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The Expanding Role and Presence of Neuromelanins in the Human Brain – Why Gray Matter is Gray

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The presence of melanins in internal tissues of the body, e.g. the inner ear, brain, etc, has challenged scientists for decades with respect to understanding their putative function(s) in those tissues. It is not too difficult to comprehend how melanins in the skin, hair and eyes play important roles in camouflage, thermal regulation, photoprotection, sexual attraction, etc, but what about their roles within the body, in tissues not visible or exposed to the environment, where color would be of no obvious advantage? We have gotten teasing glimpses of the importance of melanins in unexpected directions, e.g. with respect to their role in the developmental routing of neurons in the optic chiasm (which is disrupted in patients with OCA1-type albinism) and their importance in catecholaminergic neurons (which is disrupted in patients with Parkinson's disease). But what are these pigmented biopolymers actually doing and what function(s) might they have that are so critically important to such diverse physiological processes?

Major clues to the role of melanins in catecholaminergic neurons (found in the substantia nigra and locus coeruleus) have been uncovered in the past decade as the chemical properties of melanin to bind toxic metals, to remove toxic intermediates and to scavenge reactive oxygen species have been revealed (Sulzer et al., 2000; Zecca et al., 2002; Zucca et al., 2004; Double, 2006). Those pigments, termed neuromelanins, are synthesized via the catecholamine pathway, which involves tyrosine hydroxylase (a distinct enzyme that catalyzes a similar reaction as tyrosinase) and DOPA decarboxylase. The latter enzyme generates DOPamine, the basic building block of epinephrine and norepinephrine, but can also lead to the production of melanic pigments due to the further oxidation of DOPamine and its interaction with cysteine to produce pheomelanin-like biopolymers. In fact, melanic pigments produced in the substantia nigra and locus coeruleus were shown to be derived from DOPamine, producing eumelanin-like and pheomelanin-like polymers (the latter from the intermediate cysteinyl-DOPamine) (Wakamatsu et al., 2003). These findings provided a strong basis upon which to understand how the presence of melanic pigments in neurons is important to their survival when faced with difficult environmental stresses, and equally important, how the decreased content and function of neuromelanins eventually leads to disrupted neural function.

Zecca and colleagues assembled an international Who's Who of melanin experts to push their studies to new limits. In their most recent study (Zecca et al., 2008), they used a multidisciplinary approach to characterize melanic pigments found in other regions of the human brain, including the putamen, cortex, cerebellum, etc. In brief, they found that melanic pigments were present in those tissues and were also deposited in granules, and interestingly, that the content of those melanic pigments normally accumulates with age. In pathological diseases, the rate of loss of neuromelanins is greatly accelerated due to the loss of neurons containing neuromelanin and to the reduced content of neuromelanin in surviving neurons of Parkinson disease patients (Kastner et al., 1992; Zecca et al., 2002). Those pigment granules contained not only melanic components, but also contained significant quantities of lipids and

peptides. Their studies support the concept that, as in the catecholaminergic tissues, the synthesis and presence of neuromelanins in other brain tissues serves a similar function, i.e. binding/removal of reactive quinones and metals that would otherwise be highly toxic to the neurons in those tissues.

The study by Zecca et al (2008) used chemical approaches (HPLC analysis as well as EPR and NMR spectroscopy) to analyze the components of neuromelanins, physical methods (transmission and scanning electron microscopy) to characterize the size and structure of the neuromelanin granules, and complimentary approaches to examine their physiological functions, particularly with respect to the binding of various potentially toxic metals. The sum of their results shows quite conclusively that the neuromelanin pigments play an important protective role in neural tissues by binding and sequestering toxic metals in stable complexes that prevent neuronal toxicity.

An interesting consideration is how are the neuromelanins in these other brain tissues produced since tyrosinase function in those tissues is lacking or minimal at best (Eisenhofer et al., 2003). Tyrosine hydroxylase is known to be present in those tissues and (similarly to the critical role of tyrosinase for melanin synthesis in melanocytes) presumably is responsible for the generation of DOPA required to seed neuromelanin synthesis. The difference may lie in the function of DOPA decarboxylase, which rapidly decarboxylates the nascent DOPA to DOPamine in the substantia nigra and locus coeruleus. Low or functionally insignificant levels of that enzyme in the other brain tissues may lead to the persistence of DOPA in those tissues required for synthesis of the DOPA-based neuromelanins found there (although this is conjectural at the moment).

Regardless of the mechanism of formation of neuromelanins, the key point is their presence and protective function throughout the brain. The formation of neuromelanins provides a double advantage to the survival of neurons, quickly removing the reactive quinones present in the cells and sequestering them in a stable complex, which can also then bind toxic metals to further reduce the toxic stresses on those cells. The challenge now is to find ways to stabilize neuromelanin content in the brain to optimize its inherent and important functions to the organism, and future work will no doubt continue to be targeted in that direction.

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