

Brain temperature as a measure of misfolded proteins metabolism

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Rango et al demonstrated significant higher brain temperature in patients with early Parkinson's disease (PD) compared to controls in different brain areas such as hypothalamus, posterior cingulate gyrus and centrum semiovale, despite comparable body temperature. The Authors focused on the consequences of increased brain temperature in damaging neurons and suggest that lowering brain temperature could be considered as a potential target to prevent neurodegeneration [1].

Brain temperature directly depends on the balance between heat production and heat loss to the external environment [2]. Namely, heat is generated by cell metabolism and is removed by cerebral venous blood flow, cerebrospinal fluid circulation and probably by the newly acknowledged lymphatic system. Magnetic resonance spectroscopy estimates brain temperature in vivo comparing water and N-acetyl aspartate methyl resonance frequencies.

Mitochondrial uncoupling of oxidative phosphorylation is considered the most important mechanism determining increased brain temperature [1-4]. However, an alternative hypothesis could explain why brain temperature is increased in patients with Parkinson's disease.

Many neurodegenerative disorders are associated with the expression of proteins that misfold and need additional processing effort by the cell machinery. Parkinson's disease as well as Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis and polyglutamine disease are characterized by the chronic expression of disease-associated proteins [5]. During the early stages of the neurodegenerative process, these abnormal proteins trigger cellular mechanisms such as unfolded protein response, ubiquitination, chaperones processing and finally degradation, all requiring energy [5]. Adenosine triphosphate hydrolysis is considered the main energy source for all these processes. While about 33% of energy is dissipated as heat in mitochondria during ATP production, the remaining 67% is dissipated during consecutive futile cycles ultimately leading to proteolysis.

Most of the processes leading to the loss of dopaminergic neurons in PD take place before symptoms appear. We can assume that such processes continue during early stages of the disease, until cellular effort to clear misfolded proteins falters, giving way to the overt appearance of protein aggregates. Indeed in PD, alpha-synuclein may interfere with proteolytic systems efficiency, finally decreasing the overall proteolytic activity of the proteasome [6].

We thus suggest that brain temperature could be related to increased energy expenditure in the early stages of neurodegenerative disorders and maybe have a role in the diagnostic process.

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