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The role of purinergic pathways in the pathophysiology of gut diseases: Pharmacological modulation and potential therapeutic applications

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ABSTRACT

Gut homeostasis results from complex neuro-immune interactions aimed at triggering stereotypical and specific programs of coordinated mucosal secretion and powerful motor propulsion. A prominent role in the regulation of this highly integrated network, comprising a variety of immune/inflammatory cells and the enteric nervous system, is played by purinergic mediators. The cells of the digestive tract are literally plunged into a "biological sea" of functionally active nucleotides and nucleosides, which carry out the critical task of driving regulatory interventions on cellular functions through the activation of P1 and P2 receptors. Intensive research efforts are being made to achieve an integrated view of the purinergic system, since it is emerging that the various components of purinergic pathways (i.e., enzymes, transporters, mediators and receptors) are mutually linked entities, deputed to finely modulating the magnitude and the duration of purinergic signaling, and that alterations occurring in this balanced network could be intimately involved in the pathophysiology of several gut disorders. This review article intends to provide a critical appraisal of current knowledge on the purinergic system role in the regulation of gastrointestinal functions, considering these pathways as a whole integrated network, which is capable of finely controlling the levels of bioactive nucleotides and nucleosides in the biophase of their respective receptors. Special attention is paid to the mechanisms through which alterations in the various compartments of the purinergic system could contribute to the pathophysiology of gut disorders, and to the possibility of counteracting such dysfunctions by means of pharmacological interventions on purinergic molecular targets.

Abbreviations: *A-317491*, 5-[[[(3-Phenoxyphenyl)methyl][(1S)-1,2,3,4-tetrahydro-1-naphthalenyl]amino]carbonyl]-1,2,4 benzenetricarboxylic acid; *ARL-67156*, 6-*N*,*N*-Diethyl-D-β,γ-dibromomethylene ATP; *ATL-801*, *N*-[5-(1-cyclopropyl-2,6-dioxo-3-propyl-2,3,6,7-tetrahydro-1*H*-purin-8-yl)-pyridin-2-yl]-*N*-ethyl-nicotinamide; *ATP-γ-S*, Adenosine-5′-(γ-thio)-triphosphate; IBDs, inflammatory bowel diseases; *ATPDase*, adenosine 5′-triphosphate diphosphohydrolase; ATPase, adenosine 5′ triphosphatase; *ADPβS*, adenosine 5-O-(2-thiodiphosphate); *β-NAD*, β-nicotinamide adenine dinucleotide; *CD39*, Ectonucleoside triphosphate diphosphohydrolase 1; *CD73*, ecto-5′-nucleotidase; *CFTR*, cystic fibrosis transmembrane conductance regulator; *CGS 21680*, 4-[2-[[6-Amino-9-(*N*-ethyl-β-D-ribofuranuronamidosyl)-9*H*-purin-yl]amino]ethyl] benzene propanoic acid; *CNTs*, concentrative nucleoside transporters; *DRG*, dorsal root ganglion; *DSS*, dextran sulfate sodium; *ENS*, enteric nervous system; *ENTs*, equilibrative nucleoside transporters; *ERK*, Extracellular signal-regulated kinase; *GP515*, {4-amino-1-(5-amino-5-deoxy-1-β-D-ribofuranosyl)-3-bromo-pyrazol[3,4-*d*] pyrimidine; *FK352*, [(R)-1-[(E)-3-(2-phenylpyrazolo[1,5-a]pyridin-3-yl) acryloyl]-piperidin-2-yl acetic acid; *DPCPX*, 8-cyclopentyl-1,3-dipropylxanthine; *IB-MECA*, 1-Deoxy-1-[6-[[(3-iodophenyl)methyl]amino]-9*H*-purin-9-yl]-*N*-methyl-β-D-ribofuranuronamide; *IBS*, irritable bowel syndrome; *ICC*, interstitial cells of Cajal; *IJP*, inhibitory junction potential; *IPANs*, intrinsic primary afferent neurons; *L-NAME*, Nω-nitro-L-arginine methylester; *MR2279*, (1R,2S,4S,5S)-4-[2-Chloro-6-(methylamino)-9H-purin-9-yl]-2(phosphonooxy) bicyclohexane-1-methanol dihydrogen phosphate ester; *MRS 1754*, *N*-(4-Cyanophenyl)-2-[4-(2,3,6,7-tetrahydro-2,6-dioxo-1,3-dipropyl-1*H*-purin-8-yl)phenoxy]-acetamide; *MRS2179*, 2′-Deoxy-*N*6-methyladenosine 3′,5′-bisphosphate; *MRS2365*, [[(1R,2R,3S,4R,5S)-4-[6-Amino-2-(methylthio)-9H-purin-9-yl]-2,3dihydroxybicyclohex-1-yl]methyl] diphosphoric acid mono ester; *MRS2500*, (1R,2S,4S,5S)-4-[2-Iodo-6-(methylamino)-9H-purin-9-yl]-2(phosphonooxy)bicyclohexane-1-methanol dihydrogen phosphate ester; *NANC*, non-adrenergic non-cholinergic; *NECA*, 1-(6-Amino-9*H*-purin-9-yl)-1-deoxy-*N*-ethyl-β-D-ribofuranuronamide; *NO*, nitric oxide; *NOS*, nitric oxide synthase; *PKC*, protein kinase C; *PPADS*, Pyridoxalphosphate-6-azophenyl-2′,4′-disulfonic acid; *PSB1115*, 4-(2,3,6,7-Tetrahydro-2,6-dioxo-1-propyl-1*H*-purin-8-yl)-benzenesulfonic acid; PSB06126, 1-Amino-4-(1-naphthyl)aminoanthraquinone-2-sulfonic acid; *ROS*, reactive oxygen species; *SNAP*, synaptosomal-associated protein; *SNARE*, N-ethylmaleimide-sensitive factor attachment receptor; *8-SPT*, 8-(p-Sulfophenyl)theophylline hydrate; *TNBS*, trinitrobenzenesulfonic acid; *TNP-ATP*, 2′,3′-O-(2,4,6-Trinitrophenyl) adenosine 5′-triphosphate; *TTX*, tetrodotoxin; *VAMP*, vesicle-associated membrane protein; *VIP*, vasoactive intestinal peptide; *NPY*, neuropeptide Y; *ZM 241385*, 4-(2-[7-Amino-2-(2-furyl)[1,2,4]triazolo[2,3-*a*][1,3,5] triazin-5-ylamino]ethyl)phenol.

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Contents

1. Introduction

The relevance of purine nucleotides/nucleosides in the physiological control of digestive functions was initially appreciated in the early 1970s, when Prof. Geoffrey Burnstock provided evidence that adenosine triphosphate (ATP) and its related nucleotides/nucleosides (i.e., adenosine diphosphate, ADP, adenosine monophosphate, AMP, and adenosine), previously considered merely as ubiquitous biochemical sources of energy, could behave as transmitters at the intestinal level (Burnstock, 1976; Burnstock et al., 1970). Subsequently, despite harsh criticisms, the existence of specific receptors, designated as purinergic receptors and classified as P1 and P2 (for adenosine and ATP/ADP,

Table 1
Purinergic receptors and selective ligands.

Receptor	Endogenous ligand	Signaling	Selective agonists	Selective antagonists	Non selective agonists	Non selective antagonists
P2 receptors						
$P2X_1$	ATP	Ligand-gated ion channel	L-β,γ-meATP,	NF023, NF449, PPNDS, Ro 0437626, MRS2159, phenol red	2-MeSATP, α,β-meATP, PAPET-ATP, CTP, BzATP, Ap_5A, HT-AMP	TNP-ATP, Ip_5I, NF 279, NF157, IsoPPADS, suramin
$P2X_2$	ATP	Ligand-gated ion channel	Ap_4A	–	2-MeSATP, ATPγS	NF279, PPADS, RB-2, suramin, TNP-ATP
$P2X_3$	ATP	Ligand-gated ion channel	D-β,γ-Me-ATP	A317491, RO3, NF110, spinorphin, TC-P 262	2-MeSATP, α,β-meATP, BzATP, Ap_5A, HT-AMP, PAPET-ATP	TNP-ATP
$P2X_4$	ATP	Ligand-gated ion channel	–	Phenolphtalein, 5-BDBD	2-MeSATP, ATPγS, CTP	BBG, TNP-ATP
$P2X_5$	ATP	Ligand-gated ion channel	–	–	2-MeSATP, α,β-meATP, BzATP	
$P2X_6$	ATP	Ligand-gated ion channel	–	–	α,β-meATP	Iso-PPADS, TNP-ATP
$P2X_7$	ATP	Ligand-gated ion channel	–	A804598, A839977, decavanadate, KN62, KN-04, BBG, chelerythrine, oxidized-ATP, A740003, A438079, AZ10606110, AZ11645373	2-MeSATP, BzATP	
$P2Y_1$	ADP	G_q	MRS 2365	MRS2500, MRS2279, MRS2179, NF157	BzATP, ADPβS, 2-MeSADP, PIT	
$P2Y_2$	ATP/UTP	G_q	UTPγS, Ap4A, 2-thioUTP, MRS2768, PSB1114	–		
$P2Y_4$	UTP	G_q	UTPγS, MRS4062	ATP		
$P2Y_6$	UDP	G_q	5-iodoUDP, PSB0474, MRS2693, MRS2957, 5-OMe-UDP, UDP	MRS2578		
$P2Y_{11}$	ATP	G_q	NF546, ARC67085, NAADP, NAD^+	NF157, NF340		NF157,
$P2Y_{12}$	ADP	G_i	–	AR-C 66096, ATP, ARL66096, ticlopidine, clopidogrel	2-MeSADP, ADP	
$P2Y_{13}$	ADP	G_i	2-MeSADP	MRS2211	2-MeSADP	
$P2Y_{14}$	UDP-glucose	G_i	MRS2690	–		
P1 receptors						
A_1	Adenosine	$G_{i/0}$	R-PIA, GW493838, CHA, CPA, CCPA, TCPA, 2′-Me-CCPA, GR79236, selodenoson, capadenoson, tecadenoson, GS9667	PSB36, DPCPX, CPFPX, KW-3902, toponafylline, FK-453, SLV320	NECA	
A_{2A}	Adenosine	G_s	CGS21680, ATL-313, ATL-146e, UK-432097, sonedenoson, binodenoson, regadenoson	KW6002, CSC, MSX-2, SYN-115, BIIB014, ST-1535, SCH442416, ZM241385, SCH58261, preladenant	NECA	
A_{2B}	Adenosine	G_s, G_q	Bay 60-6583	PSB603, PSB 1115, ATL 802, LAS8096, MRS1754, CVT-6883, MRE-2029-F20	NECA	
A_3	Adenosine, inosine	G_s, G_q	CF-101, CF-102, CF-502, CO 608,039, HEMADO, MRS 5151, IB-MECA	KF26777, PSB-10, PSB-11, MRE-3008-F20, MRS1220, VUF5574, MRS1523, MRS1191	NECA	