Question/Biological Problem (10 points)

Essential Tremor (ET) is a neurological disorder that causes involuntary and rhythmic shaking of the hands, head, trunk, voice, or legs. It is often confused with Parkinson's disease. ET is usually not a dangerous condition, but it typically worsens over time and can be severe in some people. ET is most common among people older than 65, but it can affect people at any age. The cause of ET is unknown, but about half of ET cases appear to result from a genetic mutation (familial tremor) where there is a 50% chance of a child to inherit the gene responsible for the condition if one of the parents carry it. It isn't clear what causes essential tremor in people without a known genetic mutation, but since the cerebellum controls the muscle coordination, one theory suggests that the cerebellum and other parts of the brain are not communicating correctly [1][2].

AIM: To build a model to verify if the reason of the shaking could be due to an abnormality of the electrical property of cortical neurons [3].

Research Model and Plan (10 points)

- Collect fibroblast cells from 10 patients with ET and from 10 subjects without ET and derive human (control) induced pluripotent stem (hiPS) cells from them. I think this is the safest approach without invasively taken a biopsy directly from the brain tissue.
- Derive cortical glutamatergic cultures from the hiPS cells using 2D differentiation.
- Use Optopatch, a co-expression vector that contains QuasAr1 or 2 and CheRiff proteins, on the derived and control cultures. QuasAr1 and 2 are genetically engineered archaerhodopsin-based voltage indicators, which show improved brightness and voltage sensitivity, microsecond response times, and produce no photocurrent. CheRiff is a genetically engineered channelrhodopsin actuator, which shows improved light sensitivity and kinetics, and spectral orthogonality to the QuasArs.
- Use a digital micromirror device (DMD) system that can target an optical stimulation (using blue light) to either a dendrite or the soma, and that is also capable to record the fluorescence dynamics at a 1 kHz frame rate.
- Stimulate and monitor the derived and control cultures for a period of 3 weeks to avoid working with senescent cells.
- Compare these two cultures and try to identify a fluorescence property difference between them, like the rate of spontaneous Action Potentials (AP), and AP propagation dynamics after blue light stimulation.
- If a fluorescence property difference is very well defined, then apply medications commonly used to treat ET to see if they help to reverse the dynamics of the derived culture. The medications to use are beta blockers such as propranolol (Inderal); anti-seizure medications such as primidone (Mysoline), gabapentin (Gralise, Neurontin) and topiramate (Topamax, Qudexy XR); tranquilizers such as clonazepam (Klonopin); and OnabotulinumtoxinA (Botox) injections.

References

[1] Essential Tremor Disorder. Johns Hopkins Medicine.

https://www.hopkinsmedicine.org/health/conditions-and-diseases/essential-tremor-disorder

[2] Essential tremor. Mayo Clinic.

https://www.mayoclinic.org/diseases-conditions/essential-tremor/symptoms-causes/syc-20350534

[3] Khan, T. A., Revah, O., Gordon, A., Yoon, S., Krawisz, A. K., Goold, C., Sun, Y., Kim, C., Tian, Y., Li, M., Schaepe, J. M., Ikeda, K., Amin, N. D., Sakai, N., Yazawa, M., Kushan, L., Nishino, S., Porteus, M. H., Rapoport, J. L. … Paşca, S. (2020). Neuronal defects in a human cellular model of 22q11.2 deletion syndrome. Nature Medicine. doi: 10.1038/s41591-020-1043-9

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