Emerging role of glial cells in the control of body weight

Cristina García-Cáceres a,c, Esther Fuente-Martín b,c, Jesús Argente b,c,d, Julie A. Chowen b,c,*

ABSTRACT

Glia are the most abundant cell type in the brain and are indispensable for the normal execution of neuronal actions. They protect neurons from noxious insults and modulate synaptic transmission through affectation of synaptic inputs, release of glial transmitters and uptake of neurotransmitters from the synaptic cleft. They also transport nutrients and other circulating factors into the brain thus controlling the energy sources and signals reaching neurons. Moreover, glia express receptors for metabolic hormones, such as leptin and insulin, and can be activated in response to increased weight gain and dietary challenges. However, chronic glial activation can be detrimental to neurons, with hypothalamic astrocyte activation or gliosis suggested to be involved in the perpetuation of obesity and the onset of secondary complications. It is now accepted that glia may be a very important participant in metabolic control and a possible therapeutical target. Here we briefly review this rapidly advancing field.

Keywords: Astrocytes; Gliosis; Metabolic control; Hypothalamus; Obesity

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Paper Overview

* Types of Glia and their known/proposed functions

*Glia's role in metabolic sensing in the brain (Lipid Transporters, Hormone Receptors, Glucose and Glutamate Transporters.)

* Role of Glial cells in metabolic Disruptions (Genetic Obesity, Leptin Signaling deficiency Models, Diet induced Obesity)
What is Glia? Where are they? and What types do we know about?

- Glia-- Greek! for "glue"

- Different from nerve cells.

- The major distinction is that glia do not participate directly in synaptic interactions and electrical signaling.

- Their supportive functions help define synaptic contacts and maintain the signaling abilities of neurons.

- Glia are more numerous than nerve cells in the brain, outnumbering them by a ratio of perhaps 3 to 1.

- The term glia (from the Greek word meaning “glue”) reflects the nineteenth-century presumption that these cells held the nervous system together in some way. The word has survived, despite the lack of any evidence that binding nerve cells together is among the many functions of glial cells.

- Glial roles that are well-established include maintaining the ionic milieu of nerve cells, modulating the rate of nerve signal propagation, modulating synaptic action by controlling the uptake of neurotransmitters, providing a scaffold for some aspects of neural development, and aiding in (or preventing, in some instances) recovery from neural injury.

CNS Glia

**Microglia:**
remove waste, function as part of the immune system

**Macroglia:**

**Oligodendrocytes** - Build myelin sheaths that surround/insulate axon, assist neuronal connectivity

**Astrocytes** - blood brain barrier assistance, linked to blood flow in brain, involved in neuronal circuits and nutrition

**Ependymal cells** - creation/secretion of cerebrospinal fluid

**Radial glia** - neuronal progenitors, involved with synaptic plasticity
PNS Glia

Schwann cells- Myelination to peripheral nervous system axons

Satellite cells- can help regulate the external/chemical environment, highly sensitive to inflammation

Enteric glial cells- related to homeostasis and muscular digestive processes
Astrocytes...aka the Big Guns of Glia

- The most numerous cells in mammalian brain, Morphologically/ functionally diverse

- In the adult brain, it is well accepted that astrocytes influence multiple aspects of synaptic transmission by maintaining extracellular homeostasis (Parpura and Haydon 2009). As a result, astrocytes are critical to promoting neuronal survival in the context of neuroinflammation (Saijo et al. 2009) and hypoxia (Vangeison and Rempe 2009)

- likely that these cells are involved with many neurological diseases

- Very controversial, but astrocytes may even engage in information processing (like neurons)
Microglia

Microglia are considered macrophages BUT can to switch to activated state assisting neurons in similar ways as astrocytes.

Both of these cells can have beneficial effects on neurons unless there is long term activation.

Origin of microglia is debatable (either neuroepithelia or monocytes).

Astrocytes and microglia have been shown to be activated in response to metabolic signals.
Glia and All their Glory!
Glial Activation

- Glial activation AKA gliosis --- is a process by which astrocytes and microglia develop a hypertrophic (overgrowth/activation) reactive phenotype.
- Most astrocytes contain an exclusive protein called glial fibrillary acidic protein (GFAP)== acts as an intermediate filament and is up-regulated in reactive astrocytes.
- Microglia—like macrophages that can switch to an activated state undergoing structural and function transformations depending on conditions ad stress.
- Both astrocytes and microglia respond to injury or disease by developing this reactive phenotype that can lead to functional changes—can be beneficial to the brain since there is a clearance of damaged or dead cells, or reducing oxidative stress (Recall Dr. B's "chemistry" show of free radicals lol)
Brain Sensitivity to Metabolic Fluctuations

- These metabolites are transported into and within the CNS mainly by astrocytes. Energy requirements are met depending on the types of nutrients available with astrocytes playing a crucial role in this process by modulating local environment of specialized nutrient sensing neurons in the HYPOTHALMAUS.
Glia, Sleep, and Toxins
Lipid Transporters

• Apolipoprotein E (ApoE) in the most abundant lipid transporter in CNS
• produced mainly by astrocytes
• circulating long-chain fatty acids act as signals of nutrient surplus in the hypothalamus.


Hypothalamic fatty acid metabolism: a housekeeping pathway that regulates food intake.
López M¹, Lelliott CJ, Vidal-Puig A.

Abstract
The hypothalamus is a specialized area in the brain that integrates the control of energy homeostasis. More than 70 years ago, it was proposed that the central nervous system sensed circulating levels of metabolites such as glucose, lipids and amino acids and modified feeding according to the levels of those molecules. This led to the formulation of the Glucostatic, Lipostatic and Aminostatic Hypotheses. It has taken almost that much time to demonstrate that circulating long-chain fatty acids act as signals of nutrient surplus in the hypothalamus. Moreover, pharmacological and/or genetic inhibition of fatty acid synthase, AMP-activated protein kinase and carnitine palmitoyltransferase 1 results in profound decrease in feeding and body weight in rodents. The molecular mechanism behind these actions depends on changes in the cellular pool of malonyl-CoA and fatty acyl-CoAs. Current evidence also suggests that this pathway may play a major role in the physiological regulation of feeding, by integrating hormonal and nutrient-derived signals in the hypothalamus. Here, we summarize what is known about hypothalamic fatty acid metabolism and feeding control and provide future directions for research. Understanding these molecular mechanisms could provide new targets for the treatment of obesity and related disorders.
Lipid Transporters continued...

Normal conditions astrocytes are the primary source of lipoproteins that enable synaptogenesis, synaptic remodeling, and axonal growth.

Inhibitory effects of leptin on feeding are partially mediated through ApoE, central ApoE levels are reduced in both fasting and obesity can be restored by leptin treatment.

A critical sensor of lipid concentrations in the brain we have yet to talk about is the Peroxisome Proliferator-Activated Receptor gamma (PPARγ), which is expressed by astrocytes and neurons.
PPARγ involved in central regulation of energy metabolism when you are leptin resistant.

- demonstrated that HFD intake -> induces PPARγ expression in HYPOTHALAMUS -> reduces ROS production in POMC neurons -> alters the ability to inhibit food intake in lean mice on HFD.

- ATP-binding cassette transporters (ABCA) also participate in cellular lipid processes in the brain. These transporters are expressed by both astrocytes and neurons and mediate the release of ApoE-containing glial lipoproteins such as cholesterol.
PPARγ Global Effects

Metabolic organs

Immune system
- Dendritic cell: ↑Lipid metabolism, ↑Insulin sensitization, ↑Activation, ↑Migration
- Treg cell: ↑Insulin sensitization, ↓Inflammation
- Macrophage: ↓Inflammation, ↑M2 or M1

Skeletal muscle
- ↑Glucose-stimulated insulin secretion

Pancreas
- ↑Glucose-stimulated insulin secretion

Liver
- ↑Lipid storage, ↑Gluconeogenesis

White adipose
- ↑Adipogenesis, ↑Lipid metabolism, ↑Glucose homeostasis, ↑Remodeling, ↑Browning

Brown adipose
- ↑Adipogenesis, ↑Lipid metabolism

Heart
- ↑Growth, ↑Lipid storage, ↓Inflammation

Kidney
- ↑Sodium and fluid retention, ↓Diabetic nephropathy

Bone
- ↓Osteoblastogenesis, ↑Osteoclastogenesis

Brain
- ↑Food intake, ↓Inflammation

Side effects
Ketone Bodies

Ketone bodies (can be taken up from the bloodstream or produced through FA oxidation by astrocytes,) are another important energy source for the brain.

Ketone bodies have been shown to have direct effects on energy homeostasis and glucose metabolism through modulation of both leptin and insulin signaling in the hypothalamus.
Ketone Bodies continued....

The main transporter of ketone bodies into and out of cells in the CNS is monocarboxylate transporter (MCT)-1.

Brain MCT-1 levels can be enhanced by HFD intake in response to the increased concentration of circulating ketone bodies.
Hormone Receptors Revisited

ASTROCYTES express various isoforms of the leptin receptor!

Leptin resistance could be due to impaired transport of leptin across the blood-brain barrier or the reduction of leptin signaling due to presence of suppressors of leptin.

diet-induced obesity results in opposite changes of leptin receptor (LepR) in hypothalamic neurons and astrocytes, with an increase being found in these glial cells and a decrease in neurons suggests that both cell types are involved in central leptin responsiveness.
Not all equal

Figure 1 in paper

ME = Median Eminence  □ PVN = Paraventricular Nucleus  □ Hippo = Hippocampus □ CTX = Cortex □ Arc = Hypothalamic Arcuate Nucleus
Figure 1-7  Major subdivisions of the human hypophysis (the neurohypophysis and the adenohypophysis) and their relationship to the brain. The pars tuberalis, pars distalis, and pars intermedia all are part of the adenohypophysis. In adult humans, the pars intermedia is often absent. OC, optic chiasma (nerves from the eyes). Anterior is to the left.
Glucose Transporters

Glucose is the primary metabolite for the brain and is stored in astrocytes as glycogen to safeguard against hyperglycemia.

Astrocytes also participate in glucose transport and metabolism by modulating peripheral and central glucose levels and providing glucose to the extracellular space in the brain for uptake by neurons.

Astrocytes are the main metabolizers of glucose in the brain...
GLUT-1 Receptors

Expressed by astrocytes surrounding capillaries

Hyperglycemia reduces GLUT-1 expression in hypothalamic glial cells

Affects the ability of the hypothalamus to regulate systemic glucose levels

diabetes-related hyperglycemia reduces GLUT-1 expression in hypothalamic glial cells.

Astrocytes, through GLUT-1 and GLUT-2, capture and store glucose as glycogen from which they produce lactate that is transferred to neurons as an energy substrate.
Astrocytes in action

Fig. 2: Schematic representation of glucose and glutamate transport, metabolism and secretion by astrocytes and neurons. The glutamate/glutamine cycle is tightly coupled to glucose oxidation in astrocytes, which then release lactate to be taken up by neurons and be oxidized. Lac: lactate; Pyr: pyruvate; Glu: glutamate; MCT: monocarboxylate transporter; GLAST: glutamate/aspartate transporter; GLUT: glucose transporter; GS: glutamine synthetase; Gin: glutamine.
A closer look at the synapse

Leptin can modulate the morphology of astrocytes in the arcuate nucleus, increasing the length of their projections, which is associated with a decrease in synaptic protein concentrations.
Implication of Glial Cells in Metabolic Disruptions

- Concentration of metabolic nutrients in plasma affects the brain
- When levels are too low or too high this can have negative effects on target cells

- Glial cells play a huge factor in the inflammatory process
- Expressing metabolite sensors
- Modulating neuron environment
Genetic Obesity

- ob/ob mice are leptin resistant
- db/db mice have global mutations in leptin receptor
- Lack of leptin signaling results in reduction of hypothalamic glial proteins
- ob/ob mice have more excitatory synapses on NPY and POMC neurons
- Leptin affects astrocyte morphology

Remember?

NPY/AgRP neurons also inhibit POMC neurons via synaptic release of the neurotransmitter GABA. ARC, arcuate nucleus; LepRb, leptin receptor; Mc3r/Mc4r, melanocortin-3/4 receptor.

The hypothalamic ARC contains neuropeptide Y and agouti-related peptide (NPY/AgRP) neurons that stimulate food intake and are inhibited by leptin, and proopiomelanocortin (POMC) neurons that reduce food intake and are stimulated by leptin.

Morton, G. J. and Schwartz, M.
The Agouti Viable Yellow Mouse Model

Mice express two different phenotypic features: adult onset obesity and agouti coat color

Vary from ob/ob mice who are leptin deficient

Neuronal reduction of LepR expression in hypothalamus but and increase of LepR expression in astrocytes

When astrocyte activity inhibited, leptin signaling is restored

In case you were curious...
Diet-Induced Obesity

Communication between inflammatory/metabolic cells plays a huge factor in obesity

obesity = Inflammation (especially in brain) = changes in leptin/insulin sensitivity

Inflammatory response primarily promoted by microglia/astrocytes
Long term exposure to HFD exceeds glial ability to protect
Why is oxidative stress bad?

Neural disorders (Alzheimers, Parkinsons)

“Hypothalamic inflammation is now thought to be an important process in both the development and perpetuation of obesity and glial cells are a fundamental player in these inflammatory processes” (p. 37)

Exercise can help reduce toxicity to the brain, along with neurological function improvement and antioxidants (all of the factors reduce oxidative stress)
Fun Fact

Einstein's Brain
"Now we can see scores of ways in which astrocytes could be involved in many cognitive processes," Fields says. "And now it's not so crazy to find that there were abnormally high numbers of astrocytes in the parts of Einstein's brain involved in imagery and mathematical ability and that sort of thing."

-Doug Fields, a brain researcher at the National Institutes of Health.