Contents

Preface xvii
About the Authors xxi
Abbreviations xxv
About the Companion Website xxxii

1 History of Neuroscience and the Dawn of Research in Neuroglia 1
1.1 The miraculous human brain: localising the brain functions 1
1.2 Cellular organisation of the brain 10
1.3 Mechanisms of communications in neural networks 14
  1.3.1 Electrical/ionic nature of excitability 14
  1.3.2 Chemical signalling between neural cells 26
1.4 The concept of neuroglia 27
1.5 Beginning of the modern era 47
1.6 Concluding remarks 49
References 49

2 General Overview of Signalling in the Nervous System 59
2.1 Intercellular signalling: wiring and volume modes of transmission 59
2.2 Cellular signalling: receptors 62
2.3 Intracellular signalling: second messengers 67
2.4 Calcium signalling 67
  2.4.1 Cellular Ca\(^{2+}\) regulation 69
2.5 Concluding remarks 72

3 Neuroglia: Definition, Classification, Evolution, Numbers, Development 73
3.1 Definition of neuroglia as homeostatic cells of the nervous system 74
3.2 Classification 75
3.3 Evolution of neuroglia

3.3.1 Evolution of astrocytes

(i) Nematoda: neuroglia in Caenorhabditis elegans

(ii) Annelida: astroglia in leech

(iii) Arthropoda: astrocytes in Drosophila and other insects

(iv) Neuroglia in early Deuterostomia (Hemichordata and Echinodermata)

(v) Neuroglia in low vertebrates

(vi) Glial advance in higher vertebrates

3.3.2 Evolution of myelination

3.3.3 Evolution of microglia

3.4 Numbers: how many glial cells are in the brain?

3.5 Embryogenesis and development of neuroglia in mammals

3.5.1 Macrogial cells

3.5.2 Astroglial cells are brain stem cells

3.5.3 Peripheral glia and schwann cell lineage

3.5.4 Microglial cell lineage

3.6 Concluding remarks

References

4 Astroglia

4.1 Definition and heterogeneity

4.2 Morphology of the main types of astroglia

4.3 How to identify astrocytes in the nervous tissue

4.4 Astroglial syncytial networks

4.4.1 Gap junctions, connexons and connexins

4.4.2 Astroglial networks

4.5 Physiology of astroglia

4.5.1 Membrane potential and ion distribution

4.5.2 Ion channels

(i) Potassium channels

(ii) Voltage-operated sodium channels (Na<sub>v</sub>)

(iii) Calcium channels

(iv) Transient receptor potential or TRP channels

(v) Anion/chloride channels

(vi) Aquaporins

4.5.3 Receptors to neurotransmitters and neuromodulators

(i) Glutamate receptors

(ii) Purinoceptors

(iii) γ-aminobutiric acid receptors (GABA) receptors

(iv) Glycine receptors

(v) Acetylcholine receptors

(vi) Adrenergic receptors

(vii) Serotonin receptors

(viii) Histamine receptors

(ix) Cannabinoid receptors
4.5.4 Astroglial membrane transporters 152
(i) ATP-dependent transporters 153
(ii) Secondary transporters 154

4.5.5 Calcium signalling in astroglia 156
(i) Endoplasmic reticulum provides for Ca\(^{2+}\) excitability of astrocytes 156
(ii) Store-operated Ca\(^{2+}\) entry in astrocytes 158
(iii) Ionotropic Ca\(^{2+}\) permeable receptors in astrocytes 158
(iv) Sodium/calcium exchanger in astroglial Ca\(^{2+}\) signalling 159
(v) Mitochondria in astroglial Ca\(^{2+}\) signalling 159
(vi) Calcium waves in astrocytes 159

4.5.6 Sodium signalling in astrocytes 164

4.5.7 Release of neurotransmitters and neuromodulators from astroglia 165
(i) Exocytotic release of neurotransmitters from astrocytes 167
(ii) Diffusional release of neurotransmitters from astrocytes 172
(iii) Transporter-mediated neurotransmitter release from astrocytes 173
(iv) Astrocytes as a main source of adenosine in the CNS 174
(v) Physiological role of astroglial release of neurotransmitters 174

4.6 Functions of astroglia 175

4.6.1 Developmental function: neurogenesis and gliogenesis 176
(i) Embryonic neurogenesis and gliogenesis 176
(ii) Neurogenesis and gliogenesis in the adult brain 178

4.6.2 Neuronal guidance 179

4.6.3 Regulation of synaptogenesis and control of synaptic maintenance and elimination 182

4.6.4 Structural function: astrocytes define the micro-architecture of the grey matter and create neurovascular units 185

4.6.5 Structural function: astrocytes and the brain-blood barrier 186

4.6.6 Astrocytes regulate brain microcirculation 192

4.6.7 Brain energetics and neuronal metabolic support 195

4.6.8 Astroglia and neuroimaging 200

4.6.9 Ion homeostasis in the extracellular space 200
(i) Astrocytes and extracellular potassium homeostasis 200
(ii) Astrocytes and chloride homeostasis 204
(iii) Astrocytes and extracellular Ca\(^{2+}\) 204
(iv) Astrocytes and regulation of pH 205
(v) Astrocytes and zinc homeostasis 206
4.6.10 Astrocytes and homeostasis of reactive oxygen species 206
4.6.11 Water homeostasis and regulation of the extracellular space volume 207
   (i) Regulation of water homeostasis 207
   (ii) Regulatory volume decrease in astrocytes 208
   (iii) Redistribution of water during neuronal activity and dynamic regulation of the extracellular space 208
4.6.12 Neurotransmitters homeostasis 209
   (i) Astroglia control glutamate homeostasis and glutamatergic transmission in the CNS 209
   (ii) Astroglia and GABA-ergic transmission 213
   (iii) Astroglia and adenosine homeostasis 214
4.6.13 Astroglia in synaptic transmission 215
   (i) The astroglial synaptic compartment: concept of the tripartite synapse 215
   (ii) The astroglial synaptic compartment: concept of the astroglial cradle 219
   (iii) Morphological plasticity of the astroglial synaptic compartment 221
   (iv) What is the role of astroglia in regulation of synaptic transmission? 222
4.6.14 Astroglia and central chemosensation of pH and CO₂ 224
4.6.15 Astrocytes in regulation of systemic sodium homeostasis 224
4.6.16 Astroglia and glucose sensing 225
4.6.17 Astroglia and circadian rhythms 226
4.6.18 Astroglia and sleep 227
4.6.19 Astroglia and control of reproduction 228
4.6.20 Müller glial cells as light guides in retina 228
4.6.21 Astroglia in ageing 228
4.6.22 Astrocytes as a cellular substrate of memory and consciousness? 230
4.7 Concluding remarks 231
References 231

5 Oligodendrocytes 245
5.1 Oligodendrocyte anatomy 247
   5.1.1 The generalised structure of a myelinating oligodendrocyte 247
   5.1.2 Subtypes of myelinating oligodendrocytes 249
   5.1.3 Non-myelinating oligodendrocytes 251
5.2 Myelin structure and function 252
   5.2.1 Myelin and saltatory conduction 252
   5.2.2 Oligodendrocyte-axon interactions and nodes of Ranvier 256
   5.2.3 Myelin structure and metabolism 257
   5.2.4 Myelin biochemistry 258
      (i) Lipids 258
      (ii) Proteins 261
5.2.5 Myelin transport 265

5.3 Physiology of oligodendrocytes 266
  5.3.1 Voltage-operated ion channels 270
    (i) Outwardly rectifying potassium channels 270
    (ii) Inward rectifier potassium channels (Kir) 271
    (iii) Voltage-operated sodium channels (Nav) 272
    (iv) Voltage-operated calcium channels (VOCC, Cav) 272
    (v) Chloride and acid-sensing ion channels (ASIC) 273
  5.3.2 Glutamate receptors 273
    (i) Ionotropic glutamate receptors (iGluRs) 273
    (ii) Metabotropic glutamate receptors (mGluRs) 275
  5.3.3 Purinergic receptors 275
    (i) P1 purinergic receptors 275
    (ii) P2X receptors 276
    (iii) P2Y receptors 276
  5.3.4 GABA receptors 277
  5.3.5 Other neurotransmitter receptors 278
  5.3.6 Transporters and exchangers 279
  5.3.7 Gap junctions 279
  5.3.8 Intracellular calcium 280

5.4 Oligodendrocyte development 283
  5.4.1 Developmental origins of oligodendrocytes 284
  5.4.2 Stages of oligodendrocyte differentiation 284
  5.4.3 Trophic factors and oligodendrocyte differentiation 286
  5.4.4 Regulation of oligodendrocyte differentiation 288
  5.4.5 Axoglial interactions regulating oligodendrocyte differentiation and myelination 293
  5.4.6 Downstream signalling cascades that regulate oligodendrocyte differentiation and myelination 297

5.5 Concluding remarks 299
References 299

6 NG2-glial Cells 321

6.1 Definition of NG2-glia 321

6.2 Structure of NG2-glia 324
  6.2.1 Identification 324
  6.2.2 Morphology and distribution 325
  6.2.3 Relationship of NG2-glia with neuroglial domains 326
  6.2.4 NG2-glia and synapses 326

6.3 Physiology of NG2-glia 327
  6.3.1 Membrane properties 328
  6.3.2 Gap junctional coupling 328
  6.3.3 Voltage-operated ion channels 330
  6.3.4 Neurotransmitter receptors 330
  6.3.5 Neurone-NG2-glial cell signalling at synapses 331
6.4 Proliferation of NG2-glia and generation of oligodendrocytes
6.4.1 Normal adult brain
6.4.2 Are NG2-glia multipotent stem cells?
6.4.3 Response of NG2-glia to injury and demyelination
6.5 Relationship between NG2-glia and CNS pericytes
6.5.1 Identification of pericytes
6.5.2 Developmental origin of pericytes
6.5.3 Pericytes are multipotent stem cells in the adult brain
6.6 Evolution of NG2-glia
6.7 Concluding remarks
References

7 Microglia
7.1 Definition of microglia
7.2 Microglial origin and development
7.3 Morphology of microglia
7.3.1 Morphology in the healthy tissue: resting or surveillant phenotype
7.3.2 Morphology in pathological tissue: activated phenotype
7.3.3 Morphology in the dish
7.3.4 Identification of microglial cells in neural tissues
7.4 General physiology of microglia
7.4.1 Membrane potential and ion distribution
7.4.2 Ion channels in microglia
7.4.3 Calcium signalling in microglia
7.4.4 Neurotransmitter receptors
7.4.5 Receptors for neurohormones and neuromodulators
7.4.6 Cytokines and chemokines receptors
7.4.7 Pattern-recognition receptors
7.4.8 Other receptor systems
7.4.9 Microglial plasmalemmal transporters
7.5 Microglial migration and motility
7.6 Physiological functions of microglia: role in synaptic transmission and plasticity
8 Peripheral Glial Cells

8.1 Peripheral nervous system
8.1.1 Basic structure
8.1.2 Development
8.1.3 The CNS-PNS interface
  (i) Structure of the CNS-PNS interface
  (ii) Development of the CNS-PNS interface
  (iii) CNS-PNS interface in degeneration and regeneration
8.2 Schwann cells
  8.2.1 Schwann cell subtypes
  8.2.2 Development of Schwann cells
    (i) Stages of Schwann cell differentiation
    (ii) Regulation of Schwann cell differentiation
    (iii) Control of myelination
  8.2.3 Axoglial interactions and myelination
    (i) The Schwann cell basal lamina
    (ii) Organisation of nodes of Ranvier in the PNS
    (iii) Schwann cell perinodal microvilli
  8.2.4 PNS myelin structure and biochemistry
    (i) Lipids
    (ii) Proteins
  8.2.5 Physiology of Schwann Cells
    (i) Ion channels and neurotransmitter receptors
    (ii) Ca$^{2+}$ signalling in Schwann cells
    (iii) Schwann cells and pain
8.3 Satellite glial cells
  8.3.1 Organisation of sensory and autonomic ganglia
  8.3.2 Satellite glia in sensory and autonomic ganglia
  8.3.3 Physiology of satellite glia
    (i) Electrical properties
    (ii) Homeostatic function
    (iii) Ca$^{2+}$ signalling
    (iv) Other receptors in SGCs
    (v) Neurotrophic function of SGC
  8.3.4 Injury response of satellite glia
  8.3.5 Sensory satellite glia and pain
8.4 Enteric glia
  8.4.1 Organisation of the enteric nervous system
  8.4.2 Development of enteric glia
  8.4.3 Structure of enteric glia
  8.4.4 Physiology of enteric glia
8.4.5 Functions of EGCs

(i) Homeostatic functions 416
(ii) Barrier function 417
(iii) Immune functions 418
(iv) Enteric glia in intestinal diseases 418

8.5 Olfactory ensheathing cells (OECs)

8.5.1 Organisation and structure of OECs 418
8.5.2 Physiology of OECs 419
(i) Electrical properties 419
(ii) Ca$^{2+}$ signalling 420
8.5.3 OECs facilitate olfactory neurogenesis throughout life 420
8.5.4 OECs and regeneration 421
8.5.5 OECs and remyelination 422

8.6 Concluding remarks

References 422

9 General Pathophysiology of Neuroglia

9.1 Neurological disorders as gliopathologies 431
9.2 Reactive astrogliosis 433
9.3 Wallerian degeneration 439
9.4 Excitotoxic vulnerability of oligodendrocytes: the death of white matter 442
9.5 Activation of microglia 444
9.5.1 Pathological potential of activated microglia 449

9.6 Concluding remarks

References 449

10 Neuroglia in Neurological Diseases

10.1 Introduction 454
10.2 Genetic astrogliopathy: Alexander disease 456
10.3 Stroke and ischaemia
   10.3.1 Glial cell death during ischaemia 460
   10.3.2 Astroglia protect the brain against ischaemia 463
   10.3.3 Astrocytes may exacerbate brain damage in ischaemia 465
   10.3.4 Oligodendrocytes and microglia in stroke 467
10.4 Migraine and spreading depression 467
10.5 CNS oedema 469
   10.5.1 Traumatic oedema 470
   10.5.2 Ischaemic oedema 470
   10.5.3 Oedema in hepatic encephalopathy 471
   10.5.4 Hyponatremia 471
10.6 Metabolic disorders
   10.6.1 Hepatic encephalopathy 471
10.6.2 Congenital glutamine deficiency with glutamine synthetase mutations 472
10.6.3 Pyruvate carboxylase deficiency 472
10.6.4 Niemann-pick type C disease 473
10.6.5 Aceruloplasminemia 473

10.7 Toxic encephalopathies 473
10.7.1 Methylmercury toxic encephalopathy 473
10.7.2 Lead toxic encephalopathy 474
10.7.3 Manganese neurotoxicity 474
10.7.4 Aluminium toxic encephalopathy 474

10.8 Neurodegenerative diseases 474
10.8.1 Post-stroke dementia 475
10.8.2 Amyotrophic lateral sclerosis 477
10.8.3 Wernicke encephalopathy 479
10.8.4 Fronto-temporal, thalamic, HIV-associated and other non-Alzheimer’s type dementias 479
10.8.5 Alzheimer’s disease (AD) 480
   (i) Astrogliosis and astroglial degeneration in AD 482
   (ii) Astroglia and β-amyloid 483
   (iii) The neuro-vascular unit in AD: role for astrocytes 483
   (iv) Metabolic remodelling of astroglia in AD 484
   (v) Microglia in AD 484
10.8.6 Parkinson’s disease 485
10.8.7 Huntington’s disease 486
10.8.8 Infantile neuroaxonal dystrophy 486
10.8.9 Nasu-Hakola disease: microglial pre-senile dementia 486

10.9 Leukodystrophies 487
10.9.1 Megalencephalic leukoencephalopathy with subcortical cysts 487
10.9.2 Vanishing white matter disease 487

10.10 Epilepsy 488
10.11 Psychiatric diseases 490
10.12 Autistic disorders 491
   10.12.1 Autism 491
   10.12.2 Fragile X syndrome 491
   10.12.3 Rett syndrome 491

10.13 Neuropathic pain 492
10.14 Demyelinating diseases 494
   10.14.1 Multiple sclerosis 494
   10.14.2 Neuromyelitis optica 496

10.15 Infectious diseases 496
   10.15.1 Bacterial and viral infections 496
   10.15.2 Human immunodeficiency virus (HIV) infection 497
   10.15.3 Human T-lymphotropic virus type-1 498
   10.15.4 Human herpes virus-6 499
10.16 Peripheral neuropathies 499
  10.16.1 Hereditary neuropathies 499
  10.16.2 Acquired inflammatory neuropathies 500
  10.16.3 Diabetic neuropathies 500
  10.16.4 Leprosy 501

10.17 Gliomas 501
  10.17.1 Glial complications of glioma therapy 504

10.18 Concluding remarks
  References 504

Author Index 513

Subject Index 517