, but the compounds showing the highest affinity are generally basic organic amines and metal ions (Larsson and Tjalve 1979; Larsson 1993; Karlsson and Lindquist 2013). Amines are common functional groups in drugs, and therefore, melanin binds several classes of pharmaceutical drugs, e.g., antibiotics, anesthetics and β-blockers (Larsson 1993; Leblanc et al. 1998). Also other types of compounds (e.g., herbicides, illicit drugs, alkaloids, toxins) have melanin affinity (Larsson and Tjalve 1979; Larsson 1993; Karlsson and Lindquist 2013). Several mechanisms are thought

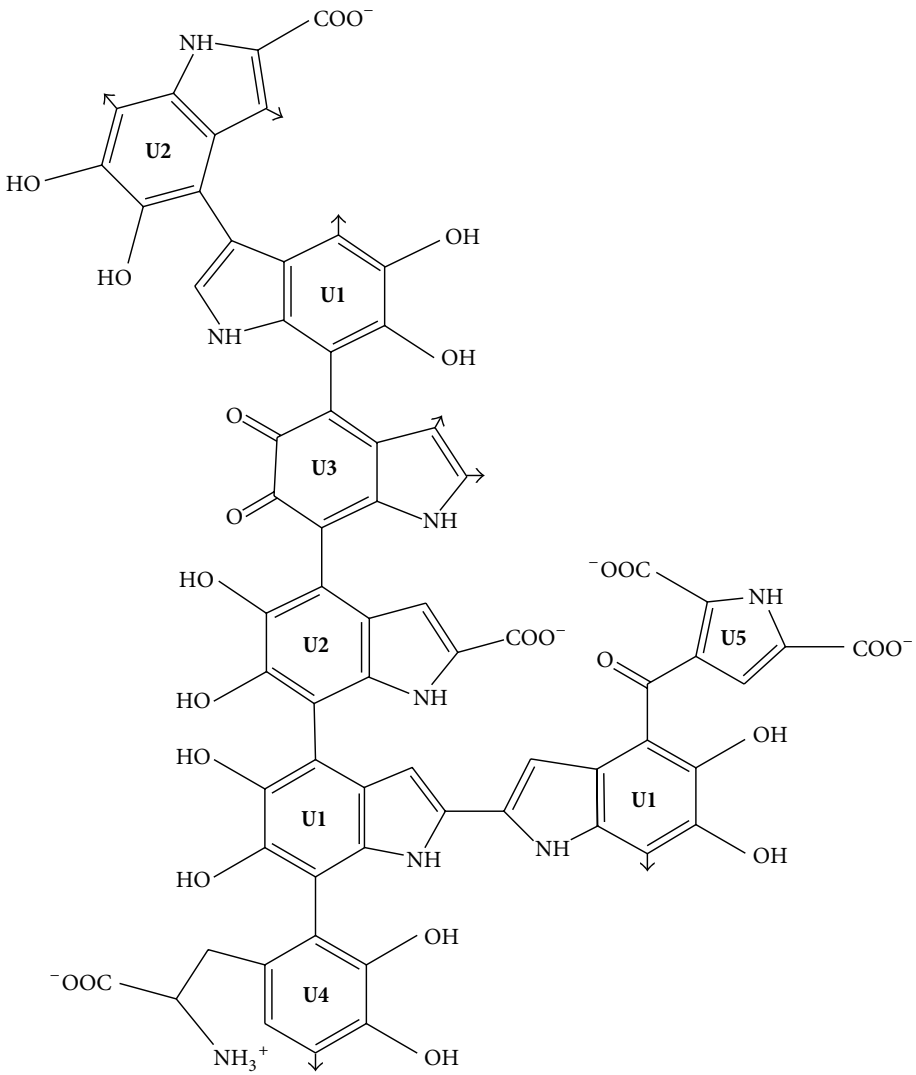

Fig. 1 Classical model of eumelanin structure. Most elements are indolic, and the abundant units are DHI (5,6-dihydroxyindole, **U1**) and the 2-carboxylated analog DHICA (5,6-dihydroxyindole-2-carboxylic acid, **U2**) that both are derived from L-dopaquinone. Oxidized units of IQ (5,6-indolequinone, **U3**), unaltered L-dopa units (**U4**) and carboxylated pyrroles (**U5**) can also be incorporated during the polymerization. *Arrows* indicate possible points for polymer growth. Pheomelanin has a similar polymeric structure but consists of the two main units benzothiazines and benzothiazoles that are derived from the addition of L-cysteine to L-dopaquinone. Neuromelanin is a mixed melanin consisting of both indole and benzothiazine units derived from dopamine-quinone (Adapted from Solano T, Melanins: Skin pigments and much more—types, structural models, biological functions, and formation routes. New Journal of Science. 2014, Article ID 498276)

to be important for the binding properties of melanin. The great number of free and negatively charged carboxylic acid residues and semiquinones in the polymer is responsible for cation exchange properties and provides most of the ionic bindings sites in melanin. Hydrogen bonds, van der Waal's attractions and hydrophobic interactions are also suggested to contribute to melanin's scavenger properties (Larsson and Tjalve 1979). In addition, pi-stacking interactions between aromatic rings of the binding compound and the highly aromatic melanin structure appear to be important (Reilly et al. 2015). Because of the chemical properties, pheomelanin is significantly less efficient in binding drugs and metal ions than eumelanin where cysteinyldopa is not included in the polymer (Mars and Larsson 1999).

The physiological role of this phenomenon is not fully known. The binding of toxicants to melanin probably protects the cells and surrounding tissues initially. However, the binding is usually reversible and melanin may therefore serve as a depot that accumulates the toxicant and gradually releases it into the cytosol (Larsson 1993; Lindquist et al. 1987). In the 1950s, a new type of drug-induced toxic chorioretinopathy involving pigmentary changes was reported for certain phenothiazine tranquilizers (e.g., thioridazine) and the antimalarial compound chloroquine (for reviews, see Dayhaw-Barker 2002; Lindquist 1973). Apart from the ocular damages, these compounds were also reported to cause pigmentary changes in the skin. Potts and coworkers demonstrated in a series of studies that the cause of the ocular toxicity was likely to be a consequence of the strong melanin affinity of these compounds (Potts 1962a, b, 1964a, b). The detailed pathophysiologic mechanisms still remain a topic of further research (Tzekov 2005; Kellner et al. 2008; Mecklenburg and Schraermeyer 2007; Schroeder and Gerber 2014). Neuromelanin shares most properties with peripheral melanin. In the *substantia nigra* of normal subjects, neuromelanin is proposed to be neuroprotective since its synthesis removes excess of harmful oxidized catechols (Sulzer et al. 2000; Zucca et al.

2015) and due to the binding and accumulation of a large amount of various drugs, metals and toxicants (Larsson 1993; Lindquist 1973; Zecca et al. 2003, 2008a). However, in accordance with the binding of compounds to melanin, binding to neuromelanin has also been suggested to be deleterious (Lyden et al. 1982; Aubry 2002).

Antipsychotics, neuromelanin interaction and extrapyramidal symptoms

The conventional or typical antipsychotic drugs such as haloperidol and certain phenothiazines (e.g., fluphenazine) could cause extrapyramidal symptoms (EPS) even at clinically effective doses. These symptoms include dystonia, akathisia, parkinsonism (e.g., rigidity, bradykinesia, and tremor) and tardive dyskinesia. With introduction of atypical antipsychotics, the pharmacological effects of the treatments could be achieved with a significantly lower risk of EPS (Tandon and Jibson 2002). The mechanism behind this adverse drug reaction is unknown, but it has been hypothesized that it is associated with the neuromelanin affinity of these drugs (Lyden et al. 1982; Aubry 2002). This is supported by a recent study revealing that the melanin affinity of seven antipsychotic drugs, determined by a novel magnetic beads method, correlated significantly ($R = 0.89$) with the potential to induce EPS (Marszall et al. 2011). The association between antipsychotics binding to melanin and EPS was also evident using an affinity chromatography method (Michal Piotr et al. 2013).

Neuromelanin and neurodegenerative disorders

Parkinson's disease (PD) is a neurodegenerative disorder second only to Alzheimer's disease in prevalence. This movement disorder is characterized by progressive bradykinesia, rigidity, rest tremor and postural disturbances. Neuropathological hallmarks of PD are the selective loss of dopaminergic neurons containing neuromelanin as well as accumulation of α-synuclein and other proteins in intraneuronal inclusions called Lewy bodies (Kastner et al. 1992; Hirsch et al. 1988). Heavily pigmented A9 neurons in *substantia nigra pars compacta* are most affected (Halliday et al. 2005). Severe neuronal loss in *locus coeruleus* has also been reported (Zarow et al. 2003). Despite the discovery of several important genes and environmental risk or protective factors, the etiology of the disease remains poorly understood (de Lau and Breteler 2006). Familiar forms of PD that are due to mutations of genes including SNCA, PINK1, PARKIN and LRRK2 are accounting for no more than 10 % of cases. The vast majority of cases are sporadic with unknown cause (Thomas and Beal 2007; Coppedè et al. 2006). Studies of monozygotic and dizygotic pairs of twins conclude that environmental factors are a major etiologic component (Tanner et al. 1999; Wirdefeldt et al. 2008). For example, epidemiological studies implicate the exposure to pesticides, metals, solvents and other chemicals as risk factors for PD (Franco et al. 2010). In most sporadic cases of neurodegenerative disorders, environmental factors in combination with genetic susceptibility likely contribute to the onset of the disorder. Increasing attention has been given to neuromelanin because of its possible role in the etiology and pathogenesis of PD. An early accumulation and overload of redox active iron, which can lead to increased oxidative stress, is observed in neuromelanin in the *substantia nigra* of PD patients and may be important for the pathological processes (Double et al. 2003; Faucheux et al. 2003; Jellinger et al. 1993; Zucca et al. 2015). Neuromelanin has also been demonstrated to interact with α-synuclein and may contribute to a vicious cycle of neuroinflammation/neurodegeneration. Moreover, some toxicants that bind to neuromelanin have been suggested to be involved in PD and parkinsonism (Lyden et al. 1983; Lindquist et al. 1986, 1988; Karlsson et al. 2009).

MPTP, neuromelanin binding and parkinsonism

MPTP (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine) is an illicit drug contaminant causally linked with specific dopaminergic denervation and parkinsonism in humans (Langston et al. 1983). This neurotoxin selectively damages dopaminergic neurons primarily in the *substantia nigra pars compacta* causing parkinsonism also in nonhuman primates. The active uptake of the metabolite MPP^+ (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine ion) in dopaminergic nerve terminals via the dopamine transporter is one important factor for this selectivity (Schmidt and Ferger 2001). In addition, both MPTP and MPP^+ have high affinity for neuromelanin which appears to be important for the toxicity. After the first report by Lyden et al. (1983) that MPTP have high affinity for melanin, MPTP-induced degeneration of dopaminergic neurons in monkeys has been correlated with the neuromelanin content in these cells (D'Amato et al. 1986; Herrero et al. 1993; McCormack et al. 2004). Moreover, Langston and co-workers observed ongoing nerve cell loss in humans decades after exposure to MPTP and suggest that MPP^+ bound to neuromelanin continues to exert toxicity as it is gradually released (Langston et al. 1999). Pretreatment with chloroquine partially prevents MPTP-induced parkinsonism in monkeys, possibly by blocking binding sites on the neuromelanin polymer, which further supports the importance of neuromelanin binding in MPTP-induced toxicity (D'Amato et al. 1987). In addition, nicotine that also has high affinity for melanin and has been suggested to be protective against the development of PD in humans

is neuroprotective when administrated before but not after MPTP in monkeys (Huang et al. 2009). *In vivo* studies of MPTP in mice and rats do not take the significant interaction of MPTP and neuromelanin into account as they lack the pigment in the brain (Barden and Levine 1983; Marsden 1961). Notably, the nigrostriatal tissue damage of MPTP is less prominent and permanent parkinsonian symptoms rarely appear in rodents that lack neuromelanin (Kitamura et al. 2000; Kopin and Markey 1988).

Neuromelanin affinity, retinal pigment epitheliopathy and neurodegeneration

Since the discovery of the ability of MPTP to reproduce many of the features of PD, research has been more focused on finding other environmental risk factors implicated in the etiology of PD as well as other neurodegenerative disorders. Occupational exposures to pesticides such as paraquat (1,1′-dimethyl-4,4′-bipyridinium dichloride) have increasingly been reported in epidemiological studies to enhance the risk of developing PD (Furlong et al. 2015; Franco et al. 2010). The toxicity of paraquat is well described regarding the effects to the main target organ, the lungs (Dinis-Oliveira et al. 2008). The mechanisms of paraquat-induced neurotoxicity are not fully known, but several pathways have been proposed: induction of oxidative stress, mitochondrial dysfunction, apoptosis and autophagy, inhibition of the ubiquitin–proteasome system, induction of synucleinopathy and tauopathy (Baltazar et al. 2014; Franco et al. 2010). Paraquat is structurally similar to the MPTP metabolite MPP^+ and has been shown to accumulate in neuromelanin-containing neurons (Lindquist et al. 1988). Hence, as for MPTP, the neuromelanin binding and interaction may be mechanistically important also for the neurotoxic effects of paraquat.

Amyotrophic lateral sclerosis/parkinsonism–dementia complex (ALS/PDC) is an enigmatic neurological disease with no obvious pattern of inheritance, primarily found on the island of Guam. Over 50 % of the ALS/PDC patients also have a rare retinal disease, a pigmentary retinopathy that is often bilateral (Campbell et al. 1993; Cox et al. 1989). The combination of a very uncommon ocular disease that affects melanin and PDC with degeneration of the neuromelanin-containing neurons in *substantia nigra* could indicate a common link. Dietary exposure to the cycad toxin β-N-methylamino-L-alanine (BMAA) has been proposed to be involved in the etiology of ALS/PDC (Banack and Cox 2003; Spencer et al. 1987; Reed et al. 1987; Whiting 1963). Interestingly, studies have revealed that BMAA interacts with melanin and neuromelanin to the extent that pigmented cells and tissues such as the eye and neurons had the highest and most persistent level in the body after a single administration of ^{3}H-BMAA to mice and frogs (Karlsson et al. 2009). *In vitro* experiments confirmed the binding of ^{3}H-BMAA to melanin and indicated an incorporation of BMAA into the melanin polymer as a false precursor (Karlsson et al. 2009). This indicates that long-term exposure to the neurotoxin BMAA may lead to accumulation in melanin- and neuromelanin-containing cells causing high intracellular levels and potentially changed melanin characteristics, e.g., binding capacity of metals or chemicals (Karlsson et al. 2009; Mars and Larsson 1999). Hence, the interaction of BMAA with melanin could be a possible link between PDC and pigmentary retinopathy. However, ALS/PDC is likely to have a multifactorial etiology with both genetic and environmental risk factors and it should be noted that the role of BMAA in the etiology of the disease has been debated (Spencer et al. 2009; Cruz-Aguado and Shaw 2009; Bradley et al. 2009; Borenstein et al. 2009; Steele and McGeer 2008; Cox et al. 2016; Karlsson et al. 2015).

Neuromelanin and a vicious cycle of neuroinflammation

During the recent years, evidence for an immunologic background of PD has started to accumulate (Koutsilieri et al. 2013). Neuromelanin released by damaged dopaminergic neurons is suspected to play a key role in brain inflammation associated with PD (Viceconte et al. 2015). Extracellular neuromelanin can activate the CNS immune cells, microglia, and may therefore induce neurodegeneration via inflammatory pathways (Wilms et al. 2003; Zecca et al. 2008b; Zhang et al. 2011, 2013). A recent study reports that neuromelanin activates proinflammatory microglia through a caspase-8-dependent mechanism (Viceconte et al. 2015). In humans, extracellular neuromelanin has been detected close to activated microglia cells in brains from patients suffering from PD as well as MPTP-induced parkinsonism (Ishikawa and Takahashi 1998; Langston et al. 1999). Moreover, studies have shown that neuromelanin is recognized by dendritic cells and triggers their maturation (Oberlander et al. 2011). This could initiate an adaptive autoimmune response directed against neuromelanin rich structures as dendritic cells are the major cell type for inducing T- and B cell responses (Koutsilieri et al. 2013). The immunogenic role of neuromelanin in PD pathogenesis is further strengthened by the detection of a specific humoral anti-neuromelanin response in PD patients (Double et al. 2009). This indicates that neuromelanin is involved in the progression of the neurodegenerative process. After neuron damage due to an environmental or a genetic factor, extracellular neuromelanin may release neurotoxic substances, initiate an adaptive autoimmune response and activate microglia. This could damage other neurons and lead to a vicious cycle of neuroinflammation and neurodegeneration. Neuromelanin-containing neurons

can also be targeted by $CD8^+$ cytotoxic T cells as they express major histocompatibility complex class I (MHC-I) molecules on their cell membranes (Cebrian et al. 2014).

Neuromelanin and α-synuclein interactions

Besides the progressive degeneration of neuromelanin-containing dopaminergic neurons in the *substantia nigra*, PD is characterized by the intraneuronal cytoplasmic inclusions, Lewy bodies, mainly consisting of the protein α-synuclein (Ma et al. 2003). To date, six point mutations in the gene SNCA encoding for this protein are associated with familial PD (Polymeropoulos et al. 1997; Xu and Chan 2015) and over-expressed wild-type α-synuclein causes neuronal cell death (Zhou et al. 2002). Several studies have reported important interactions between neuromelanin and α-synuclein. Studies suggest that age-related accumulation of neuromelanin could induce α-synuclein overexpression and thereby make the neurons more sensitive to injuries (Xuan et al. 2011; Li et al. 2012; Xu and Chan 2015). Peripheral melanin may also induce the expression of α-synuclein as this protein is expressed in melanoma and nevous, but not in normal skin or non-melanocytic cutaneous carcinoma (Matsuo and Kamitani 2010). Although growing evidence support that neuromelanin could induce α-synuclein expression, the mechanism is unclear. Neuromelanin overloaded with toxic metals or other compounds such as paraquat can potentially produce many free radical species and increased oxidative insult that may increase α-synuclein expression (Double et al. 2002; Segura-Aguilar et al. 2014). The degradation of proteins could also be obstructed as neuromelanin is reported to inhibit the 26S proteasome (Shamoto-Nagai et al. 2004), causing accumulation of abnormal proteins such as α-synuclein aggregates. Another interesting finding is that numerous of epidemiological studies have established an increased incidence of melanoma in PD patients, but the pathogenic pathways behind the connection remains to be determined (Liu et al. 2011; Bertoni et al. 2010; Gao et al. 2009). It has been suggested that the link between the diseases resides in genes that regulate pigmentation and could involve neuromelanin as well as α-synuclein (Herrero Hernandez 2009; Pan et al. 2012). However, the genetic control of neuromelanisation in humans is currently unknown (see above).

Concluding remarks

Although there is little doubt regarding melanin's photoprotective role in skin and eye, the reason for pigmentation elsewhere in the mammalian remains somewhat elusive. After the first reports showing that drugs with melanin affinity may cause lesions in the eye and skin melanin/neuromelanin has been proposed to be linked to a range of pathologies in association with drug/compound binding. Neuromelanin has attracted increasing attention because of its possible role in neurodegeneration and in particular PD. The majority (>90 %) of PD cases are sporadic, and environmental risk factors (e.g., pesticide exposure) together with genetic predisposition probably contribute to the onset of the disorder, but the specific causative agents and the underlying mechanisms are not fully understood. Research indicates that neuromelanin and its interaction with toxicants may play a significant part both in the initiation and in the progression of neurodegeneration. MPTP/MPP^+ that has been casually linked with parkinsonism has high affinity for neuromelanin, and the induced dopaminergic denervation correlates with the neuromelanin content in the cells. The age-related accumulation of neuromelanin, overloaded with toxic metals or other compounds, could potentially lead to an increased oxidative stress, decreased sequestration of toxic dopamine metabolites, and release of active toxicants. Furthermore, neuromelanin, in particular if it is loaded with neurotoxic substances, may also induce the expression and aggregation of α-synuclein, making the neuromelanin-containing neurons even more vulnerable. Neuromelanin that leaks from degenerating neurons can contribute to a vicious cycle of neuroinflammation and degeneration of dopamine neurons by activating microglia and possibly by initiating an adaptive autoimmune response. Today most research has focused on genetic risk factors for PD, which accounts for less than 10 % of all cases. The above-described findings make further studies of the role of neuromelanin in PD and parkinsonism warranted. However, the lack of neuromelanin in the *substantia nigra* of mice and rats (Barden and Levine 1983; Marsden 1961) and the restricted use of primates as animal models makes it challenging to determine the importance of neuromelanin in neurodegeneration and to examine interactions with genetic predisposition, metals and environmental toxicants.

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