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Molecular Mechanisms Coronary Flow Regulation by Adenosine

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Assistant Dean for Research
Robert C. Byrd Professor
Dept. Physiology and Pharmacology
and Basic Pharmaceutical Sciences
WVU Health Sciences Center
Morgantown, West Virginia, USA

Clinical Applications

- Adenocard® (Adenosine)-SVT
- Adenoscan® (Adenosine)-myocardial perfusion imaging

Investigational Use: Treatment during PTCA (to reduce the myocardial reperfusion injury in patients with myocardial infarction.

- Better myocardial salvage and thus prevention of left ventricular remodeling, ejection fraction, decreased infarct size, and ST-segment elevation resolution.

- But not conclusive and needs larger clinical trials.

0022-3565/80/2143-0496$02.00/0
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Vol. 214, No. 3
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Binding of Adenosine to the Crude Plasma Membrane Fraction Isolated from Dog Coronary and Carotid Arteries[1]

PURABI DUTTA[2] and S. JAMAL MUSTAFA
Department of Pharmacology, College of Medicine, University of South Alabama, Mobile, Alabama
Accepted for publication May 20, 1980

ABSTRACT

Dutta, Purabi and S. Jamal Mustafa: *Binding of adenosine to crude plasma membrane fraction isolated from dog coronary and carotid arteries.* J. Pharmacol. Exp. Ther. **214:** 496–502, 1980.

In an attempt to elucidate the mechanism of action of adenosine, specific adenosine binding was determined by using plasma membrane rich microsomal fraction of dog coronary and carotid arteries. The binding of adenosine to both coronary and carotid preparations was temperature as well as pH dependent and was inhibited by aminophylline and adenosine nucleotides. Scatchard analysis of the saturable binding data on carotid arteries exhibited a single species of binding sites with a K_d value of 1.34×10^{-6} M and binding capacity of 140 pmol/mg of protein. The first order dissociation rate constant of adenosine binding to carotid preparation was 0.0247 min^{-1}. The nonlinearity of equilibrium binding data (Scatched Plot) and dissociation curve of binding to coronary arteries suggested the presence of more than one population of binding sites. The data suggest that the binding sites located in the microsomal fraction of coronary and carotid arteries possess the basic characteristics of the receptors which might be involved in the vasodilatory action of adenosine.

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Evidence Suggesting an R_a-Type Adenosine Receptor in Bovine Coronary Arteries[1]

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Department of Pharmacology, School of Medicine, East Carolina University, Greenville, North Carolina
Accepted for publication September 24, 1984

ABSTRACT

It has been reported that adenosine has two extracellular membrane receptors depending upon the activation (R_a) or inhibition (R_i) of the adenylate cyclase system. At the R_a site, 5′-N-ethylcarboxamideadenosine is more potent than N^6-L-phenylisopropyladenosine (L-PIA) and the reverse is true for the R_i site. Therefore, the aim of this investigation was to characterize the subtype of adenosine receptor in bovine coronary arteries with the use of several adenosine analogs. The order of potency for several of these analogs was found to be: 5′-N-ethylcarboxamideadenosine > 5′-N-cyclopropylcarboxamideadenosine > L-PIA > N^6-cyclohexyladenosine > 2-Cl-adenosine > adenosine > D-PIA. The concentration-response curves were parallel to each other, which suggests the same receptor site. L-Adenosine, L-5′-N-ethylcarboxamideadenosine, and methyl-N^6-cyclohexyladenosine and 2′-5′-dideoxyadenosine (P site analog) were found to be ineffective in relaxing the bovine coronary arteries. The difference between L- and D-PIA was less than 100-fold. This hierarchy suggested the existence of R_a subtype adenosine receptor in bovine coronary arteries. Both theophylline and 8-phenyltheophylline antagonized the relaxing effect of various analogs and shifted the concentration-response curve to the right in parallel. 8-Phenyltheophylline was severalfold more potent in its antagonistic effect than theophylline. In addition, inosine caused the dilation of both large and small coronary arteries at 1×10^{-4} M and 1×10^{-3} M concentrations (adenosine would cause a similar relaxation at 500-fold less concentration). Inosine dilated the large vessels more than small vessels. 8-Phenyltheophylline (2×10^{-5} M) had no effect on the inosine-induced relaxations in either large or small vessels. Adenosine deaminase rapidly reversed the adenosine-induced relaxation, whereas the reversal of inosine-induced relaxation by nucleoside phosphorylase was slower in onset. These data suggest extracellular sites for their action. However, it is likely that inosine may be causing its effect through some metabolic processes in addition. The data further suggest the existence of an R_a subtype adenosine receptor, which may mediate the physiological relaxation and the existence of an extracellular site for the action of inosine.

- Lexiscan® (A_{2A} selective agonist, regadenoson): approved (April, 2008) myocardial perfusion imaging based on our work for almost 30 years ago.

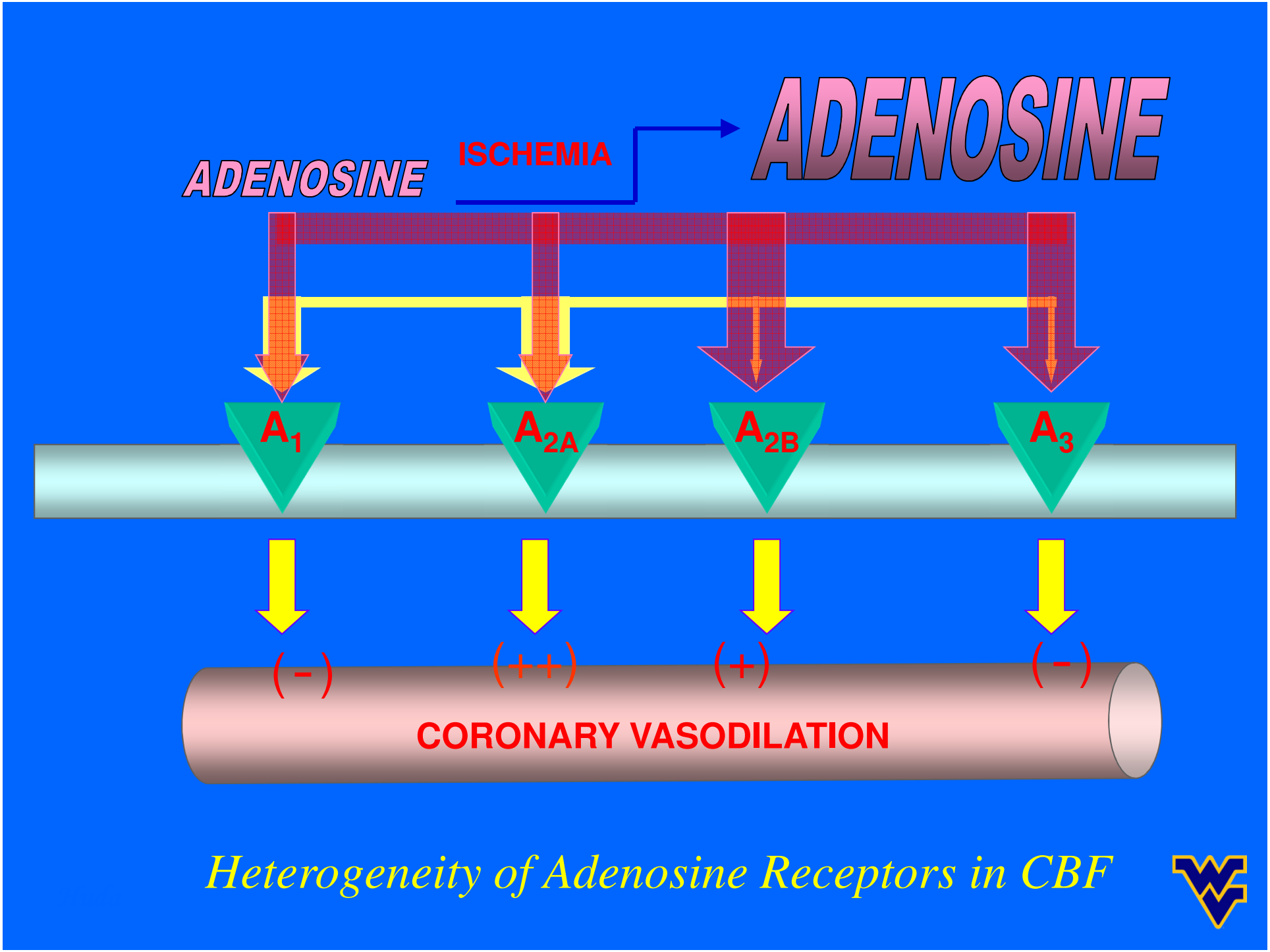


Adenosine Receptor Pharmacology

Receptor Subtype	A_1	A_{2A}	A_{2B}	A_3
Deduced molecular size				
Amino acids	326	410-412	332	320
Kilodaltons	36.7	46.2	36.4	36.6
G-protein coupling	Go, Gi	Gs	Gs	Go, Gi
Agonist potency	CCPA > CPA > NECA >> CGS 21680	CGS 21680 ≥ NECA > CV 1808 > R-PIA > CPA	NECA Bay 60-6583 LUF5835[a]	2-Cl-IBMECA >> R-PIA= NECA >> CGS21680
Antagonists	DPCPX, 8-PST, CPT	ZM 241385, SCH 58261, CSC, KF 17837	MRS-1754 MRS-1706 PSB-1115 compound 16[a] CVT-6883	MRS-1220, MRS-1191, MRS-1523,
Clone designation	M 69045 (rat) M 64299 (rat) X 14051 (dog) M 86261 (cow) X 63592 (cow)	M 97370 (human) X 14052 (dog)	M 97759 (human) M 91466 (rat)	M 94152 (rat)
Distribution	Brain, testis, adipose tissue, heart, lung, mast cells	Striatum, olfactory tubercule, heart, blood vessels (including endothelial cells)	Brain, heart, lung, mast cells, blood vessels (including endothelial cells)	Testis, brain, lung, mast cells, heart

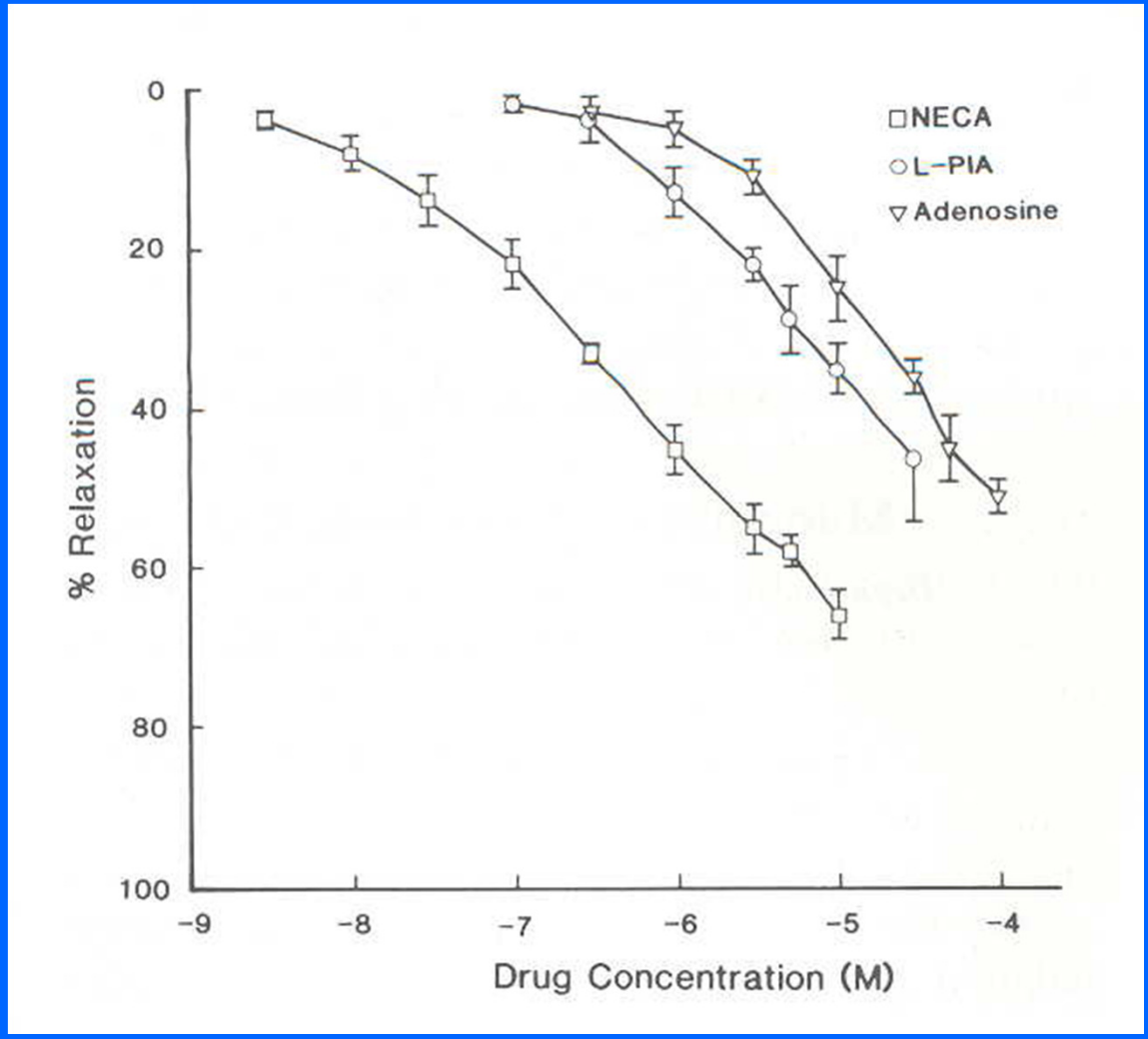
*'A novel adenosine receptor, tentatively designated A4, has been described on the basis of ['H]CV 1808 binding [Cornfield et al., 19921. Several binding proteins for NECA that are unrelated to A2 receptors have been described (see Schwabe et al., [19921; Linden et al. 1993 for further information on adenosine receptor clones). CPA, N6-cyclopentyl adenosine; CCPA, 2-chloro CPA; NECA, 5'N-ethylcarboxamino adenosine. Modified from **ABBRACCHIO et.al DRUG DEVELOPMENT RESEARCH 28:207,1993**

[a] **Beukers et al; Med Res Rev. 26:667-98, 2006.**



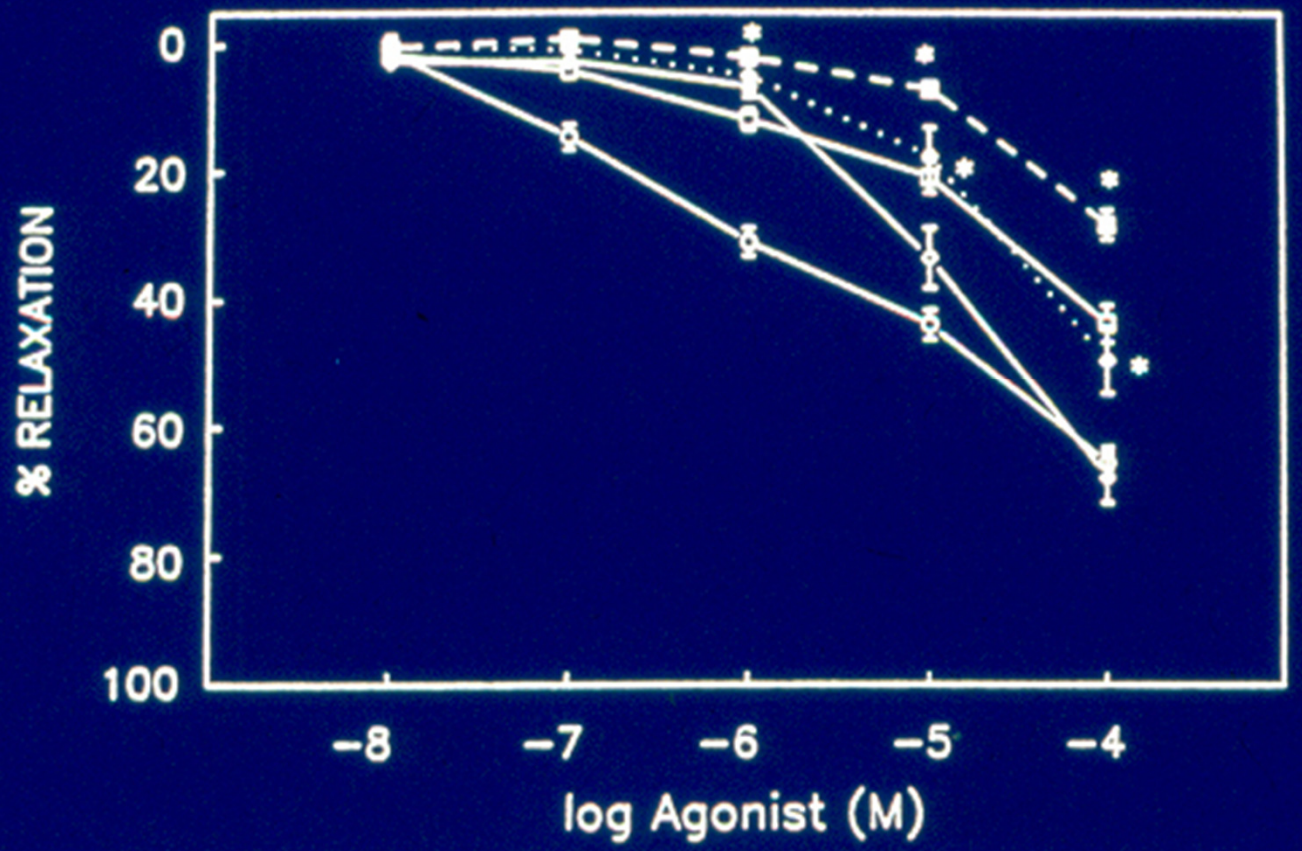
Heterogeneity of Adenosine Receptors in CBF

Ramagopal, Chitwood and Mustafa (European J. Pharmacology 151: 483, 1988)



Concentration-response curves for the relaxation of adenosine and its analogs in human coronary artery ring preparations pre-contracted with prostaglandin $F_{2\alpha}$ (10^{-6} M) in the presence of diltiazem (10^{-6} M). Each point represents the mean of six vascular rings from four human hearts ± S.E.M.

Mustafa *et.al.* (European J. Pharmacology 221: 243, 1992)



The antagonistic effects of CGS 15943A (◆ ... ◆) on the relaxations produced by CGS 22492 (◇ ——— ◇); antagonistic effects of CGS 15943A (■ – – – ■) on the relaxations produced by CGS 21680 (□ ——— □) vasodilatory effects of NECA (○ ——— ○) on 35 mM KCl-contracted human coronary rings. Each point is a mean ± S.E. representing 16–41 rings from four hearts. * Indicates significance from control ($P < 0.05$).

Driver *et.al.*
Chest 107: 346-351, 1995

Driver et al. (Chest vol. 107, p. 346-351)

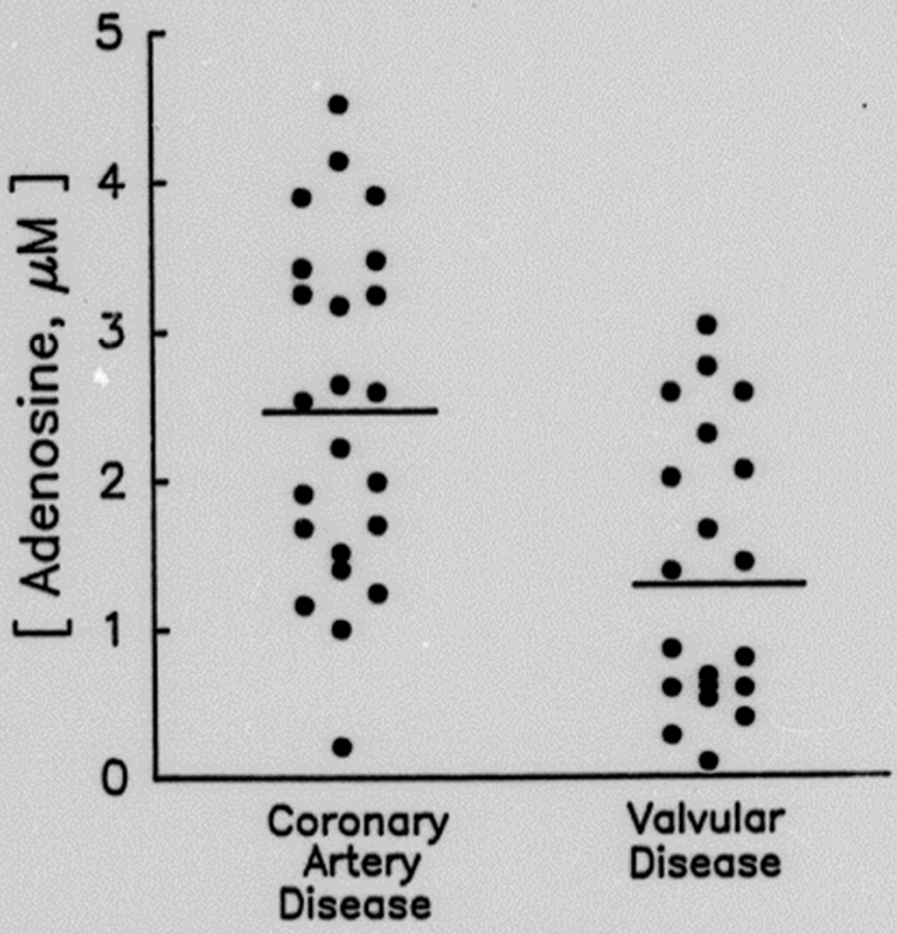


FIGURE 1. Distribution of adenosine concentrations in pericardial fluid in subjects with coronary artery disease and valvular heart disease. The horizontal lines indicate the mean of group.

Dr. Morrison

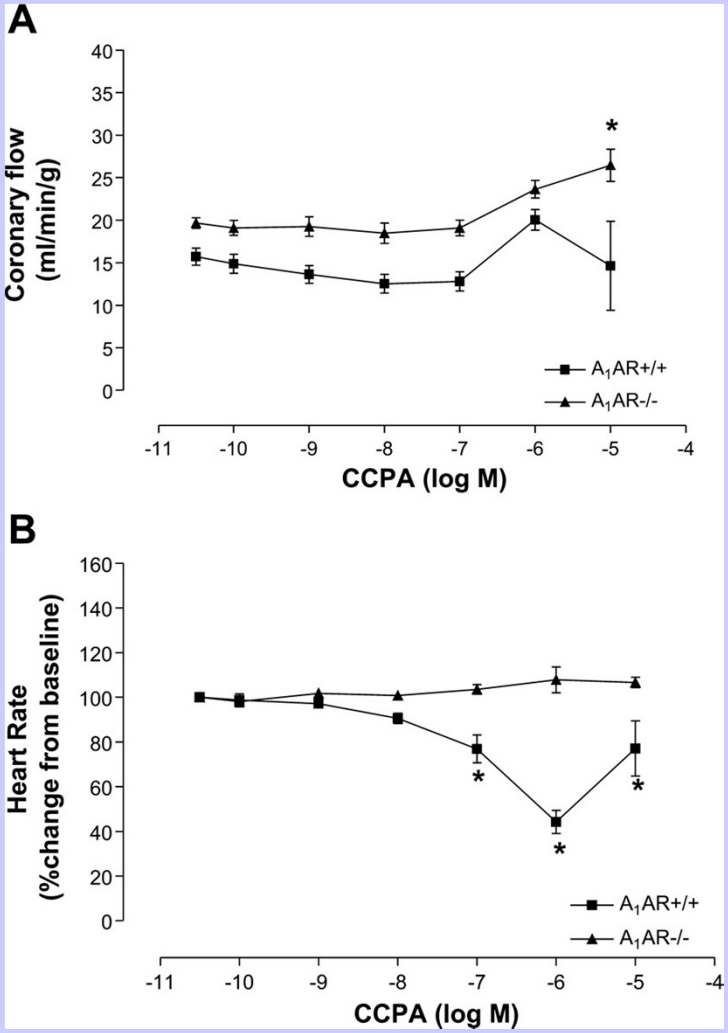
Men to Mice

- Advent of targeted gene modification
- “Knockout”, “knockin”, transgenic models
- among the most useful models for dissection of physiological pathways



Role of A_1 Adenosine Receptor in CBF Regulation (using A_1 KO)

Concentration-response curves for 2-chloro-N6-cyclopentyladenosine (CCPA) on coronary flow (A) and heart rate (B) in isolated perfused hearts from A1AR+/+ and A1AR-/- mice



Tawfik, H. E. et al. Am J Physiol Heart Circ Physiol 291: H467-H472 2006.

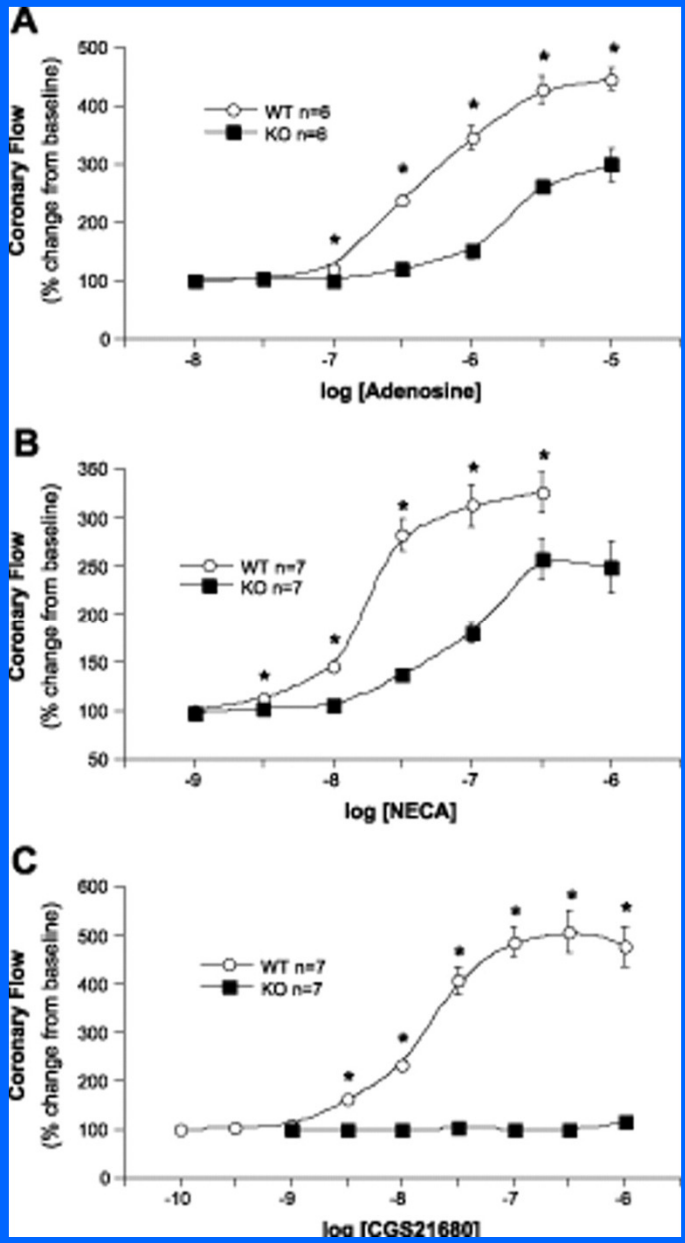
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Role of A_{2A} Adenosine Receptor in CBF Regulation (using A_{2A} KO)

Concentration-response curves for coronary flow (expressed as percent change from baseline) for adenosine (A), NECA (B), and CGS-21680 (C) in isolated perfused mouse hearts.

Open circles represent wild-type (WT) hearts and closed squares represent A2AR KO . *Significant differences between WT and A2AKO groups, $P < 0.05$.

Support A_{2A} and possibly A_{2B} and others?

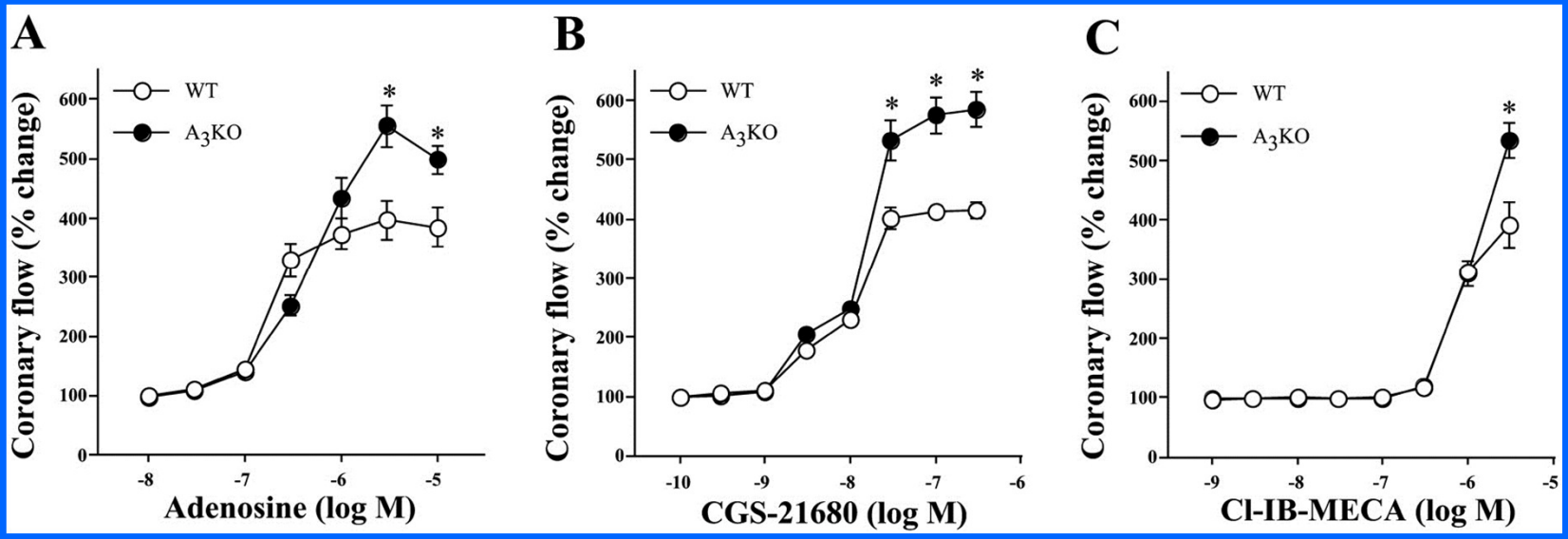


R. Ray Morrison et al. Am J Physiol Heart Circ Physiol 2002;282:H437-H444

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Role of A_3 Adenosine Receptor in CBF Regulation (using A_3 KO)

Concentration-dependent coronary vascular effects of adenosine (A), 2-[p-(2-carboxyethyl)]phenylethylamino-5′-N-ethylcarboxyamido-adenosine (CGS-21680) (B), and 2-chloro-N 6-(3-iodobenzyl)-adenosine-5′-N-methyluronamide (Cl-IB-MECA) (C) in isolated hearts.



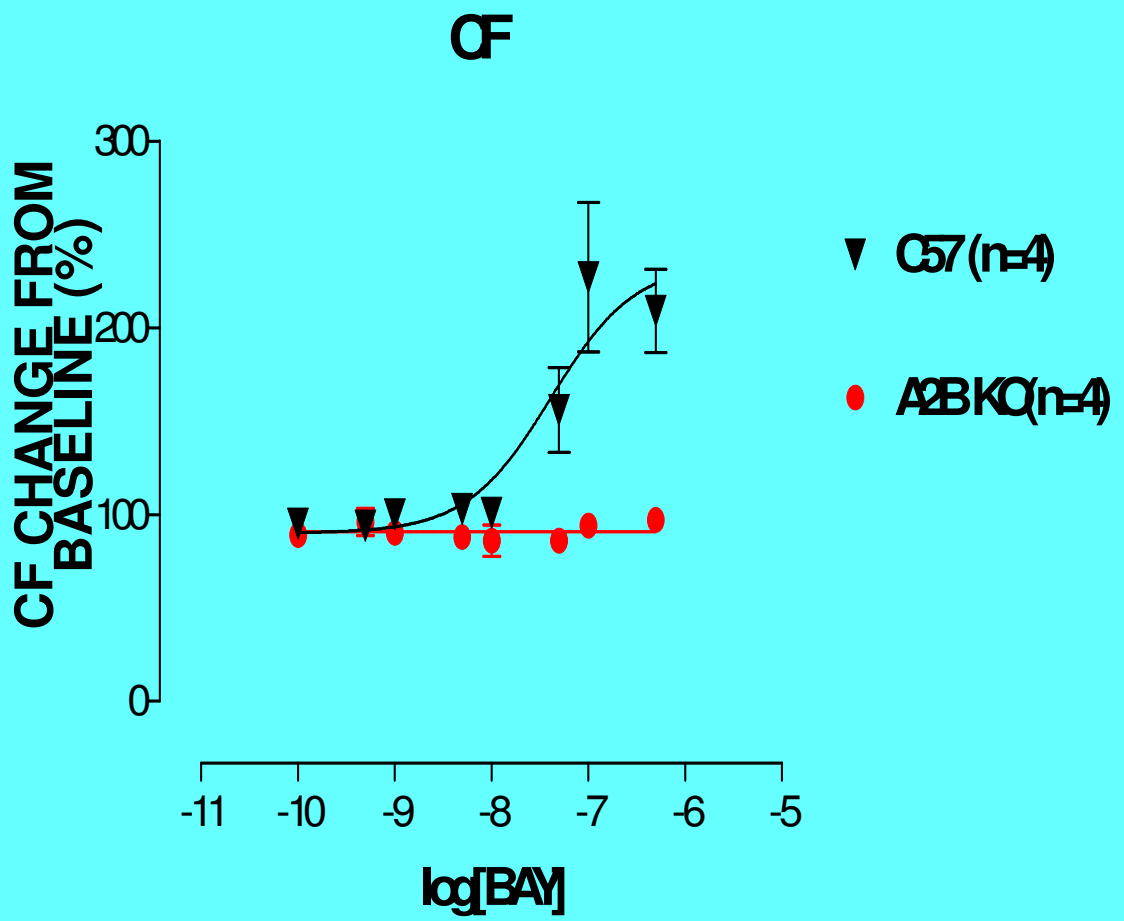
CF response curves adenosine (*A*), CGS-21680 (*B*), and Cl-IB-MECA (*C*) in isolated hearts from WT and A3AR KO, negative role) mice. **P* 0.05 vs. corresponding WT value.

M. A. Hassan Talukder et al. Am J Physiol Heart Circ Physiol 2002;282:H2183-H2189

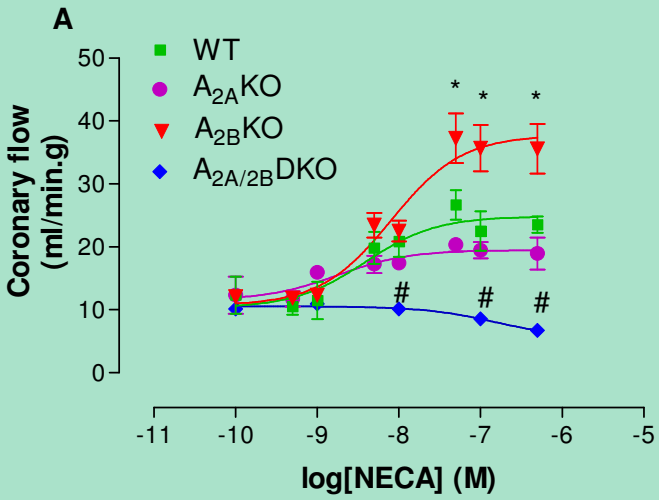
©2002 by American Physiological Society

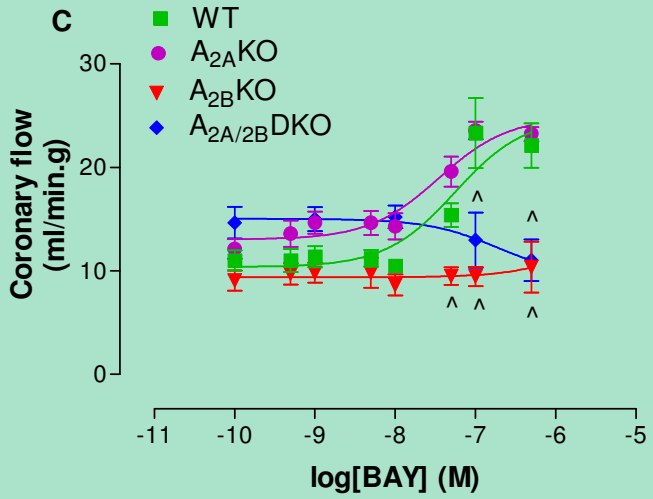
Role of A_{2B} Adenosine Receptor in Coronary Flow Regulation (using A_{2B} KO)

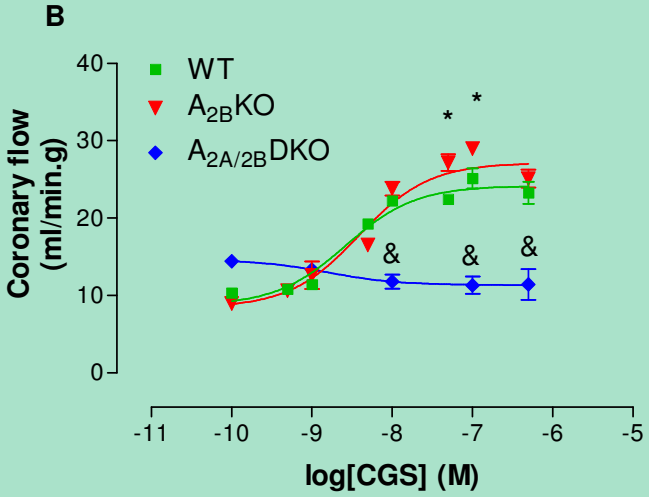
Effect of BAY 60-6583 (A_{2B} selective agonist) in Isolated Heart from A_{2B} KO and WT mice



Maryam Sharifi Sanjani et al. Am J Physiol Heart Circ Physiol. 301:H2322-H2333, 2011.







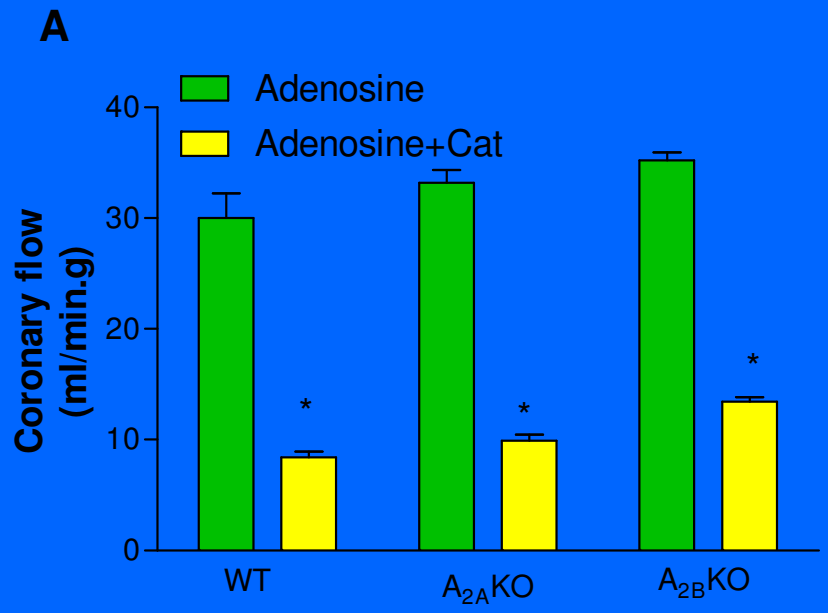
Role of A_{2A} and A_{2B}ARs in the regulation of coronary flow.

Values are means±S.E.M. *Significant difference compared to WT, A_{2A}KO, and $A_{2A/2B}$DKO, #Significant difference compared to WT, A_{2A}KO, and A_{2B}KO, ∞Significant difference compared to WT, $A_{2A/2B}$DKO, &Significant difference compared to WT, A_{2B}KO, ^Significant difference compared to WT, A_{2A}KO, $p<0.05$.

Maryam Sharifi Sanjani et al. Am J Physiol Heart Circ Physiol. 301:H2322-H2333, 2011.

Role of H_2O_2 in Adenosine Receptor-Mediated Increase in Coronary Flow Regulation (using AR KOs)

Involvement of H_2O_2 in A_2 adenosine receptors-mediated increase in coronary flow



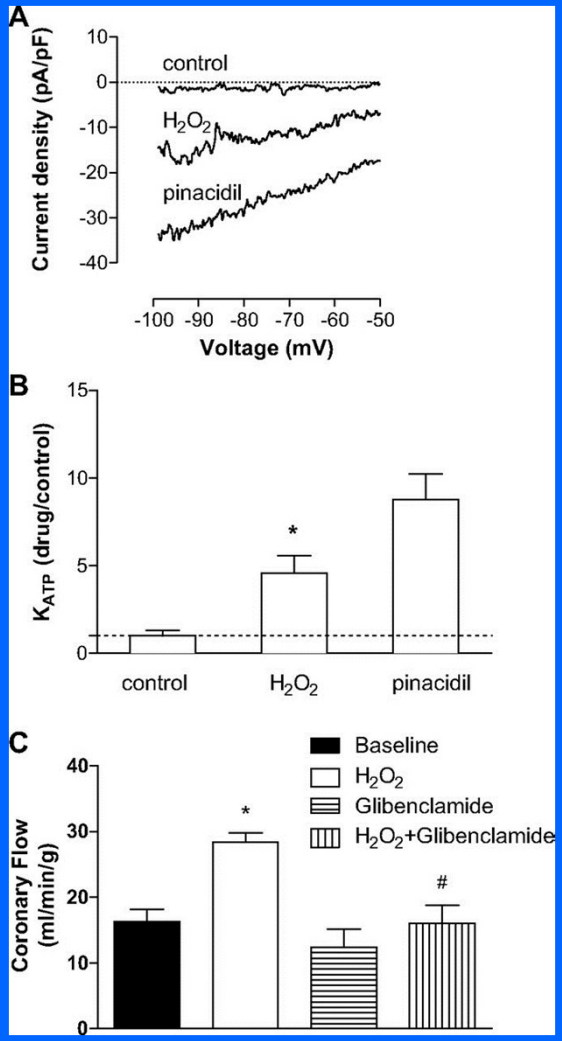
Catalase (CAT)

$H_2O_2 \rightarrow H_2O+O_2$

Maryam Sharifi-Sanjani et al. Am J Physiol Heart Circ Physiol. 304:H1294-H1301, 2013.

Role of K^+_{ATP} Channels in AR-Mediated Increase in Coronary Flow Regulation/Reactive Hyperemia (using AR KOs) through H_2O_2

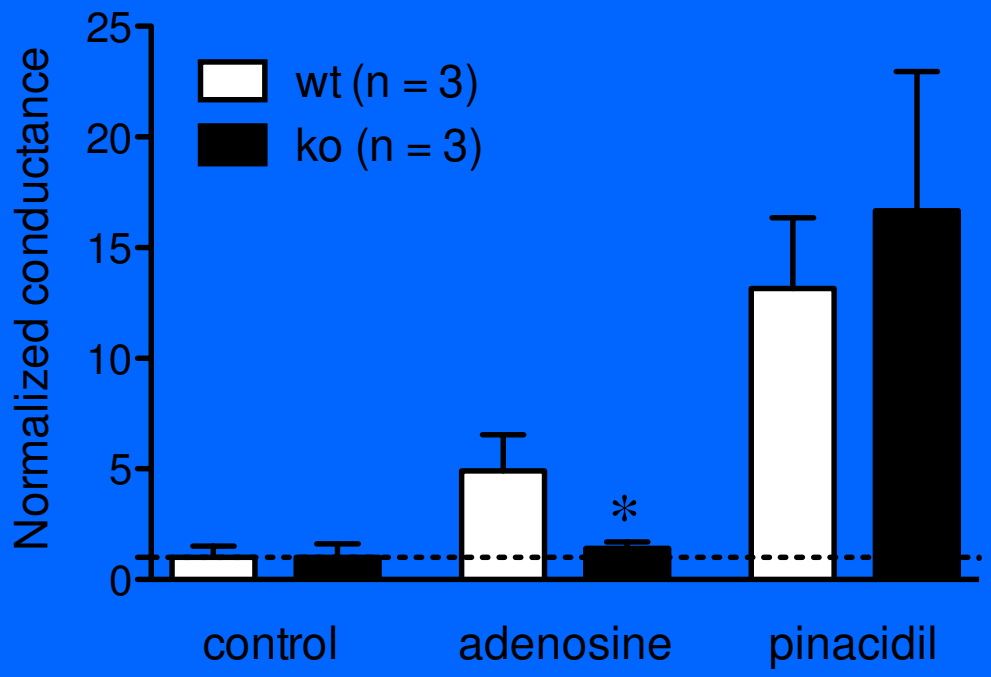
H2O2 activates KATP channels in smooth muscle cells.



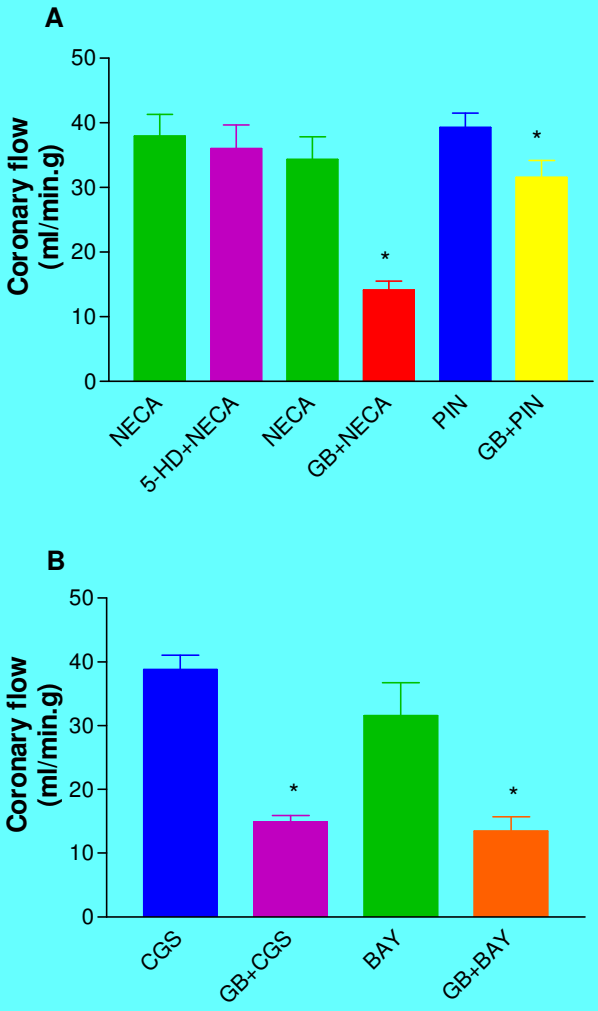
Maryam Sharifi-Sanjani et al. Am J Physiol Heart Circ Physiol. 304:H1294-H1301, 2013.

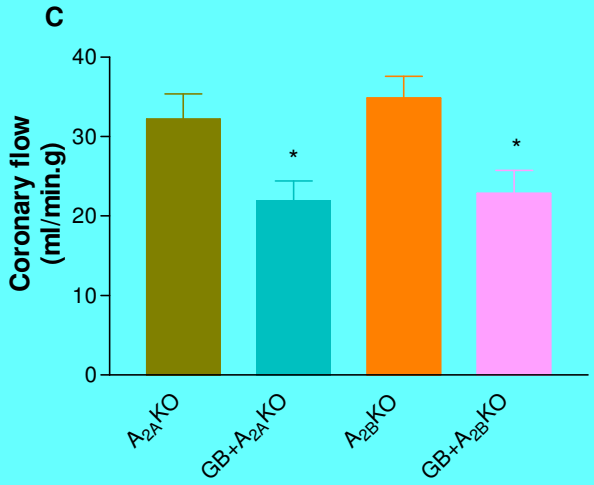
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Adenosine induces opening of K_{ATP} channels in SMC through A_2 ARs ($A_{2A/2B}$DKO)



Collaborators: Dick GM and Asano C.

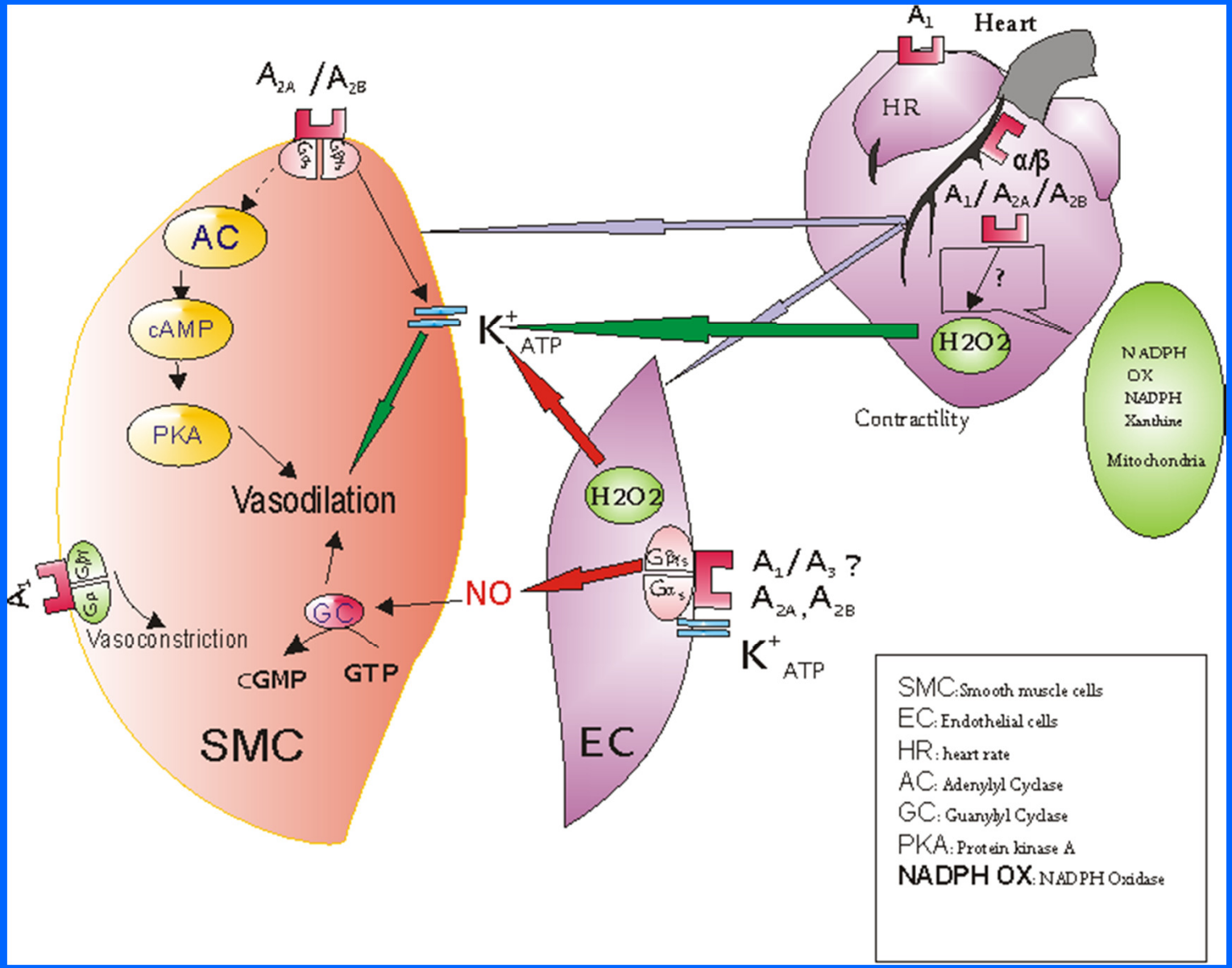




Effect of 5-HD and glibenclamide (GB) on NECA and pinacidil (A, PIN), CGS 21680/BAY (B)-mediated increase in CF in WT mice (B). Effect of GB on NECA-mediated increase in CF in A_{2A}KO and A_{2B}KO mice (C).Values are means±S.E.M. *Significant difference in drug-mediated effects in the presence of antagonist compared to their corresponding controls, $p<0.05$.

Involvement of non-mitochondrial K_{ATP} channels in A_{2A} and A_{2B}ARs-mediated increase in coronary flow.

Maryam Sharifi-Sanjani et al. Am J Physiol Heart Circ Physiol. 304:H1294-H1301, 2013.


A1
Heart
A2A /A2B
HR
α/β
A1/ A2A/ A2B
?
AC
cAMP
PKA
K+ ATP
H2O2
Contractility
NADPH
OX
NADPH
Xanthine
Mitochondria
Vasodilation
H2O2
A1
Vasoconstriction
GC
NO
A1/A3 ?
A2A, A2B
K+ ATP
cGMP
GTP
SMC
EC
SMC: Smooth muscle cells
EC: Endothelial cells
HR: heart rate
AC: Adenylyl Cyclase
GC: Guanylyl Cyclase
PKA: Protein kinase A
NADPH OX: NADPH Oxidase

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Swati Kunduri, M. S.

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C. Ledent, Ph. D. (Belgium)

Greg Dick, Ph. D. (WVU)

Al Driver, M. D.

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Hasan Talukder, M. D., Ph. D.

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Thanks' for your kind attention!!!!!!



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