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Current Genomics, 2020, *21*, 525-530

REVIEW ARTICLE

The Long-Term Effect of Medically Enhancing Melanin Intrinsic Bioenergetics Capacity in Prematurity

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ARTICLE HISTORY

Received: June 12, 2019
Revised: August 09, 2019
Accepted: March 16, 2020

DOI:
10.2174/1389202921999200417172817

Abstract: ***Background*:** The ability of the human body to produce metabolic energy from light modifies fundamental concepts of biochemistry.

***Objective*:** This review discusses the relationships between the long-accepted concept is that glucose has a unique dual role as an energy source and as the main source of carbon chains that are precursors of all organic matter. The capability of melanin to produce energy challenges this premise.

***Methods*:** The prevalent biochemical concept, therefore, needs to be adjusted to incorporate a newly discovered state of Nature based on melanin's ability to dissociate water to produce energy and to reform water from molecular hydrogen and oxygen.

***Results and Discussion*:** Our findings regarding the potential implication of QIAPI-1 as a melanin precursor that has bioenergetics capabilities.

***Conclusion*:** Specifically, we reported its promising application as a means for treating retinopathy of prematurity (ROP). The instant report focuses on the long-term treatment medical effects of melanin in treating ROP.

Keywords: Melanin, energy, retina, oxygen, hydrogen, prematurity, retinopathy of prematurity.

1. INTRODUCTION

Oxygen is supplied to the human retina *via* the retinal and choroid vasculature. It is consumed by the retinal tissue as per metabolic demands. Irregularities in oxygen supply or metabolism are thought to play significant roles in common retinal diseases such as diabetic retinopathy, retinopathy of prematurity, vascular occlusion, and age-related macular degeneration [1].

A study involving stable heart-failure patients showed a mean (SEM) frequency of episodes of diminished nocturnal oxygen saturation (SaO_2) exceeding 4 percent. The rate was 10.3 (0.9) per hour in the patients, compared to 4.8 (0.6) in normal controls ($p < 0.005$) [2]. Upper airway size plays a secondary role, as suggested by the lack of post-adenotonsillectomy oxygen saturation improvement [3]. Nocturnal hypoxemia may precipitate vascular occlusion in the lungs as well as in the bone marrow, with progressive parenchymal lung injury and poor gas exchange [4].

Experiments on cats showed that the electrical activity in the inner (proximal) retina is unaffected by systemic hypoxia if the arterial oxygen tension (PaO_2) is above 40 mmHg. This results from effectively regulating the inner retinal tissue PaO_2 by retinal circulation. In contrast, some electrical signals generated in the outer (distal) retina change when PaO_2 falls below 70–80 mmHg. The outer retinal responses are generated by the retinal pigment epithelium. Their susceptibility to hypoxia is due primarily to their dependence on the photoreceptors.

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1389-2029/20 $65.00+.00

Photoreceptor metabolism is sensitive to hypoxia because of the high oxygen consumption rates and reliance on the choroid circulation, which is unable to regulate outer retina PaO_2. Retinal electrophysiology and oxygen distribution are altered by intraocular pressure elevation as well as hypoxia. These results raise the question of how to preserve the inner retinal function when the outer retinal function is altered [5].

The analysis of oxygen concentration on layers of retinal tissue is not straightforward. Results from various published reports seem to contradict one another. However, the presence of oxygen in the retinal tissue does not depend solely on retinal blood flow: Retinal cells have melanin granules (melanosomes) that can dissociate water molecules, generating molecular hydrogen (H_2) and oxygen (O_2). Therefore, it is reasonable to consider oxygen concentration in blood as an indirect indicator of molecular hydrogen concentrations in tissue.

The finding that glucose is oxidized to produce energy can be traced to Lavoisier in Paris and Priestley in London more than 200 years ago. Their conjecture was that atmospheric oxygen is absorbed into the blood and distributed throughout the body by the circulatory system. However, the standard model is still in debate. For example, it had been shown that glucose could not diffuse through the cell membrane: specific proteins must transport it. From there, glucose is phosphorylated by ATP to form glucose 6-phosphate. Unfortunately, glucose 6-phosphate cannot diffuse through the cell membrane due its negative charge. However, the phosphoryl group catalyzes further metabolism and supports carbon chains.

2. MOLECULAR HYDROGEN AND RETINAL PHOTORECEPTORS

The photoreceptor layer of the eye (Fig. **1A, B**) requires significant energy to function. For comparison, it requires 10 times more energy than the cerebral cortex, 6 times more energy than the cardiac muscle, and 3 times more energy than the renal cortex. Paradoxically, under normal conditions it is devoid of blood vessels. Therefore, energy cannot be provided by glucose, as there are no means for its transport. The oxygen levels on this layer (photoreceptors) can be explained by the proximity of the retinal pigment epithelium and the choroid layer. Both layers have one of the highest concentrations of melanin of the human body (*e.g.,* 40 percent more than skin).

The absence of blood vessels in tissue with the highest energy requirements is a conundrum. It has been observed, in both the photoreceptors layer and the central bone marrow, that they can produce around 2.5 million cells per second, which casts further doubt on the notion that glucose is the sole source of energy. Energy production by melanin in the form of molecular hydrogen and high energy electrons is illustrated in Fig. (**1B**).

The movement of gases sketched here shows that the hydrogen released by melanin is transported by simple diffusion due to the concentration gradient. The close proximity of photoreceptors and retinal pigment epithelium enables rods and cones to capture molecular hydrogen almost immediately upon being freed from water by melanin.

The histological findings are compatible with our claim that the tissues receive energy from light via the intrinsic ability of melanin to dissociate water molecules. Admittedly, glucose provides the carbon backbone to replenish the organic matter fed by the bloodstream.

3. MELANIN AND RETINOPATHY OF PREMATURITY

There is a deep-rooted belief that blindness resulting from retinopathy of prematurity (ROP) is strongly associated with the development of retinal neovascularization (NV). Although the pathogenesis of the retinal NV is unknown, retinal hypoxia is commonly thought to be its cause [1]. Therefore, one of the main aims of ROP therapy has been to control the angiogenic threat. The development of retinal NV leads to retinal detachment, which is frequently irreversible in infants. Another important issue is the development of myopia resulting from structural and functional changes [6].

The Cryo-ROP and ETROP trials have reported a marked increase in myopia following peripheral retinal ablation in

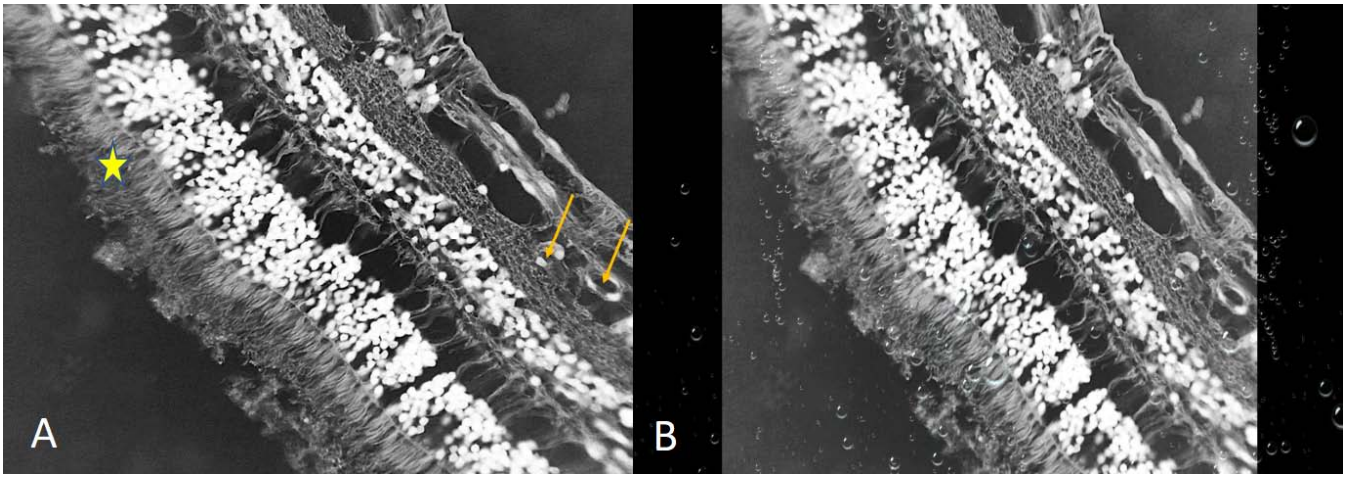

Fig. (1). Hematoxylin & Eosin (H&E) stained histological section of human retina. (**A**) The yellow star indicates the photoreceptor layer, devoid of blood vessels. The orange arrows indicate two blood vessels between the outer plexiform and the ganglion cell layers. (**B**) The same area under the higher resolution. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

ROP [7], with similar outcomes using cryotherapy or laser photocoagulation. Furthermore, there is a direct relationship between laser photocoagulation use and the severity of myopia.

Some clinical trials compared laser photocoagulation and cryotherapy with the intravitreal injection of anti-VEGF agents, such as Bevacizumab. The relative advantages of Bevacizumab on the outcome in myopia are insignificant, taking into account the local and systemic secondary effects of anti-VEGF agents: cataracts, infectious endophthalmitis, and recurrence of ROP. Statistically significant increases in severe psychomotor delay have been observed as well. The reported complications after the intravitreal injection of bevacizumab typically are severe [8].

ROP causes blindness in prematurely born infants worldwide [9, 10]. Although increased oxygen supply to premature infants results in increased survival and reduced frequency of cerebral palsy, there is a concomitant increased incidence of ROP [9]. A better understanding of the role of melanin lends itself to therapies that potentially can prevent ROP-induced childhood blindness. Sadly, childhood blindness shows increasing global incidence, particularly in the middle-income countries [10].

Major risk factors are poor neonatal care quality and oxygen supply control. Yet, the optimal level of oxygen supply to preterm infants is still unknown. This is surprising given ROP was first described in the late 1700s. Notwithstanding these points, restricted oxygen delivery reduced ROP rates but increased rates of mortality [11] and cerebral palsy [12]. With SpO_2 values below 90 percent, fewer infants needed ROP treatment but mortality increased [13]. With increasing rates of survival of prematurely born babies, there is an associated risk for further increases in the incidence of ROP. Pragmatically, it is important for neonatologists to refer very sick infants with long periods of high or fluctuating oxygen levels for ROP screening.

4. RETINOPATHY OF PREMATURITY AND OXYGEN LEVELS

Whenever energy is involved in a system, there is a risk of failure. Patients requiring oxygen supplementation can reasonably be considered as at risk of multiple failures. It is not a coincidence that, despite the best efforts of clinicians and researchers, a causal relationship between oxygen level and ROP remains obscure. We suggest that the failure is systemic in nature and that energy failure explains it reasonably well. What needs to be changed is the dogma that our body relies entirely on reaction of oxygen with glucose for energy production.

Moreover, glucose is unable to provide the energy for its own metabolism. We suggest that the energy that boosts metabolism in the human body is generated from water dissociated by melanin using visible and invisible light. Blood oxygen saturation, therefore, is an indirect indicator of the dissociation levels of the water molecule and does not represent oxygen being transported from the atmosphere to tissues via the bloodstream. Supplemental oxygen does not alter partial oxygen saturation in the blood significantly. The effectiveness of supplemental oxygen may be to unbalance the water dissociation process, which stimulates the organism to respond by raising the blood oxygen level. Unfortunately, this is simply symptomatic relief. The underlying problem persists, which is the disruption of energy generation and distribution *via* melanin, not glucose [14-16].

We may describe the water dissociation by melanin as follows:

$$2H_2O \rightarrow 2H_2 + O_2$$

To this point, the process is similar to photosynthesis in chlorophyll. However, the reaction in plants is irreversible because the oxygen is expelled into the atmosphere. The reaction involving melanin, however, is reversible, taking place as follows:

$$2H_2O \rightarrow 2H_2 + O_2 \rightarrow 2H_2O + 4e^-$$

For every two molecules of re-formed water, 4 high energy electrons are generated.

These processes (dissociation and re-formation) can be disrupted by environmental factors such as pollution in air, water, and food. Exacerbating factors include pesticides, herbicides, fertilizers, metals, plastics, industrial wastes, solvents, alcohol, recreational drugs, extreme weather, physical trauma, supplementary oxygen, *etc*. When supplementary oxygen is administered to a newborn, the equation goes into imbalance as follows:

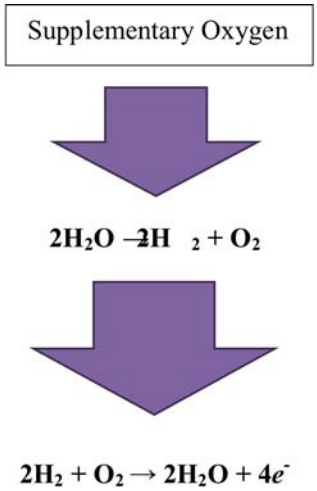

Fig. (2). Changing the concentration of reactants by providing supplementary oxygen. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

The proportion of products changes depending on the conditions, more water is starting to be produced than it dissociates, resulting in edema. Hydrogen is being consumed to form water, which would be consuming energy in an abnormal, non-physiological form. In turn, this may result in significant damage to forming tissues in one way or another. The belief that administering the supplementary oxygen raises tissue saturation is incorrect, as well as the notion that the body uses oxygen to generate energy by combining it with glucose (Fig. **2**).

Despite the many decades of ROP research, its etiopathogenesis is not yet understood fully. The role of oxygen may provide some insights. The discovery of the unexpected

bioenergetics role of melanin opens the door to different explanations for systemic and local alterations, such as eye fibrosis. A case study involving the use of QIAPI 1® had been published previously [17], Figs. (**3** and **4**) show the patient's dynamics throughout 9 years of continuous treatment.

5. CLINICAL CHALLENGE

The problem of premature and congenitally ill infants is not novel. Scholarly papers on the topic had been first published as early as the 17th and 18th centuries. It was not until 1922, however, that hospitals started organizing specialized areas, generally known as the Neonatal Intensive Care Unit (NICU).

Prior to the Industrial Revolution, premature and ill infants were born and cared for at home without medical intervention. In the mid-19th century, the infant incubator was first developed, based on incubators used for chicken eggs. Dr. Stephane Tarnier is considered to be the father of the incubator, referred to as an *isolette*, having developed it to attempt to keep premature infants warm in a Paris maternity ward. Other methods had been attempted previously, but this was the first closed model. In addition, Dr. Tarnier was able to show that the incubator actually helped the infants. Subsequently, France became a forerunner in helping premature infants survive.

Concomitantly, physicians took an increasing role in childbirth from the 18th century onwards. Mothers and midwives continued playing a major role in caring for the newborn. Some incubators, similar to those used for hatching chicks, were devised in the late 19th century and shown with newborns in the United States at commercial exhibitions.

In 1931, Dr. A. Robert Bauer at Henry Ford Hospital in Detroit, Michigan, demonstrated an incubator that successfully combined oxygen, heat, humidity, ease of accessibility, and ease of nursing care. Although facing initial opposition, after quadruplets were successfully delivered at Southmead Hospital, Bristol in 1948 and nursed in such a unit, obstetricians and pediatricians gradually accepted the technology. ***"In previous times, the problems of the newborn child have been the province of the obstetrician, a field in which he has taken comparatively little interest and to which he has contributed little. As pediatricians we have but scratched the surface." C.G. Grulee, 1939*** [2].

Fig. (3). Case study of a premature infant prescribed with QIAPI 1®. (**A**) The patient on the first days after hospitalization, QIAPI 1 is given at least six times daily in the dose of three drops per ounce since Day 1; (**B**) The Intensive Care Unit setting; (**C**) The initial condition of the patient was poor, requiring continuous treatment. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

Fig. (4). Case study of a premature infant prescribed with QIAPI 1® (cont'd)**. (A)** The patient at age 4, still undergoing continuous treatment with QIAPI 1®; (**B**) The patient at age 9, showing signs of normal physical and mental development. QIAPI 1® had been given at least four times daily since birth. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

Oxygen was frequently administered until the late 1950s, when it was shown that high concentrations inside incubators resulted in blindness. This common sense philosophy of *"if a little is good, a lot should be better"* resulted in many preterm infants developing ROP. Formerly referred to as retrolental fibroplasia, as itis the most severe form, is associated with retinal scarring or detachment.

The role of oxygen in ROP has been well documented by William Silverman [14]. The disorder cannot be identified until the retinal blood vessels reach initial maturity at about Week 6 postpartum, making it the last symptom of prematurity to be discerned. As ROP was found to be associated with the use of oxygen, the use of 100 percent oxygen was prohibited. Incubators of that era were designed so that no more than 40 percent oxygen could be delivered unless a baffle on the back of the incubator was closed.

At one time, severe stages of ROP inevitably resulted in blindness, but in the past 35 years, considerable improvement can be seen. In 1988, a preliminary report on improved outcomes in severe ROP using cryotherapy provided promising results. Now it is possible to treat and even prevent not only ROP but the associated systemic co-morbidities by administering QIAPI 1® to pregnant women [16-18].

CONCLUSION

Many biochemical processes remain mysteries beyond comprehension. The so-called "hypoxic theory" relative to treating premature infants has not been supported fully. Furthermore, the current results are controversial due to retinal oxygenation response to inhalation being taken, albeit erroneously, into consideration as a measure of the retinal circulation to supply oxygen while not reflecting changes in the oxygen consumption [15].

Available experimental data do not explain the two hypotheses commonly put forth (location and critical levels) to explain how hypoxia may stimulate retinal neovascularization. It is not currently possible to test these alternative hypotheses comprehensively. Hence, the possibility that retinal hypoxia is a necessary but not sufficient condition needed for developing ROP and systemic co-morbidities.

Importantly, the knowledge that melanin can produce energy by the dissociation of water offers many avenues for additional research. The main product of water dissociation is molecular hydrogen (H_2), which is the most common energy carrier in Nature.

Therefore, oxygen levels must be considered as an indirect indicator of hydrogen generation, as both elements are produced through the same mechanism: water dissociation. Oxygen is not transported across tissues via the bloodstream from the atmosphere [16]. In addition, oxygen is toxic, making it *"unavoidable"* for human life.

Finally, the biochemistry should research and incorporate findings that the human organism takes the compounds needed to replenish organic molecules from glucose in food. Nevertheless, the energy necessary to initiate the highly complex and diverse biochemical reactions and processes can be obtained from light, thanks to melanin [19, 20].

LIST OF ABBREVIATIONS

ROP = Retinopathy of Prematurity

ETROP = Early Treatment Retinopathy of Prematurity

VEGF = Vascular Endothelial Growth Factor

AUTHORS' CONTRIBUTIONS

Arturo Solís Herrera (ASH), Paola E. Solís Arias (PSA), María del Carmen Arias Esparza (MdCAE), Luis Fernando Torres Bernal (LFTB), and Gjumrakch Aliev (GA) conceptualized and designed the study. ASH, PSA, MdCAE, and LFTB, and GA collected and analyzed the data. ASH, PSA, MdCAE , LFTB, Andrey D. Bondarev (ADB), Vladimir N. Chubarev (VNC), Nina N. Minyaeva (NNM), Liudmila M. Mikhaleva (LMM), Vadim V. Tarasov (VVT), Siva G. Somasundaram (SGS), Cecil E. Kirkland (CEK), and GA discussed the analyses, the results and their interpretation. ASH, LFTB, NNM, LMM, SGS, CEK, and GA wrote the original manuscript draft. All authors have reviewed and approved the manuscript before submission.

CONSENT FOR PUBLICATION

The parents of the patient in the case study included have expressed informed written consent.

FUNDING

This work was funded by Human Photosynthesis® Research Centre, Aguascalientes 20000, México. This work also supported by Russian Academic Excellence project "5-100" for the Sechenov University, Moscow, Russia.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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