Neuroendocrine

BRIEFING

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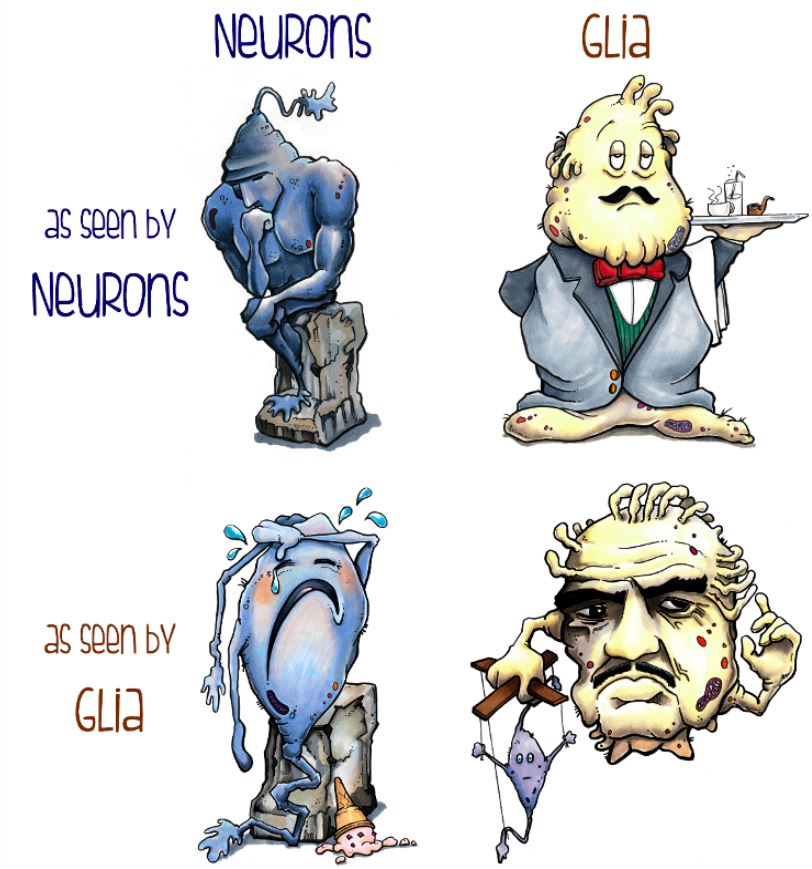
SUMMARY

Glia is the collective term for a class of non-neuronal cells in the brain. First described in the 1850's by Rudolf Virchow, these cells were thought to hold neurons in place, and not have much function beyond this. In the last 35 years it is increasingly being appreciated that glia, including the subclass astroglia, play an important role in behaviour and health, including in neuroendocrinology.

Astroglia - rising stars in neuroendocrinology



A brief history

The central nervous system (CNS) controls behaviours essential for sustaining life. Historically, the role of glia in regulating physiology and behaviour has been under-appreciated. Glia evolved concurrently with the CNS and are present throughout the animal kingdom from nematode worms, up to humans. Loss of astroglia results in neurodegeneration and paralysis, while depletion of other glial subclasses causes axonal damage, seizures, ataxia, and weight loss. In contrast to neurons, glia swiftly repopulate the CNS after ablation and reverse any adverse effects seen. The restoration of function upon repopulation suggests a vital role in orchestrating information transduction in the brain beyond just supporting neuronal survival. These studies provided compelling evidence that glia play a critical integrative role the CNS, leading to the discovery that they are involved in conveying information

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in many essential processes, including multiple neuroendocrine systems. The role of astroglia as a key constituent of the blood-brain barrier allows them to respond rapidly and directly to peripheral stimuli, including hormones. They express receptors for many hormones, and influence neuronal communication by mechanisms including: regulating neurotransmitter availability via modulation of production, uptake from the synaptic cleft, and recycling; releasing gliotransmitters; regulating synaptic ensheathment and stability; and controlling access to the CNS through modulating the permeability of the blood brain barrier.

Food for thought

Multiple hormones regulate food intake through acting on distinct neuronal subsets. Perhaps two of the best known hormones being leptin and ghrelin. Via receptors expressed in the CNS, leptin activates hypothalamic pro-opiomelanocortin (POMC) neurons and inhibits neuropeptide Y/agouti-related protein (NPY/AgRP) neurons to reduce feeding. Ghrelin, via growth-hormone secretagogue receptor 1 (GHSR-1), activates hypothalamic NPY/AgRP neurons, increasing feeding. Experiments in rodents indicate astroglia also play a role in regulating when and how much they eat. Astroglia express both the leptin receptor and GHSR-1. As such, they can respond directly to circulating leptin and ghrelin. Loss of leptin receptors from astroglia prevents the appetite supressing effects of leptin and promotes ghrelin-induced feeding in mice, suggesting a role for astroglia in integration of hormonal cues regulating feeding. Both diet-induced and genetic obesity increase astroglial expression of leptin receptors. Interestingly, extended exposure of astroglia to leptin promotes rearrangement of the cytoskeletal protein, glial fibrillary acidic protein (GFAP), and increases astroglial process length. This increases ensheathment of POMC neurons by astroglia, leading to physical disruption of neuronal synapses that reduce feeding behaviours. Overexposure to leptin may contribute to the development of obesity through these actions. This demonstrates the importance of astroglia in leptin signalling.

The appetite stimulating hormone ghrelin can also directly impact astroglial activity. Ghrelin increases GFAP, glucose and glutamate transporter expression in astroglia. This increases uptake of glucose and glutamate, leading to changes in astroglial metabolism and neurotransmitter turnover. Artificial activation of astroglial intracellular calcium signalling (using chemogenetic technology) reduces nocturnal feeding and ghrelin-induced food intake while promoting leptin-induced satiety, possibly through inhibiting AgRP neurons. However, another research group using a similar methodology found that AgRP neurons were excited by astroglial calcium signalling, and this increased food intake. These differences may be due to in the activation state of astroglia in these studies.

Keeping blood sugars in check

Emerging evidence suggests that astroglia play an integral role in maintaining circulating blood glucose levels, partly through regulation of food intake, but also by direct glucose sensing, and mediating the glucoregulatory hormone release and action. Insulin reduces blood sugar when it is too high by promoting storage of glucose as glycogen or fat inside cells. Conversely, adrenaline and glucagon are important in increasing blood glucose when it is too low, through driving breakdown of glycogen and fat. Release of these hormones is regulated partially by astroglia. Experiments in the hindbrain of rodents show that calcium signalling is induced in astroglia by insufficient glucose. This signalling is essential for activation of neighbouring catecholamine neurons, which are important for the release of adrenaline in response to low glucose. Further to this, loss of glial energy metabolism reduces the body's ability to respond appropriately to low blood glucose. Loss of the glucose sensing glucose transporter, GLUT2, from all brain cells prevents the breakdown of astroglial glycogen stores during low blood glucose. This response can be restored by re-expression of GLUT2 in astroglia, demonstrating that astroglial glucose sensing is sufficient for maintaining glucose homeostasis. Loss of insulin receptors from astroglia also disrupts the response to glucose availability and reduces POMC neuronal signalling which is normally stimulated by insulin, and induction of diabetes activates astroglia in mice. This suggests that astroglia integrate information from the endocrine system and nutrient levels to maintain glucose homeostasis.

Much more work to be done

Astroglia are also involved other neuroendocrine systems including reproduction, the hypothalamic-pituitary-adrenal axis, circadian rhythms and the thyroid axis. There are many unknowns regarding the role of astroglia in all of these systems, including the ones discussed here. Further to this, much of what is known is mainly from rodent experiments. Fully understanding the function of astroglia in these systems in humans is essential in the development of better treatments of neuroendocrine diseases as they play an integral role.

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