Thermal Physics and Glaucoma: From Thermodynamic to Biophysical Considerations to Designing Future Therapies

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Thermal Physics and Glaucoma: From Thermodynamic to Biophysical Considerations to Designing Future Therapies

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Abstract: This paper presents a theoretical approach to glaucoma, with the aim of improving the comprehension of the biophysical bases for new possible therapies. The approach is based on a non-equilibrium thermodynamic model. The results point to the fundamental role of the membrane's electric potential and of its relation with inflammation and ion fluxes. A new viewpoint is suggested to consider anti-inflammation and photobiomodulation as possible therapies for glaucoma.

Keywords: biophysics; glaucoma; non-equilibrium thermodynamics; ions fluxes; transport theory; thermodynamics of bio-systems

1. Introduction

Glaucoma is a disease of the visual system that, over a long period in the life of patients, can lead to irreversible blindness. It has been estimated that 112 million of people will loose their vision due to glaucoma by 2040 [1,2]; indeed, it affects around 1% of people aged over 40 years, 5% of people over aged 70 years and older, and 10% of those older than 80 years [1].

The most widespread type of this disease is open-angle glaucoma, which is caused by a degeneration of the trabecular meshwork, with a related increase of intraocular pressure (IOP). This ocular hypertension generates an impairment of the axons of retinal ganglion cells, which make up the optical nerve: the result is a progressive loss of retinal ganglion cells. After a long time of asymptomatic development, visual loss is first peripheral and then central.

Current treatments consist in lowering intraocular pressure in order to increase the time of vision.

Recently, it has been pointed out that other biological mechanisms are involved in the development and progression of the glaucoma.

This is evident in the glaucoma progression observed in 15–25% of patients who present normal intraocular pressure [3–5]: there is continuous growing evidence on the relation between glaucoma and the central nervous system [1,6].

One of the consequence of high values of intraocular pressure is a reduction in neuronal metabolic activities and changes in the expression patterns of several synaptic plasticities [7,8].

Optic nerve regeneration represents a current new area of research in the treatment of patients with optic neuropathy [9]. However, there are a great number of constraints against optic regeneration in mammals [9] that can be summarized as follows:

- With age, the central nervous system loses the capacity for axonal regrowth;
- Axonal injury triggers some cycles of apoptosis.

However, a deeper comprehension of the mechanisms for regeneration could allow us to overcome these biological limits and cause ocular nerve cells to regenerate. To do so, we try to introduce a new viewpoint [10] based on biophysical thermodynamics. Recently, we developed a thermodynamic analysis of the glaucoma, pointing out that [11,12]:

- There is a relation between the temperature of the ocular anterior chamber and the intraocular pressure;
- There is a relation between the cornea temperature and the temperature of the ocular anterior chamber;
- There is a relation between the cornea temperature and its elastic behavior;
- There is a relation between the IOP and cornea thickness.

Thus, any heat applied to, or work performed on, the cornea could change its thermo-elastic properties with the result of generating possible variation in eye pressure. Moreover, we have experimentally proven the analytical model obtained by analyzing the temperature–IOP variation during cross-linking surgery in keratokonus treatment [13].

In this paper, we develop an improvement of the previous thermodynamic approach, based on non-equilibrium thermodynamics, in order to highlight the thermophysical properties of the optical nerve, studied as cell systems in relation to their ion transfer from a thermodynamic viewpoint. The results obtained could represent a starting point for new biophysical therapies for open angle glaucoma.

2. Materials and Methods

The living cell membrane is characterized by different permeabilities in relation to distinct ions (Na^+, K^+, Cl^-, Ca^{2+}, etc.), which cause an electric potential difference $\Delta\phi$ between the cytoplasm and the extracellular environment, measured in reference to the environment [14].

Moreover, the fundamental role of the membrane's electric potential has recently been highlighted in relation to the control of critical cell functions (proliferation, migration, and differentiation) [15–17]. In this context, the role of ion fluxes has also been highlighted.

The membrane electric potential can be theoretically described by the Goldman–Hodgkin–Katz equation [18–21]:

$$\Delta\phi = \frac{RT}{F} \ln\left(\frac{P_{Na^+}[Na^+]_{outside} + P_{K^+}[K^+]_{outside} + P_{Cl^-}[Cl^-]_{outside}}{P_{Na^+}[Na^+]_{inside} + P_{K^+}[K^+]_{inside} + P_{Cl^-}[Cl^-]_{inside}}\right) \quad (1)$$

where [A] is the concentration of the ion A in mol m^{-3}, $R = 8.314$ J $mol^{-1}K^{-1}$ is the universal constant of ideal gasses, T is the absolute temperature, F is the Faraday constant, and P is the relative permeability, such that $P_{Na^+} = 0.04$, $P_{K^+} = 1$, and $P_{Cl^-} = 0.45$.

In order to develop a non-equilibrium thermodynamic analysis [22,23], we follow the Onsager approach; hence, we introduce the following phenomenological equations [24–26]:

$$\begin{cases} \mathbf{J}_e = -L_{11}\frac{\nabla\phi}{T} - L_{12}\frac{\nabla T}{T^2} \\ \mathbf{J}_u = -L_{21}\frac{\nabla\phi}{T} - L_{22}\frac{\nabla T}{T^2} \end{cases} \quad (2)$$

where $\mathbf{J}_e$ is the current density [A m^{-2}], $\mathbf{J}_u$ is the heat flux [W m^{-2}], T is the living cell temperature, and L_{ij} are the phenomenological coefficients, such that $L_{12} = L_{21}$ in absence of magnetic fields, and $L_{11} \geq 0$ and $L_{22} \geq 0$, and $L_{11}L_{22} - L_{12}^2 > 0$ [27].

When ion fluxes occur $\mathbf{J}_e \neq \mathbf{0}$, so [24,25]:

$$\frac{dc_i}{dt} = -\nabla \cdot \mathbf{J}_i \quad (3)$$

where c_i is the concentration of the i-th ion (Na^+, K^+, Ca^{2+}, Cl^-, etc.) in C m^{-3}, t is the time and $\mathbf{J}_i$ is the current density of the i-th ion. In this condition, considering Equation (2), it follows that [24–26]:

$$\frac{d\phi}{dT} = -\frac{L_{21}}{L_{11}}\frac{1}{T} \tag{4}$$

which highlights that a Peltier-like effect occurs [24]. Considering Onsager's coefficients for the Peltier effect [28], Equation (4) becomes:

$$d\phi = -\kappa\, dT \tag{5}$$

where κ is the absolute thermoelectric power. A related heat flux is also generated [24,25]:

$$\frac{du}{dt} = -\nabla \cdot \mathbf{J}_u \tag{6}$$

where u is the specific internal energy and $\mathbf{J}_u$ is the heat flux in W m^{-2}. We can highlight that any increase in the cell temperature generates a decrease in the membrane electric potential: a case is represented by inflammation. Living cells exchange heat power towards their environment by convection, so following the first law of thermodynamics we can write [29]:

$$\frac{du}{dt}\, dV = \delta\dot{Q} \quad \Rightarrow \nabla \cdot \mathbf{J}_u = \frac{\delta\dot{Q}}{dV} \tag{7}$$

where V is the cell volume and $\dot{Q}$ is the heat power. The model obtained allows us to describe a continued metabolic generation [29–31], characterized by a relation between the ion fluxes and heat power density generated. Consequently, a specific entropy rate is produced [26,31,32]:

$$T\frac{ds}{dt} = \nabla \cdot \left(\mathbf{J}_u - \sum_{i=1}^{3} \mu_i \mathbf{J}_i\right) - \sum_{i=1}^{3} \mathbf{J}_i \cdot \nabla\mu_i \tag{8}$$

where s is the specific entropy, T is the temperature, $\mathbf{J}_S = \mathbf{J}_u - \sum_{i=1}^{3} \mu_i \mathbf{J}_i$ is the contribution of the inflows and outflows, with $i = 1,2,3$ means Cl^--, Na^+-, K^+-fluxes, $T\sigma = -\sum_{i=1}^{3} \mathbf{J}_i \cdot \nabla\mu_i$ is the dissipation function [24], and μ is the chemical potential, defined as:

$$\mu_i = \left(\frac{\partial G}{\partial n_i}\right)_{T,p,n_{k\neq i}} \tag{9}$$

where G is the Gibbs energy, n is the number of moles, and p is the pressure. The entropy outflow σ is fundamental in order to generate order from disorder, as Schrödinger himself pointed out [33].

In relation to the ion fluxes, we rewrite Equation (10) as follows:

$$T\frac{ds}{dt} = -\nabla \cdot \left(\mathbf{J}_u - \sum_{i=1}^{3} \mu_i \mathbf{J}_i\right) \tag{10}$$

which, considering T constant and following Prigogine ($ds/dt = 0$) [34], becomes:

$$\nabla \cdot \left(\mathbf{J}_u - \sum_{i=1}^{3} \mu_i \mathbf{J}_i\right) = 0 \tag{11}$$

Now, considering Equation (7), we obtain:

$$\nabla \cdot \left(\sum_{i=1}^{3} \mu_i \mathbf{J}_i\right) = \frac{\delta\dot{Q}}{dV} \tag{12}$$

which relates the ion fluxes to the power density generated, which must be wasted.

3. Results

In this paper, we developed a non-equilibrium thermodynamic analysis of the cell membrane electric potential, in order to obtain an analytical model for the comprehension of the role of the ion fluxes in relation to glaucoma.

We can point out that during the signal transmission in the optic nerve, the membrane ion potential is strictly related to a Peltier-like effect, with a dependence on temperature. Consequently, an inflammation causes an increase in temperature and a related depolarization of the cells, with a progressing removal of the normal behavior of the nerve.

Moreover, a thermal flux is generated with a related requirement of energy production, which determines an alteration in the generation and use of energy; thus, a metabolic alteration occurs.

Now, we consider that any change in the ion concentration changes both the membrane electric potential and the related pH of the cytoplasm due to the relation between the concentration of a chemical species and the pH [35,36]:

$$c_{out} = c_{in} \exp\left(\frac{F\Delta\phi}{R\,T}\right) \tag{13}$$

where c is the concentration, R is the universal constant of ideal gas, F is the Faraday constant, T is the temperature, and in and out mean inside and outside the eye nerve cell, respectively. Then, we also consider the Nernst equation [20]:

$$\Delta G = F\,\Delta\phi - 2.3\,RT\,\Delta(\mathrm{pH}) = V\Delta p - \int S dT + \sum_i \mu_i \frac{n_i}{V} \tag{14}$$

where G is the Gibbs potential, F is the Faradys constant, 2.3 ΔpH is the physiological concentration gradient, S is the entropy, T is the temperature, n is the number of moles of the i-th ion, and p is the intraocular pressure (IOP). Thus, considering the eye isotherm, we can link the result obtained here to the IOP, p, as follows [12]:

$$\Delta p = \frac{RT}{V}\ln\left(\frac{c_{out}}{c_{in}}\right) - 2.3\frac{RT}{V}\Delta\mathrm{pH} - \int dt \sum_i \nabla\cdot\left(\mu_i \mathbf{J}_i\right) = \frac{RT}{V}\ln\left(\frac{c_{out}}{c_{in}}\right) - 2.3\frac{RT}{V}\Delta\mathrm{pH} - \frac{Q}{V} \tag{15}$$

which relates the intraocular pressure variation with the fluxes previously introduced, and where Q is the heat exchanged with the eye environment.

4. Discussion and Conclusions

A great number of experiments highlighted the role of neuroinflammation in the pathophysiology of glaucoma. However, up to now, the causes of this inflammatory response have not been understood [37,38].

Our results allow us to suggest a possible response to this open problem. Indeed, the relationship between the temperature variation caused by inflammation and the nerve membrane's electric potential points to the modification of the behavior of the optical nerve, due to the change in the membrane's electric potential due to the temperature increase.

Moreover, considering the symmetry of Equation (5) it is possible to argue that if the inflammation is controlled, then the membrane's electric potential can be restored by a decrease in temperature. This result agrees with the results presented in the literature, in which anti-inflammatory treatments are highlighted as new effective therapeutic strategies [39].

Lastly, a control of the membrane's electric potential can also produce regeneration; indeed, an interesting way to produce variation in the membrane's electric potential is to consider Equation (12):

supplying energy in the form of heat, ion fluxes are generated, and these fluxes change the membrane's electric potential. A possible way to supply energy is to use light; indeed, photostimulation has recently been highlighted as aiding regeneration and functionality after nerve injury [40].

Our results represent a new viewpoint to improve these new therapies, providing a non-equilibrium thermodynamic approach to improve the biophysical comprehension of these possible future therapies.

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