UNDERSTANDING AND MANIPULATING NEURON-GLIA INTERACTIONS

Anvika Singhal
Eastside Preparatory School • Independent Study • Fall 2024 • Dr. Duffy

REFERENCES

INTRODUCTION

Neurons play an incredibly important role in the brain, but supporting glial cells are much less talked and equally significant. This course begins with an analysis of ways to study neuron-glia interactions. It then goes on to detail the role of glia in the cause and progression of different diseases including Attention-Deficit/Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), epilepsy and seizure disorders, as well as their effect on sleep and behavior. Methods of manipulating the effect on neuron-glia interactions are also discussed including functional probes and optogenics and how glial cells can be harnessed to treat neuropsychiatric diseases and for neuronal regneration.

BACKGROUND

Extensive roles of glial cells in the nervous system:
- control ion balance and rate of action potentials
- impact reuptake of neurtransmitters in synaptic cleft
- foster neuron recovery/regeneration after injury

Astrocytes and microglia are the most studied types.
Why C. Elegans is a model organism for glial study:
- mapped connectome (neuron and glia connections)
- easy genetic modification, sequencing and primers
- clear cuticle, image cell and behavior simultaneously

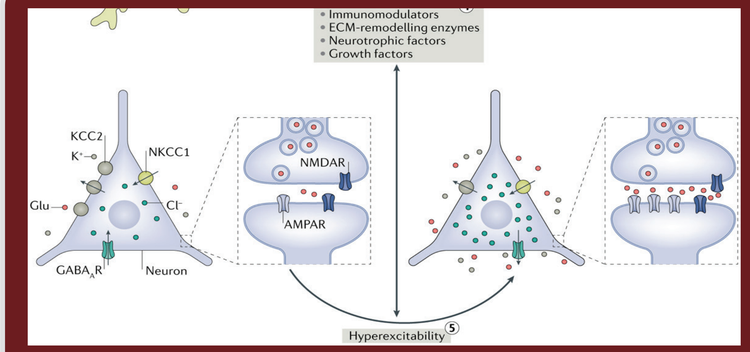

FIGURE 2

Glial activation leads to hyperexcitability, seizures caused by K+, Cl– and glutamate buffering impairments and excitatory/inhibitory imbalance. Seizures can aggravate the glia further (make them mroe reactive), starting the vicious cycle of gliosis and seizures.

PATHOPHYSIOLOGY OF DISEASES

ADHD and AUTISM SPECTRUM DISORDER:
- microglia and astrocytes in central nervous system (CNS) cause neuroinflammation
  - activated (amoeboid) present in high quantities in mothers of children w/ ASD
  - cytotoxic to neurons/glia, cause synaptic elimination, anti-inflammatory cytokines
- cause increased exitation and reduced inhibition in patients with ADHD

EPILEPSY:
- gliotic scarring caused by trauma leads to damaged blood-brain barrier (BBB)
  - reduced inhibitory neurotransmitter (glutamate) uptake, more action potentials

SLEEP and BEHAVIOR:
- known link between glial cells and sensory processing in humans and other organisms
  - by determing link between sleep and sensory processing in C. Elegans, can begin to show how sleep behavior is impacted/controlled by glia in humans

MANIPULATING GLIA:

FUNCTIONAL PROBES: detect glial response to stimuli allowing real time tracking and manipulation
CELL ADHESION MOLECULES: creates targets to support and change how glia impact synapse/BBB regeneration
OPTOGENETICS: engineering light-sensitive proteins (opsins) into glia allows control over the activation/inhibition of individual cells, applications in epilepsy
NEUROPSYCHIATRIC DISEASES: glial drug development
- affect depression, bipolar disorder, schizophrenia
- better understand which drugs are most effective
  - targeting glia instead of just typical neurons

NEURONAL REGENERATION: response to injury
- ties between glia (Schwann cells) and regeneration
- work to support similar glial regeneration in CNS

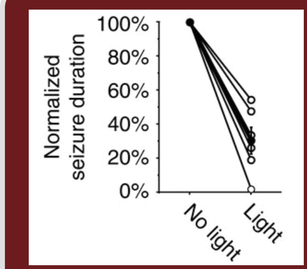

FIGURE 3

reduced seizure duration with optogenetics in mice

Normalized seizure duration with light application as function of control. Filled circles represent averaged data. In one case, seizures stopped within 1 sec.

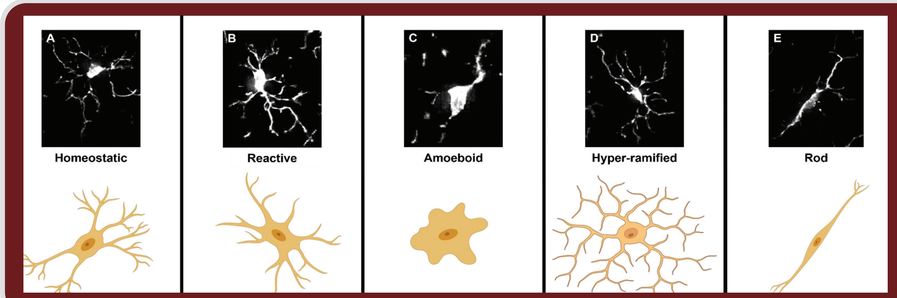

FIGURE 1

representations of the five microglial morphologies

(A) Homeostatic (normal) form with long processes (arms) and small somas (bodies). **(B)** Reactive form with retracted processes, larger soma. **(C)** Amoeboid form w/o processes, this is activated form. **(D)** Hyper-ramified "bushy" form are intermediate form between homeostatic and reactive. **(E)** Rod-shaped microglia have polarized structure, thin somas, extended processes.

PROCESS AND ACKNOWLEDGEMENTS:

The beauty of studying the human body is how everything has a purpose. The most amazing part of this project was at the end of each section when everything fell into place: the role of glia, the connection to the disease, the possibilities that the discovery unlock. Despite the copious amounts of reading and subsequent extrapolation that took much more time than anticipated, I am excited for the future of glial cell studies and the treatments and therapies that they will unlock. Thank you to Dr. Liza Severs at Fred Hutch and to Dr. Duffy for their inspiration and guidence.