Review

Adenosine and bone metabolism

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Bone is a dynamic organ that undergoes continuous remodeling while maintaining a balance between bone formation and resorption. Osteoblasts, which synthesize and mineralize new bone, and osteoclasts, the cells that resorb bone, act in concert to maintain bone homeostasis. In recent years, there has been increasing appreciation of purinergic regulation of bone metabolism. Adenosine, released locally, mediates its physiologic and pharmacologic actions via interactions with G protein-coupled receptors, and recent work has indicated that these receptors are involved in the regulation of osteoclast differentiation and function, as well as in osteoblast differentiation and bone formation. Moreover, adenosine receptors also regulate chondrocyte and cartilage homeostasis. These recent findings underscore the potential therapeutic importance of adenosine receptors in regulating bone physiology and pathology.

Purinergic receptors

Extracellular purines (adenosine, ATP, and ADP) and pyrimidines (UDP and UTP) comprise a family of molecules that exert a variety of important physiological functions via the activation of cell-surface receptors termed purine receptors. Although the physiologic effects of adenosine and ATP have been recognized for over 80 years [1] purinergic receptors were first described in 1976 [2] and two subfamilies were identified: P1 or adenosine receptors, and P2 or nucleotide receptors (Box 1). In this review, we will primarily discuss the role of adenosine receptors in regulating bone metabolism.

P1 or adenosine receptors

Adenosine is generated both intracellularly and extracellularly from the hydrolysis of adenine nucleotides (Figure 1), and acts locally to exert its extracellular physiologic and pharmacologic effects via activation of specific cell-surface G protein-coupled receptors (A_1, A_{2A}, A_{2B}, and A_3), proteins with unique pharmacological profiles, tissue distributions, and effector coupling [3]. Because extracellular adenosine levels differ among tissues and in response to varying degrees of stress, the basal stimulation of each receptor by endogenous agonist varies [4]. Human adenosine receptors share 39–61% sequence homology with each other and 8–11% homology within the transmembrane domains (TMI–TMVII) of P2Y receptors [5]. Classically, adenosine receptors (AR) have been divided on the basis of their ability to inhibit (A_1R and A_3R) or stimulate (A_{2A}R and A_{2B}R) adenylyl cyclase activity [6–8]. The increase in cAMP levels following activation of A_{2A}R and A_{2B}R, or the inhibition of cAMP generation by A_1R, leads to activation of other signaling systems such as several types of K^+ or Ca^{2+} channels, phospholipase Cβ, and mitogen-activated protein kinases (MAPKs) [3,4,9]. In some cell types, such as DDT_1MF-2, HEK93, and CHO cells, adenosine receptors activate MAPKs – serine/threonine-specific kinases, which

Glossary

Adenosine: purine nucleoside form of a molecule of adenine attached to a ribose sugar moiety via a β-N_9-glycosidic bond.
Adenosine receptors: a class of purinergic receptors comprising G protein-coupled receptors with adenosine as the endogenous ligand.
Bone formation (osteogenesis): begins during prenatal development and persists throughout adulthood. There are two ways in which osteogenesis occurs: intramembranous ossification and endochondral ossification. Osteoblasts are mainly involved in intramembranous ossification whereas osteoclasts are involved in bone remodeling following formation.
Bone resorption: the process by which osteoclasts break down bone.
M-CSF: macrophage colony-stimulating factor, a secreted cytokine which influences hematopoietic stem cells to differentiate into macrophages or other related cell types.
Osteoarthritis: a group of mechanical abnormalities involving degradation of joints, including articular cartilage and subchondral bone. When bone surfaces become unprotected by cartilage, bone can be damaged, resulting in a decreased movement secondary to pain, regional muscle atrophy, and lax ligaments.
Osteoblasts: mononuclear cells responsible for bone formation. They are specialized mesenchymal cells that express bone sialoprotein and osteocalcin. Osteoblasts produce a matrix of osteoid, which is composed mainly of type I collagen.
Osteoclasts: large, multinucleated cells derived from hematopoietic stem cells that are responsible for resorbing bone by removing the mineralized matrix and breaking up the organic bone. Osteoclasts are formed by the fusion of cells of the monocyte–macrophage cell line and are characterized by high expression of tartrate-resistant acid phosphatase (TRAP) and cathepsin K.
Osteoprotegerin (OPG): also known as osteoclastogenesis inhibitory factor (OCIF), or tumor necrosis factor receptor superfamily member 11B (TNFRSF11B), OPG a decoy protein that binds to RANK and inhibits osteoclast differentiation.
RANKL: receptor activator of NF-κB ligand, also known as tumor necrosis factor ligand superfamily member 11 (TNFSF11), TNF-related activation-induced cytokine (TRANCE), osteoprotegerin ligand (OPGL), and osteoclast differentiation factor (ODF), is critical for adequate bone metabolism. It is secreted by the osteoblasts and serves to activate osteoclasts by binding to its specific surface-bound membrane receptor RANK (receptor activator of NF-κB).
Rheumatoid arthritis: a chronic, systemic autoimmune inflammatory disorder that principally affects synovial joints. The pathogenesis of rheumatoid arthritis involves inflammation of the synovium with destruction of the articular cartilage and bone. Extra-articular manifestations of rheumatoid arthritis include inflammatory lesions of the lungs, pericardium, pleura, and sclera.

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Box 1. P2 or nucleotide receptors

There are two classes of P2 receptors: ligand-gated ion channels (P2X receptor, ionotropic receptors) and G protein-coupled receptors (P2Y receptors, metabotropic receptors) [2,5,69]. P1 and P2 receptors have different pharmacological profiles and tissue distributions. Classically, P2X receptors are potently activated by stable ATP analogs such as α,β-methylene ATP (α,β-meATP) and β,γ-meATP, whereas P2Y receptors are activated by 2-methylthio ATP (2MeSATP) [70,71]. To date, seven mammalian P2X receptors, $P2X_{1-7}$, and eight P2Y receptors $P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$, $P2Y_{11}$, $P2Y_{12}$, $P2Y_{13}$, and $P2Y_{14}$, have been cloned, characterized pharmacologically, and accepted as valid members of the P2 receptor family [72] (Table I). P2X receptors are ATP-gated ion channels which mediate rapid (within 10 ms) and selective permeability to cations such as Na^+, K^+, and Ca^{2+} [73].

P2Y receptors are expressed on the surface of all cell types. Nevertheless, $P2Y_{11}$, $P2Y_{12}$, $P2Y_{13}$, and $P2Y_{14}$ receptors are known for their specific role in the stimulation of platelet aggregation and vascular tone [74]. P2Y receptors are primarily coupled by G_q to phospholipase C (PLC), with subsequent formation of inositol triphosphate (IP3) and diacylglycerol (DAG). $P2Y_{13}$and $P2Y_{14}$ are also negatively coupled to adenylate cyclase through G_i, and $P2Y_1$ and $P2Y_2$ are also coupled to the RhoA/ROCK-I and ERK1/2 pathways [75].

Table I. P2 or nucleotide receptors

Receptor		Agonist (rank potency)	Antagonist (rank potency)	Transduction mechanism	Refs
P2X	$P2X_1$	Bz-ATP >> 2-MeSATP ≥ ATP > α,β-MeATP >> ADP	NF449 > IP5I > TNP-ATP > RO 0437626 > NF279, NF023, RO1, MRS2159	Intrinsic cation channel (Ca^{2+} and Na^+)	[2,5,69–73]
	$P2X_2$	ATP ≥ ATPγS ≥ 2-MeSATP >> α,β-meATP	PSB-1011 > RB2, isoPPADS > PPADS > Suramin, NF770, NF778, aminoglycoside	Intrinsic ion channel (particularly Ca^{2+})	[2,5,69–73]
	$P2X_3$	Bz-ATP >> 2-MeSATP > ATP = α,β-MeATP	TNP-ATP, isoPPADS > A317491 > NF110 > PPADS, Ip5I, phenol red, RO4, RN-1838, Spinorphin, AF353	Intrinsic cation channel	[2,5,69–74]
	$P2X_4$	UDP = 5Br-UDP >> UTP > 2-MeSADPBz-ATP = ATP	5-BDBD >> TNP-ATP, PPADS > BBG, Paroxetine, phenolphthalein,	Intrinsic ion channel (especially Ca^{2+})	[2,5,69–74]
	$P2X_5$	ATP >> α,β-meATP > ADP	BBG > PPADS, Suramin	Intrinsic ion channel	[2,5,69–74]
	$P2X_6$	ATP > 2-MeSATP > ADP		Intrinsic ion channel	[2,5,69–74]
	$P2X_7$	Bz-ATP > ATP ≥ 2-MeSATP >> α,β-meATP	KN62, BBG, KN04, MRS2427, O-ATP, RN-6189, AZ10606120, A740003, A-438079, A-804598, GSK-1370319, Compound 31 (GSK), AZD-9056, CE-224535	Intrinsic cation channel and a large pore with prolonged activation	[2,5,69–74]
P2Y	$P2Y_1$	(*N*)-mc-2-MeSADP > 2-MeSADP > ADP = ADPβS >> ATP2-MeSATP > ADP > ATP2-MeSADP = 2-MeSATP > ADP2-MeSATP > 2Cl-ATP > ATP	MRS2500 > MRS2279 > MRS2179, PIT, A3P5P	G_q/G_{11} PLCβ activation	[2,5,69–71,73–75]
	$P2Y_2$	UTP = ATP > INS37217 > Ap4A > ATPγS > UTP ≥ ATP > ADP > 2-MeSATP UTP > ITP > ATP > UDP UTP = ATP > CTP > GTP UTP = ATP > Ap_4A	AR-C126313 > Suramin > RB2, PSB-716, MRS2576	G_q/G11 and possibly G_i PLCβ activation	[2,5,69–76]
	$P2Y_4$	UTP > UTPγS UTP = ATP = ITP = Ap_4A UTP = ATP	ATP (human) > Reactive Blue 2 > Suramin, MRS2577, PPADS	G_q/G_{11} and possibly G_i PLCβ activation	[2,5,69–71,73,74]
	$P2Y_6$	UDP = 5Br-UDP >> UTP > 2-MeSADP UDP > UTP > ADP > 2-MeSATP UDP > UTP > ADP > 2-MeSATP	MRS2578 > Reactive Blue 2, PPADS, MRS2567, MRS2575 (human)	G_q/G_{11} PLCβ activation	[2,5,69–71,73,74]
	$P2Y_{11}$	ARC67085 ≥ ATPγS = BzATP > ATP > 2-MeSATP ADPβS = 2-MeSADP ≥ 2-MeSATP > ATP	NF157 > Suramin > RB2, 50-AMPS, NF340, AMP-α-5,	G_q/G_{11} and G_s PLCβ activation	[2,5,69–71,73,74]
	$P2Y_{12}$	2-MeSADP > ADP >> (N)-mc-2-MeSADP 2-MeSADP >> ADP, ATP 2-MeSADP > ADP > ATP 2-MeSADP > ADP > ADPβS	AR-C69931MX > AZD6140, INS50589 > RB2 > 2-MeSAMP, AR-C66096, CT50547, PSB-0413, carbanucleosides, MRS2395, AR-C67085	G_i inhibition of adenylate cyclase	[2,5,69–71,73,74]
	$P2Y_{13}$	2-MeSADP ≥ ADP > ADPβS ADP > 2-MeSADP >> ATP ADP = 2-MeSADP = ADPβS > ATP	AR-C69931MX > AR-C67085 > MRS2211, 2-MeSAMP	G_i	[2,5,69–71,73,74]
	$P2Y_{14}$	UDP-glucose > UDP-galactose		$G_{i/o}$	[2,5,69–71,73,74]