

## Review

# Melanin and nicotine: A review of the literature

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**The role of melanin in nicotine uptake and metabolism has received little attention. Because nicotine has been shown to accumulate in tissues containing melanin, exploring links between melanin and nicotine may provide additional clues to understanding smoking behavior and disease effects. To examine the scientific literature on the relationship between melanin and nicotine, we conducted a PubMed search. We also searched online archives of internal tobacco industry documents. We retrieved and reviewed 82 published research papers related to melanin and nicotine or melanin and metabolism of other drugs, and 150 relevant internal tobacco industry documents. The published literature suggests that nicotine may accumulate in human tissues containing melanin and this retention may increase melanin synthesis. Existing research on the relationship between melanin and nicotine lacks an adequate consideration of this relationship's potential impact, if any, on nicotine metabolism, level of nicotine dependence, and ability to quit smoking. Differential accumulation of nicotine in melanin-containing tissues could have implications for individuals with high levels of melanin.**

## Introduction

Melanin's relationship to nicotine has been studied inadequately to date. Melanin is a pigment that gives color to the skin, eyes, and hair (Freedberg & Fitzpatrick, 1999, p.936; Hedin & Larsson, 1978). Its amount in the skin determines the level of pigmentation observed in individuals (Diffey, Oliver, & Farr, 1984; Kollias & Baqer, 1986; Shriver & Parra, 2000). Research on nicotine's distribution in animal tissues that was conducted during the 1970s revealed an accumulation of nicotine in melanin-containing tissues (Larsson, Olsson, Szuts, & Ullberg, 1979; Lindquist & Ullberg, 1974; Waddell & Marlowe, 1976).

Melanin is produced exclusively inside melanosomes, which are synthesized by highly specialized cells called melanocytes (Baker & Joseph, 1960;

Freedberg & Fitzpatrick, 1999, p.209; Seiji, Fitzpatrick, Simpson, & Birbeck, 1963). It is well established that no racial or ethnic differences exist in the number of melanocytes (Soames, 1974; Squier & Waterhouse, 1967; Staricco & Pinkus, 1957; Szabo, 1954; Zelickson, 1967). Those components having a significant role in the final appearance of human skin color are total melanin content, melanin composition, and melanosome size (Alaluf et al., 2002; Ito & Wakamatsu, 2003; Szabo, 1959). The degree of pigmentation results from a complex process that includes melanin synthesis, the subsequent transfer of melanin from the melanosomes to the neighboring keratinocytes (another population of cells located in the skin and oral mucosa), and the distribution of these melanin-loaded keratinocytes (Boissy, 2003; Hearing, 1999; Hedin & Larsson, 1984; Olson, Nordquist, & Everett, 1970; Schroeder, 1969; Squier & Waterhouse, 1967).

There are two types of skin pigmentation. Constitutive skin color, which is determined genetically and not directly affected by sun exposure, has photoprotective properties (Kollias, Sayre, Zeise, & Chedekel, 1991) and is seen in areas of the body that are habitually shielded from light (Freedberg &

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Fitzpatrick, 1999, p. 194). Facultative skin color, or “tan,” is induced by direct exposure of the skin to ultraviolet radiation (Fitzpatrick, Pathak, & Shiseido, 1974), hormonal changes, or disease (Freedberg & Fitzpatrick, 1999, p. 194). When compared with lighter skin, darker skin tends to have more and larger melanosomes of the type that are individually bound within a membrane. Lighter skin has less melanin than darker skin and contains smaller melanosomes (Alaluf et al., 2002; Quevedo, Fitzpatrick, Pathak, & Jimbow, 1975), which tend to be aggregated and bound in groups as complexes (Konrad & Wolff, 1973; Olson, Gaylor, & Everett, 1973; Thong, Jee, Sun, & Boissy, 2003; Toda, Pathak, Parrish, Fitzpatrick, & Quevedo, 1972).

Melanin-containing tissues have been located in various parts of the human body outside the skin complex, including in the heart, lungs, liver, brain (Altschule & Hegedus, 1976), lymphocytes (Wassermann, 1964), and inner ear (Breathnach, 1988). The black-brown pigment located in the human central nervous system is called neuromelanin (Wassermann, 1965) and has been shown to accumulate in the substantial nigra of the brain during aging (Bogerts, 1981; Cotzias, Papavasiliou, Vanwoert, & Sakamoto, 1964; Graham, 1979; Mann & Yates, 1974). Melanocytes have been located in nasal mucosa (Zak & Lawson, 1974), the oral cavity (Laidlaw & Cahn, 1932), the larynx (Goldman, Lawson, Zak, & Roffman, 1972), and esophagus (De La Pava, Nigogosyan, Pickren, & Cabrera, 1963). In dark-skinned ethnic groups, melanin also has been found in the lymphatic system draining the skin (Okuma & Seiji, 1973).

## Method

To better understand nicotine’s accumulation in melanin-containing tissues, we examined literature on the relationship between melanin and nicotine. A literature search for articles published in English pertaining to the accumulation of nicotine in animal tissue was conducted on PubMed. The studies were published between 1974 and 2003. Searches also were performed for additional authors and for studies identified in the references of the initially selected articles. We combined MeSH search terms *melanins*, *pigments*, *melanocytes*, *melanosomes*, *autoradiography*, or *hair with nicotine*, *cotinine*, *smoking*, *tobacco*, *cigarette* (non-MeSH term), or *drugs*. The search yielded 982 citations. We screened these to identify studies that presented research findings or discussed possible mechanisms of the accumulation of nicotine or other drugs in human or animal melanin-containing tissues. We augmented this search by reviewing studies that addressed melanin’s interactions with drugs other than nicotine. This resulted in a set of

264 articles. After eliminating duplicates, reviews, letters, those not written in English, and articles found not to be relevant, a total of 82 publications were selected for this review, including 43 articles addressing drug-melanin interactions. Table 1 shows the 38 studies relevant to melanin and nicotine. Articles on neuromelanin were not included in the review because neuromelanin is structurally distinct.

In addition, we conducted searches of internal tobacco company documents made publicly available through the 1998 Master Settlement Agreement (available in the Legacy Tobacco Documents Library at [www.legacy.library.ucsf.edu](http://www.legacy.library.ucsf.edu); Balbach, Gasior, & Barbeau, 2002; Malone & Balbach, 2000). We combined the terms *melanin* and *nicotine* in our initial search of the tobacco documents archives. We then used a “snowball approach” to conduct further searches on names of individuals identified in pertinent documents and materials from their files. We reviewed approximately 150 internal company documents. We also reviewed background literature on melanin.

## Results

### *Autoradiographic studies*

The distribution of nicotine in the body has been of interest to investigators since 1851 (U.S. Department of Health and Human Services [USDHHS], 1988). However, it was not until the 1960s that a team of Swedish researchers, using whole-body autoradiography (Ullberg, 1954), would be able to visualize nicotine’s distribution in animal tissue (Hansson & Schmitterlow, 1962). In 1972, based on in vitro experiments that had provided evidence that nicotine accumulated in tissues containing melanin, the Swedish researchers conducted autoradiographic studies on pigmented animals “to investigate whether this affinity [attraction of nicotine for melanin] can be observed in vivo and if so how persistent” (Ullberg, 1972). This research continued for the next several years, providing additional evidence that nicotine accumulated differentially in melanin-containing tissues (Larsson et al., 1979; Lindquist & Ullberg, 1974). Additionally, research on animal fetuses suggested that fetal tissues containing melanin might be more sensitive to nicotine than the corresponding adult structures (Larsson et al., 1979; Szuts et al., 1978).

During the 1970s in the United States, Waddell and Marlowe (1976) also used whole-body autoradiography to study nicotine distribution in animal tissue. Though they noted no differences between pigmented and albino mice in the pattern of how nicotine was distributed in the bronchi, kidney, urine, salivary gland, liver, bile, and contents of the

**Table 1.** Summary of melanin and nicotine research.

Autoradiography	Year	Author	Summary of findings related to melanin
Mouse	1974	Lindquist & Ullberg	Strong and persistent accumulation of nicotine in tissues containing melanin.
Mouse	1976	Waddell & Marlowe	Nicotine has a remarkable accumulation in melanin-containing tissues.
Mouse	1978	Szuts et al.	Consistently high concentration of nicotine found in melanin-containing tissues; melanin has lower binding capacity with cotinine than it does with nicotine.
Mouse	1979	Larsson et al.	Nicotine accepted as a precursor in the formation of melanin; uptake of nicotine likely to be higher in fetal melanin than in maternal melanin.
Mouse	1980	Brittebo & Tjalve	NNN metabolites bind to melanin in eye and hair in vivo and in vitro.
Mouse	1980	Waddell & Marlowe	NNN localizes in melanin-containing tissues; little probability that NNN metabolizes to reactive metabolite.
Hamster	1983	Tjalve & Castonguay	NNK and its metabolites bind to eye melanin; somewhat exceed the level in blood
Mouse	1984	Castonguay et al.	Metabolites of NNN and NNK localized in eye melanin.
Marmoset monkey	1985	Castonguay et al.	NNN and NNK accumulate in melanin of eyes and hair follicles of skin.
Miniature pig	1987	Domellof et al.	NNN accumulates in melanin of eyes and skin.
Mouse and hamster	1996	Roberto et al.	Pronounced retention of polycyclic aromatic hydrocarbons, e.g. benzo(a)pyrene, in melanin-containing structures of eyes and hair follicles.
In vitro experiments			Summary of findings related to melanin
Mouse tissue	1979	Larsson et al.	Intact nicotine accumulation in newly formed melanin.
Toad and frog tissue	1986	Hedin & Larsson	Nicotine activated amphibian dermal melanocytes.
In vitro	2001	Claffey et al.	Explored drug (including nicotine)-melanin interactions. Nicotine has much tighter association with melanin than did the other drugs tested in this study.
In vitro	2001	Dehn et al.	Pigmentation influences drug incorporation into hair; study provides evidence of a nicotine-melanin association.
Nicotine hair analysis: Human			Summary of findings related to melanin
36 Japanese subjects	1993	Mizuno et al. <sup>a</sup>	Concentration of nicotine in white hair was much lower than that in black hair collected from same subject.
22 Japanese subjects	1993	Uematsu	Concentration of nicotine in white hair was much lower than that in black hair collected from same subject.
26 Japanese subjects	1995	Uematsu et al.	Slow dissociation of nicotine from melanin in hair when compared to other drugs; higher nicotine content in black hairs than in white hairs of same subject.
80 European male subjects	1996	Zahlsen et al.	Relative affinity of nicotine for hair pigments is not known.
150 mother-child pair hair samples	2003	Pichini et al.	Hair nicotine concentration of newborns can be due to differences including melanin content.
Nicotine hair analysis: Animal			Summary of findings related to melanin
Rat	1993	Mizuno et al. <sup>a</sup>	Mean concentration of nicotine in whitish hair was lower than that in brown hair collected from same animal.
Rat	1995	Gerstenberg et al.	Nicotine concentrations were 20 times higher in pigmented than in unpigmented hair.
Mouse	1999	Stout & Ruth	Explored drug (including nicotine)-melanin interactions. Results suggest darker-haired individuals are likely to accumulate and retain more drugs in their hair. Systemically administered drugs are more strongly retained in forming hair than are drugs from environmental exposure.
Mouse	2000	Claffey et al.	Results demonstrate a significant interaction of nicotine with melanin.
Clinical and histological examination			Summary of findings related to melanin
214 Swedish subjects	1977	Hedin	Increased oral melanin pigmentation in 25.5%–31.0% of smokers.
30,118 Swedish subjects	1982	Axell & Hedin	Presence of oral melanin pigmentation among tobacco smokers was 21.5%, compared with 3% among non-tobacco users.
195 Japanese male subjects	1983	Araki et al.	Increased oral melanin pigmentation in 17% of smokers and in 24% of smokers 4 years later.

Table 1. (Continued.)

Autoradiography	Year	Author	Summary of findings related to melanin
15 Swedish subjects	1984	Hedin & Larsson	Tobacco smoking increases oral pigmentation in smokers by affecting basic mechanisms of melanin formation.
15 Swedish subjects	1987	Hedin & Larsson	Large melanosome complexes seen in smokers, due to increased melanin production.
920 Swedish subjects	1990	Salonen et al.	Positive correlation between tobacco use and oral lesions, including excessive melanin pigmentation.
1 White subject	1991	F. H. Brown & Houston	Increased melanin pigmentation in gingivae due to tobacco smoking.
467 Thai, Malaysian subjects	1991	Hedin & Axell	Tobacco smoking stimulates oral melanocytes to a higher melanin production; also in dark-skinned ethnic groups.
106 subjects, Black predominately	1991	Natali et al.	Increased oral mucosal pigment changes primarily due to tobacco use, enhanced by alcohol use.
2191 Swedish subjects, previous smokers	1993	Hedin et al.	Increased oral melanin pigmentation in 11.4% between 2 and 3 months after smoking cessation; dropping to 6% between 7 and 24 months after smoking cessation; dropping to 3% between 3 and 30 years after cessation.
91 Filipino women (reverse and conventional smokers)	1996	Ortiz et al.	Oral mucosal changes, including pigmentation, seen in 96.7% reverse smokers and 26.7% conventional smokers.
16 Spanish subjects	1997	Gonzalez-Vela et al.	Activated melanocytes associated with tobacco use.
1 Black subject	1997	Ramer & Burakoff	Increased oral pigmentation in smoker involving the tongue.
496 Turkish subjects	2001	Unsal et al.	Increased oral melanin pigmentation in 27% of smokers.
49 Indian subjects	2003	Sarswathi et al.	Increased oral melanin pigmentation in 95% of smokers.

Note. NNN, N'-nitrosornicotine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. <sup>a</sup>Same study.

stomach and upper intestine, they, too, noted an intense localization of nicotine in the melanin of the pigmented mice. "The black pigment in the eye, hair follicles, and in the meninges of the brain had the most intense accumulation of any site in this strain ... There was no accumulation of [radioactive nicotine] in these sites in the [albino] strain" (University of Kentucky, Tobacco and Health Research Institute, 1973). Their subsequent research supported these findings (Waddell & Marlowe, 1976, 1980).

In one study nicotine was shown to be retained in melanin-containing tissues for up to 30 days after a single intravenous injection (Lindquist & Ullberg, 1974). Other studies also found accumulation and long-term retention of nicotine in melanin-containing structures (Barza, Kane, & Baum, 1979; Lindquist & Ullberg, 1975; Mizuno, Uematsu, Ishikawa, Yoshimine, & Nakashima, 1997; Szuts et al., 1978). Larsson et al. (1979) hypothesized that nicotine's retention in melanin-pigmented tissues involved nicotine being accepted as a precursor in the formation of new melanin, because of a structural resemblance between melanin and nicotine's main precursor, indole-5,6-quinone. More recently, investigators have suggested that the melanin-nicotine relationship may stem from irreversible bonding (Claffey, Stout, & Ruth, 2001; Dehn, Claffey, Duncan, & Ruth, 2001).

#### Nicotine hair analysis

Investigators have observed the role of melanin pigmentation in the accumulation of various drugs, including nicotine, in hair analyses (Claffey & Ruth, 2001; Hold, Hubbard, Wilkins, & Rollins, 1998; Ishiyama, Nagai, & Toshida, 1983; Mizuno, Uematsu, Oshima, Nakamura, & Nakashima, 1993; Reid, O'Connor, Deakin, Ivery, & Crayton, 1996; Rothe, Pragst, Thor, & Hunger, 1997; Sato, Uematsu, Yamada, & Nakashima, 1993; Slawson, Wilkins, & Rollins, 1998; Stout & Ruth, 1999; Uematsu, Miyazawa, Okazaki, & Nakashima, 1992; Uematsu, Sato, Fujimori, & Nakashima, 1990). When a drug displays an affinity for melanin in the hair, it also will have an affinity for the melanin located in skin and other tissues (Harrison, Gray, & Solomon, 1973).

More recently, researchers have been interested in the use of hair as a potential biomarker to assess systemic uptake and accumulation of nicotine (Gerstenberg, Schepers, Voncken, & Volkel, 1995), chronic exposure to second-hand smoke (Dimich-Ward, Gee, Brauer, & Leung, 1997; J. J. Jaakkola, Jaakkola, & Zahlsen, 2001; M. S. Jaakkola & Jaakkola, 1997; Klein & Koren, 1999; Nafstad et al., 1995; Pichini, Altieri, Pellegrini, Pacifici, & Zuccaro, 1997; Woodruff, Conway, Edwards, &

Hovell, 2003), and smoking status (Uematsu, Mizuno, Nagashima, Oshima, & Nakamura, 1995). These studies and others have indicated that the interaction of drugs with melanin has implications in assaying hair samples (Potsch, Skopp, & Moeller, 1997) and interpreting results (Hold et al., 1998). Compared with lightly colored hair, dark hair accumulates and retains larger amounts of nicotine (Stout & Ruth, 1999; Uematsu et al., 1995), consistent with earlier findings of nicotine's affinity with and slow dissociation from melanin (Mizuno et al., 1997). An extensive literature review on the use of hair as a biomarker for exposure to tobacco smoke included a discussion of systemic and external hair uptake of nicotine and other drugs, and acknowledged the need for further studies to investigate the relationship between hair melanin and nicotine uptake (Al-Delaimy, 2002).

#### *Clinical and histological examinations*

"Melanosis gingivae," melanin pigmentation in the mouth, is often seen in individuals of dark-skinned ethnic groups (Becker, 1969; T. Brown, 1964; Dummet, 1966) but seldom seen among White Europeans (P. L. McCarthy & Shklar, 1964). However, "smoker's melanosis" is a phenomenon that has been reported among tobacco smokers from fair-skinned and dark-skinned ethnic groups (Axell & Hedin, 1982; Hedin, 1977; Ramer & Burakoff, 1997; Unsal, Paksoy, Soykan, Elhan, & Sahin, 2001). The amount of this increased oral pigmentation is directly correlated with the number of cigarettes consumed each day (Axell & Hedin, 1982). Although several diseases are characterized by increased pigmentation in the oral mucosa (P. L. McCarthy & Shklar, 1964), smoker's melanosis is hypothesized to be either the result of nicotine's ability to stimulate melanocyte activity and melanin production or related to the binding of melanin to noxious substances in the tobacco smoke (Hedin, 1977, 1991; Iwata, Inui, & Takeuchi, 1981; Sarswathi, Kumar, & Kavitha, 2003; Taybos, 2003).

#### *Tobacco-specific carcinogens*

Nicotine is not the only substance found in tobacco that has been shown to accumulate in melanin-containing tissues. The *N*-nitrosamines *N'*-nitroso-nornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) are the most abundant carcinogens in tobacco smoke (Hoffmann, Adams, Brunnemann, & Hecht, 1979; Keeney, Waddell, & Perraut, 1982) and have been shown in animal studies to accumulate in melanin-containing tissues (Brittebo & Tjalve, 1980, 1981; Domellof et al., 1987; Iwata et al., 1981; Tjalve & Castonguay, 1983; Waddell & Marlowe, 1980). These tobacco-specific

carcinogens have been shown to lead to the development of lung adenomas and squamous cell carcinomas when administered orally, topically, subcutaneously, or intraperitoneally (Carbone, 1992; Hecht, 1999; Hecht et al., 1993). It has been hypothesized that NNN becomes carcinogenic when its reactive metabolites interact with genetic material. However, if the melanocytes have an enzymatic capacity to degrade the NNN, then high local concentration of NNN, reversibly bound to melanin, may constitute a hazard (Brittebo & Tjalve, 1980). NNK metabolites have been shown to bind to the tissues of nasal mucosa and lung, indicating NNK metabolism has occurred in these tissues. Unbound metabolites distribute in the body and reach various tissues to eventually be excreted, primarily in the urine. However, accumulation of tissue-bound metabolites has been suggested to be correlated to the susceptibility of some laboratory animals to carcinogenicity of NNK (Castonguay, Tjalve, & Hecht, 1983).

The polycyclic aromatic hydrocarbons (PAHs) are another group of tobacco-specific compounds. Among the PAHs, benzo(a)pyrene is the most extensively studied compound (Hecht, 1999). It is listed among cigarette smoke carcinogens evaluated by the International Agency for Research on Cancer (IARC; Hoffmann & Hoffmann, 1997). Benzo(a)pyrene also has been shown to accumulate in melanin-containing tissues, and its presence in these tissues may induce carcinogenesis (Roberto, Larsson, & Tjalve, 1996). Its ability to induce lung tumors upon local administration or inhalation is well documented (IARC, 1972, 1983; Thyssen, Althoff, Kimmerle, & Mohr, 1981; Wolterbeek, Schoevers, Rutten, & Feron, 1995), and there is sufficient evidence of its carcinogenicity in laboratory animals and humans (Hoffmann & Hoffmann, 1997). Benzo(a)pyrene increases the bioactivity of the melanocytes (Iwata et al., 1981; Lindquist & Ullberg, 1975), whereby human melanocytes in culture have been found to convert benzo(a)pyrene to its carcinogenic metabolite benzo(a)pyrene-7,8-diol (IARC, 1985).

Perhaps problematic for smokers of mentholated cigarettes is the fact that menthol combustion produces benzo(a)pyrene (Schmeltz & Schlotzhauer, 1968) and smoking menthol cigarettes might generate carcinogenic components responsible for lung cancer (W. J. McCarthy et al., 1995). Smoking menthol cigarettes may result in greater exposure to a smoker's respiratory tract and greater transfer of tobacco smoke toxins into the pulmonary circulation (Garten & Falkner, 2004). If smoking menthol cigarettes results in exposure to benzo(a)pyrene and its carcinogenic metabolite, these substances may accumulate in melanin-containing tissues.

*Mechanisms of melanin-drug interactions*

Understanding the mechanisms involved in how other drugs interact with melanin may provide additional insight into the interaction between melanin and nicotine. Drugs travel via the arteriovenous or lymphatic circulation, thereby gaining access to melanocytes (Harrison, Gray, & Solomon, 1974; Takahashi & Fitzpatrick, 1966). Depending on its affinity for melanin, a drug will either bind directly to melanin or become entrapped inside the melanocyte during melanin synthesis (Potsch et al., 1997). When a drug enters a melanocyte, it then enters the melanosome and interacts with melanosomal proteins. These structural proteins of the melanosome are firmly associated with melanin (Sharma, Wagh, & Govindarajan, 2002) and play a role in entrapping drugs within the melanin granules. These drug-entrapped melanin granules are then carried outside of the melanocyte, where circulating lymphocytes are capable of transporting them to other sites (Ishizaki & Belter, 1960; Sundberg, 1956; Wassermann, 1963, 1965).

Though not referring specifically to the drugs' interaction with melanin-containing tissues, a 1929 human study demonstrated racial differences in how several drugs affected pupil dilation. When compared with the pupils of Whites, the pupils of dark-skinned individuals were less responsive (Chen & Poth, 1929). The investigators reported that the pigments interfered with the penetration of the drugs. Since then, many drugs have been demonstrated to have an affinity for the melanin-containing tissues of the eye (Brittebo & Tjalve, 1980; Castonguay, Tjalve, Trushin, & Hecht, 1984; Domellof et al., 1987; Roberto et al., 1996; Tjalve & Castonguay, 1983). Drug-induced lesions in melanin-containing tissues of the eye, inner ear, and brain stem are related to the drug's accumulation and retention in those tissues (Lindquist, 1973; Lindquist & Ullberg, 1972; Lyden, Larsson, & Lindquist, 1982; Potts, 1962). Lindquist and colleagues noted that several drugs accumulate in melanin for months, and that in some cases these drugs could be retained for years (Lindquist, 1973; Lindquist & Ullberg, 1974). Long-term exposure of noxious chemicals may lead to high levels being stored in melanin, which ultimately may cause degeneration in the melanin-containing cells and lesions developing in the surrounding tissues (Larsson, 1993). Specific drugs shown not to have a high affinity for melanin include buprenorphine (Wilkins, Valdez, Nagasawa, Gygi, & Rollins, 1998), amphetamines, catecholamines (Harrison et al., 1974), cocaine (Claffey et al., 2001; Joseph, Hold, Wilkins, Rollins, & Cone, 1999; Joseph, Tsai, Tsao, Su, & Cone, 1997), codeine (Gygi, Joseph, Cone, Wilkins, & Rollins, 1996; Joseph et al., 1999), haloperidol (Lyden et al., 1982), methadone (Green

& Wilson, 1996), and several neuroleptic drugs (Lindquist, 1973; Lindquist & Ullberg, 1972; Potts, 1962, 1964).

Melanin's ability to bind to drugs and chemicals may be detoxifying and protective by absorbing potentially harmful substances (Ortonne, 2002). One investigator suggested that the "harmless stimulation of the pigmentary system [skin] with chemical drugs may prevent toxic destruction of [this] melanin-containing tissue" (Hedin, 1991). However, regular intake of nicotine, which is lipid soluble and readily permeates cell membranes (Eliopoulos et al., 1994), may induce the same type of lesions shown to occur with long-term use of other drugs with an affinity for melanin (Szuts et al., 1978), as well as other adverse effects (Creel, 1980).

*Tobacco industry documents and industry knowledge*

Most of the internal tobacco industry documents we reviewed were copies of published articles already discussed in this review. The documents showed that the tobacco industry funded studies of nicotine distribution (Kastenbaum, 1975; Larsson et al., 1979; Marlowe & Waddell, 1975; Szuts, Olsson, Lindquist, & Ullberg, 1978; Ullberg, 1972) and revealed industry interest in this line of research (Anderson, Applegren, Hansson, Hoffmann, & Schmitterlow, 1966; Council for Tobacco Research, 1983, 1984; DeBardeleben, 1988; Ford, 1977; McKennis, 1974, 1975; H. Zahn, 1980; L. Zahn, 1974). However, we found no evidence in the documents to date that the tobacco industry considered any potential implications of this research for people who have higher concentrations of melanin.

**Discussion**

This review of the scientific literature highlights important aspects of the relationship between nicotine and melanin that may warrant further study. The studies included in the review are primarily animal studies, and interspecies differences in nicotine's affinity for melanin-containing tissues have been documented (Leeds & Turner, 1977; Tsujimoto, Nakashima, Tanino, Dohi, & Kuroguchi, 1975). Such differences may become especially critical when attempting to predict nicotine uptake and deposition in human tissues (Plowchalk, Andersen, & de Bethizy, 1992); thus it is premature to assert anything about possible nicotine-melanin interactions in humans. However, if melanin's relationship to nicotine and other tobacco smoke components as documented in animals holds true in humans, there may be possible adverse health implications for those individuals with higher concentrations of melanin. Thus it may be fruitful to theorize how this might occur.

Chronic nicotine exposure from smoking is associated with numerous adverse health consequences. The potential accumulation in melanin-containing tissues of nicotine and tobacco-specific compounds may be a concern for any individual who is chronically exposed to tobacco smoke. However, those individuals who have higher concentrations of melanin might be at increased risk, if it can be shown that the retention of nicotine and tobacco-specific carcinogens in melanin-containing tissues results in greater exposure to these substances.

The 1988 surgeon general's report on nicotine addiction and its appendix on nicotine toxicity discussed the distribution and retention of nicotine and its metabolites in various body tissues, citing the earlier studies on nicotine distribution (USDHHS, 1988). However, the report did not discuss possible implications of nicotine accumulation in melanin-containing tissues in humans.

Though it is not clear what role, if any, menthol may play in an increased risk of cancer among smokers of mentholated cigarettes, menthol may enhance the absorption of nicotine and other tobacco smoke components (Ahijevych, Gillespie, Demirci, & Jagadeesh, 1996; Caraballo et al., 1998; Clark, Gautam, & Gerson, 1996; Jarvik, Tashkin, Caskey, McCarthy, & Rosenblatt, 1994; Pérez-Stable, Herrera, Jacob, & Benowitz, 1998). This may contribute to greater cancer risk either by increasing systemic exposure to tobacco smoke toxins or by affecting the metabolism of nicotine or tobacco smoke carcinogens (Benowitz, Herrera, & Jacob, 2004; Brooks, Palmer, Strom, & Rosenberg, 2003; Garten & Falkner, 2004). The present review suggests that the tobacco smoke components nicotine, NNN, NNK, and benzo(a)pyrene may accumulate in human melanin-containing tissues.

It may be argued that melanin's detoxifying and protective properties (Hedin, 1991; Ortonne, 2002; Schallreuter, Hordinsky, & Wood, 1987) may be advantageous to those individuals who have higher levels of it. However, it may be equally plausible that the possible melanin-related sequestering of nicotine and of the tobacco-specific compounds NNN, NNK, and benzo(a)pyrene may lead to a constant exposure to these substances. It has been suggested that long-term exposure of smokers to these carcinogens and the potential cumulative damage produced in years of smoking would be substantial (Hecht, 1999).

Many important, unanswered questions remain about nicotine's affinity for melanin that might inform future research. For example, investigators have reported that, compared with other racial/ethnic groups, Blacks have a higher intake of nicotine per cigarette and increased nicotine absorption (Caraballo et al., 1998; Clark et al., 1996; Pérez-Stable et al., 1998; Wagenknecht et al., 1990) and

have suggested that this higher nicotine absorption could help explain their lower quitting rates (Centers for Disease Control and Prevention, 1993). These studies did not specifically address nicotine's accumulation in melanin, but if such an accumulation can be documented in humans as it has in animals, it could aid in understanding whether melanin-specific differences in nicotine metabolism play a role in these racial differences. Blacks as a group tend to have higher levels of melanin. Furthermore, 75%–80% of Black adult smokers consume menthol cigarettes (Ahijevych, Tyndale, Dhatt, Weed, & Browning, 2002; Clark et al., 1996; Cummings, Giovino, & Mendicino, 1987; Gardiner, 2004; USDHHS, 1998), which increases their exposure to benzo(a)pyrene and its accumulation in melanin-containing tissues.

Other questions include (a) Does the accumulation of nicotine in melanin-containing tissues have an impact on nicotine metabolism, the level of nicotine dependence, or consequential health risks? and (b) Does the sequestering of nicotine in melanin-containing tissues prolong its half-life, thereby leading to chronic exposure to nicotine and increased nicotine dependence, or is it a protective mechanism that aids in detoxification?

Interest in neuromelanin is growing. Though neuromelanin is believed to be related to the melanins located outside the central nervous system, many questions remain unanswered about its structure and functions (de Marco et al., 2004; Fedorow et al., 2005). One area that may be worthy of exploration is the triad of melanin, nicotine, and melatonin. Melatonin is a hormone released by the pineal gland that has numerous cellular actions, including inhibiting melanin synthesis (Logan & Weatherhead, 1980; Slominski & Pruski, 1993) and modifying dopamine levels. Melatonin also has modulating effects on many physiological, endocrine, and behavioral functions in the brain (Cassone, 1990; de Prado, Reiter, & Mora, 2003; Krause & Dubocovich, 1990; Reiter, 1991), and acts on parts of the brain that are also influenced by nicotine (Dani & Heinemann, 1996; Paredes et al., 1999). Nicotine has been shown to stimulate the release of dopamine, which has been implicated in the sensation of reward (Dani & Heinemann, 1996), and melatonin has the ability to inhibit nicotine-stimulated dopamine release (Schiller, Champney, Reiter, & Dohrman, 2003). Although a review of the melatonin-melanin-nicotine relationship is beyond the scope of this paper, it could be relevant in teasing out mechanisms related to nicotine absorption and metabolism.

An extensive literature suggests that nicotine and tobacco-specific compounds may accumulate in tissues containing melanin and that this retention may affect melanin synthesis. Existing work lacks an

adequate consideration of the potential impact, if any, of this phenomenon on nicotine metabolism, level of nicotine dependence, and cessation success. Speculatively, could accumulation of nicotine and tobacco-specific compounds in melanin-containing tissues be relevant in developing better models to explain tobacco-related health disparities affecting some communities of color?

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