Diverse Roles and Inflammatory Situations
A Glia Story

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Emerging Role Of Glial Cells in the Control of Body Weight

• Background
  – History and Current Outlook
  – A Compilation of Glial Dossiers

• Glia cells’ role in Metabolism
  – Lipid Transporters - Hormone Receptors
  – Glucose Transporters - Glutamate Transport
  – Glucose and Glutamate Transport in Tanycytes

• Implications of Glial Cells in Metabolic Disruptions
  – Physical Activity and Caloric Restriction - Genetic Obesity
  – Diet-Induced Obesity
"Originally, neuroscientists didn't think glial cells did anything of importance. Believing neurons communicated to each other, represented our thoughts, and that glia were kind of like stucco and mortar holding the house together. They were considered simple insulators for neuron communication."

Merely providing just passive support for the neurons?! BAH!

Nothing more than cellular "glue" you say??
A Better Understanding

• As it turns out we’d be utterly lost without our glial cells

• Glia are the most abundant cell type in the brain and depending on their cellular origin, glial cells can be generalized as either macroglia or microglia
Glial Cells: Origin Stories...

- Macrogia are derived from the neuroectoderm and include both astrocytes and oligodendrocytes.

- Microglia have eluded our efforts to clearly define their origins... but we can suggest that they may be derived from either neuroepithelia or from hematopoietic cells [codename: monocytes].
Oligodendrocytes, they’ll sheathe you real nice

Oligodendrocytes are in charge of myelination in the central nervous system

Our operatives tell us that this fella plays a major role in insulating axons with myelin

Hey there axon. you look cold... Let me wrap you in my fatty sheath
• Oligodendrocytes are the myelinating cells of the central nervous system (CNS). They are the end product of a cell lineage which has to undergo a complex and precisely timed program of proliferation, migration, differentiation, and myelination to finally produce the insulating sheath of axons.

• The myelin sheath these fellas create to insulate neuronal axons are composed of lipids and proteins
Astrocytes, hardest working stars in the business.

Astrocytes are stellate cells with several protrusions that will make contact with blood vessels, other astrocytes, or as ensheathment of neuronal somas or synapses.

Our covert operatives tell us that most astrocytes contain the protein GFAP, or Glial Fibrillary Acidic Protein, that acts as an intermediate filament and is up-regulated in reactive astrocytes.
Astrocytes have diverse skill sets

- physical and metabolic support for neurons
- detoxification
- guidance during migration
- regulation of energy metabolism
- electrical insulation (for unmyelinated axons)
- transport of blood-borne material to the neuron
- reaction to injury or insult
Microglia, little cells with a big bite

Microglia are the first line of defense in the brain’s immune response.

Our operatives tell us that these microglia are considered brain macrophages, running around and eating the dangerous things in the central nervous system.
Microglia...

I mediate **immune** responses in the CNS by acting as macrophages, clearing cellular debris and dead neurons from nervous tissue through the process of phagocytosis (cell eating)

key in overall brain maintenance-eliminating damaged or unnecessary neurons and synapses, and infectious agents. They’re part of the brain’s immune system.
Glial Cells as Undertakers?! 

Both astrocytes and microglia respond to injury or disease by developing a reactive phenotype that can lead to functional changes resulting in beneficial effects on neurons, such as the removal of damaged or dead cells or reducing oxidative stress.
The Good, The Bad, and The Inflammatory Factors

Both astrocytes and microglia are activated in response to metabolic signals.

BUT!!
Long-term activation can have detrimental consequences... including increasing tissue damage through the release of inflammatory factors like reactive oxygen species & cytokines.
An Intriguing Finding
Glial Cells and Einstein’s Brain

“After his death in 1955, Albert Einstein’s brain was studied by scientists worldwide—all wanting to gain insight into the anatomy of a genius. But it wasn’t until the 1980s when Marian Diamond noticed that Einstein had more glial cells than average. Glia, stemming from Greek for “glue”, was previously thought to have performed a strictly support role for the neurons. Now it is clear that glia may play a more active, non-electrical role in brain activity”
GLIAL CELLS ACT AS METABOLIC SENSORS IN THE BRAIN

- Lipid Transporters
- Hormone Receptors
- Glucose Transporters
- Glutamate Transporter
- Tancytes
Lipid Transporters

• Astrocytes are primary source of lipoproteins--primary control of lipid homeostasis

• Apolipoprotein E most abundant lipid transporter in the CNS (**Also a SATIETY FACTOR in the hypothalamus)

• Peroxisome proliferator activated receptor gamma (PPARγ)

ATP binding cassette transporters (ABCA)
Ketone Bodies

- Produced in the liver from fatty acids

- When the glucose concentration is low the liver breaks down fatty acids to acetyl co-A and eventually ketone bodies to provide an alternative energy source for the body

- Ketone bodies have been shown to have direct effects on energy homeostasis and glucose metabolism by affecting leptin and insulin signaling in the brain

- Monocarboxylate transporter (MCT-1) found on astrocytes to bring ketone bodies

[Chemical structures of Acetone, Acetoacetic acid, and Beta-hydroxybutyric acid]
Pyruvate
(from glycolysis, 2 molecules per glucose)

NAD⁺

CO₂

NADH + H⁺

Acetyl CoA

CoA

Citric acid cycle

FADH₂

FAD

ADP + P₁

ATP

2 CO₂

3 NAD⁺

3 NADH + 3 H⁺
Hormone Receptors

• Astrocytes and microglia express various isoforms of the leptin receptor and insulin receptor

• The distribution of the leptin receptor expression is anatomically specific

• Leptin binding to microglia can change their activation state and affect cytokine production (inflammation!)

• Insulin binding to astrocytes is important for their proliferation, promotes glycogen storage and increases the expression of glutamate transporters
HYPOTHALAMUS

MICROGLIA

CYTOKINE PRODUCTION

Y = Leptin Receptor

Y = Insulin Receptor

○ = Leptin
○ = Insulin

ASTROCYTE

• Astrocyte Proliferation
• Glycogen Storage
• ↑Glutamate transporters
Glucose Transporters

- Glucose stored as glycogen in astrocytes
- There are specialized regions in the brain designed to sense extracellular glucose--these neurons change their firing rate depending on extracellular glucose concentration
- GLUT-1 expressed on astrocytes that surround capillaries
- GLUT-2 expressed in brain areas that help control food intake
- GLUT-3 mainly expressed in neurons--how they get their energy

Astrocytes take up glucose and do anaerobic respiration (lactic acid fermentation) to form lactate as an alternative energy source.
Glutamate Transporters

- Also known as excitatory amino acid transporters (EEATs)
- GLT-1 is the glutamate transporter found almost exclusively in astrocytes
- GLAST is the glutamate aspartate transporter expressed in glia
- Glutamate transport modulated synaptic transmission and inhibits excitotoxicity
- Glutamate uptake activates astrocyte intracellular glycolysis increasing lactate production and secretion
Glutaminase

Presynaptic neuron

Reduced flux

Gln synthase

GFAP expression

GFAP+ glial cells

Spillover

mGluR1 or 5

Excitotoxicity

Glu clearance

Nature Reviews Neuroscience
Tanycytes

- Glial cells present in the lower portion and floor of the third ventricle
- Express glucose sensing genes (GLUT2, glucokinase, MCT-1/4)
- Express a wide range of receptors (neuroendocrine control?)
A

MCT1
MCT2
MCT4
GLUT2
GK

β1d

III-V

β1v

B

CSF Glucose

GLUT2 Glucose-6-P

Piruvate LDH Lactate

MCT4

β1d-tanyocyte

Neurotransmitters secretion

Satiety

GE neuron

C

CSF Glucose

GLUT2 Glucose-6-P

MCT1 Lactate

β1v-tanyocyte

GI neuron

MCT2 Lactate

Silent neuron

K+ Cl−
IMPLICATION OF GLIAL CELLS IN METABOLIC DISRUPTIONS

- Metabolic disorders, such as genetic obesity and diet-induced obesity, have helped reveal the role that glial cells play in metabolism.

- Another interesting point to look at is the effect caloric restriction and physical exercise have on glial cells even when NO metabolic disorders are present.
Physical Activity and Caloric Restriction

- Excessive intake of high fat foods increases oxidative rates in the organism and can cause detrimental effects.

  - Prolonged activation of astroglia and microglia can have damaging effects, such as the release of inflammatory factors.
  - Dietary restriction also restores the rate of neurogenesis in obese mice and reduce the age-related astrogliosis in the hypothalamus.
    ● This gliosis is often related to neuronal dysfunction in chronic neurodegenerative diseases
Physical Activity and Caloric Restriction

- Physical exercise reduces fatty acid stores, which helps reduce the stress that glial cells undergo.

- Also increases protection/improvement of neurological functions by diverse mechanisms including increasing important neurotrophic factors and antioxidants

  - Neurotrophic factors are proteins that promote growth, survival and differentiation of neurons

  - Antioxidant effects in the brain are highly coupled to astrocyte activity, since astrocytes are the main defence against excitotoxicity and other fatal cell states
Genetic Obesity: Leptin Signaling Deficient Models

- Recall: *ob/ob* and *db/db* mice.
  - *ob/ob* mice: cannot produce leptin
  - *db/db* mice: cannot produce leptin receptors
- These mice have a reduction in brain weight and in hypothalamic glial proteins such as GFAP and ApoE, which act as mediator of the inhibitory effects of leptin.
- *ob/ob* mice also have more excitatory, compared to inhibitory, synapses on NPY and POMC neurons.
Leptin deficiency and Glial cells

- In obese mice, the number of synaptic inputs to POMC neurons in the hypothalamus is inversely correlated to GFAP protein levels and astrocyte coverage of POMC neurons.

- Treatment with leptin can modulate the morphology of astrocytes in ARC, increasing the length of their projections, which decreases the synaptic protein concentrations.

- Therefore, astrocytes regulate synaptic inputs to the hypothalamic neurons that control metabolism simply through undergoing a structural change that occurs in response to
Genetic Obesity: The Agouti Viable Yellow Mouse Model ($A^{Vy}$)

- The agouti gene helps determine whether a mammal’s coat is banded (agouti) or of a solid color (non-agouti)

- $A^{Vy}$ mutation leads to melanocortin receptor signaling deficits.

- Mice with this mutation exhibited 2 main phenotypical features:
  - Agouti coat color
  - Adult-onset obesity
Genetic Obesity: The Agouti Viable Yellow Mouse Model ($A^v_y$)

- Onset of obesity in adulthood in these mice is associated with region-specific up-regulation of astrocytic LepR expression.

  - In Hypothalamus:
    - Neurons show reduction of LepR expression
    - Astrocytes show increase of LepR expression

- When astrocyte activity is inhibited, neuronal leptin signaling was enhanced.
The Agouti gene plays a crucial role in determining fur color in mice. When the gene is methylated, the agouti mRNA is briefly made during development and then silenced for the remainder of the mouse's life. This results in a healthy mouse with brown fur.

When the Agouti gene is not methylated, the agouti gene is continually active, producing mRNA across the mouse's lifespan. This leads to a mouse with yellow fur; however, it also develops obesity and diabetes during adulthood.
Diet-Induced Obesity

- Obesity induces chronic low-grade inflammation in diverse tissues, including the hypothalamus.
  - This results in alterations in insulin and leptin sensitivity.

- Microglia and Astrocytes promote central inflammatory responses.
  - Central inflammation is also a response to infection and other insults. The similar mechanism and increase of proinflammatory cytokines can induce a negative energy balance.
Diet-Induced Obesity

• Long-term HFD:
  – increases number and size of glial cells (gliosis)
  – reduces neurogenesis
  – promotes astrocyte coverage of specific neuronal populations and blood vessels

• Metabolic factors derived from HFD (such as saturated FAs) directly induce reactive gliosis and the release of pro-inflammatory cytokines in astrocytes

• Mice with diet-induced obesity (DIO) exhibit lipid imbalance in the hypothalamus, resulting in increased...
HFD

FAs
KB

Microglia

IL-6, IL-1β

Neuron

POMC

Survival in neurons involved in the metabolism

Astrocyte

GLUT-1

ABCA-1 (?)

MCT1

ApoE

GFAP

PPARγ (?)

PPARγ (?)

IL-6, TNFα

LepR
• Much more investigation is needed to understand the pivotal role glial cells play in the development of obesity.

• Some of the Glial cells functions and hormonal responses include...

• Neuronal output is closely associated to astrocytic functions throughout the brain; however, astrocytes are not identical in all brain areas, nor are neuronal functions.

• The hypothalamic gliosis associated with obesity could be one of the main causes of altered nutritional sensing in the brain, resulting in further body weight gain and secondary metabolic complications.

Rapidly accumulating evidence indicates that glial cells play a key role in the development of obesity, with some of their functions and hormonal responses summarized in Fig. 3. Neuronal output is closely associated to astrocytic functions throughout the brain; however, astrocytes are not identical in all brain areas, nor are neuronal functions. The hypothalamic gliosis associated with obesity could be one of the main causes of altered nutritional sensing in the brain, resulting in further body weight gain and secondary metabolic complications. However, much more investigation is needed to understand this process, including the signals involved in its onset and perpetuation.