
Contents

1	Introduction	1
	References	5
2	Early History of Purinergic Signalling.	7
2.1	Discovery of Purines and Pyrimidines	7
2.2	Early Studies of the Extracellular Effects of Purines	9
2.3	Early Studies of the Effects of Purines on the Nervous System	11
2.4	Early Studies of Peripheral Effects of Purines	13
2.5	Early Comparative Studies	14
2.6	Discovery of Purinergic Transmission	14
2.6.1	Non-Adrenergic, Non-Cholinergic (NANC) Nerves	14
2.6.2	ATP as a Principal Transmitter	14
2.6.3	ATP as a Cotransmitter	17
2.6.4	ATP as an Excitatory Transmitter in the CNS	19
2.6.5	Adenosine in the Nervous System	20
2.6.6	Neuromodulation by Purines	21
2.7	Receptors for Purines	22
2.7.1	Subdivision into P1 and P2 Purinoceptors	22
2.7.2	History of Adenosine (P1) Purinoceptors	23
2.7.3	History of P2 Purinoceptors	25
2.8	Concluding Remarks: The Expanding Field of Purinergic Signalling in the Past Decade	26
	References	37
3	Purinergic Cotransmission	67
3.1	Peripheral Motor Nerves	68
3.2	Sympathetic Nerves	68
3.3	Parasympathetic Nerves	70
3.4	Sensory-Motor Nerves	70
3.5	Intrinsic Neurons in the Gut and Heart	70
3.6	Nerves in the Brain and Spinal Cord	70
3.7	Physiological Significance of Cotransmission	71

3.7.1	Fast and Slow Cotransmitters: Different Firing Patterns	71
3.7.2	Different Cotransmitters Act on Different Postjunctional Cells.	73
3.7.3	Presynaptic Neuromodulation of Cotransmitter Release	73
3.7.4	Synergism	73
3.7.5	Negative Cross-Talk	74
3.7.6	Cotransmitters and Trophic Factors	74
3.7.7	Excitatory and Inhibitory Cotransmitters	74
3.7.8	False Cotransmitters	74
3.7.9	Coexisting Peptide Acting as a Neuromodulator	74
3.8	Cotransmitter Plasticity: Control of Transmitter Expression	74
3.9	Concluding Remarks	75
	References	75
4	Mechanisms of ATP Release and Inactivation	79
4.1	Introduction: General Principles of Cellular ATP Release	79
4.2	Measuring ATP Release	80
4.2.1	Luciferin–Luciferase Technique	80
4.2.2	Local ATP Measurements: Plasmalemma-Tagged Luciferase	81
4.2.3	Biosensors	82
4.2.4	The Amperometric ATP Biosensor Microelectrodes	83
4.2.5	Atomic Force Microscopy	83
4.2.6	Quinacrine-Based Fluorescence Imaging	83
4.2.7	Other Enzymatic Assays	83
4.3	Mechanisms of ATP Release	84
4.3.1	Exocytosis	84
4.3.2	Diffusional ATP Release: The Role of Plasmalemmal Channels	88
4.3.3	ATP Release Following Cell Damage	93
4.3.4	Physiological ATP Release.	93
4.3.5	Release of Uridine Nucleotides and Nucleotide Sugars	96
4.4	ATP Degradation: Roles for Ectoenzymes	96
4.4.1	Nucleoside Triphosphate Diphosphohydrolases	96
4.4.2	Nucleotide Pyrophosphatases/ Diphosphodiesterases.	102
4.4.3	Alkaline and Acid Phosphatases	102
4.4.4	Ecto-5'-Nucleotidase	103

4.4.5	Other Ecto-Enzymes Involved in Metabolism of Purines	103
4.4.6	Pharmacology of Ectonucleotidases	104
4.5	Adenosine Release	104
4.6	Concluding Remarks	105
	References	105
5	Receptors for Purines and Pyrimidines	119
5.1	Introduction	119
5.2	Adenosine (P1) Receptors	120
5.2.1	Molecular Cloning	120
5.2.2	Molecular Structure	120
5.2.3	Adenosine Receptor Oligomerisation	123
5.2.4	Adenosine Receptors, G-Proteins and Second-Messenger Systems	126
5.2.5	Distribution of Adenosine Receptors: General Overview	126
5.3	P2X Receptors	128
5.3.1	General Principles of Ionotropic Receptor Architecture	128
5.3.2	Molecular Cloning of P2X Receptors	129
5.3.3	Molecular Structure of P2X Receptors	130
5.3.4	P2X Receptors: Biophysics and Pharmacology	134
5.3.5	Distribution of P2X Receptors: General Overview	167
5.4	P2Y Receptors	168
5.4.1	Molecular Structure of P2Y Receptors	168
5.4.2	P2Y Receptor Classification	174
5.4.3	P2Y Receptor Subtypes	176
5.4.4	Molecular Pharmacology: Agonists and Antagonists	190
5.4.5	Molecular Modelling Studies	199
5.4.6	Interactions Between P2Y and Other Receptors	199
5.4.7	P2Y Receptors Distribution: General Overview	204
5.4.8	Gene Activation Regulated by P2Y Receptors	206
5.5	Concluding Remarks	209
	References	209
6	Evolution of Purinergic Signalling	245
6.1	Evolution of Chemical Intercellular Transmission	245
6.2	Tree of Life: Remarks on Taxonomy	246
6.3	Viruses	247
6.4	Bacteria	248

6.5	Eucarya	249
6.5.1	Protozoa (Amoebozoa)	249
6.5.2	Algae	252
6.5.3	Plants	253
6.5.4	Fungi	255
6.5.5	Sponges	256
6.5.6	Metazoa or Animalia	256
6.6	Evolution of the Purinergic Signalling System:	
	Generalisation	278
6.6.1	Ancient Roots of ATP Release Systems.	278
6.6.2	Purinoreceptors	279
6.6.3	Ectonucleotidases	281
	References	284
7	Peripheral Nervous System	307
7.1	Motor Nerves to Skeletal Muscle	307
7.1.1	Skeletal Neuromuscular Junction.	307
7.1.2	Schwann Cells	311
7.2	Autonomic Nervous System	313
7.2.1	Sympathetic Ganglia	314
7.2.2	Parasympathetic Ganglia	317
7.2.3	Enteric Ganglia	319
7.2.4	Autonomic Neuroeffector Transmission	329
7.2.5	Smooth Muscle	334
7.2.6	Heart	363
7.2.7	Other Cell Types	366
7.3	Diseases of Peripheral Nervous System	377
7.3.1	Skeletal Muscle Diseases	377
7.4	Concluding Remarks	388
	References	388
8	Purinergic Signalling in the Central Nervous System	433
8.1	Intercellular Communications in the Central Nervous System	434
8.2	Initial Discoveries of the Central Action of ATP	436
8.3	Mechanisms of ATP Release in CNS	437
8.3.1	Vesicular Release of ATP in the CNS	438
8.3.2	Diffusional Release of ATP	443
8.4	Neuronal P2X Receptors: ATP-Mediated Excitatory Synaptic Transmission	445
8.4.1	P2X Receptors in Central Neurons	445
8.4.2	P2X-Mediated Excitatory Postsynaptic Currents (EPSCs)	453
8.4.3	Multiple Functional Roles of Neuronal P2X Receptors	454

8.5	Neuronal P2Y-Mediated Signalling	462
8.5.1	Distribution of P2Y Receptors in the CNS	462
8.5.2	Functional Role of Neuronal P2Y Receptors	462
8.6	Neuronal Adenosine Receptor-Mediated Signalling. . .	466
8.6.1	Mechanisms of Adenosine Release in CNS	466
8.6.2	Neuronal Adenosine Receptors	468
8.7	Purinergic Signalling in Astroglia	470
8.7.1	P2X Receptors	470
8.7.2	Synaptic Activation of Astroglial P2X Receptors	476
8.7.3	Role of P2X Receptors in Astroglial Signalling	479
8.7.4	P2Y Receptors	482
8.7.5	Adenosine (P1) Receptors	488
8.8	Purinergic Signalling in Oligodendroglia	491
8.8.1	P2X Receptors	491
8.8.2	P2Y Receptors	491
8.8.3	Adenosine Receptors	492
8.9	Purinergic Signalling in Ependymal Cells	492
8.10	Purinergic Signalling in Microglia	493
8.10.1	Purinergic Signalling Controls Microglial Function	493
8.10.2	Microglial P2X Receptors	495
8.10.3	P2X ₇ Receptors and Microglial Function . . .	495
8.10.4	Microglial P2Y Receptors	499
8.10.5	Microglial Adenosine Receptors	501
8.11	Purinergic Transmission in Various Regions of the CNS	501
8.11.1	Cortex	501
8.11.2	Hippocampus	502
8.11.3	Cerebellum.	504
8.11.4	Basal Ganglia	505
8.11.5	Midbrain	506
8.11.6	Thalamus	506
8.11.7	Habenula	506
8.11.8	Spinal Cord	507
8.12	Purinergic Transmission and Higher Brain Functions	508
8.12.1	Learning and Memory	508
8.12.2	Sleep and Arousal	509
8.12.3	Locomotion	510
8.12.4	Feeding	511
8.12.5	Mood and Motivation	511

8.13	Central Control of Autonomic Function.	512
8.13.1	Brain Stem and Ventrolateral Medulla: Central Chemoreception.	512
8.13.2	Trigeminal Mesencephalic Nucleus.	513
8.13.3	Trigeminal Subnucleus Caudalis.	513
8.13.4	Area Postrema.	514
8.13.5	Locus Coeruleus.	514
8.13.6	Nucleus Tractus Solitarius.	514
8.13.7	Motor and Sensory Nuclei.	516
8.13.8	Hypothalamus.	516
8.13.9	Circadian Rhythms.	519
8.14	Purinoreceptors in Neuropathology.	519
8.14.1	Brain Injury and Neuroprotection.	519
8.14.2	Neuroinflammatory Disorders.	523
8.14.3	Neurodegenerative Diseases.	524
8.14.4	Epileptic Seizures.	528
8.14.5	Neuropsychiatric Disorders.	529
8.14.6	Neuropathic Pain.	531
8.14.7	Migraine.	534
8.14.8	Cancer.	534
8.14.9	Encephalitis.	534
8.14.10	Abnormalities in Central Control of Peripheral Function.	535
8.15	Concluding Remarks.	535
	References.	535
9	Sensory Nerves.	583
9.1	Introduction.	583
9.2	Sensory Neurons.	584
9.2.1	Dorsal Root Ganglia.	586
9.2.2	Nodose Ganglia.	588
9.2.3	Trigeminal Ganglia.	589
9.2.4	Petrosal Ganglia.	591
9.2.5	Retinal Ganglia.	591
9.2.6	Intramural Enteric Sensory Neurons.	592
9.3	Peripheral Sensory Nerve Terminals.	593
9.3.1	Carotid Body.	594
9.3.2	Lung.	595
9.3.3	Gut.	598
9.3.4	Urinary Bladder.	598
9.3.5	Skin, Muscle and Joints.	598
9.3.6	Heart.	599
9.4	Purinergic Mechanosensory Transduction.	599
9.4.1	Urinary Bladder.	599
9.4.2	Ureter.	601

9.4.3	Gut	601
9.4.4	Uterus	601
9.4.5	Tooth Pulp	602
9.4.6	Tongue	602
9.4.7	Skin and Joints	602
9.5	Purinergic Sensory Pathology	602
9.5.1	Pain	602
9.5.2	Bladder Diseases	606
9.5.3	Gut Disorders	607
9.5.4	Arthritis	607
9.5.5	Respiratory Diseases	608
9.6	Development of Purinergic Sensory Signalling	608
9.7	Evolution of Purinergic Sensory Mechanisms	611
9.8	Concluding Remarks	612
	References	614
10	Special Senses	627
10.1	Eye	627
10.1.1	Retina	627
10.1.2	Lens	638
10.1.3	Ciliary Body and Choroid	638
10.1.4	Trabecular Meshwork and Schlemme Cells: Regulation of Intra-ocular Pressure	641
10.1.5	Iris	642
10.1.6	Conjunctiva	642
10.1.7	Cornea	643
10.1.8	Vasculature	643
10.1.9	Lacrimal Gland and Tears	644
10.1.10	Development	645
10.1.11	Diseases of the Eye	646
10.2	Ear	650
10.2.1	Cochlea	652
10.2.2	Vestibule	655
10.2.3	Endolymph and Peilymph	656
10.2.4	Development and Ageing	656
10.2.5	Diseases of the Ear	657
10.3	Nasal Organs	658
10.4	Tongue	661
10.5	Concluding Remarks	663
	References	663
11	Ontogeny of Purinergic Neurotransmission	681
11.1	Central Nervous System	681
11.2	Peripheral Ganglia	687
11.3	Retina	688
11.4	Skeletal Neuromuscular Junction	690

11.5	Gastrointestinal Tract	693
11.6	Cardiovascular System	694
11.7	Lung	696
11.8	Urinary Bladder	696
11.9	Inner Ear	697
11.10	Vas Deferens and Seminal Vesicles	697
11.11	Other Organs	698
11.12	Embryonic Stem Cells.	698
11.13	Concluding Remarks	701
	References	702
Index		709

Purinergic Signalling and the Nervous System

Burnstock, G.; Verkhatsky, A.

2012, XVIII, 715 p. 135 illus., 46 illus. in color.,

Hardcover

ISBN: 978-3-642-28862-3