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MEETING REPORTS

Adenosine Receptors as Targets for Drug Discovery. National (215th) Meeting of American Chemical Society Dallas, TX, March 29 to April, 2, 1998.

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This Meeting report briefly summarizes presentations at the session on adenosine at the American Chemical Society meeting held on March 30, in Dallas, Texas. The session was chaired by P. R. McGuirk.

R. Olsson (Univ. Florida, Tampa, FL) reviewed the four known members of the adenosine class of receptors – A_1, A_{2A}, A_{2B}, and A_3. These are G-protein-coupled, 7-transmembrane-segment receptors linked to adenylate cyclase and phospholipase C. The ligands that interact with these receptors can be classified as direct (agonists and antagonists) or indirect (transport inhibitors, adenosine kinase inhibitors, and adenosine deaminase inhibitors).

The A_1 receptor is a potential therapeutic target for a number of disorders, including: atrioventricular (AV) node block and supraventricular tachyarrhythmias (adenosine agonist); AV block of cardiac arrest (adenosine antagonist); bradyarrhythmias in transplanted hearts (adenosine antagonist); diuresis (adenosine antagonist). Caffeine and theophylline are existing adenosine antagonists. Synthetic compounds include 1,3-diisopropyl-8-cyclopentylxanthine (CPX, C-101).

The A_{2A} receptor is a therapeutic target for coronary vasodilatation (adenosine agonist) and Parkinson's disease (adenosine antagonist). The existing known antagonists include CGS 15943, ZM 241385, and SCH 58261.

The A_{2B} receptor is a therapeutic target for bacterial diarrhea (through activation of a colonic chloride current) and allergic reactions. There are no known selective agonists or antagonists.

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The A_3 receptor is a therapeutic target for allergic reactions and testicular function. There are significant species differences between the rat and human A_3 receptors. Known antagonists include MRS 1191, MRS 1220, and L 249313.

Transport inhibitors include nitrobenzylthioinosine, thioguanosine, and R 75231; these are relatively nonselective in their actions.

Russell Petter (Biogen, Cambridge, MA) discussed CVT 124 [BG9719], a highly selective A_1 antagonist that is being developed as a diuretic for the treatment of congestive heart failure. It inhibits reabsorption of Na^+ and Cl^- in the proximal tubule and in the distal tubule it appears to be K^+ neutral. The K_I value for the human receptor is 0.45 nM, it is stereoselective, and it is selective for the A_1 subtype, with K_I values for A_{2A}, A_{2B}, and A_3 receptor subtypes of 1100, 198, and 4500 nM, respectively. Other known antagonists include FK 453 and KW 3902. In phase I clinical trials with 29 normal volunteers with an intravenous infusion of up to 0.3 mg/kg over 1 h Na^+ excretion increased from 64 to 152 mEq without effect on heart rate or blood pressure. The peak effect was seen within 1 h.

Marlene Jacobson (Merck, West Point, PA) discussed the A_3 receptor that is negatively coupled to adenylyl cyclase. She pointed out unique species differences between rats and humans in both expression and pharmacology. The human receptor is expressed at the highest levels in lung tissue, but not on mast cells; in the rat it is expressed in the testis and mast cells. There are significant differences in pharmacology, despite significant sequence homology. The rat receptor is not sensitive to xanthine antagonists. The A_3 receptor requires high adenosine concentrations for activation (10^{-6} M) suggesting a role under conditions of ischemic stress when adenosine concentrations rise significantly. Potential therapeutic targets include allergy (antagoni st) and inflammation, neuroprotection, and cardioprotection (agonist). Additionally, a role in cancer has been suggested, since adenosine inhibits killer lymphocyte adhesion to colon carcinoma cells. The A_3 receptor is highly expressed in human lung and its density is increased in inflamed tissue. Non-xanthine antagonists include CGS 15943, CP 66713, SCH 58261, MRS 1220, and L 249,313.

L 249,313 is approximately 1200-fold selective over A_1 receptors and some 230-fold selective over A_2 receptors. An A_3 knockout revealed no effect on development, fertility or growth, no effect on A_1 and A_{2A} receptor density, and no effect on mean arterial pressure or heart rate. In this model, adenosine failed to release hexosaminidase from bone marrow-derived mast cells.

Mark Erion (Metabasis Therapeutics, San Diego, CA) observed that it was in 1963 that Berne advanced the hypothesis that adenosine is cardioprotective and despite many years of work on adenosine receptors, only adenosine is used clinically. Erion discussed the thesis that adenosine regulatory agents affecting nucleoside transporters, adenosine deaminase, and adenosine kinase (metabolism) or 5′-nucleotidase and AMP deaminase (adenosine biosynthesis) should be site and event specific since these agents should have their greatest effects when adenosine concentrations are elevated due to pathological conditions.

GP 3269 is an adenosine kinase inhibitor that is highly bioavailable and has nanomolar potency, high selectivity, and antiseizure activity. Adenosine kinase inhibitors have an advantage over adenosine agonists since they have little effect on the cardiovascular system (relative to cyclopentyladenosine). GP 3269 is anti-inflammatory and

inhibits neutrophil adhesion and tumor necrosis factor-α production. AMP deaminase blockade serves to divert AMP into the adenosine rather than the inosine pathway. Under normoxic conditions, AMP concentrations are approximately micromolar and there is low flux through the pathway; under hypoxic conditions, AMP levels approximate millimolar amounts and there is high flux. Under hypoxic conditions, but not under resting conditions, at 10^{-10} M GP 3269 inhibits AMP deaminase and has site and event specificity. A transition-state approach was employed in the design of AMP deaminase inhibitors. The natural product, coformycin, has a K_I value of 10^{-11} M against adenosine and phosphate deaminases. Analogs were derived from coformycin in which the ribose moiety was replaced by arylcarboxylic acids, including tetranhydronaphthylethylcarboxylate, with a K_I value of 10^{-8} M that is selective for AMP deaminase.

Michael Williams (Abbott Laboratories, Chicago, IL) reviewed the P_1 (adenosine) and P_2 (purinergic) receptors, describing their nomenclature, structural, and functional classifications. He argued that workers in this field faced a number of challenges including: selecting novel targets with unmet medical needs; developing compounds where side effect liability can be overcome; using research tools to characterize targets more clearly; and proof of principle for targeted mechanisms.

The chemical names of the compounds listed in this report are:

CGS 15943: 5-amino-9-chloro-2-(2-furyl)[1,2,4]triazolo[1,5-c]quinazoline

ZM 241385: (4-(2-[7-amino-2-(2-furyl)[1,2,4]triazolo[2,3-a][1,3,5]triazin-5-yl)amino]ethyl)phenol

SCH 58261: 5-amino-7-(2-phenylethyl)-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine

MRS 1191: 2-methyl-6-phenyl-4-phenylethyl-1,4-(+/–)dihydropyridine-3,5-dicarboxylate

MRS 1220 (M-228): 9-chloro-2-(2-furanyl)-5-[(phenylacetyl)amino][1,2,4]triazolo[1,5-c]quinazoline

L 249,913: 6-carbomoxymethyl-5,9-dihydro-9-methyl-2-phenyl[1,2,4]triazolo[5,1]naphthyridine

R 75231: 2-(aminocarbonyl)-N-(4-ammo-2,6-dichlorophenyl)-4-[5,5-bis(4-fluorophenyl)pentyl]-1-piperazinyl acetamide trihydrochloride-2,5-hydrate

CVT 124: 1,3-dipropyl-8-[2-(5,6-epoxynorbonyl)]xanthine, S-enantiomer

FK 453: (+)-(R)-[(E)-3-(2-phenylpyrazolo[1,5-a]pyridin-3-yl)acryloyl]-2-piperidine ethanol

KW 3902: 1,3-N,N-diethyltetrahydropyrimidin-2-one, 4,5-imidazolyl-2′-norbornane

CP 66713: 4-amino-8-chloro-1-phenyl[1,2,4]triazolo[4,3-a]quinaxoline

GP 3269: 7-(5-deoxy-, beta, -D-ribofuranosyl)-N-(4-fluorophenyl)-5-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine