

Commentary

David Hunter Hubel, the ‘*Circe effect*’, and SARS-CoV-2 infection of the human visual system

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Abstract

David Hunter Hubel (1926–2013) was an internationally recognized neurophysiologist and vision neuroscientist noted for his life-long studies on the columnar structure and highly integrated function of the brain’s primary and secondary visual cortex. He was co-recipient with the American neuropsychologist and neurobiologist Roger Wolcott Sperry (1913–1994) and the Swedish neurophysiologist Torsten Nils Wiesel (1924–present) of the 1981 Nobel Prize in Physiology or Medicine, for their significant discoveries concerning the functional specialization of the cerebral hemispheres, the layered structure of the human cerebral visual cortex and information processing in the visual system, how the human visual cortex is organized into columns, and how this remarkable cellular organization and connectivity for the human visual system can be modified by lifestyle, experience, aging and disease. This commentary integrates these significant findings with current observations on SARS-CoV-2, the causative agent of COVID-19, and its invasion of the human visual system via the angiotensin converting enzyme 2 (ACE2) receptor.

Keywords: *Circe effect*; COVID-19; Primary visual cortex; SARS-CoV-2; Vision; Visual processing

1. Introduction

Once during a lecture in the early 1980’s, and just after receiving his Nobel prize in Physiology or Medicine Hubel described the columnar nature and the polarity of the visual circuitry of the human visual system and how signals travel from the exterior environment to the anterior surface of the eye, to the posterior of the eye, to the retina, through the optic nerves across the optic chiasm, optic tract and lateral geniculate nuclei (LGN), and on to the primary visual cortex in the occipital lobe at the posterior of the human cerebrum (Brodmann Area 17) [1,2].

2. Neurochemical gradients, visual signaling pathways and the ‘*Circe effect*’

Hubel proposed that there might be some kind of a ‘*neurochemical gradient*’ driving visual signals along this neural pathway for vision, perhaps via a series of tandem receptors—initially at a low density to a higher density of the same receptor along a visual circuit culminating at the highest density of receptors in the occipital lobe in the deepest anatomical regions of the brain. Hubel went on to further describe the concept of the ‘*Circe effect*’, a phenomenon first proposed by the American biochemist William Platt Jencks (1927–2007), as has been since widely observed in chemical and biochemical signaling reactions (https://en.wikipedia.org/wiki/Circe_effect); this process was named af-

ter the enchantress *Circe* in Homer’s *Odyssey* from Greek mythology who ‘*lured warriors to their fates*’) [3]. In modern biological chemistry the ‘*Circe effect*’ thereby involves a gradient of chemical, biochemical or biophysical components—such as receptors—from a lower to higher density that would initially attract and drive signals forward along a classical biochemical pathway involving an increasing gradient from a low to a higher molecular receptor density. Hubel provided an interesting analogy of a string of 10 lighted electrical lamp posts along a street with the faintest light at the top of the first lamp post and the brightest light along a gradient 10 lamp posts away. Hubel’s electrical or molecular signals were represented by a box full of moths. As we all know moths are attracted to light and especially to bright lights—so when the moths were first released at the lamp post with the least bright light the moths initially clustered around the faintest light but as time passed all moths moved along the lighted pathway to the brightest light source 10 lamp posts away.

The analogy of the driving force for light signals travelling from the anterior to the posterior of the human visual pathway to moths moving up a gradient of dim light to bright lights was an insightful example of Hubel’s creativity, innovation and genius. Fifty years after the Nobel laureate first proposed these innovative biological systems a very recent and exciting example is how the SARS-CoV-2 virus may move across the human visual system from the



surface of the eye through to the optic nerve and ultimately to the primary visual cortex in deeper regions of the human brain.

3. Vision and visual processing disturbances associated with COVID-19 infection

Disturbances in vision and visual processing are commonly reported by COVID-19 patients. SARS-CoV-2 RNA has been found in tears of infected COVID-19 patients, and several reports suggest that the ocular surface could serve as a portal of entry and/or serve as a reservoir for viral transmission to the upper respiratory tract via the nasolacrimal duct [4]. Besides the respiratory and digestive tracts, the ocular exterior presents an additional mucosal surface that is constantly exposed to infectious droplets and direct/indirect contact, and there is abundant data that SARS-CoV-2 is most easily spread via an aerosolized transmission and captured by the moist surface of the eye [5–7].

In addition, there are also multiple emerging reports of SARS-CoV-2 infection of the visual system with detrimental sensory consequences that include an inflammation or infection of the transparent conjunctival membrane (conjunctivitis) [4–10], photophobia and acute retinal necrosis [11–14], loss of visual acuity, visual distortion, blurred vision and disturbances in visual perception and balance [14–18] and persistent visual dysfunction and hallucinations [1,18–20]. These later pathological phenomenon are a product of highly integrated neuroanatomical regions and connections associated with the deeper regions of the visual brain [11–19,21,22]. The observation of a pathological ACE2 receptor gradient from the eye's exterior surface to the primary visual cortex, combined with the presence of SARS-CoV-2 in tear fluid and viral translocation via the nasolacrimal duct into the upper respiratory tract provides novel routes of SARS-CoV-2 transmission involving multiple anatomical elements across the human visual system.

4. Discussion

Keeping this in mind, Table 1 (Ref. [20,22,23]) shows the density of the angiotensin converting enzyme 2 (ACE2) receptor along a gradient from the anterior surface of the eye through to the primary visual cortex. ACE2 is known to be the primary and critical cell surface receptor for the SARS-CoV-2 virus essential for viral entry into host cells, necessary for successful infection, and is the causative agent for COVID-19. It appears that just like in Hubel's proposed model in line with the concept of the 'Circe effect' signaling, an increasing gradient of the ACE2 receptor might enable the single-stranded RNA (ssRNA) SARS-CoV-2 virus to travel from the exterior surface of the eye into deeper visual processing regions of the brain. There visual disturbances and dysfunction in vision and visual neuropathology may develop as a consequence of a successful SARS-CoV-2-mediated viral invasion of susceptible human host cells along these visual pathways.

Table 1. A molecular highway for SARS-CoV-2 infection of the visual system.

corneal epithelial cells	1.5
trabecular meshwork cells	4.5
non-pigmented ciliary epithelial cells	6.1
ocular choroid fibroblasts	7.7
retinal ganglion cells (RGCs)	8.1
whole retina	8.9
retinal pigment epithelial cells	10.2
optic nerve	10.6
optic chiasm	11.3
optic tract	11.5
thalamus	11.7
lateral geniculate nucleus (LGN)	12.1
occipital lobe - primary visual cortex (Brodmann area A17)	12.5

Visual signals and visual signal processing in humans typically proceeds from the outer eye and retina into deeper areas of the brain, and different cell types, tissues or anatomical structures are encountered along this major sensory pathway. The visual pathway extends from the corneal epithelial cells of the outermost layer of the cornea of the external eye through to the primary visual cortex located deep in the occipital lobe of the brain. Interestingly, SARS-CoV-2 infection is also associated with olfactory disturbances, however a similar gradient for the ACE2 receptor along single bipolar olfactory neurons from the cribriform plate of the nasal cavity into deeper brain regions of the olfactory lobe has yet to be demonstrated. The numbers in Table 1 are representative of the densities of the primary SARS-CoV-2 viral receptor, the angiotensin converting enzyme 2 (ACE2) cell surface acceptor protein, from the anterior (outer) surface of the eye to the primary visual processing center in the occipital lobe (Brodmann area 17) of the brain; ACE2 receptor abundance was determined employing an ELISA assay using a quantitative colorimetric (450 nm) sandwich ELISA specific for human ACE2 and a Fluoroskan Ascent FL Microplate Fluorometer and Luminometer (Cat no. 5200220, ThermoFisher Scientific, Waltham MA; sensitivity 1052 pg/mL; detection range 1.5 ng/mL–255 ng/mL; human ACE2 ELISA Kit ab235649; Abcam Cambridge MA, USA) as previously described in detail [20,22,23]. The numbers in Table 1 represent the statistical mean of 3–5 analyses for each visual pathway cell, tissue or anatomical structure.

5. Conclusions

From these observations we can speculate that other neuroanatomical, neurochemical and/or neurobiological pathways may utilize 'Circe effect' signaling in the transmission of biological entities or molecular-encoded information by means of specific receptor gradients in the brain and CNS both in health and during microbial infection and associated neurological disease.

Abbreviations

ACE2, angiotensin converting enzyme 2; CNS, central nervous system; COVID-19, coronavirus disease of the year 2019; ELISA, enzyme-linked immunoassay; SARS-CoV-2, severe acute respiratory syndrome coronavirus variant 2.

Ethics approval and consent to participate

The acquisition, handling, experimental, and analytical procedures involving postmortem human brain and retinal tissues were carried out in an ethical manner in strict accordance with the ethics review board policies at brain and eye tissue donor institutions (listed above) and at the Louisiana State University (LSU) Health Sciences Center. The ethical use of postmortem human brain and eye tissues and their analyses were also carried out in strict accordance with the Institutional Biosafety Committee and the Institutional Review Board Committee (IBC/IRBC) ethical guidelines IBC#18059 and IRBC#6774 at the LSU Health Sciences Center, New Orleans LA 70112 USA. Project identification codes: NIA AG18031 and NIA AG038834 (WJL).

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Conflict of interest

The author declares no conflict of interest.

References

- [1] Sperry RW, Hubel DH, Wiesel TN. The Nobel Prize in Physiology or Medicine 1981. 1981. Available at: <https://www.nobelprize.org/prizes/medicine/1981/summary/> (Accessed: 18 December 2021).
- [2] Hubel DH, Wiesel TN. Brain Mechanisms of Vision. *Scientific American*. 1979; 241: 150–162.
- [3] Jencks WP. Binding energy, specificity, and enzymic catalysis: the *circe effect*. *Advances in Enzymology and Related Areas of Molecular Biology*. 1975; 43: 219–410.
- [4] Bertoli F, Veritti D, Danese C, Samassa F, Sarao V, Rassu N, *et al*. Ocular Findings in COVID-19 Patients: a Review of Direct Manifestations and Indirect Effects on the Eye. *Journal of Ophthalmology*. 2020; 2020: 4827304.
- [5] Abobaker A, Alzwi A. The Eye: a Possible New Route of Infection in COVID-19. *Disaster Medicine and Public Health Preparedness*. 2020; 14: e25–e26.
- [6] Chen X, Yu H, Mei T, Chen B, Chen L, Li S, *et al*. SARS-CoV-2 on the ocular surface: is it truly a novel transmission route? *British Journal of Ophthalmology*. 2021; 105: 1190–1195.
- [7] Ho D, Low R, Tong L, Gupta V, Veeraghavan A, Agrawal R. COVID-19 and the Ocular Surface: a Review of Transmission and Manifestations. *Ocular Immunology and Inflammation*. 2020; 28: 726–734.
- [8] Aggarwal K, Agarwal A, Jaiswal N, Dahiya N, Ahuja A, Mahajan S, *et al*. Ocular surface manifestations of coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. *PLoS ONE*. 2020; 15: e0241661.
- [9] Hu K, Patel J, Patel BC. Ophthalmic manifestations of coronavirus (COVID-19). In: *StatPearls [Internet]*. StatPearls: Treasure Island (FL). 2020.
- [10] Loffredo L, Pacella F, Pacella E, Tiscione G, Oliva A, Violi F. Conjunctivitis and COVID-19: a meta-analysis. *Journal of Medical Virology*. 2020; 92: 1413–1414.
- [11] Marinho PM, Marcos AAA, Romano AC, Nascimento H, Belfort R. Retinal findings in patients with COVID-19. *The Lancet*. 2020; 395: 1610.
- [12] Mirfazeli FS, Sarabi-Jamab A, Jahanbakhshi A, Kordi A, Javadian P, Shariat SV, *et al*. Neuropsychiatric manifestations of COVID-19 can be clustered in three distinct symptom categories. *Scientific Reports*. 2020; 10: 20957.
- [13] Siedlecki J, Brantl V, Schworm B, Mayer WJ, Gerhardt M, Michalakis S, *et al*. COVID-19: Ophthalmological Aspects of the SARS-CoV 2 Global Pandemic. *Klinische Monatsblätter für Augenheilkunde*. 2020; 237: 675–680.
- [14] Wu P, Duan F, Luo C, Liu Q, Qu X, Liang L, *et al*. Characteristics of Ocular Findings of Patients with Coronavirus Disease 2019 (COVID-19) in Hubei Province, China. *JAMA Ophthalmology*. 2020; 138: 575.

- [15] Yagci BA, Atas F, Kaya M, Arıkan G. COVID-19 Associated Bilateral Acute Iris Transillumination. *Ocular Immunology and Inflammation*. 2021; 29: 719–721.
- [16] Gonzalez MP, Rios R, Pappaterra M, Hernandez M, Toledo A, Santos C, *et al.* Reactivation of Acute Retinal Necrosis following SARS-CoV-2 Infection. *Case Reports in Ophthalmological Medicine*. 2021; 2021: 1–4.
- [17] Al-Sharif E, Strianese D, AlMadhi NH, D’Aponte A, dell’Omo R, Di Benedetto R, *et al.* Ocular tropism of coronavirus (CoVs): a comparison of the interaction between the animal-to-human transmitted coronaviruses (SARS-CoV-1, SARS-CoV-2, MERS-CoV, CoV-229E, NL63, OC43, HKU1) and the eye. *International Ophthalmology*. 2021; 41: 349–362.
- [18] Clouden TA. Persistent Hallucinations in a 46-Year-Old Woman after COVID-19 Infection: a Case Report. *Cureus*. 2020; 12: e11993
- [19] Hixon AM, Thaker AA, Pelak VS. Persistent visual dysfunction following posterior reversible encephalopathy syndrome due to COVID-19: Case series and literature review. *European Journal of Neurology*. 2021; 28: 3289–3302.
- [20] Lukiw WJ. microRNA heterogeneity, innate-immune defense and the efficacy of SARS-CoV-2 infection. *Noncoding RNA*. 2021; 7: 37.
- [21] Lopes B, Bortolon C, Jaspal R. Paranoia, hallucinations and compulsive buying during the early phase of the COVID-19 outbreak in the United Kingdom: a preliminary experimental study. *Psychiatry Research*. 2020; 293: 113455.
- [22] Lukiw WJ, Pogue A, Hill JM. SARS-CoV-2 infectivity and neurological targets in the brain. *Cellular and Molecular Neurobiology*. 2020. (in press)
- [23] Hill JM, Clement C, Arceneaux L, Lukiw WJ. Angiotensin converting enzyme 2 (ACE2) expression in the aged brain and visual system. *Journal of Aging Science*. 2021; 9: 001.