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Alzheimer's Disease: A Thermodynamic Perspective

Umberto Lucia [1,*,†,‡], Giulia Grisolia [1,‡] and Thomas S. Deisboeck [2,‡]

[1] Dipartimento Energia "Galileo Ferraris", Politecnico di Torino, Corso Duca degli Abruzzi 24, 10129 Torino, Italy; giulia.grisolia@polito.it

[2] Department of Radiology, Harvard-MIT Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA 02129, USA; deisboec@helix.mgh.harvard.edu

* Correspondence: umberto.lucia@polito.it; Tel.: +39-011-090-4558

† Current address: Dipartimento Energia "Galileo Ferraris", Politecnico di Torino, Corso Duca degli Abruzzi 24, 10129 Torino, Italy.

‡ These authors contributed equally to this work.

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Abstract: Alzheimer's disease is investigated using a thermodynamic approach based on ion fluxes across the neuronal membrane. Our study indicates that the onset of Alzheimer's may be aided by a hyperpolarization of this membrane, because hyperpolarization-activated cyclic nucleotide gated HCN channels 1–4 conduct inward, with the consequence of depolarising Na^+/K^+ currents which in turn impacts synaptic transmission and reduces plasticity.

Keywords: Alzheimer; irreversible thermodyamics; ion fluxes; thermodynamic approach to biosystems; transport processes

1. Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative illness responsible for some 60% to 70% of all dementia cases [1]. The most common early symptom is short-term memory loss, while symptoms at later stages may include language difficulties, disorientation, mood swings, loss of motivation, diminished self-care, and behavioural issues [2]. Recent results indicate that risk factors to develop AD may include genetics, head injury, insulin resistance, and inflammation with a complex interplay between genetic and environmental exposures [3,4]. At present, the clinical focus is on the prevention of early onset based on identifying people at risk for developing the disease, designing and providing new therapies that are capable of slowing its progression [5]. Midlife risk factors considered [3,4] are:

- The cardiometabolic conditions such as diabetes, obesity and metabolic syndrome, hypertension, high cholesterol, and brain amyloid plaque;
- Lifestyle factors including smoking, alcohol, diet, physical activity, and stress;
- Other medical conditions, e.g., depression, poor sleep rhythm, and inflammation.

In AD, family history is considered a major risk factor with both clear genetic paths in early-onset and less so for the late-onset form. Out of 24 mutations, for instance PSEN2-N141I (expression N141I in presenilin-2) is inherited in an autosomal-dominant way while a mutation in APP (amyloid precursor protein) is inherited recessively. The latter increases all species of amyloid Aβ whereby the increase in Aβ_{42} is thought to determine aggregation into amyloid fibrils [6]. Consequently, the β-amyloid cascade hypothesis continues to be at the core of Alzheimer's pathogenesis.

In the healthy brain, communication between neurons is achieved through four main mechanisms [7]:

- Ca^{2+} evoked exocytosis with chemical neurotransmission;
- Gap junction electrotonic coupling;
- Secretion of neurosteroids, nitric oxide and derivatives of arachidonic acid acting in a paracrine manner;
- Cellular adhesive protein interactions with scaffold protein reorganisation.

It has been stated that [7] the fundamental structure for the integration of anisomorphic signals is the neuronal cytoskeleton which is considered to be sensitive to intense biochemical modification.

Recent clinical studies have pointed to some pathophysiological changes and signalling pathways, i.e., PI3K-GSK3β (phosphoinositide-3-kinase/glycogen synthase kinase 3 beta) signalling, neuronal stress signalling, inflammatory pathways, and metabolism damages are common in what has been termed "Type-3-Diabetes", i.e., resulting from an insulin-resistance in the brain, and AD. Moreover, there is some evidence that diet and exercise slow AD progression [8]. Although significant research has been done, still many questions remain unanswered on the shared mechanisms of AD, i.e., how upstream components of brain insulin/IGF (insuline-like growth factor) signalling are causally contributing to Alzheimer's Disease pathogenesis [8].

Recently, we have proposed a new biophysical approach to understand biosystems behaviours (with particular focus on cancer) based on the thermodynamics of energy and ion fluxes [9,10]. Growth implies organisational and thermodynamic processes and optimising them towards the maximum conversion of available energy is at the core of life itself [11–18]. Cells exchange energy and matter through their membrane in an effort to fuel the biochemical reactions producing/consuming external metabolites and connecting them with the internal ones. These fluxes of ions and molecules through the membrane, at the steady state, produce constant concentrations. The driving force of this transport mechanism is the cell's endogenous electric fields which are produced by accumulating ions in the nanometer-thin layer of water [16,19–21]. Hydrodynamic forces are generated by the electrophoresis of positive ions and, consequently, negative ions are forwarded in the opposite direction [16,22]. The human brain represents only around 2% of the body's weight, but it uses about 20% of the body's resting metabolism [23]. This significant energy demand has important implications for brain functions because its energy requirements render the brain susceptible to possible damages due to its metabolically "expensive" neural processing of information. Both information and metabolites are fluxes. In this paper, we follow this thermodynamic perspective to analyse and offer some new insights about Alzheimer's disease.

2. Materials and Methods

We first introduce a simple model of information coding to evaluate the energy consumption of the brain. It is known that, in order to process signals, a brain cell requires a Na^+-inflow, and a countering flow of K^+-outflow [19]. The consumption of one molecule of ATP (adenosine triphosphate) requires that the membrane pump extrudes 3 Na^+-ions and imports 1 K^+-ion. At the stationary state, a neuron maintains its pump current:

$$I_p = \frac{\Delta V_{Na^+} - \Delta V_m}{R_{Na^+}} + \frac{\Delta V_{K^+} - \Delta V_m}{R_{K^+}} \tag{1}$$

where ΔV_{Na^+} is the electric potential variation due to the Na^+-flux, ΔV_{K^+} is the electric potential variation due to the K^+-flux, R is the electric resistance of the ion considered during its current flux through the membrane, and ΔV_m is the membrane electric potential variation; ATP is consumed at a rate of I_p/F, where $F = 96,485$ C mol^{-1} is the Faraday constant. Consequently, the membrane potential is expressed as:

$$\Delta V_m = R_{in} \left(\frac{\Delta V_{Na^+}}{R_{Na^+}} + \frac{\Delta V_{K^+}}{R_{K^+}} \right) - R_{in}\, I_p \tag{2}$$

with

$$R_{in} = \frac{1}{\frac{1}{R_{\mathrm{Na}^+}} + \frac{1}{R_{\mathrm{K}^+}}} \tag{3}$$

and

$$\frac{d[\mathrm{Na}^+]}{dt} = -\frac{d[\mathrm{K}^+]}{dt} \tag{4}$$

where [A] is the concentration of the A-ion ($\mathrm{Na}^+/\mathrm{K}^+$) . A nonsignalling neuron exhibits a voltage across its membrane called the *resting membrane potential*, or simply the resting potential. In a resting neuron, there is no signal: this state of the neuron can be analytically described by the following analytical condition [24]:

$$\frac{d[\mathrm{Na}^+]}{dt} = \frac{d[\mathrm{K}^+]}{dt} = 0 \tag{5}$$

with

$$I_p = \frac{\Delta V_{\mathrm{Na}^+} - \Delta V_m}{3\, R_{\mathrm{Na}^+}} \tag{6}$$

Following Attwell et al. [23], considering a cell of volume Ω_{cv}, the change in the concentration of the two ions results [23]:

$$\Omega_{cv} F \frac{d[\mathrm{Na}^+]}{dt} = \frac{\Delta V_{\mathrm{Na}^+} - \Delta V_m}{R_{\mathrm{Na}^+}} - 3\Delta I_p \tag{7}$$

$$\Omega_{cv} F \frac{d[\mathrm{K}^+]}{dt} = \frac{\Delta V_{\mathrm{K}^+} - \Delta V_m}{R_{\mathrm{K}^+}} + 2\Delta I_p \tag{8}$$

The solutions of these equations are well known and they are [25]

$$\Delta V_{\mathrm{Na}^+} = -\frac{RT}{F} \ln\left(\frac{[\mathrm{Na}^+]_f}{[\mathrm{Na}^+]_i}\right) \tag{9}$$

$$\Delta V_{\mathrm{K}^+} = -\frac{RT}{F} \ln\left(\frac{[\mathrm{K}^+]_f}{[\mathrm{K}^+]_i}\right) \tag{10}$$

where $R = 8314$ Jmol^{-1} K^{-1} is the constant of the ideal gasses, f and i means final and initial respectively, and they are referred to the initial and finale state of the neuronal signalling process, and T is the temperature.

In order to maintain a normal membrane potential of around [23] -70 mV a neuron ($R_{in} = 200$ MΩ of input resistance) requires an influx of around 1.02×10^9 Na^+-K^+ ions s^{-1} ($\Delta V_{Na^+} = -50$ mV and $\Delta V_{K^+} = -100$ mV) which requires 3.42×10^8 hydrolysed ATP molecules s^{-1} [23]: it generates a pump current I_p of 1.63×10^{-10} A. Consequently, due to the very slow numbers of particles we can consider the mathematical approximation $\ln(1 + x) \approx x$, and we can approximate these relations as follows:

$$\frac{dV_{\mathrm{Na}^+}}{dt} = -\frac{RT}{F\,[\mathrm{Na}^+]_i} \frac{d[\mathrm{Na}^+]}{dt} \tag{11}$$

$$\frac{dV_{\mathrm{K}^+}}{dt} = -\frac{RT}{F\,[\mathrm{K}^+]_i} \frac{d[\mathrm{K}^+]}{dt} \tag{12}$$

where $[\mathrm{Na}^+] = 20$ mmol·L^{-1} and $[\mathrm{K}^+] = 140$ mmol·L^{-1}. From these equations it follows that:

$$\Delta[\mathrm{Na}^+](t) = \Delta[\mathrm{Na}^+](0) e^{-t/\tau} \tag{13}$$

$$\Delta[\mathrm{K}^+](t) = \Delta[\mathrm{K}^+](0) e^{-t/\tau} \tag{14}$$

where $\tau = (F/RT)\, dV_{\text{ion}}/dt$ ion = Na^+ or K^+ is the time of the process (the time characteristic of the process related to the physical and geometrical structure of the system), t is a time and 0 is referred to the initial time.

As previously highlighted, the fluxes can be generated by the hydrolysis of ATP, according to the following relation [25]:

$$\text{ATP} + \text{H}_2\text{O} \rightarrow \text{ADP} + \text{P} \tag{15}$$

$$\text{H}^+_{out} \rightarrow \text{H}^+_{in} \tag{16}$$

with a consequent variation of the pH because [25]:

$$\Delta\text{pH} = \frac{F}{2.3RT}\left(\Delta V_m - \Delta G_{\text{H}^+}\right) \tag{17}$$

where G is the Gibbs potential. Now, considering the previous relations (11) and (12), denote their ratio with the approximation $d \sim \Delta$, as usually done in engineering thermodynamics [26], we can obtain that:

$$\frac{\Delta V_{m,AD}}{\Delta V_{m,h}} = \frac{\Delta[Na^+]_{AD}}{\Delta[Na^+]_h} \tag{18}$$

where h means healthy and AD means Alzheimer's disease.

3. Results

The main, new result of this paper is Equation (18). This equation highlights that neuronal cell membrane hyperpolarisation is a fundamental characteristic of (if not even causative for) the development of AD. Indeed, hyperpolarisation-activated cyclic nucleotide gated HCN channels 1–4 conduct inward with the consequence of depolarizing Na^+/K^+ currents which control synaptic transmission [27]. Neural activity generates physiological changes in the nervous system that modulate neuronal communication through synaptic transmission. Both presynaptic and postsynaptic ion channels are involved in the process of synapse strength modulation [28]. This cell behaviour is strictly related to the energy and mass exchange between the cell and its environment [29]. In particular, insulin [30]:

- Suppresses the breakdown and build-up of glycogen, which represents the storage form of glucose;
- Blocks fat metabolism, and the release of fatty acids;
- Activates the sodium-potassium (Na-K) cellular channels.

It is therefore evident that K^+-fluxes participate in regulation and control of the cell cycle phases and this is strictly related to insulin. Conversely, insulin resistance is related to chronic inflammation and oxidative stress, and also to the metabolic syndrome [30]—all represent fundamental factors that determine the development of AD [31]. Furthermore, the membrane potential ratio in people afflicted with Alzheimer's and the healthy population, given by Equation (18):

- Frontal cortex: 1.2 ± 0.5;
- Parietal cortex: 1.2 ± 0.3;
- Cerebellum: 1.2 ± 0.4.

These numerical results which have been obtained using data summarised in Reference [32], allow us to highlight that the membrane potential in patients afflicted with AD is higher than that of healthy individuals. Consequently, also pH (Equation (17)) and the regulation of the energy use (Equation (15)) are distinctively different between AD patients and healthy individuals. Specifically, we can state that in the case of AD:

- The ratio is equal in the different brain areas, which means that the Na^+ concentration varies in an equivalent way. Consequently, there exists a difference in the pH in the presence of inflammation;

indeed, endosomal pH emerges as a target lever in amyloid disorders. This has been shown, e.g., in astrocytes when the Na^+/K^+ exchange mechanism NHE6 (sodium–hydrogen exchanger 6) has been restored which then led to alkalinizing of endosomal pH and, consequently, to a normalised Aβ clearance [33];

- The neuron membrane is hyperpolarized as compared to that of normal neurons;
- Hyperpolarization can enhance the Mg^{2+} block leading to a significantly reduced synaptic plasticity [28].

Just as synaptic plasticity is essential for learning and memory in the healthy brain [28], any decrease in these properties in the diseased stage can induce difficulties in memory tasks and learning ability. Consequently, all these effects should lead to impairments in learning hippocampus-dependent tasks.

Our results are in agreement with those reported in Reference [32].

4. Discussion and Conclusions

Several interrelated mechanisms have been presented trying to explain the pathogenesis of Alzheimer's disease, with the most prominent ones [31] being: (1) senile plaques which represent intracellular accumulations of Amyloid-β (Aβ) deposits; such deposits are accompanied by a formation of toxic oligomer aggregates and fibrils. (2) Neurofibrillary tangles (NFT) which represent the extracellular accumulation of hyperphosphorylated microtuble associated protein tau [31]. Toxic concentrations of Aβ trigger changes in tau and NFT formation. The related mechanisms of progressive neuronal damage are not well understood; still, it has been suggested that [31]: (i) aggregates of tau generate a stress response, and (ii) the microtubule stabilising function of tau is lost.

Our results highlight the fundamental role of ion transport in maintaining cell membrane potential and cellular pH; indeed, [31]:

- The metabolic syndrome (combining obesity, insulin resistance, arterial hypertension, low levels of HDL (High-Density Lipoprotein) and elevated triglycerides—principal risk factors for AD [34,35]) is being understood as a consequence of a chronic state of inflammation paired with dyslipidemia, hyperinsulinemia, and dysglycemia [36];
- The deposits of Aβ trigger an inflammatory response through microglia and astrocytes [37–39], related to the aggregation of cleared peptide, and the stimulation of the mediator's secretion which generate the damage;
- Proteins can also be modified by nonenzymatic reactions with monosaccharides (glucose or fructose), due to the formation of hydroxyl radicals OH- which determine some reactions of rearrangement, dehydration, and condensation; this in turn generates heterogeneous derivatives named AGEs (Advanced Glycation End products), that play a fundamental role in the overproduction of intracellular ROS (Reactive oxygen species) [40] and the decrease in proteasomal activity, inflammatory response, cell insensitivity to insulin and induction of neuronal nitric oxide NO [40];
- Biometals (i.e., Cu, Zn, Fe) play a physiological role to maintain normal cellular processes, but they are also linked to AD due to their interaction with the amyloid substrates; their modulation with age may initiate AD signalling pathways and deregulate the metal ions homeostasis which in turn may intensify the disease [41];
- Insulin regulates glucose and lipid metabolism in the brain and neural development and activities [42] which represent a fundamental factor in key activities such as the process of learning and the development of memory. Insulin enters the brain via a saturated transport mechanism; insulin induces its intrinsic tyrosine kinase activity, which leads to its autophosphorylation [43]. Glucose metabolism performs a fundamental role in AD and it is possible to consider it related to the Metabolism Syndrome [31]. Indeed, the deficiency of insulin signalling conditions

the PI3K/Akt (phosphoinositide 3-kinase/protein kinase B) pathway, thereby increasing APP processing, Aβ levels, and tau phosphorylation. Moreover, insulin inhibits IDE (Insulin-degrading enzyme) [31] damaging Aβ with a consequent increase of its neurotoxicity.

Furthermore, mitochondrial dysfunction and oxidative stress [44] have been shown to play an important role in the early pathology of Alzheimer's Disease [44]. Minor changes in the mitochondrial membrane potential due to activity of potassium channels may play a crucial role, i.e., ROS synthesis, which plays an executive role in mitochondria upon channel activation or inhibition. Moreover, the functionality of mitochondrial large-conductance calcium-activated potassium channels allows us to understand the fundamental signalling role of calcium ions within the cell [45]. The spontaneous oscillations of neuronal microtubules (at a frequency of around 1 MHz oscillation of electrical dipole moments of free electrons and conformational switching) generate wave interference, shown by a characteristic shape in the electroencephalographic signal of 4–40 Hz nested gestalts, knows as beat frequencies [46–48], explained by Bandyopadhyay [48–50] as the amplification of a resonance electromagnetic interaction between external electromagnetic waves and cell microtubules, with a related microtubules synchronisation [50]. Our results represent a theoretical explanation of these experimental findings, as deeply analysed in Reference [51] in relation to transport processes and free energy transporting matter, energy and ions [14–16,22,52–56] and the selective processes of interactions between cells and their environment.

Any biochemical process requires energy, and any energy conversion generates outflows of energy, due to the second law of thermodynamics. So, the fundamental thermodynamic approach to help decipher the behaviour of cellular systems is to consider inflows and outflows of energy and masses (ions included). Indeed, in support of our results we can summarise some experimental facts reported in the literature [14–16,57–71]:

- Cell cycles often require increases in K^+-channel expression and activity at the G1/S boundary;
- Ca^{2+}-fluxes modulate expression and activity of transcription factors which control G1 cyclin expression and as such effect associated proteins;
- Ions-fluxes modulate and determine internal/external cellular pH variation with a concomitant variation of the cell's metabolism.

In conclusion, our thermodynamic perspective lends credence to a fundamental role of neuronal cell membrane hyperpolarization in the pathogenesis of Alzheimer's disease. Importantly, these results further suggest that a possible therapeutic strategy should include reducing this hyperpolarization via reduction of the cytosolic Ca^{2+} levels and alterations in the kinase/phosphatase activity by neuromodulators in accordance with References [72–76]. Our findings therefore conceptually support experimental-clinical forays such as reported in Reference [77].

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Nomenclature

Latin symbols	
ADP	Adenosine Diphosphate
ATP	Adenosine Diphosphate
F	Faraday's constant 96485 [C mol^{-1}]
H	Hydrogen
K	Potassium
Na	Sodium
I	Current A
R	Electric resistance [Ω] and Universal gas constant 8214 [Jmol^{-1}K^{-1}]
t	time [s]
V	Electric potential [V]
Greek symbols	
Ω	Volume [m^3]
Δ	Variation
Symbols	
$[\cdot]$	Concentration [mol]
Subscript	
AD	Alzheimer's Disease
h	Healthy
p	pump

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