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Review article

Ferritin and neuromelanin "quantum dot" array structures in dopamine neurons of the *substantia nigra pars compacta* and norepinephrine neurons of the *locus coeruleus*

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A R T I C L E I N F O

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A B S T R A C T

In this review, the author shows that ferritin has documented quantum dot material properties that have been reported in numerous independent studies, and can enable quantum mechanical electron transport over substantial distances. In addition, neuromelanin is a pi-conjugated polymer, and quantum dot/pi-conjugated polymer combinations have been reported in numerous independent studies to facilitate electron transport for solar photovoltaic and other applications. Both ferritin and neuromelanin are present in large quantities in the dopamine neurons of the *substantia nigra pars compacta*and the norepinephrine neurons of the *locus coeruleus*. The unique structure of subgroups of these neurons that have a large number of axon branches and synapses may have evolved to take advantage of this electron transport mechanism, if it is present, such as to coordinate conscious action, or for other purposes. Independent clinical and laboratory studies are also reviewed that corroborate this theory of coordinated action in these neuron groups. Research to validate the theory using charge transport measurements, materials characterization, existing fluorescent probe material and reaction time testing is proposed.

1. Introduction

Neuromelanin and ferritin are found in certain groups of catecholaminergic neurons, such as those of the *substantia nigra pars compacta* (SNc) and the *locus coeruleus* (LC). In this review, extensive evidence from independent research is discussed that shows that neuromelanin and ferritin have physical characteristics of quantum dots (QDs) and form a random array of QDs that could support the formation of one or more electron transport mechanisms that are capable of transferring electrons between neurons. This electron transport could be further facilitated by ferritin in the intercellular fluid between those neurons, in combination with the generation of internal cell voltages and possibly pressures. The electron transport, if present, could be associated with a function performed by the neuron groups. One possible function would be to cause electrons to transfer to a neuron having an axon that presents the lowest impedance path to ground, as a function of the extracellular field of downstream neurons. This hypothesized configuration would effectively form a gate circuit that senses the impedance of each of the available axon paths to ground and conducts energy to the neuron that is best situated to activate, to assist with formation of the action potential for that neuron, under certain circumstances. The neurological function of this gate circuit would enable multiple parallel processes to be performed by the neural network of the brain and to allow for selection of the "best" of those processes under those circumstances, such as when action potential generation is not capable of being driven only by dendritic innervation, which would correlate to the experience of conscious selection of an action under those conditions. Other possible timing-related functions might also or alternatively be associated with the hypothesized electron transport. Clinical and laboratory evidence is discussed that appears to corroborate this theory of function. Test are proposed that could be used to validate the theory, including charge transport measurements, materials characterization, fluorescent probes and reaction time testing.

2. Review

2.1. Ferritin QD properties

The technical literature clearly shows that ferritin has the physical properties of a QD. QDs were discovered in 1981 by Ekimov and Onushchenko (Ornes, 2016) who studied color formation in semiconductor doped glass and observed that the absorption frequency of

Abbreviations: LC, *locus coeruleus*; QD, quantum dot; SN, c*substantia nigra pars compacta*; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

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light in such doped glass was lower than expected. This effect was subsequently found to be caused by the quantum confinement of electron-hole pairs, also called "excitons," in small semiconductor crystals. QDs can be spherical and are usually 50 nm in diameter or smaller, although the size requirements for a specific QD are related to the Bohr radius of the excitons associated with the QD (Hennequin, 2008).

Ferritin is a spherical molecule with a diameter of approximately 12 nm and has an inner core of ferrihydrite that is approximately 8 nm (Kell and Pretorius, 2014). It was recognized as early as 1992 as having measurable quantum mechanical effects that are representative of QDs (Awschalom et al., 1992)—an observation that has been subsequently confirmed (Tejada et al., 1997; Schäfer-Nolte et al., 2014; He and Marles-Wright, 2015). Ferritin is a magnetic nanoparticle (Fittipaldi et al., 2011) and includes iron in a form that is antiferromagnetic at room temperature (Kaur, 2009). Antiferromagnetism has been shown to extend coherence lifetimes in QDs under certain conditions (Tackeuchi et al., 2006; Papaefthymiou, 2010; Cole and Hollenberg, 2009; Moro et al., 2015; Caram et al., 2014). Ferritin has both direct and indirect electron band gaps, meaning that it can generate excitons either due only to an electric field and in the absence of photons or as a function of photon energy. Measured band gaps range from approximately 2.1 eV to 3.07 eV and vary as a function of the number of iron atoms stored and the presence of different anionic elements or compounds (Colton et al., 2014; Smith, 2015). This prior work has thus established that the properties of naturally occurring ferritin can be used to generate quantum mechanical effects similar to those of man-made QDs; it has also established that ferritin can generate excitons due to an applied electric field, or due to other mechanisms. Electron transport in QD structures using electron flux, coherent tunneling, sequential tunneling, and hopping (quantum mechanical electron transport mechanisms) has been generated under laboratory conditions using ferritin with differing iron content levels (Axford and Davis, 2007; Rakshit and Mukhopadhyay, 2012; Bostick et al., 2018; Kumar et al., 2016).

2.2. Neuromelanin QD properties

Although the technical literature does not appear to have addressed whether neuromelanin is a QD, melanin in sheet form has been studied for its semiconducting properties and for possible use as an organic semiconductor. Neuromelanin, a combination of eumelanin and pheomelanin, is a molecule that is approximately 30 nm in diameter and is found in certain catecholaminergic neurons, including dopamine neurons of the SNc and norepinephrine neurons of the LC (Schwartz and Roth, 2008; Oades and Halliday, 1987; Margolis et al., 2006; Damier et al., 1999). Neuromelanin has been extensively studied, but no consensus has been reached on its function or even its properties. Some observers have suggested that it is detritus that accumulates with age (Haining and Achat-Mendes, 2017). Others have suggested that it might function to collect heavy metals and other material that might otherwise damage the neuron (Zecca et al., 2008). Some studies have estimated the band gap of melanin to range from 2.5 eV to 3.4 eV (Crippa et al., 1978; Obeid and Hussain, 2013), but at least one study concluded that the electrical behavior of melanin can be explained as an electronic-ionic hybrid conductor. (Mostert et al., 2012). These observations are consistent with the pi-conjugated structure of melanin, because pi-conjugated polymers can have conductive or semiconductive properties (Haining and Achat-Mendes, 2017; Ito, 2006). In addition, one documented function of neuromelanin is its ability to attract ferritin, as ferritin has been demonstrated to be present in proximity to the neuromelanin of the SNc (Tribl et al., 2009). Neuromelanin is formed by the reaction of iron with excess cytosolic catecholamines not accumulated in synaptic vesicles (Zecca et al., 2001), such that the presence of $Fe2+$ in the intracellular environment could contribute to the formation and accumulation of neuromelanin.

2.3. Concentration of ferritin and neuromelanin in catecholaminergic neurons

Neuromelanin is found in organelles in catecholaminergic neurons, and it is found in the SNc and LC in greater proportion than in any other areas of the brain (Kumar et al., 2016). One study reported that neuromelanin organelles make up 50% of the image area of dorsal SN neurons, where the density of SN neurons is lower, and 25% of the image area of ventral SN neurons, where the density is greater (Halliday et al., 2005; Gibb and Lees, 1991). These observations suggest that neuromelanin content is lower in dopamine neurons in areas where they have greater density, where a lower density of neuromelanin and ferritin would be required to support electron transport, and greater in areas where these neurons have lower density and would require a higher density of neuromelanin and ferritin to support electron transport. Based on an average estimated number of 1000 neuromelanin organelles per neuron, 100 neuromelanin molecules per neuromelanin organelle and a cell body diameter of 25 μm, the average distance between neuromelanin molecules within the SNc and LC cell bodies is 50 nm, although it is noted that neuromelanin molecules aggregate in neuromelanin organelles and are not evenly distributed throughout the cell body.

Ferritin has been observed in large quantities in SNc cell bodies, adjacent to neuromelanin organelles, using immunogold markers, and with an estimated density on the same order of magnitude as neuromelanin (Tribl et al., 2009). Serum ferritin has a low normal concentration in men (350 ng mL^{-1}) and women (150 ng mL^{-1}), which equates to a concentration of approximately $5 \times 10^{11}/2.2 \times 10^{11}$ molecules per mL, or a separation distance of approximately 2 μm between molecules, but the concentration of ferritin is higher in the intercellular fluid of the SNc and LC. For example, one study estimated that the concentration of ferritin molecules in the SNc in healthy subjects is approximately 3 ferritin cores per 0.003 μm^3, which works out to a spacing of approximately 100 nm between ferritin cores, on average (Bertini et al., 2012). This is similar to the spacing of ferritin molecules as studied for application in the qubit-structured QD array, reported by Choi et al. (2005), and would support electron transport between these molecules.

2.4. QD electron transport

The quantum mechanical characteristics of QDs are physical characteristics and have been tested in materials that are similar to the *in vivo* environment, such as celluloid hydrogels (Khabibullin et al., 2017), and have been demonstrated to function within cells (Tyner et al., 2007). The effects of QDs formed from different materials and sizes on the quantum mechanical properties of structures formed from those QDs have been extensively studied, as have systems of multiple similar QDs (Dolde et al., 2013; Burkard et al., 1999). The effect of random variations in size and spacing of QDs has also been studied (Mahler and Wawer, 1998; Gomez et al., 2002; Nozik et al., 2010). These studies demonstrated the existence of electron transport in random/non-regimented QD arrays that is observed more prominently in regimented QD arrays but which is still present at functional levels in such disordered arrays. One of these electron transport mechanisms is coherent electron bands, also referred to as mini-bands (Sun et al., 2008; Lazarenkova and Balandin, 2002). This effect was also demonstrated in a quantum well structure (which is a structure that constrains electron movement in two dimensions, instead of three dimensions, like a QD). In that structure, a spatially extended, two-dimensional electron probability wave function was demonstrated to exist when there was no applied electric field, which formed a coherent electron band (Bradshaw and Leavitt, 1998). As the electric field surrounding the quantum well structure was increased, the electron wave function reduced in extent (known as the Wannier-Stark regime) until it became fully localized into a single quantum well at a high electric field. This