The Role of Glia in Stress

Polyamines and Brain Disorders

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KEYWORDS

• Stress • Brain disorders • Glia • Polyamines

KEY POINTS

- Polyamines (PAs) are one of the principal differences between glia and neurons, because they are stored, but not synthesized, almost exclusively in glial cells, from which they can be released to regulate neuronal synaptic activity.
- PAs have not yet been a focus of much glial research.
- PAs affect many neuronal and glial receptors, channels, and transporters.
- PAs are key elements in the development of many diseases and syndromes, thus forming the rationale for PA-focused and glia-focused therapy for these conditions.

GLIA VERSUS NEURONS

Ramón y Cajal[1] predicted how glia could help in health and disease by saying that glia are "insulating the neurons and switching their signaling." His work has been analyzed by many scientists.[2–9] Ramón y Cajal knew that glia were more than just connective tissue but could never prove this. He was able to highlight novel features of glial cells. These observations can be considered to be the discovery of the importance of glia as the second brain. Ramón y Cajal, who has been considered by many to be the father of modern neuroscience, made a principal glial discovery: he visualized what are now known as radial glial cells (RGCs). Recent studies have shown that these cells are of ectodermic origin, which means that RGCs are universal precursors for both neurons and glia. This finding broke the dogma that glia and neurons have separate origins and lineages.[10] Then came the studies that neurogenesis was observed in adult human[11] and rat[12] brains, shattering yet another dogma, that neurogenesis was absent in the mature brain.

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Abbreviations	
A/N ratio	Ratio of astrocytes to neurons
AChR	Acetylcholine receptor
AMPAR	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
ATP	Adenosine triphosphate
Ca	Calcium
CA	Cornu ammonis area
Ca^{2+}	Extracellular calcium
Cl^{+}	Extracellular chloride
CNS	Central nervous system
CSF	Cerebral spinal fluid
Cx	Connexin
G/N ratio	Ratio of glial cells to neurons
Glu	Glutamate
H^{+}	Extracellular hydrogen
Ir K = Kir	Inwardly rectifying potassium
K^{+}	Extracellular potassium
Na^{+}	Extracellular sodium
NMDA	*N*-Methyl-D-aspartate
NMDAR	*N*-Methyl-D-aspartate receptor
OCT	Organic cation transporter
ODC	Ornithine decarboxylase
Panx	Pannexin
PAs	Polyamines
PUT	Putrescine
RGCs	Radial glial cells
SPD	Spermidine
SpdS	Spermidine synthase
SPM	Spermine
TRPV1	Transient receptor potential cation channel, subfamily V, member 1

There is increasing evidence that RGCs build the brain by accommodating in the inner and outer subventricular zone to send their processes into the ventricular zone. RGCs show polarity and are the stem cells of the developing brain.[13–16] Several morphologically distinct subtypes of RGCs in fetal macaque neocortex produce neurons and are guides for the migration of neural progenitors.[17]

Therefore, there are many different types of glial cells that are of RGC origin: NG-2, astrocytes, oligodendrocytes, tanycytes (in whole brain), Müller glia (in retina), and Bergmann glia (in cerebellum), as well as ependymal cells (in the ventricular surface). These cells represent the major neuroglial population in the adult central nervous system (CNS). On the other hand, peripheral glial cells, such as Schwann cells, satellite glia (in the sympathetic, parasympathetic, and sensory ganglia), enteric glia (in the ganglia of the digestive system), and pituicytes (astrocytic glia in the posterior pituitary), are also types of neuroglia. Although there are the microglia (mesodermal origin), which are macrophages in the brain, in this review, the microglia are not discussed. One of the major differences between glia and neurons is accumulation of biogenic polyamines; astrocytes expressing arginine decarboxylase can produce agmatine, a principal element in brain PA-exchange, and therefore, glial cells can be agmatine reservoirs.[18] In general, the ratio of astrocytes to neurons (A/N) increases in evolution with increasing brain size,[19] and the highest glial cell (G) to neuron (G/N) ratio is found in brainstem,[20] where the most important controls of body functions occur, for example control of respiration.[21,22] On the other hand, there is also evidence that the frontal cortex has the highest G/N ratio. RGCs, as well as astrocytes, are filled with the