Further Observations on Visual Perception: The Influence of Pathologies Upon the Absorption of Light and Emission of Bioluminescence

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Abstract: The absorption and emission of light by biological systems is a dilemma for the research community which remains transfixed upon the bottom-up systems biology approach. Many health care professionals do not yet accept that photosensitivity is an essential aspect of the body's function.

This article highlights that light is often required to activate enzymes and/or proteins in biological systems. Inadequate levels of exposure to light may be responsible, at least in part, for the uncoiled nature of proteins found in diabetes mellitus, Alzheimer's disease, and other conditions. Moreover the emission of light, the consequence of protein reactions with reactive substrates or of reactive oxygen species, is an often observed characteristic of pathologies and influences the visual perception of colour. It illustrates that a significant diagnostic principle exists by measuring the levels of light absorbed and/or the bioluminescence released from fluorescent pathologies.

Keywords: Bioluminescence, colour perception.

1. INTRODUCTION

There is not yet any significant level of understanding of the mechanisms which regulate the body's function. We now know that genes produce our proteins and possess our genetic template but we do not yet know how this is regulated. Many genes produce more than one protein however the mechanisms for the production of one or other protein are not yet known.

The recognition that sense perception, and in particular colour perception, is linked to the function of the autonomic nervous system (top-down systems biology) appears to challenge the most fundamental concepts of reductionist biomedical research which focuses upon the symptoms of pathology and excludes any significant consideration of sensory input and the mechanisms which naturally regulate the body's function (bottom-up systems biology).

That colour is linked to the function of all cellular processes has been recognised in plant research since Ott [1] first recognised that the colours blue and red influenced the flow and/or function of chloroplasts (plant photoreceptors) and plant growth. In humans the link between colour vision and autonomic nervous system has been recognised since 1941 [2] e.g. the administration of adrenaline and pilocarpine are accompanied by alterations to colour perception.

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2. THE REGULATORY INFLUENCE OF LIGHT

The body responds to sensory input through touch, sight, hearing, smell, and taste. It may be essential for life [3]. Inadequate levels of sensory input lead to increased morbidity and mortality. Sensory input influences the autonomic nervous system. The sympathetic and parasympathetic nervous systems are influenced by GPCRs. An estimated 30-70% of drugs are based upon the function of GPCRs. They are involved in the processing and regulation of data from the external and internal environments. In vision, the opsin family of GPCRs convert light into cellular signals [4]; and in smell, olfactory receptors bind smells and pheromones. GPCRs are also involved in the regulation of behaviour and mood, immune system function, blood pressure and digestive processes. Any direct or indirect influences upon such proteins and their reactive substrates will modify sense perception and in particular visual perception. Alterations to their level, influenced by upstream biochemistries, or suppressed by the prevailing reaction conditions e.g. pH, temperature, plasma viscosity, levels of minerals, cofactors, hormones, neurotransmitters, *etc*; will influence the rate at which proteins react and, ultimately, visual perception. In addition most drugs and disease(s) are associated with cognitive deficits, often involving colour perception. This associates them with protein function [5].

A good example is that of PDE5 which is influenced by Viagra. The *phosphodiesterase 5 enzyme* (found in several tissues including (but not solely) the rod and cone photoreceptor cells of the retina) catalyze the hydrolysis of cAMP and cGMP. PDE5 absorbs and degrades cGMP. Sildenafil (Viagra) and other similar drugs inhibit this

1876-3928/11

enzyme. Consequently, many people who take Viagra notice a change in the way they perceive green and blue colors, or they see the world with a bluish tinge for several hours. For this reason, (i) pilots are prohibited from taking Viagra within 12 hours of a flight and (ii) policemen are advised to take special care when driving and negotiating their passage at traffic lights if they have recently taken Viagra. Viagra [6] activates or suppresses the processes which alter colour perception. If the latter this should be accompanied by lessened colour contrast in addition to altered colour perception. If the former this is likely to be accompanied by increased visual contrast and the emergence of specific colours in the visual spectrum. Both options are plausible. In the case of Viagra the latter seems more plausible. As this family of phosphodiesterase enzymes are genetically encoded it follows that epigenetic influences may decrease or increase the levels of gene expression and hence influence colour perception. In addition it is worth noting that PDE5 is not solely associated with visual function. It is also found in smooth muscle, lung tissues, the penis/erectile function and has been implicated in processes associated with learning and memory. Such enzymes are not solely devoted to visual transduction.

- PDE6 is light-activated. Suppression of its function by drugs reduces colour perception [7]. Moreover, most PDE5 inhibitors also inhibit PDE6 [8,9]. PDEs are implicated in the etiology of atherosclerosis and cardiovascular disease [10-12].
- cGMP is the substrate for PDE6. Regulation of cGMP levels and of associated reaction conditions such as pH, levels of minerals, *etc*; is therefore a prerequisite for normal function of transduction in the optic pathways.
- The enzymes PDE5 and PDE6 require divalent metal ions, in particular Zinc, to facilitate their function. Accordingly a zinc deficiency will influence signal transduction in the visual pathways.
- cGMP, which is produced by soluble guanylyl cyclase (sGC) in response to nitric oxide [13] is an important signaling molecule in axonal development.
- Light is a trigger for the delivery of Nitric Oxide [14] and subsequent stimulation of vasodilation. Moreover the therapeutic use of light (near infrared, 890 nm) to stimulate vasodilation is a commercial reality (Anodyne Therapy System) approved by the US FDA.
- Chronically altered biochemistry leads to genetic mutations in the phototransduction signaling process/cascade thereby influencing the function of retinal structures and the neurovisual pathways.
- Nitric Oxide plays a distinct role in cardiology [15-17].
- The body's function is multi-systemic and complex [18-21].

The role of light upon the body's physiology has been the subject of research for many researchers and has been extensively described in many articles by the author [22-25].

3. THE INFLUENCE OF LIGHT UPON THE BODY'S PHYSIOLOGY

Mono-chromatic light influences many of the body's physiological processes. It may be essential for the body's normal and regulated function i.e. without sunlight morbidity and mortality will be significantly enhanced. The precise selection of light and/or colour selects those neurons which are sensitised and part of neurophysiological processes [26]. It influences the function of neurons in the brain and biological processes in the visceral organs e.g.

- it regulates the function of retinal photoreceptors [27]. This use of light has been able to halt brain activity in specific neurons using different colours [28] and influence the firing of neurons.
- it activates the expression of proteins [29] and enhances mitochondrial DNA replication [30].
- it regulates the autonomic nervous system [2,31] and the stability of the physiological systems.
- it regulates Bilirubin metabolism [32,33] and its various isomers.
- it regulates the production of Calcitriol [34,35]. The action of light upon the skin activates processes which produce Calcitriol (Vitamin D_3). This is involved in neural biochemistries including the synthesis of neurotransmitters, brain detoxification pathways, and has a significant immunomodulatory effect [36, 37].
- it activates enzymes, which catalyse the body's function [38,39].
- it influences the production of Nitric Oxide [13,40] and subsequent regulation of blood pressure, lipid peroxidation, blood flow [41] and heart rate [42].
- and many other biological processes including (but not limited to) the migration of stem cells [43]; rate of wound healing [44-46]; rate at which proteins translocate to the cell membrane; function of the lymphatic system [47]; regulation of intercellular pH balance [48,49]; sperm motility [50] and sexual function [51]; and immune function [52-54], *etc*.
- the effect of light upon nitric oxide formation may have potential anti-cancer application [55].

There is an immense amount of data which illustrates the therapeutic effect of light including that summarised in articles by the author [21,23,56-59].

Proteins exist in multi-level, multi-energetic states. They require energy to be activated and often release energy as they decay into lower energy states following their reaction.

Some proteins do not fold correctly unless glycosylated. As discussed [60] light plays a significant role activating such proteins and moreover the light emitted may change following the protein reaction. The principle appears increasingly evident. Monochromatic light, received from the environment (and/or generated and transmitted *in vivo*), raises proteins/enzymes to their activated state. This is not a novel finding and has been reported by many researchers. Nevertheless the understanding that light may be essential

for their subsequent reaction and can influence differing biochemistries is most significant. The delivery of monochromatic light stimulates specific biochemical processes and regulates the function of the physiological systems [22, 23]. It synchronises the activity of groups of neurons [61] and their electrical impulses [62].

Lower levels of such proteins, arising from reduced genetic expression of proteins and /or the consequence of stress, and less favourable reaction conditions will reduce the number and rate of protein reactions e.g. firefly luciferin is oxidised by the enzyme luciferase in the presence of Magnesium, oxygen and ATP and yields a photon of light. This forms the basis of an assay for ATP however altered biochemical pathways - due to the adverse effects of pH, temperature, levels of minerals (in particular of Mg) and viscosity - influence the rate at which reactions proceed and may influence subsequent biochemical outcomes. They may alter the genetic profile and create genetic mutations [63,64].

Many proteins other than GPCRs are visually active. Knowledge of their chemiluminescent properties has been used to develop analogues with greater fluorescence but with the intention of measuring levels of biochemical markers rather than rate of reaction e.g. a bioluminescent assay has been proposed as a general method for the study of protein glycosylation [65]. Moreover the modification of chemical structure will modulate the ability of each biochemical or analogue to absorb light of a particular frequency or colour.

This alone may be considered to be a reasonable explanation for the phenomena of colour perception however such explanation does not adequately explain all known and related phenomena. In particular, the influence of bioluminescence upon colour perception. The ability to diagnose disease from its presymptomatic origins (a feature of Virtual Scanning) indicates that such bioluminescence must be generated by pathologies as a consequence of the light emitted from catalytic enzymes and reactive oxygen species as they decay into lower energy states.

There are numerous observed precedents linking colour perception to disease. One of the most striking precedents is that light is not solely absorbed through the neurovisual channels. It is also absorbed by the skin e.g. in the case of Vitamin D. It is assumed that these are the only two mechanisms for the absorption of light however researchers have established that blue light when applied to the back of the knee alters human circadian rhythm. Subsequent research [66] has indicated that the skin may act as an extra-retinal photoreceptor able to influence circadian rhythm. Light also influences the function of the pineal gland and, like the skin, influences circadian rhythms [67]. The production of melatonin by the pineal gland is stimulated by darkness and inhibited by light [68]. Although there is not yet a clear understanding of the role of the pineal gland (and hence of melatonin and serotonin) it is perceived to rise and fall in response to natural sunlight (during the day and night), and to seasonal fluctuations i.e. it may act to compensate or adjust for different levels of natural sunlight. In addition, different wavelengths are able to penetrate tissue to different depths [69, 70] i.e. at sufficient depth to influence the function of visceral organs.

The conventional explanation fails to explain how the number of colour-sensitive retinal cones can differ significantly but that colour perception can be unaltered. This indicates that colour perception is also influenced by our brains, and associated neurovisual pathways, and not solely by our eyes [71]. Similarly, those from tropical regions of the world where light is more intense have inherent genetic traits which are able to compensate for regional variation i.e. our visual perception is context dependent. In addition, the receipt of sensory input alone cannot explain the influence of stress and of the stress response upon the body's physiology. This can only be explained by considering how sensory input is processed by the brain. The neural response to stress is manifest as pathologies and subsequently influences colour perception i.e. the cumulative association of sensory input from the various senses is manifest as a physiological response of differing levels of intensity.

4. THE INFLUENCE OF PATHOLOGY-RELATED BIOLUMINESCENCE UPON COLOUR PERCEPTION

The phenomena of bioluminescence is considered to be associated with the excitation of substrates by enzymatic catalysis or by oxidative stress involving reactive oxygen species [72-75].

The evolutionary processes create or adopt physiological phenomena or developments which are passed onwards throughout subsequent generations. From life's origins as plant species, through marine sea life, light has been adapted from its earliest creation of life. The emission of natural bioluminescence is seen in marine life, in deep sea marine species; in fire-flies, glow worms, and insect larvae; and in vertebrates. It would be unusual in the extreme if evolution, in the human, had discarded such a valuable principle.

This emission of bioluminescence may have significant diagnostic potential [76]. Light influences the function of all cellular processes however the absorption of light may be primarily a therapeutic principle i.e. that light of specific frequency(s) stimulates specific biochemistries and systems. Nevertheless the measurement of light absorbed may be used to make diagnostic conclusions. The data presented in this article illustrates the ways in which pathologies influence the primary visual mechanisms and alter colour perception however this may not fully explain all of the aspects of colour perception.

The emission of light from protein-substrate reactions represents a diagnostic principle which, if adapted, may lead to a measure of rate of reaction rather than the diagnosis of the level of a specific biomarker. In principle, this may be a significantly more precise method of diagnosing the progression of disease [21,23]. It illustrates that the emission of pathology-related bioluminescence could influence or reduce the light absorbed by the optic mechanism and hence inhibit the perception of colour and colour contrast but it does not explain that the perceived visual intensity of such colours increases with the emergence of pathology.

The body literally glows with energy [77]. Moreover the locations from which light is released differs from the locations from which heat is released thereby illustrating that there may be distinctly different mechanisms. Blood and most body fluids are fluorescent e.g. forensic scientists use

ultraviolet lights at crime scenes to find blood, urine, or semen.

The principle(s) that light is emitted by protein-substrate reactions is recognised in several precedents e.g.

- BioAstral, part funded by the DTI, a spin-off from the University of Leicester [78].
- Fluorescent light illuminates blood sugar disorders in patients. The Dutch company DiagnOptics has developed a device that may be able to identify diabetes risk simply by shining a fluorescent light on a patch of skin below the elbow. The technique illuminates advanced glycation end products [79].
- Increased biophoton emission has been linked to the progression of disease e.g. in multiple sclerosis [80].
- Systemic parameters are linked to diabetic retinopathy [81-87].

Various articles elucidate the link between natural fluorescence, glycation and diabetes [88-92] and in subsequent cardiovascular developments [93-96]. Biophoton emission may be linked to current DM indicators such as HbA1c [97,98]; and the detection of other medical conditions [89] including gastrointestinal disease(s) [99-101], cancers [102-107], conditions of unknown origin [108,109], and as an early marker of retinal deterioration [110, 111]. Albumin is naturally bioluminescent. The glycated form of albumin has been proposed as an alternative to HbA1c in the measurement of diabetes [112, 113].

The loss of blue-yellow colour vision has been shown to be an indicator of the onset of type 1 diabetes mellitus [112, 114-122]. The loss of other colours in the visual spectrum are associated with coronary heart disease [123], migraine [124-126] and may also be implicated in the diagnosis of other heart conditions [127-129].

Light is partially absorbed and emitted by haemoglobin, albumin and their glycated analogues. Similarly ATP [130-132] and other nucleotides [133] may exhibit the same property of being able to weakly absorb and emit light and/or that biologically generated analogues may be fluorescent. Other potentially fluorescent biomarkers include NADH, FAD, tryptophan, collagen, and endogenous porphyrins [134].

5. DISCUSSION

The objective of this article is to demonstrate the existence of a significant scientific principle i.e. that the light absorbed by proteins and the bioluminescent released from many protein-substrate reactions can be used diagnostically and is the principle upon which Virtual Scanning is based. The idea of linking visual perception to pathology arose out of Grakov's research re the medical application of industrial lasers [135] conducted at the University of Novosibirsk in the period 1980-2000. This first development, Virtual Scanning, is now being followed by other commercial developments which seek to adapt the absorption and emission spectra of biological phenomena.

Monochromatic light has long been known to activate biological systems [136-138]. (Alexander Gurwitsch, V.P.Kazmacheyev and others established that every living cell emits light). Most proteins are visually active and/or naturally bioluminescent [136,137]. A similar principle appears to be used in non-linear interferometric vibrational imaging [139, 140] which, like Virtual Scanning, has taken many years to be developed.

Proteins react with substrates. Light provides the energy of activation required to energise the protein and/or its substrate into their reactive conformations [138]. In most cases this will release energy as heat however, as outlined in this article, it may also be accompanied by the release of electromagnetic radiation in the IR, Visible and UV spectrum. Moreover, many marine organisms have adapted light in various ways. Some mammals have no colour perception or have vision which preferentially absorbs in the IR or UV.

In some cases the protein may be activated to different energy states by light of different energy/colour. This stimulates different biochemistries and may be accompanied by the release of energy as heat or as light of different wavelengths. Some proteins may be relatively benign i.e. they are not visually active or are only weakly active, however their conversion to analogues may increase their inherent fluorescence. The development of problems re the regulation of blood glucose, which we recognise as diabetic mellitus, leads to a biochemical cascade involving the production of reactive oxygen species which release light according to the energetic states of the functional molecule(s) and glycated, or other, analogues.

Every genetic change will influence the level and structure of proteins expressed and of subsequent biochemical analogues (and their light absorbing or emitting properties).

Moreover the eye is a parabolic photoreceptor. It focuses and amplifies sensori-visual input. Whilst it routinely detects about 10^9 photons per second during daylight it also detects the light intensity of specific colours at as low as 50 photons per second [141]. It is a detector of extraordinary flexibility and scope. As outlined, its function is influenced by the release of fluorescence from blood i.e. by the bioluminescence of specific pathologies.

This illustrates that light perform a role which is analogous to that of software for our biochemical hardware. The phenomena is not unique to marine species but may be a necessary requirement for all intercellular commmunication and hence for the regulation and organisation of all forms of life.

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COMPETING INTERESTS

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