Astrocyte – Neuron Cross Talk

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Anatomy, AIIMS
Neuroglia (Kitt)

Camillo Golgi

Rudolf Virchow

Ramon Cajal
Astrocytes – form & distribution

Fibrous astrocyte

Very long thread like process
GFAP +
Surface of brain, spinal cord, white matter, hippocampus, ant./ dorsal horn of sp. Cord except substantia gelatinosa

Protoplasmic astrocyte

Short sinuous process with cluster of lamellar appendages of grey matter
Astrocytes – form & distribution

Special forms
Radial glia
Bergmann glia
Muller cells (GFAP + after injury in rats, +ve in goldfish)
tanycytes

Pituicytes
GFAP +
Posterior pituitary
Interstitial cells of pineal
Neuronal Migration & Glia

Radial glial cells in developing brain
Vimentin, GFAP, S100

Pial surface

Bergmann glia

laminin

VZ

AMOG

Granule cells
Specific cues for axonal trajectories provided by glial cells

lessons from retinotectal pathway
Glucose requirement in brain

Indispensable

Logistic challenge
Glucose metabolism in neuronal cells & astrocytes

- Glycogen
- Glucose
- EMP
- Pyruvate
- LDH – 5 lactate
- Pyruvate
- Acetoacetate
- Hydroxybutyrate
- MCT – 1
- MCT – 2 (monocarboxylate transporter)
- Lactate
- LDH – 1
- Pyruvate
- TCA cycle
- CO2 + H2O

2 ATP

VIP, noradrenaline

GLIA

NEURON

H+
Glia as carbon dioxide sinks

$\text{CO}_2 + \text{H}_2\text{O} \rightarrow \text{H}_2\text{CO}_3 \rightarrow \text{H}^+ + \text{HCO}_3^-$

1 Na$^+$ / 2 HCO$_3^-$; 25 – 33% energy savings
Glutamate receptors

Ionotropic receptors
(ligand gated ion channels)

Alternative splicing

AMPA

Kainate

(DRG, Hippocampus)

NMDA

(Muller Cells, Visual cortex, Bergmann glia)
Ionotropic receptors

- AMPA
- K+
- Na+
- L-glu
- Mg++
- MK-801 (dizocilpine)
- glycine
- NMDA
- Ca++
Glutamate receptors

Metabotropic receptors

Gs / Gi

IP3 ----- Ca++

Ca fluctuation – role in circadian rhythm
Tripartite synapse – glia, the unclaimed partner

Astrocytes listen & ? talk to synapses

Slow inward current

NMDAR / non NMDAR depolarization

1 glu, 3 Na+, 1 H+
EAAT 1(GLAST)
EAAT 2 (GLT –2)

pre
post

Ca++

K+

Astrocytes

glu

1 glucose, 3 sodium, 1 hydrogen
Metabolic trafficking between astrocytes and neurons

Ketoglutarate ---- succinate

Glutamate + NH3

Glutamine

GABA

GABA

GAD

GLDH

AAT

PAG

Glutamine

Glu
Structural neuron – glia plasticity

Parturition

Lactation

Osmotic stimulation

Astrocytic coverage of magnocellular neurons of SON/ PVN

Pituicyte contraction

Highly sialylated weakly adhesional isoform of PSA - NCAM
Glutamate receptor mediated signalling to nucleus

Activation of AMPA in Bergmann Glia

Ca++

AP –1 (activator protein)

IEG activation (c-fos, c-jun c-myc, NGPI – A)
Neurovascular coupling

- Cerebral blood vessel
- Glutamate
- NMDA
- PSD 93, PSD 95
- NOS
- PLA2
- AA
- Cox2
- H+, K+, Adenosine
- NO
- PG
- NOS + cox2 + Cyt p450 epoxyxygenase
- Epoxyeicosatrienoic acid
Glial Cells

Diagram showing various types of glial cells and their interactions with neurons.
Glial limiting membrane

continuous lining separating brain from mesenchymal structures with intervening basal lamina

Blood Brain Barrier

Insects – glial cells

Sharks, skates, rays – open endothelial layer & tight junction between astrocyte end – feet & capillary

Human – tight endothelial junction with surveillance from end–feet of astrocyte
Astrocytes release neurotransmitters

Bradykinin
Aminocyclopentanedicarboxylate (ACPD)
Ca++
Astrocyte

ATP
Glutamate
Calcium metabolism in astrocyte

Are glial cells excitable cells?
Effect of intra-astrocytic calcium

Local calcium oscillation

Gap junction (dye coupling, freeze fracture)

(Cx 43, Cx30)

long distance signalling of calcium wave (GJIC)

Low resistance pathways

Increased cytosolic calcium implicated in hypoxia, hypoglycemia, HIV gp120
Glial membrane potential

High permeability to K+ ions

20 mV more ( - ) RMP than neuron

Glial cells hyperpolarise during onset of neuronal activity

? Inadequate number of Na+ channels

Glia – neuron dialogue in chemosensitive brain areas -↑ discharge in response to↓ pH
Potassium spatial buffering

High neuronal activity (mesencephalic reticular formation)

\([K+]_e = 3.5 \text{ mV} - 12 \text{ mV}\)

Astrocytes help in siphoning K+ from ECS

No explosive voltage dependent conductance

Slow potential shifts (SPS)
Is brain insulated from effects of immune system?

Brain grafts

BBB

Absence of lymphatics

TGF β, neuropeptide, ganglioside – immune suppressor

Low expression of MHC

Apoptotic elimination of T cells
Th 1 vs. Th 2 response

Th 1

CD 4+ Th 1

APC  IL-2, γ-IFN, TNF β

Th 2

IL-4, IL-10, IL-13

Downregulate Th 1 response
Microglia – Tissue guardians of brain

Ontogenically ~ mononuclear phagocyte lineage

? Neuroectodermal origin

• Resting microglia

• Activated microglia
Activated glia

Highly plastic

Stereotypic activation

Rod shaped (syphilitic paralysis)

Nodules (spinal neurons of anterior horn in poliomyelitis)

Foam laden macrophages

Gitter cells
Activated glia
Receptors on microglial cell surface

ATP

ACh

K+

microglia
Mitosis of microglia

Resting microglia

Activated microglia

NF κ B, CREB

IL-3
GM – CSF
M - CSF

P 50 / P 65

am

am
Microglia in CNS inflammation

1. IL-1, TNF α, IL-12
   IL-10, TGF β, PGE2
   (proinfl) (antiinfl)

2. Recruitment of leukocyte

3. Class II MHC / CD 11a, CD 40, CD 54, CD 80, CD 86
   T cell restimulation
Cytotoxicity vs. tissue remodelling
microglial perspective

CR 3
MHC I / MHC II
B 7
TNFα / γ IFN
TGFβ / IL –4
Plasminogen, U-PA

thrombospondin
Functions of microglia

1. Professional phagocytes – ORF, NO, proteases
   (microorganisms, debris)

2. Wound healing

2. Demyelinating diseases

3. ? Alzheimer’s disease

4. Delayed hypersensitivity
Astrocyte in CNS inflammation

- PGE2, TGF $\beta$ – Th 2 response
  - limit inflammation & support neuron survival
- IL – 4 --- NGF
- MCP –1, IP- 10, RANTES
  - recruitment of cells
Gliosis vs. fibrosis

↑ GFAP expression by astrocytes in brain damage

IL – 1β → astrocyte mitosis if BBB disrupted

Scrapie → IL –1 / TNF α – intense gliosis

Glial scar & epileptogenesis
Gliosis

- During fibrillogenesis, is uptake of glutamate inhibited?
- ECF excitotoxicity & penumbra in infarcted area
- Are the glial cells derived from site of injury or have they migrated?
- Can the glial cells secrete stromyelesin to digest brain versican?
Injury to brain

- MPTP $\rightarrow$ MPP+ (Parkinson’s disease)

- 3-HAO (in astrocyte) $\rightarrow$ quinolinic acid

damages neurons in Huntington’s disease
Brain edema in hepatic encephalopathy

- Na+
- H+
- Cl-
- HCO3-
- NaCl accumulation
- H2O
- NH3
- SCFA
- Mercaptan

Cirrhosis of liver
Reye’s syndrome
Alzheimer’s type II astrocytes
(cerebral cortex, basal ganglia)
Role of astrocytes in regeneration in CNS

GDNF - regeneration of dopaminergic neurons

Olfactory glia – role in CNS regeneration
Thank You