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em Farmacologia e Terapêutica

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Uma iniciativa para uso da estrutura de vídeo e web-conferências da Rede Universitária de Telemedicina (RUTE-MCT) ***para reduzir as distâncias geográficas e integrar ações em ensino e pesquisa em farmacologia e terapêutica no Brasil***

Apoio SBFTE

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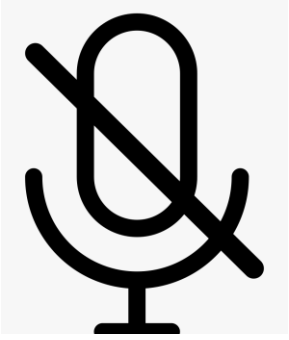
- Durante a sessão: A todos os participantes:



Mantenham os **microfones da videoconferência no MUDO enquanto não estiverem falando**, medida que se faz necessária para evitar ruídos e perda de qualidade de áudio durante a conferência.

Perguntas, Comentários ***pelo Chat***
Inscrições para perguntas por audio ***pelo Chat*** (nome, instituição)

Estrutura da sessão

1. Boas vindas – informações gerais : ~5 min

2. Apresentação do tema e palestrante : ~3 min

3. Apresentação do palestrante: ~30-35 min

4. Debate do tema com participantes: ~40 min

5. Encerramento e Registro Participação: ~5 min

Ambiente Restrito:
AS SESSÕES NESSE AMBIENTE SÃO GRAVADAS
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3) Selecione o SIG: Farmacologia e Terapêutica

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- Informe a senha e clique em “Registrar Presença – Etapa 2”

- Avalie a sessão após registrar sua presença
- O registro deve ser feito no mesmo dia (até 23h59) da sessão
- Em caso de dúvidas ou suporte, contate o e-mail: sig@rute.rnp.br

Conceitos em Farmacologia
Sinalização intra- e extracelular do cAMP: papéis complementares ou diferenciais?

Palestrante:
Profa. Dra. Rosely O. Godinho (Unifesp-EPM)

Coordenadores da Sessão:
Maria Christina W. Avellar (SIG-Farmaco, Unifesp-EPM)
Emiliano Barreto (SIG-Farmaco, UFAL)

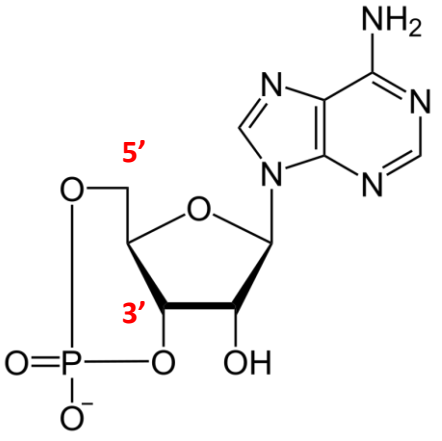
Paulo Ghedini (SIG-Farmaco, UFG)
François G. Noel (SIG-Farmaco, UFRJ)

The relationship of epinephrine and glucagon to liver phosphorylase. Rall TW., Sutherland, EW & Berthet J. (1957). *J Biol Chem.* 224, 463–475.

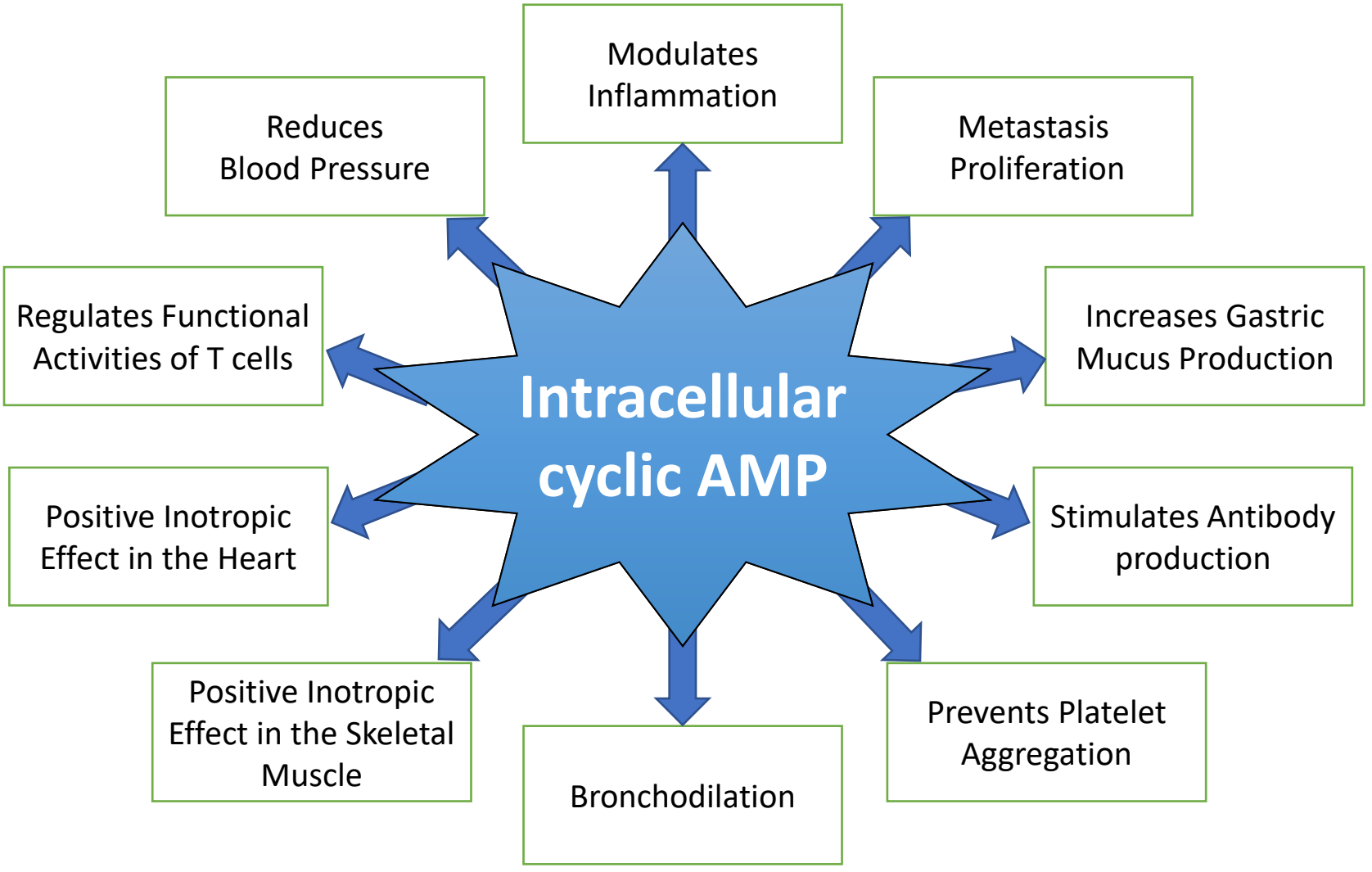
The response to the hormones in liver homogenates was separated into two phases:

- first, the ***formation of an active factor in particulate fractions*** in the presence of the hormones and,
- In the second stage, this factor ***stimulated the formation of liver phosphorylase*** *in* ***supernatant fractions of homogenates in which the hormones themselves were inactive***.
- The active factor was ***heat-stable, dialyzable***, and was purified considerably by chromatography on anion and cation exchange resins.

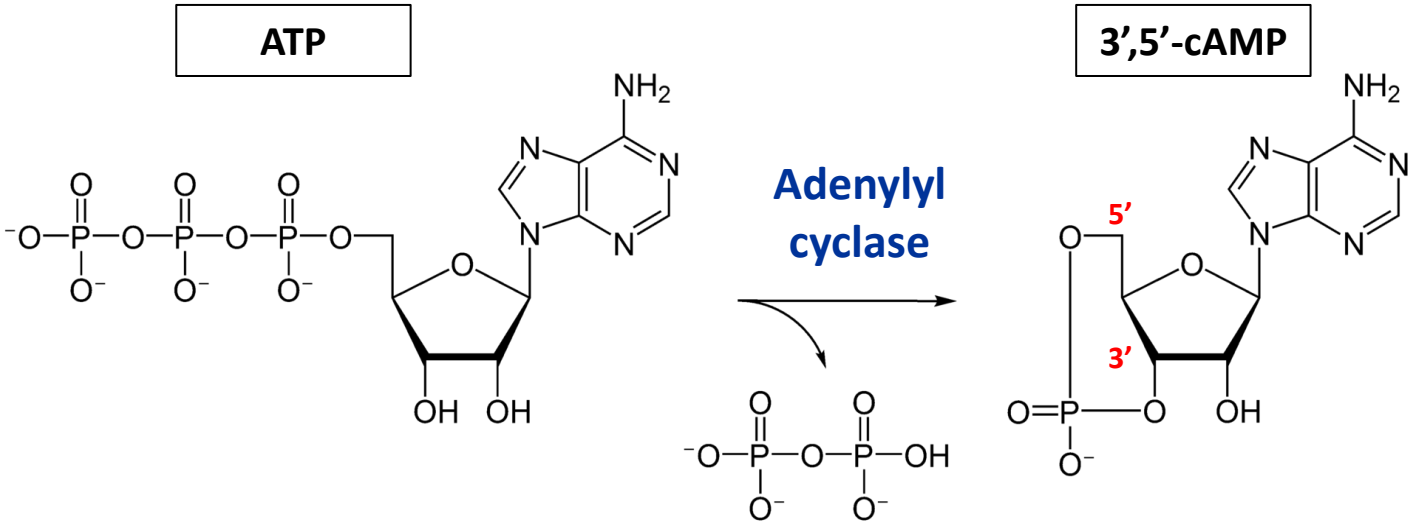
3',5'-cyclic adenosine monophosphate
or cylic AMP



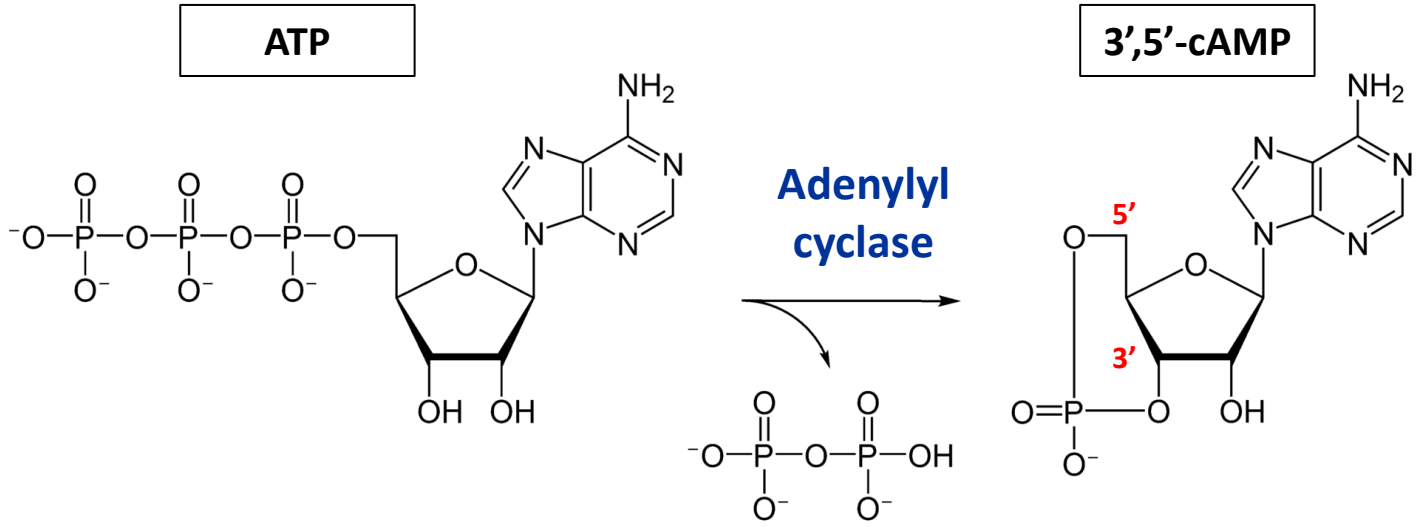
3’,5’- cAMP Function

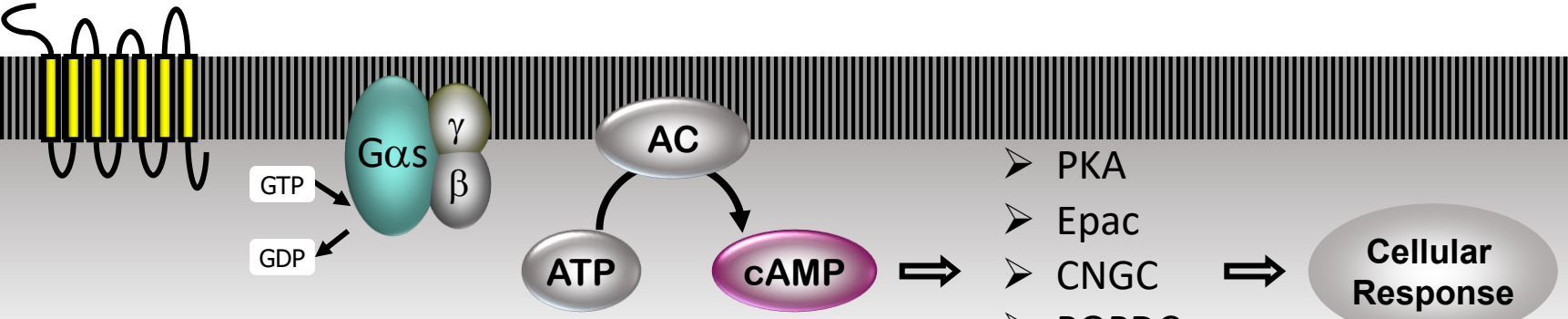


Synthesis of cAMP



Synthesis of cAMP





- PKA
- Epac
- CNGC
- POPDC
- CRIS

⇒ **Cellular Response**

PKA = *protein kinase A*
EPACs = *exchange protein directly activated by cAMP*
CNGC = *cyclic nucleotide-gated ion channels*
POPDC = *Popeye domain-containing proteins*
CRIS = *cyclic nucleotide receptor involved in sperm function*

Receptors coupled to stimulatory G protein (Gαs)

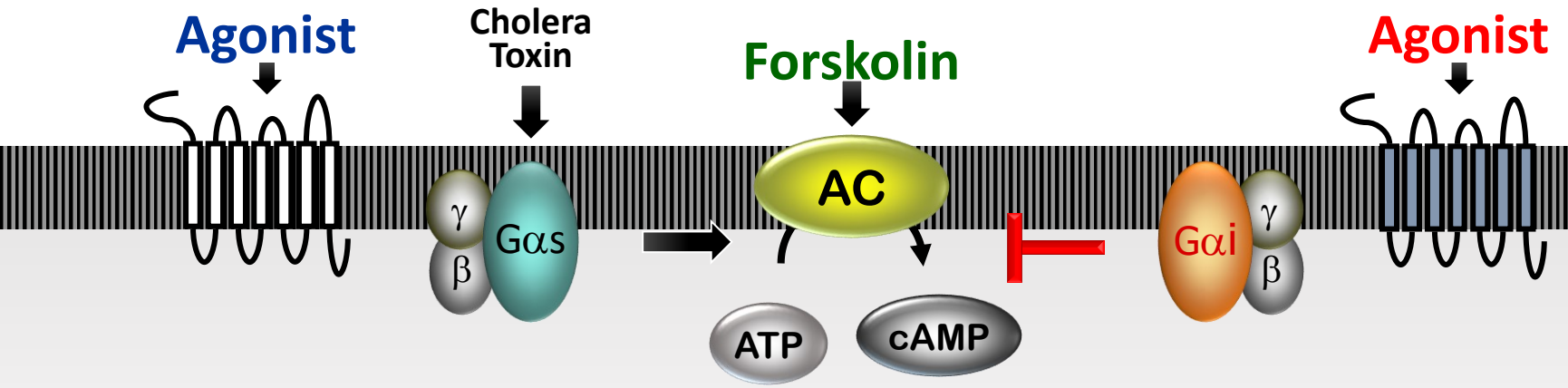
5-Hydroxytryptamine: 5-HT_4, 5-HT_6 - 5-HT_7
Adenosine: A_{2A}, A_{2B}
Adrenoceptor (β): β_1-β_3
Bile acid
Calcitonin: CGRP, AM_1 - AM_2, CT, AMY_1 -AMY_3,
Cholecystokinin: CCK_1, CCK_2
Corticotropin-releasing factor: CRF_1, CRF_2
Dopamine: D_1, D_5
Endothelin: ET_A
Estrogen (G protein-coupled): GPER
Glucagon: glucagon, GLP-1 - GLP-2, GIP, GHRH, secretin
Glycoprotein hormones: FSH, LH
Histamine: H_2
Lysophospholipid (LPA): LPA_3-LPA_4
Sphingosine 1-phosphate (S1P): $S1P_2$ - $S1P_4$
Melanocortin: MC_1 - MC_5
Neuropeptide S: NPS
Odorants: ~400 functional receptors
Purinergic P2Y: $P2Y_{11}$
Parathyroid hormone: PTH_1 - PTH_2
Prostanoid: DP_1, EP_2, EP_4
Relaxin family peptide (RXFP): RXFP1- RXFP2
Trace Amino: TA_1
Vasopressin and Oxytocin receptors: V_2
Vasoactive intestinal peptide and PACAP: $VPAC_1$, $VPAC_2$, PAC_1
Orphans: GPR3-GPR4, GPR6, GPR26, GPR61, GPR65, GPR132, TAAR2, GPR78, GPR174

Godinho *et al.*, Front Pharmacol, 6:58. 2015
doi: 10.3389/fphar.2015.00058.

Receptors coupled to inhibitory G protein (Gαi)

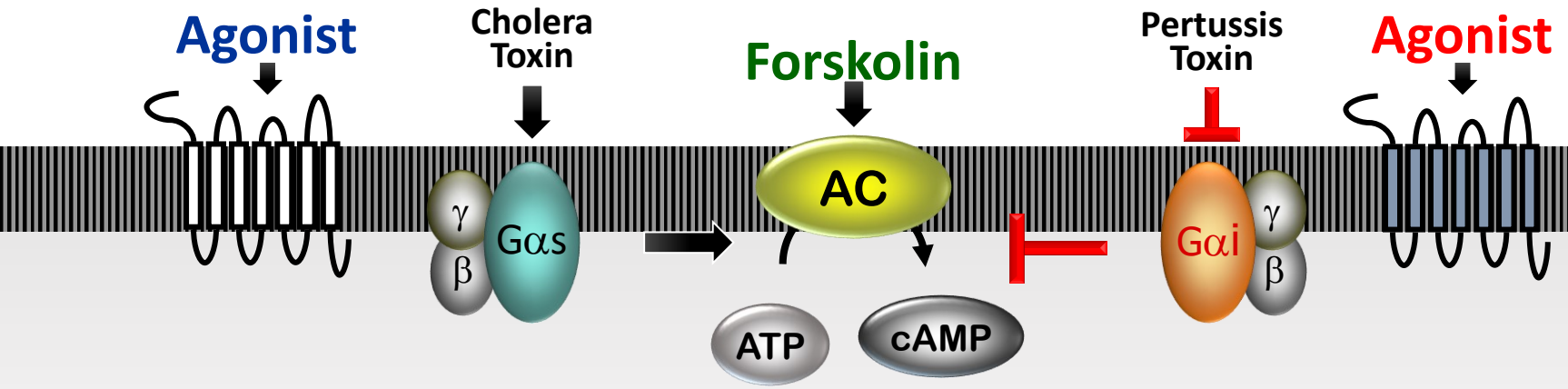
Acetylcholine (Muscarinic): M_2, M_4	**Leukotriene/lipoxin/oxoeicosanoids**: BLT_1-BLT_2, FPR_2/ALX, OXE
Adenosine: A_1, A_3	**Lysophospholipid (LPA):** LPA_1-LPA_4
Adrenoceptor (α): α_{2A}, α_{2B}, α_{2C}	**Sphingosine 1-phosphate (S1P):** $S1P_1$, $S1P_3$ - $S1P_5$
Angiotensin: AT_2	**Melanin-concentrating hormone (MCH):** MCH_1
Apelin	**Melatonin:** MT_1 - MT_2
Calcium sensing: CaS	**Metabotropic glutamate (mGlu)**: $mGlu_2$ - $mGlu_4$; $mGlu_6$ - $mGlu_8$
Cannabinoid: CB_1, CB_2	**Neuropeptide FF/neuropeptide AF**: NPFF2
Chemokine: CCR_1-CCR_{10}, $CXCR_1$-$CXCR_6$, CX_3CR1, XCR1	**Neuropeptide W/neuropeptide B**: NPBW1 - NPBW2
Complement peptide: C3a, $C5a_1$	**Neuropeptide Y:** Y_1 - Y_2, Y_4 - Y_6
Dopamine: D_2, D_3, D_4	**Opioid**: δ, κ, μ, NOP
Endothelin: ET_B	**Purinergic P2Y**: $P2Y_{12}$ - $P2Y_{13}$
Formylpeptide: FPR1, FPR2/ALX	**Peptide P518**: QRFP
Free fatty acid: FFA3, FFA2, FFA5	**Platelet-activating factor**: PAF
Gaba: $Gaba_B$	**Prostanoid**: DP_2, EP_3
Galanin: GAL_1, GAL_2, GAL_3	**Proteinase-activated (PARs):** PAR1, PAR2, PAR4
Glycoprotein hormone: TSH, LH	**Relaxin family peptide (RXFP):** RXFP3 - RXFP4
N-araquidonilglicina (GPR18)	**Somatostatin (sst):** sst_1 - sst_5
Histamine: H_3, H_4	**Vasopressin and Oxytocin**: OT
Hydroxycarboxylic acid: HCA_1, HCA_2, HCA_3	**5-Hydroxytryptamine:** 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D} - 5-HT_{1F}, 5-HT_{5a}
Orphans: GPR22, GPR34, GPR37, GPR84,1 MRGPRD, GPR33, GPR37L1, OPN5	

Godinho *et al.*, Front Pharmacol, 6:58. 2015
doi: 10.3389/fphar.2015.00058.



Mammal Adenylyl Cyclases		
Isoforms	**Activators**	**Inhibitors**
AC 1	**Gαs**, **Forskolin**, Ca^{2+}/CAM, PKC,	**Gαi**, Gβγ
AC 2	**Gαs**, **Forskolin**, Gβγ, PKC,	
AC 3	**Gαs**, **Forskolin**, Ca^{2+}/CAM, PKC	Gβγ
AC 4	**Gαs**, **Forskolin**, Gβγ	PKC
AC 5	**Gαs**, **Forskolin**,	**Gαi**, Ca^{2+}, PKA
AC 6	**Gαs**, **Forskolin**,	**Gαi**, Ca^{2+}, PKC, PKA
AC 7	**Gαs**, **Forskolin**, Gβγ	
AC 8	**Gαs**, **Forskolin**, Ca^{2+}/CAM	Gβγ
AC 9	**Gαs**	
Soluble AC	**HCO_3^-**, Ca^{2+}	

adapted from Sadana & Dessauer, Neurosignals 2009;17:5–22
https://doi.org/10.1159/000166277



Mammal Adenylyl Cyclases		
Isoforms	**Activators**	**Inhibitors**
~~**AC 1**~~	**Gαs**, **Forskolin**, Ca^{2+}/CAM, PKC,	**Gαi**, Gβγ
AC 2	**Gαs**, **Forskolin**, Gβγ, PKC,	
AC 3	**Gαs**, **Forskolin**, Ca^{2+}/CAM, PKC	Gβγ
AC 4	**Gαs**, **Forskolin**, Gβγ	PKC
~~**AC 5**~~	**Gαs**, **Forskolin**,	**Gαi**, Ca^{2+}, PKA
~~**AC 6**~~	**Gαs**, **Forskolin**,	**Gαi**, Ca^{2+}, PKC, PKA
AC 7	**Gαs**, **Forskolin**, Gβγ	
AC 8	**Gαs**, **Forskolin**, Ca^{2+}/CAM	Gβγ
AC 9	**Gαs**	
Soluble AC	HCO_3^-, Ca^{2+}	

adapted from Sadana & Dessauer, Neurosignals 2009;17:5–22
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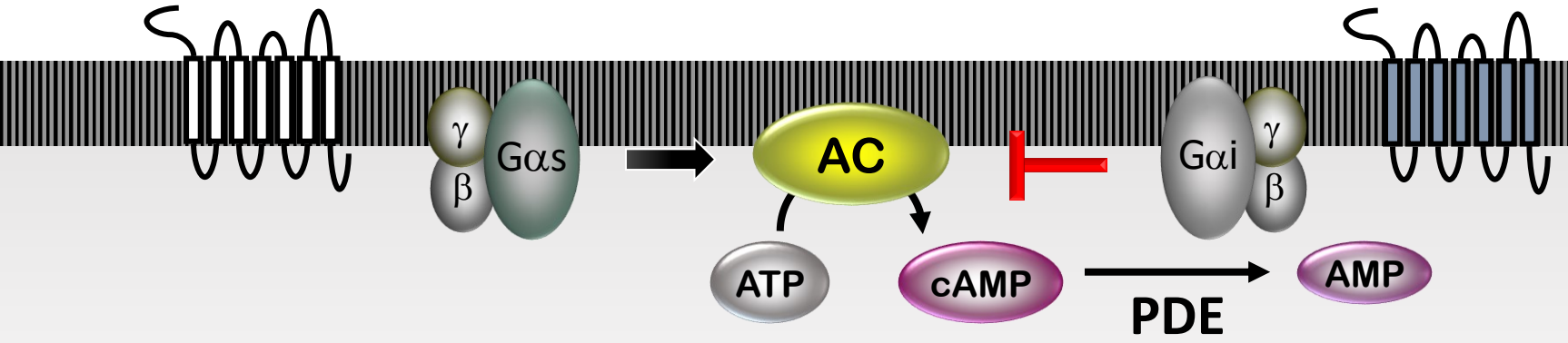
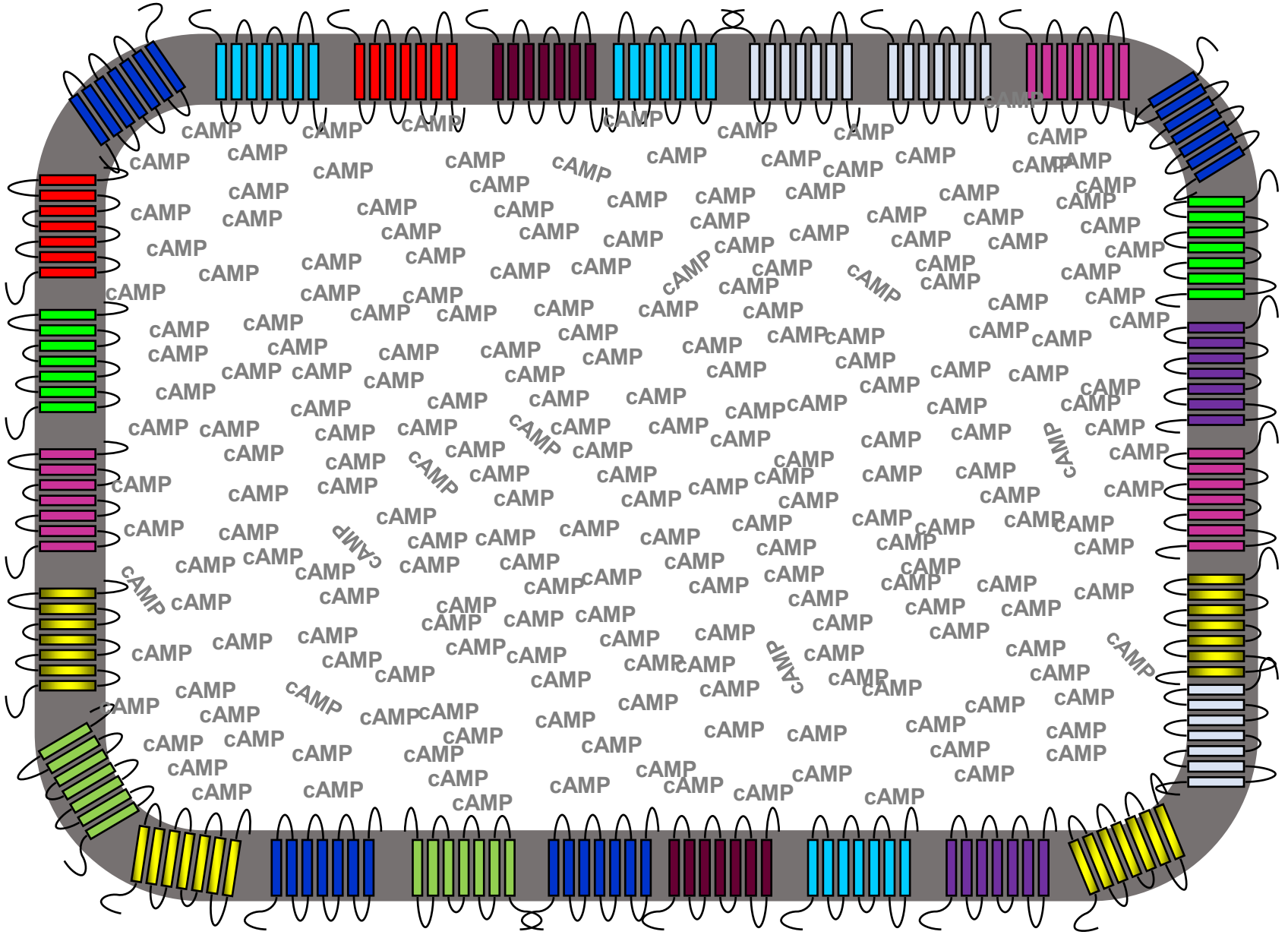
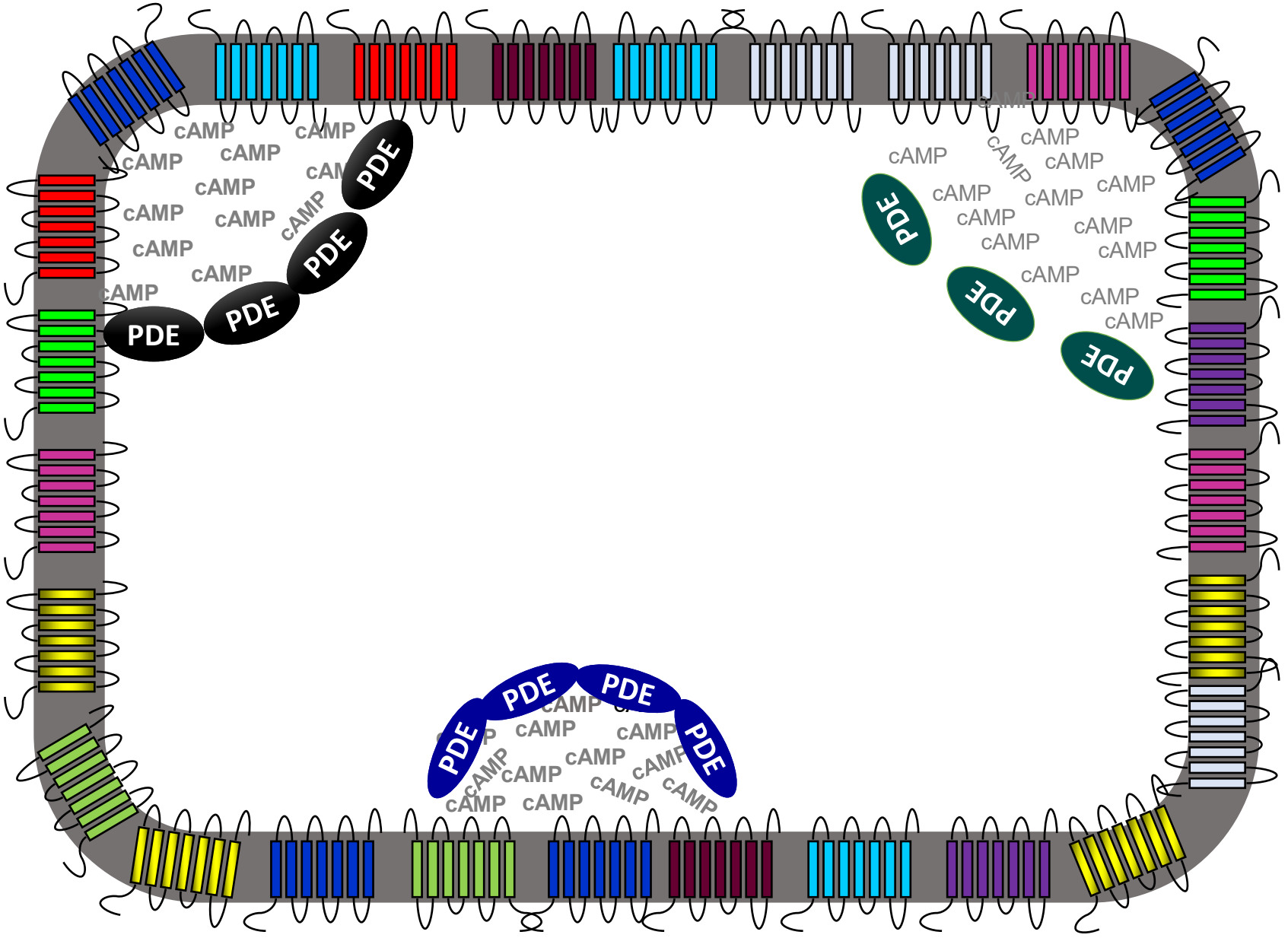


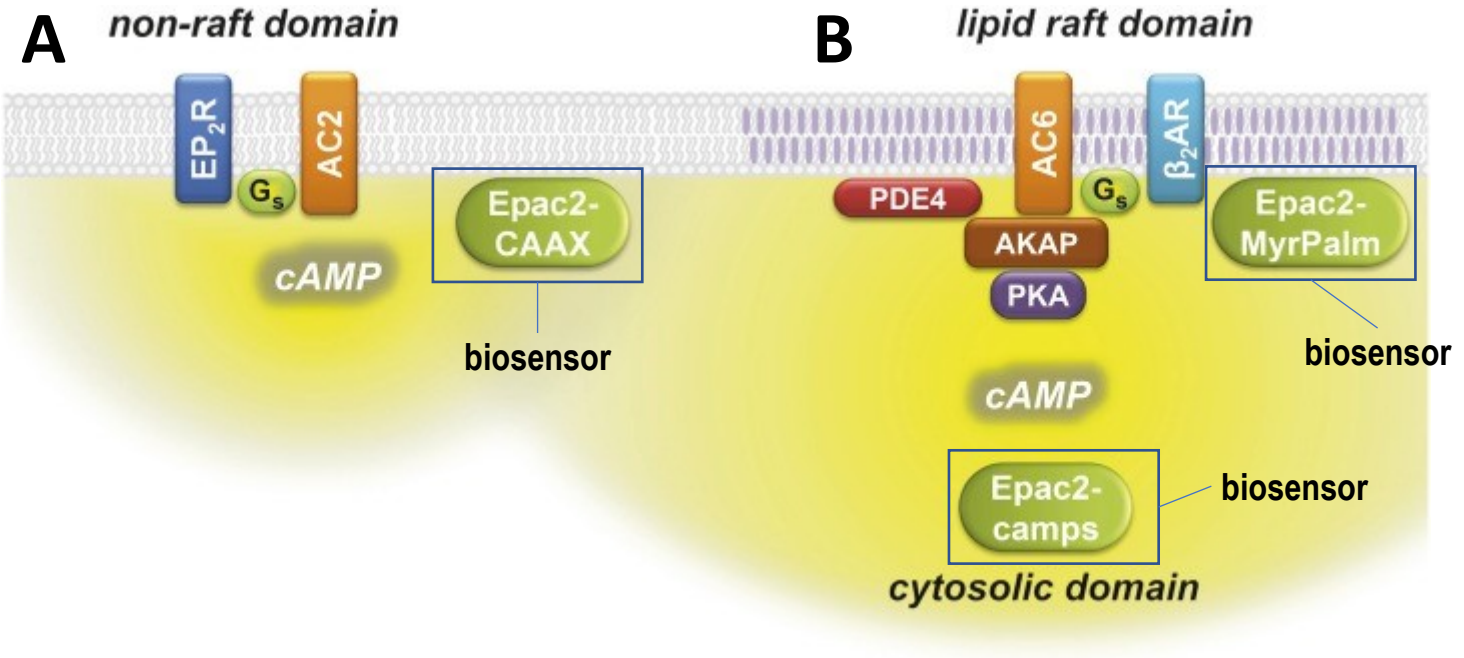
Mammalian Phosphodiesterases (PDE)		
Families	**Targets**	**Inhibitors**
PDE 1	**cAMP, cGMP**	Vinpocetine
PDE 2	**cAMP, cGMP**	EHNA (?)
PDE 3	**cAMP, cGMP**	Milrinone
PDE 4	**cAMP**	Rolipram
PDE 5	**cGMP**	Sildenafil
PDE 6	**cGMP**	Zaprinast (5/6/9/11)
PDE 7	**cAMP**	BRL 50481
PDE 8	**cAMP**	PF 04671536
PDE 9	**cGMP**	PF 04449613
PDE 10	**cAMP, cGMP**	TC-E 5005 (A)
PDE 11	**cAMP, cGMP**	Zaprinast (5/6/9/11)

PDEs play crucial roles in controlling the amplitude, duration, and compartmentalization of cyclic nucleotide signaling.


cAMP


cAMP
PDE

cAMP may remain confined in microdomains near the sites of its synthesis

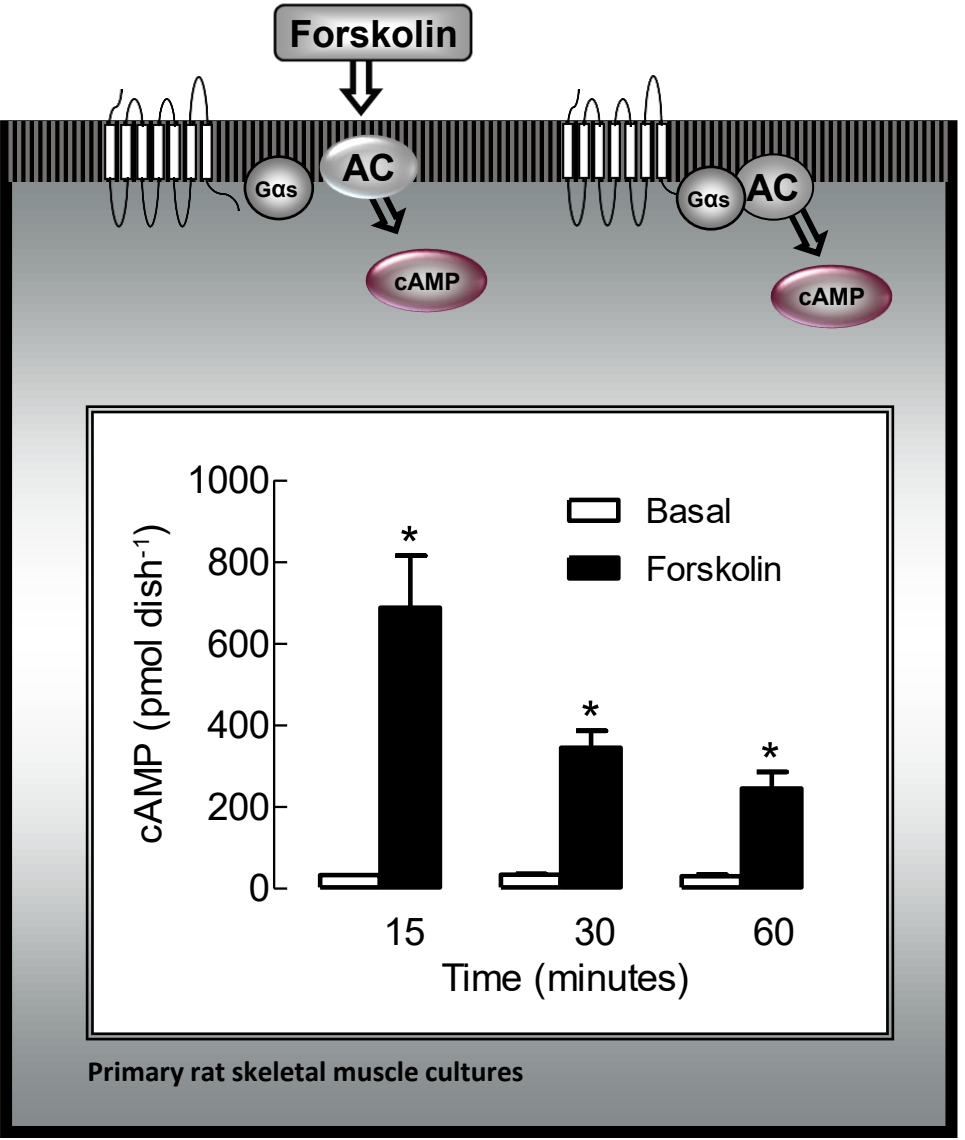


Compartmentalized cAMP signaling in human airway smooth muscle cells. β_2AR stimulation of AC6 produces cAMP that is most readily detected by the Epac2-MyrPalm biosensor, which is targeted to lipid raft domains of the plasma membrane, and the Epac2-camps biosensor, which is expressed throughout the cytosolic domain. AKAPs contribute to the formation of a signaling complex that includes β_2ARs, AC6, type II PKA, and PDE4 associated with lipid raft membrane domains. EP_2Rs stimulation of AC type 2 (AC2) produces cAMP that is most readily detected by the Epac2-CAAX biosensor, which is targeted to nonraft membrane domains.

Agarwal et al., J Pharmacol Exp Ther. 2019 Jul; 370(1): 104–110.
doi: 10.1124/jpet.119.256594

3’,5’-cAMP efflux

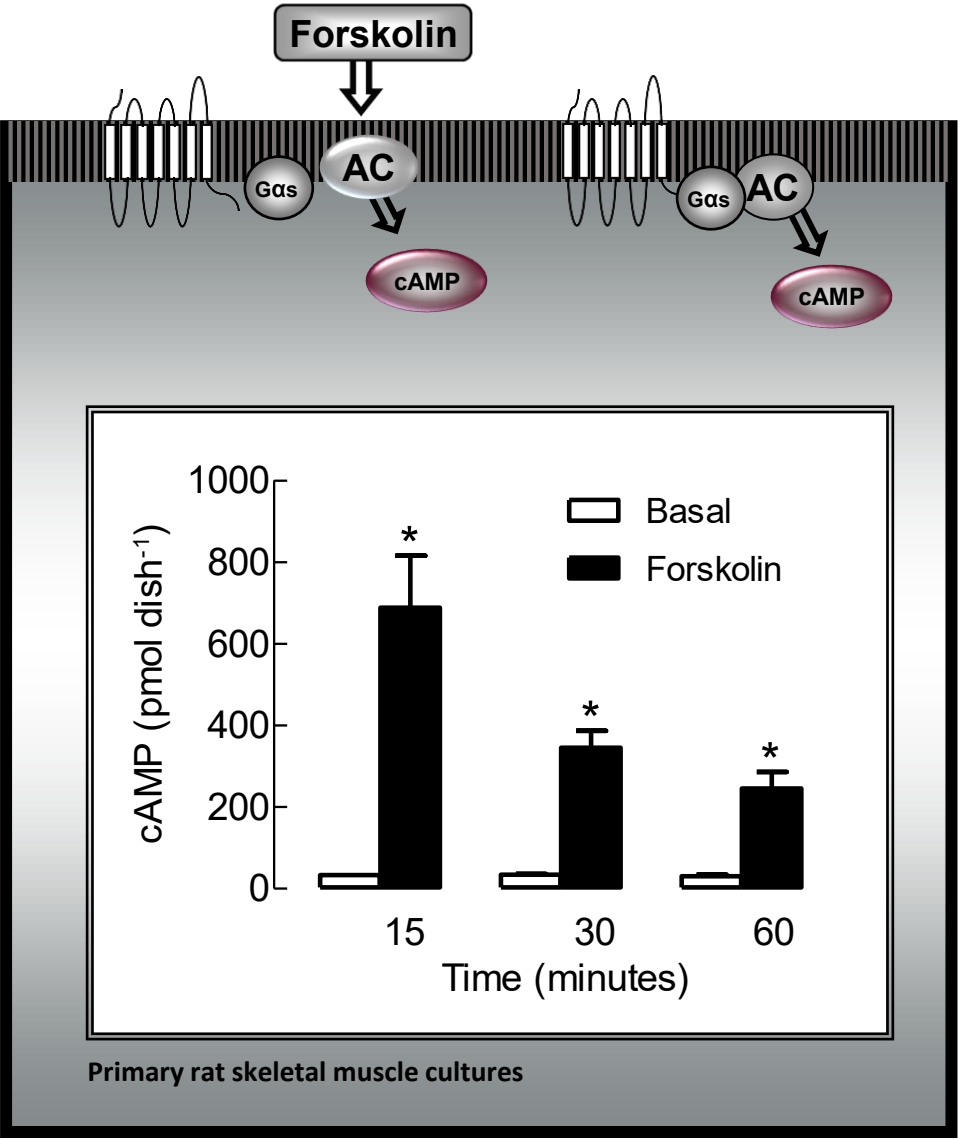
Intact Cell



Primary rat skeletal muscle cultures

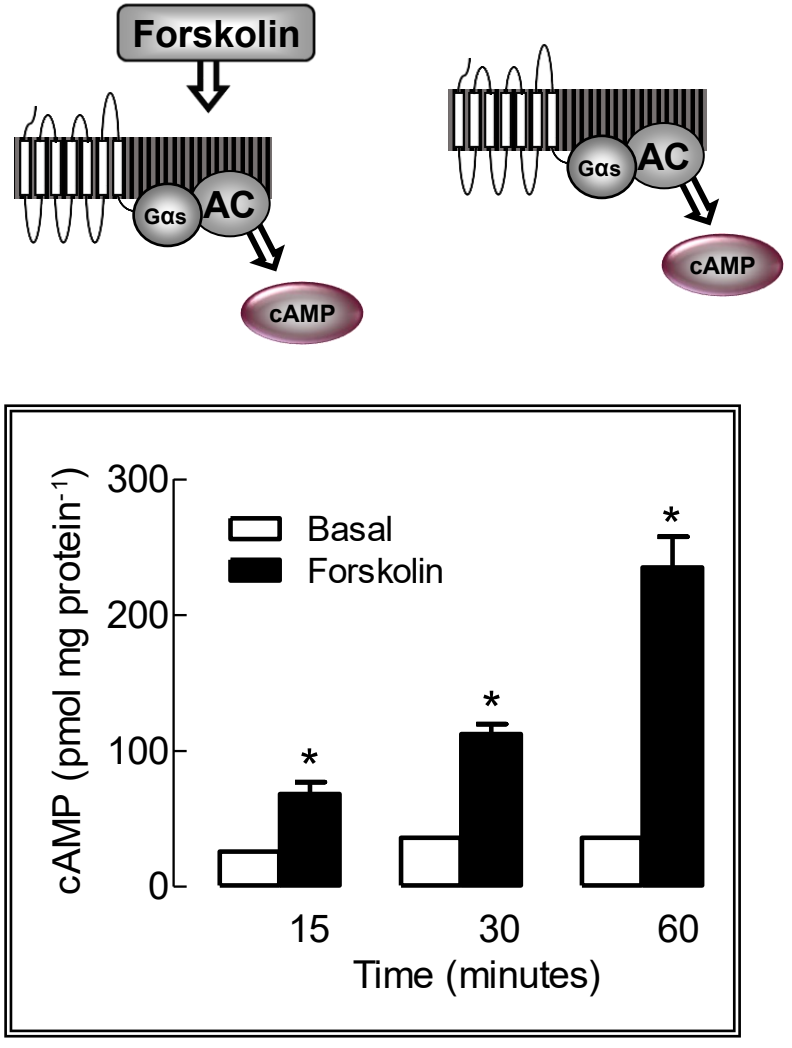
Godinho & Costa Jr. , *Br J Pharmacol.* 138(5):995, 2003
doi: 10.1038/sj.bjp.0705130

Intact Cell



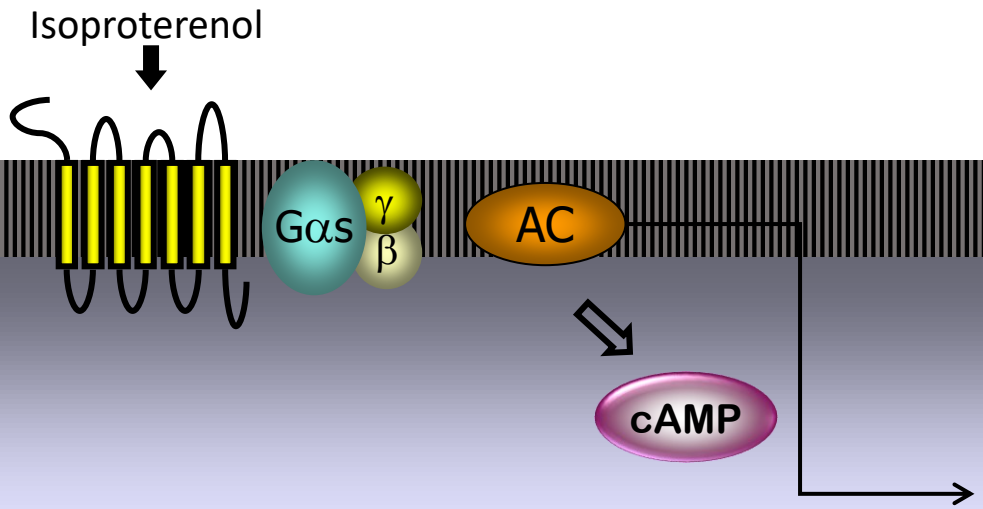
Primary rat skeletal muscle cultures

Cell Membranes



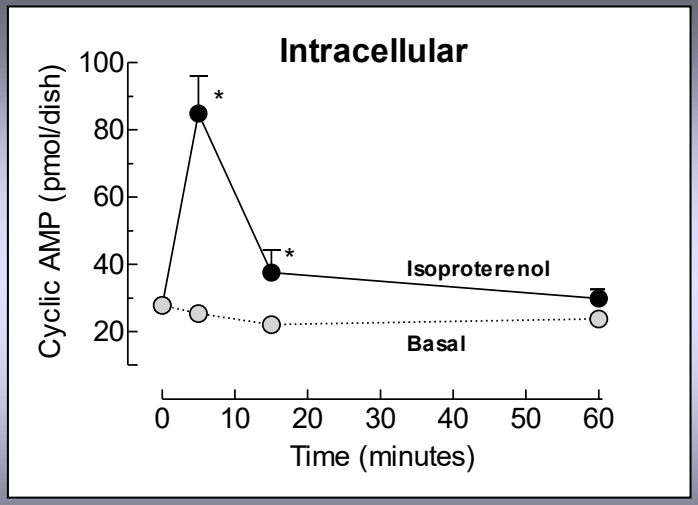
Godinho & Costa Jr. , *Br J Pharmacol.* 138(5):995, 2003
doi: 10.1038/sj.bjp.0705130

β adrenoceptor-dependent generation of cAMP



extracellular

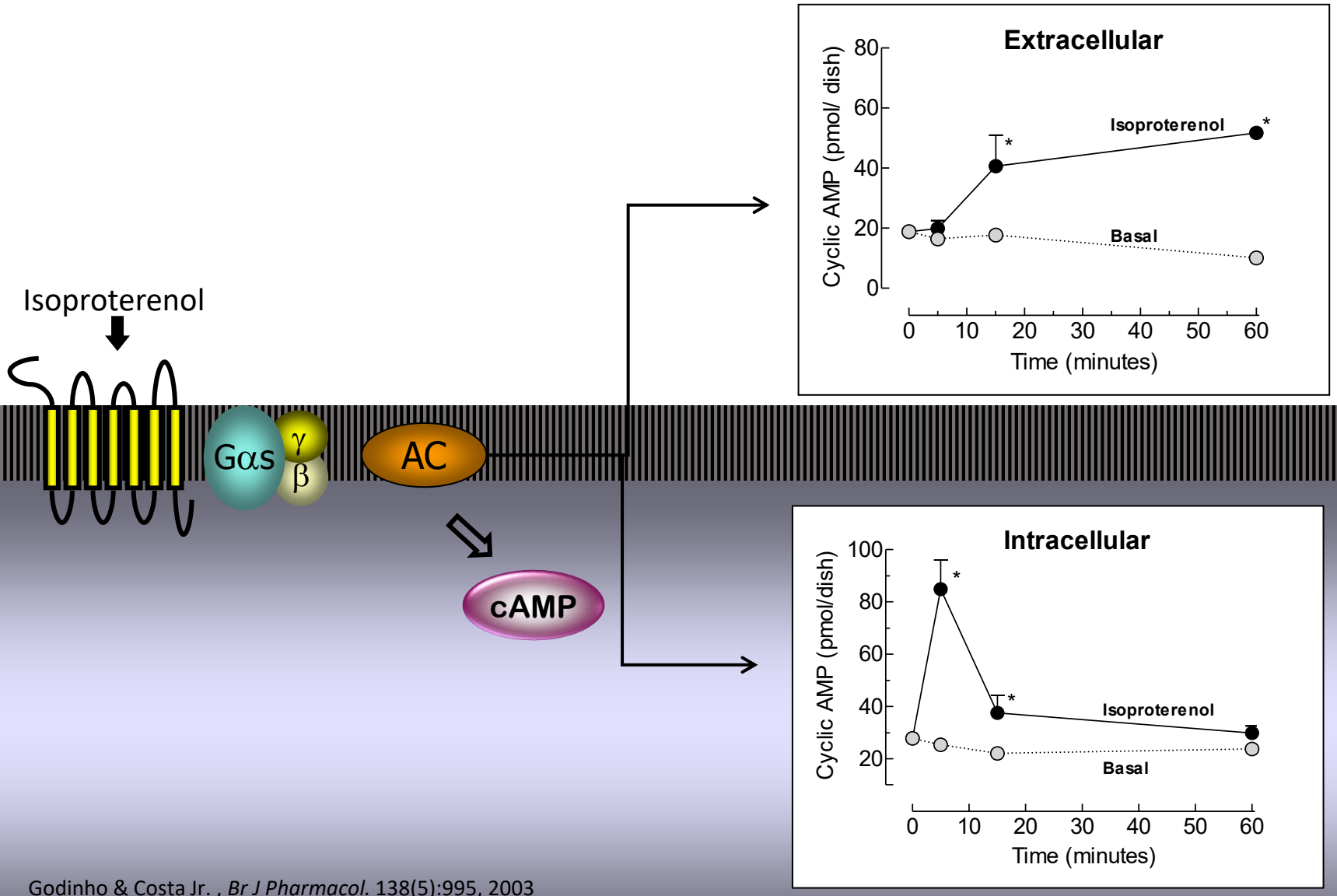
intracellular



Primary rat skeletal muscle cultures

Godinho & Costa Jr. , *Br J Pharmacol.* 138(5):995, 2003
doi: 10.1038/sj.bjp.0705130

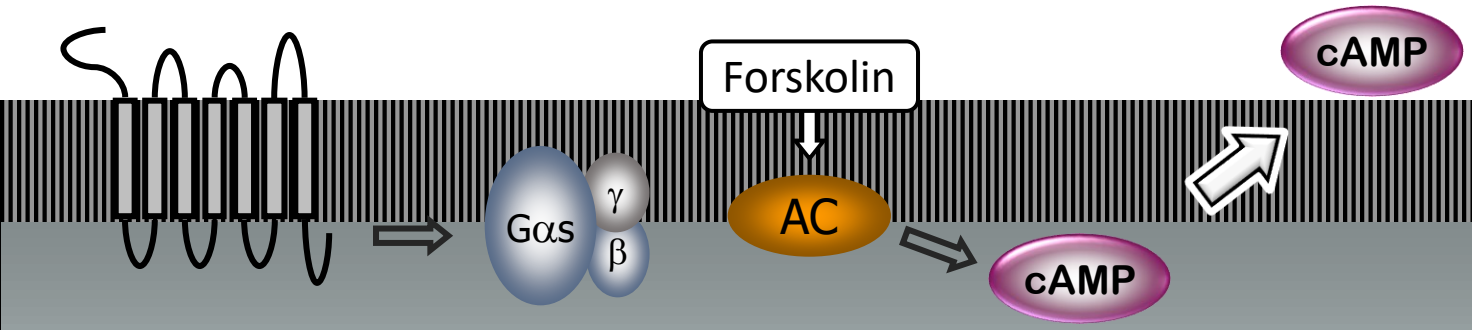
β-adrenoceptor-dependent generation of cAMP is followed by extracellular accumulation of cyclic nucleotide



Godinho & Costa Jr. , *Br J Pharmacol.* 138(5):995, 2003
doi: 10.1038/sj.bjp.0705130

Primary rat skeletal muscle cultures

Forskolin increases intra- and extracellular cyclic AMP levels



Forskolin (μM)	Cyclic AMP		
	Total	Intracellular	Extracellular
	pmol dish^{-1}	% of Total	% of Total
0	10.8 ± 1.7	100.0	---
1.0	36.8 ± 2.6	83.2	16.8
3.0	82.0 ± 8.2	83.7	16.3
10	209.0 ± 7.8	83.3	16.7
30	281.3 ± 22.0	83.6	16.4
100	395.0 ± 61.6	77.4	22.6
300	241.1 ± 13.7	76.2	23.8

~ 20%

Cultured skeletal muscle cells were treated with 0.1 – 300 μM forskolin for 30 min at 37°C, in the presence of 100 μM IBMX.

Chiavegatti *et al.*,
Br J Pharmacol (2008) 153, 1331
doi:10.1038/sj.bjp.0707648

J Biol. Chem 238:3009-15 (1963)

THE EFFECT OF L-EPINEPHRINE AND OTHER AGENTS ON THE SYNTHESIS AND RELEASE OF ADENOSINE 3',5'-PHOSPHATE BY WHOLE PIGEON ERYTHROCYTES

P R DAVOREN, E W SUTHERLAND

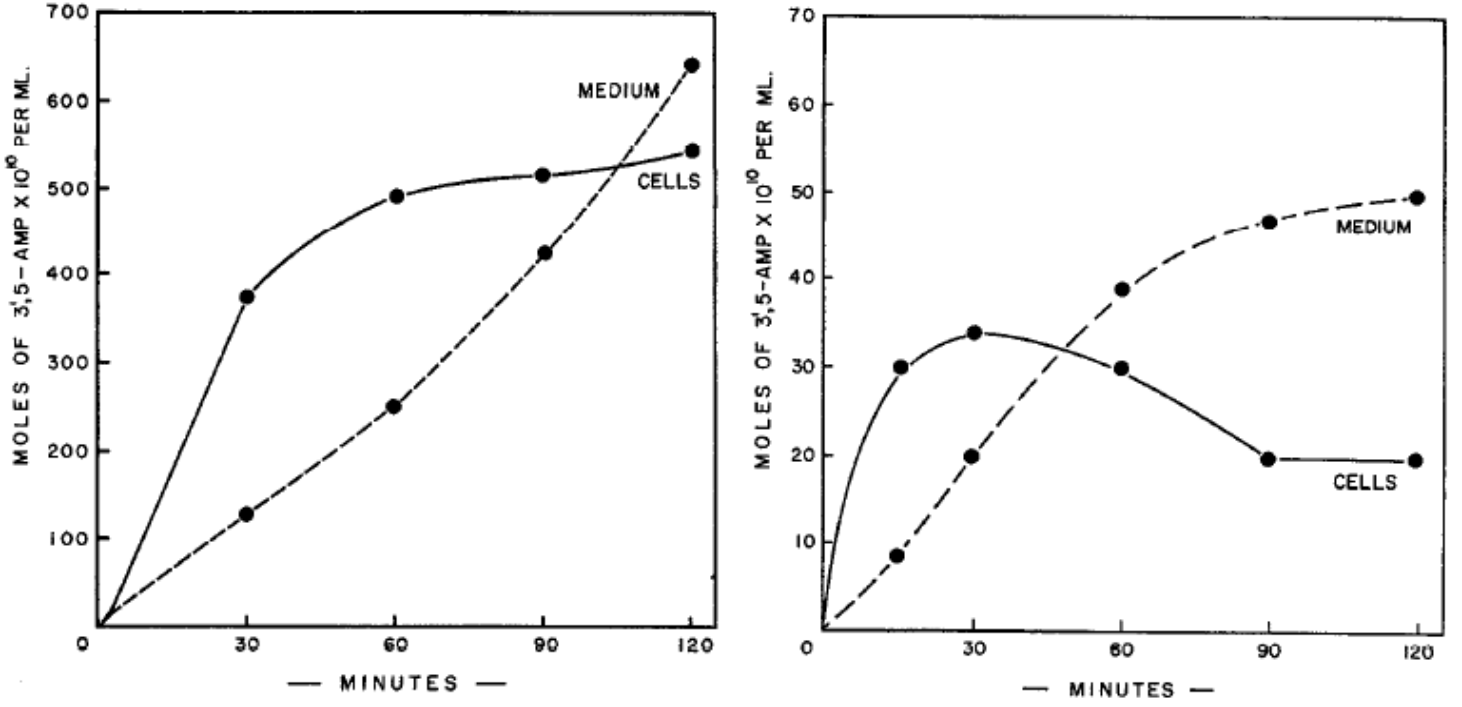


FIG. 2. The synthesis and release of cyclic 3′,5′-AMP by pigeon erythrocytes. Each 2-ml aliquot of incubation mixture contained 1 ml of packed erythrocytes and 1 ml of medium. The cyclic 3′,5′-AMP content of cell lysates and of media are expressed per ml of packed cells and per ml of medium. *Left*, results when the L-epinephrine concentration in the system was 5×10^{-5} M; *right* results for a concentration of 5×10^{-7} M.

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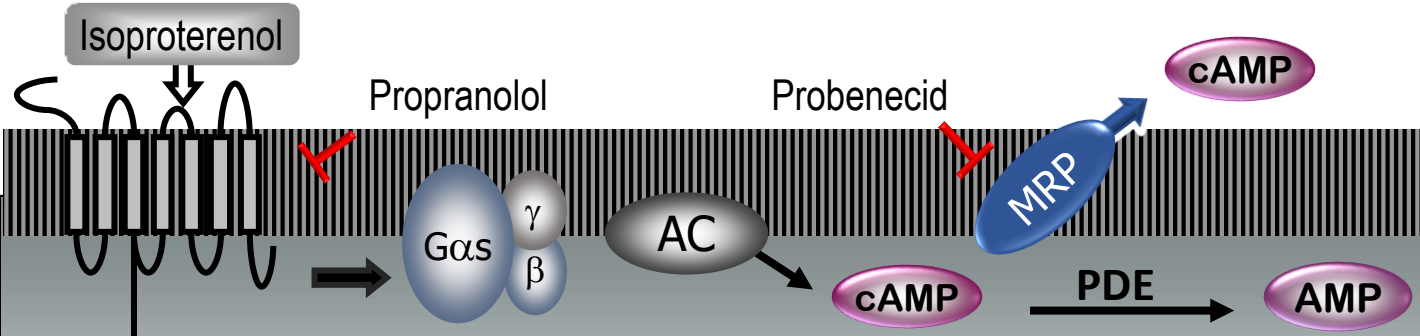
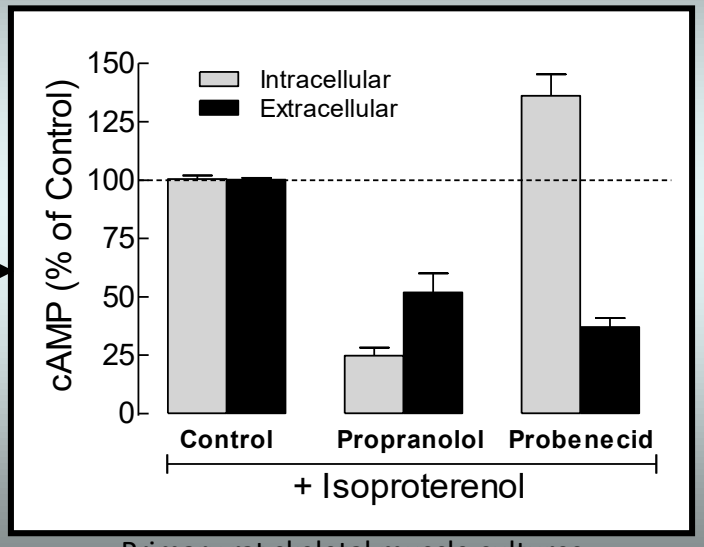
Vol. 278, No. 20, Issue of May 16, pp. 17664–17671, 2003
Printed in U.S.A.

Characterization of the MRP4- and MRP5-mediated Transport of Cyclic Nucleotides from Intact Cells*

Received for publication, December 13, 2002, and in revised form, February 12, 2003
Published, JBC Papers in Press, March 13, 2003, DOI 10.1074/jbc.M212723200

Peter R. Wielinga‡, Ingrid van der Heijden‡, Glen Reid‡, Jos H. Beijnen§, Jan Wijnholds¶, and Piet Borst‡‖

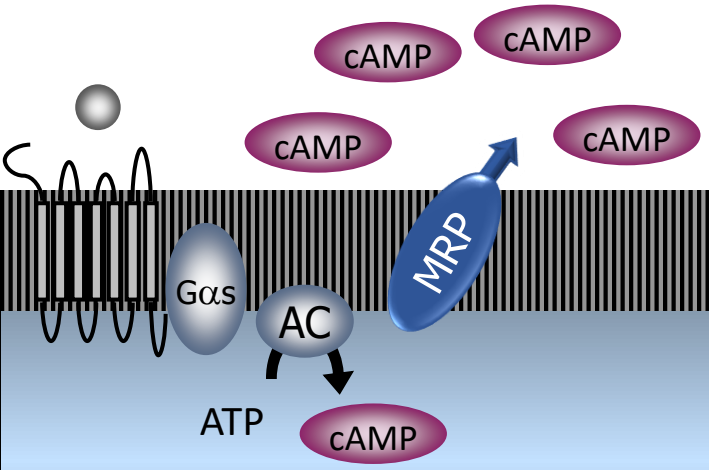




Primary rat skeletal muscle cultures

Chiavegatti *et al.*,
Br J Pharmacol (2008) 153, 1331
doi:10.1038/sj.bjp.0707648

Extracellular cAMP signaling



extracelullar

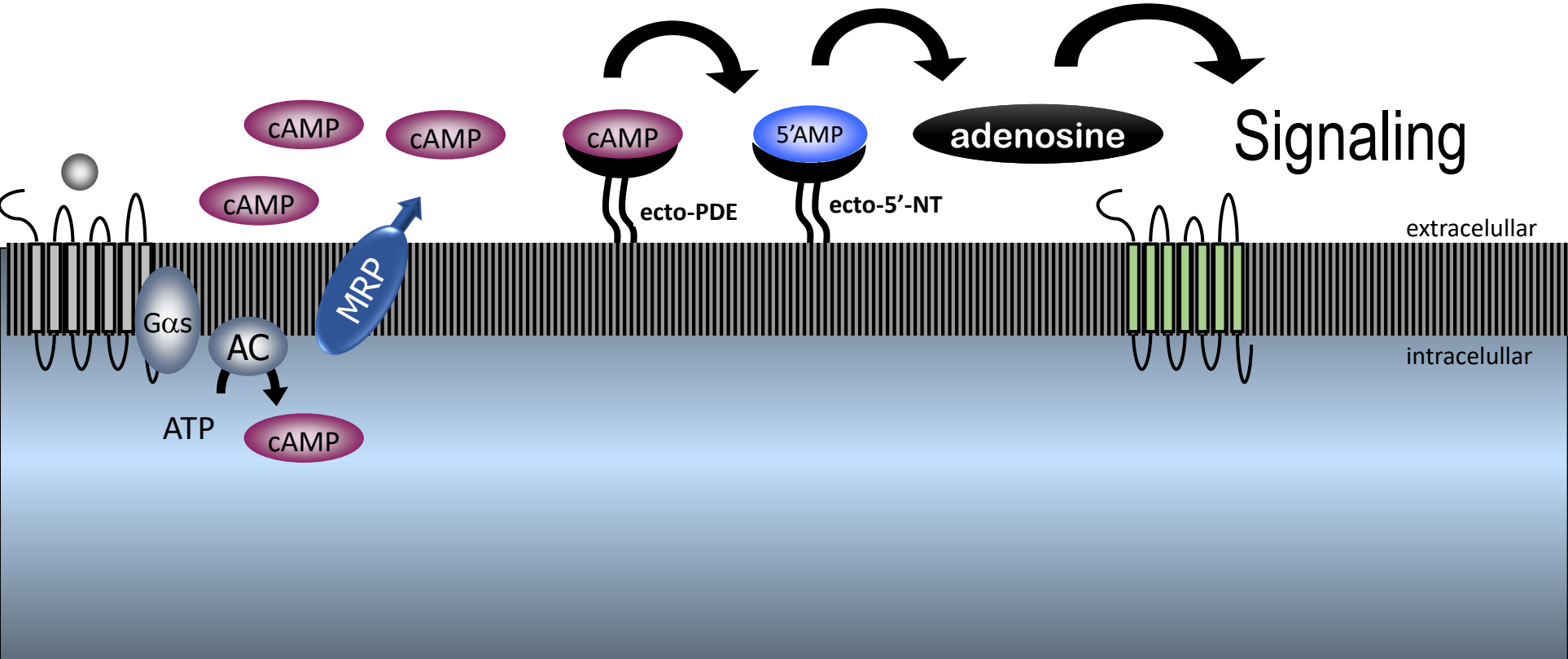
intracelullar

Hypertension
Volume 28, Issue 5, November 1996, Pages 765-771
https://doi.org/10.1161/01.HYP.28.5.765

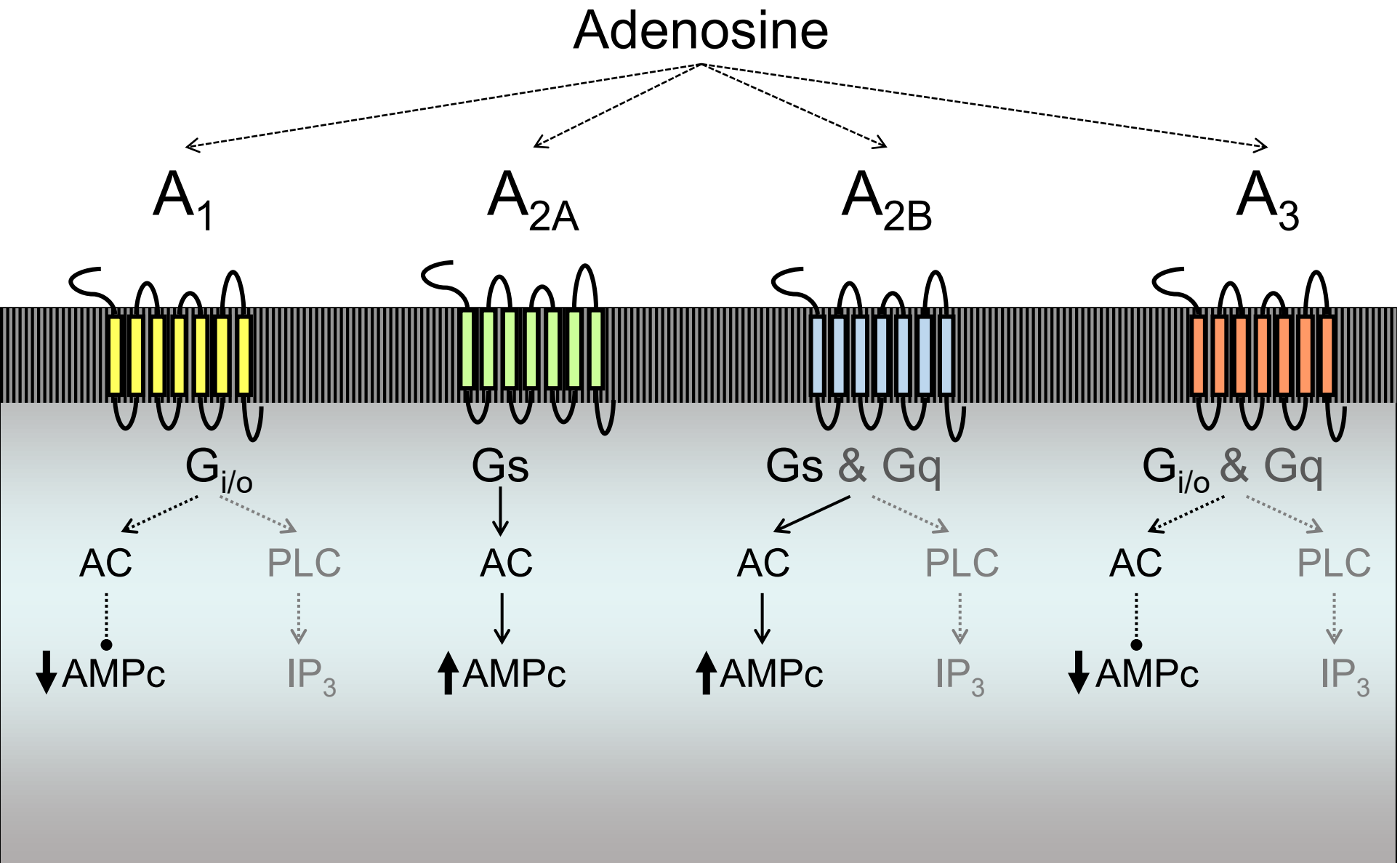
ARTICLE

Cyclic AMP–Adenosine Pathway Inhibits Vascular Smooth Muscle Cell Growth

Raghvendra K. Dubey, Zaichuan Mi, Delbert G. Gillespie, and Edwin K. Jackson

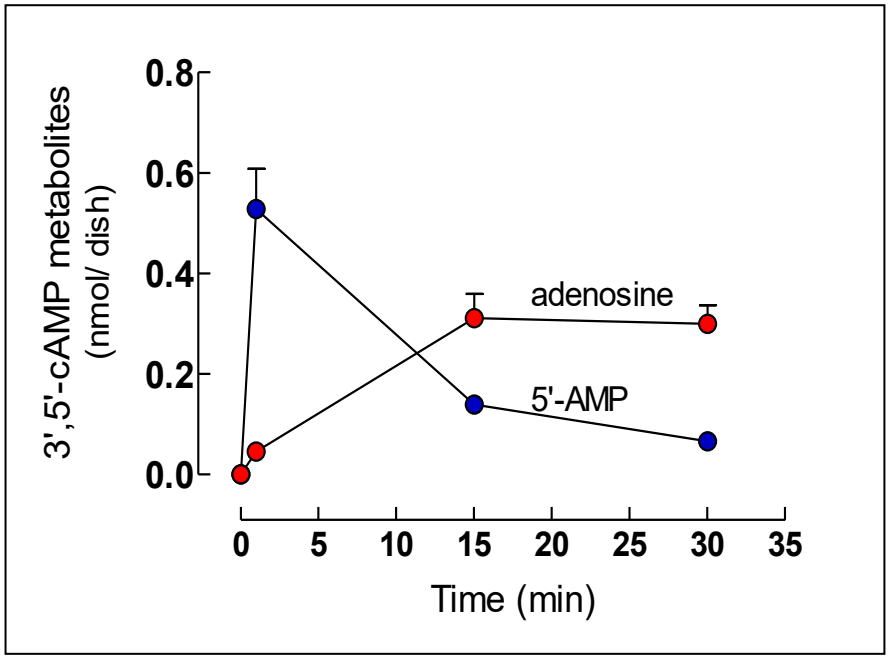


Adenosine Receptors



The extracellular 3’,5’-cAMP–adenosine pathway:

Extracellular cAMP is converted to AMP and adenosine by ectoenzymes



Primary rat skeletal muscle cultures

Chiavegatti *et al.*, Br J Pharmacol (2008) 153, 1331
doi:10.1038/sj.bjp.0707648

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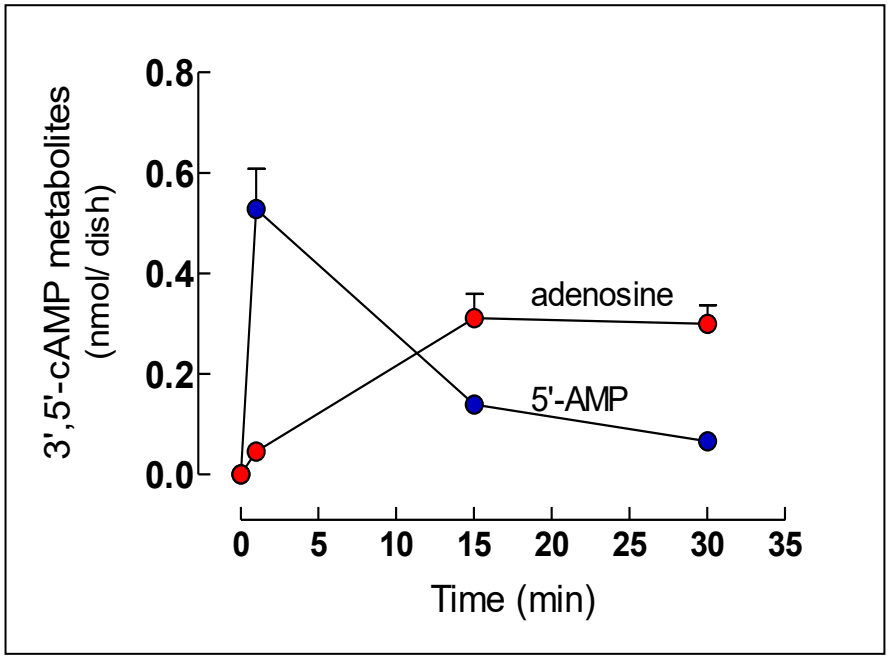

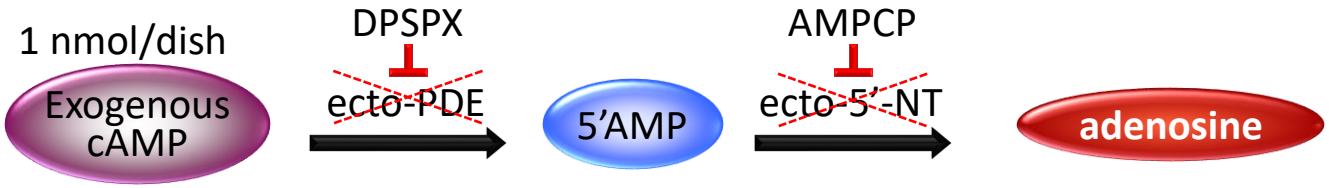

Primary rat skeletal muscle cultures

Chiavegatti *et al.*, Br J Pharmacol (2008) 153, 1331
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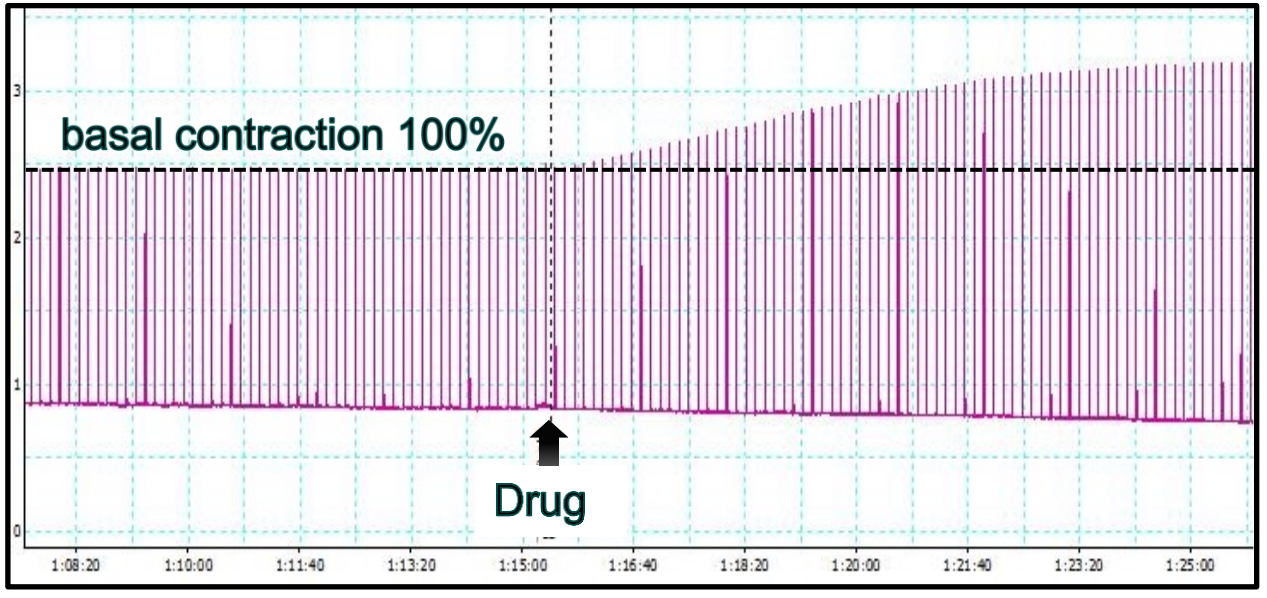
Mouse diaphragm muscle

isometric contractility

supramaximal direct electrical stimulation

0.1 Hz, 2 ms duration;



Inotropic effect

Extracellular cAMP-adenosine pathway in skeletal muscle

3',5'-cAMP does not cross the cell membrane!

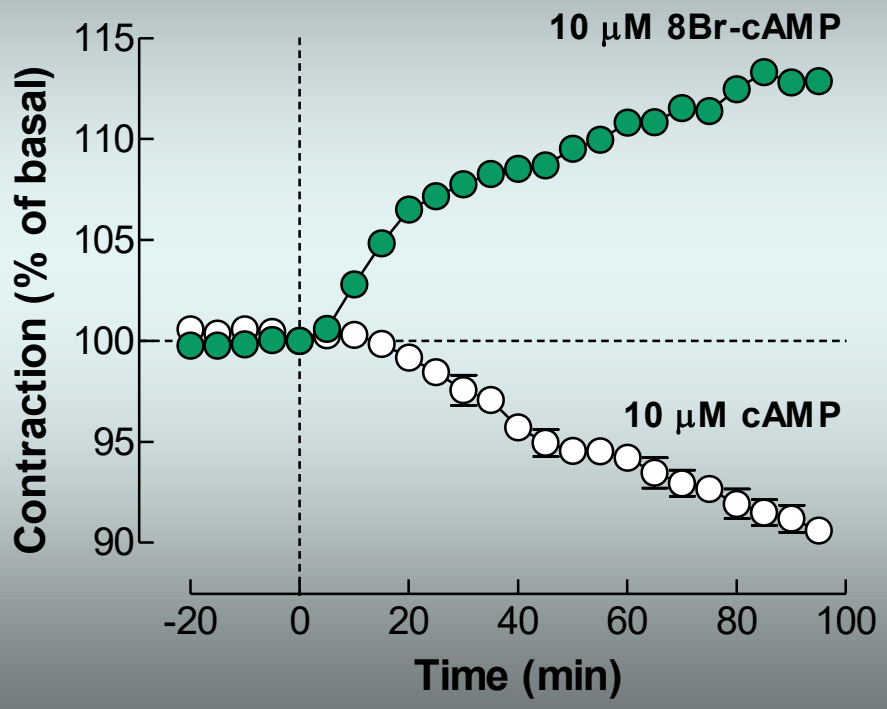
cAMP

8-Br cAMP

extracellular

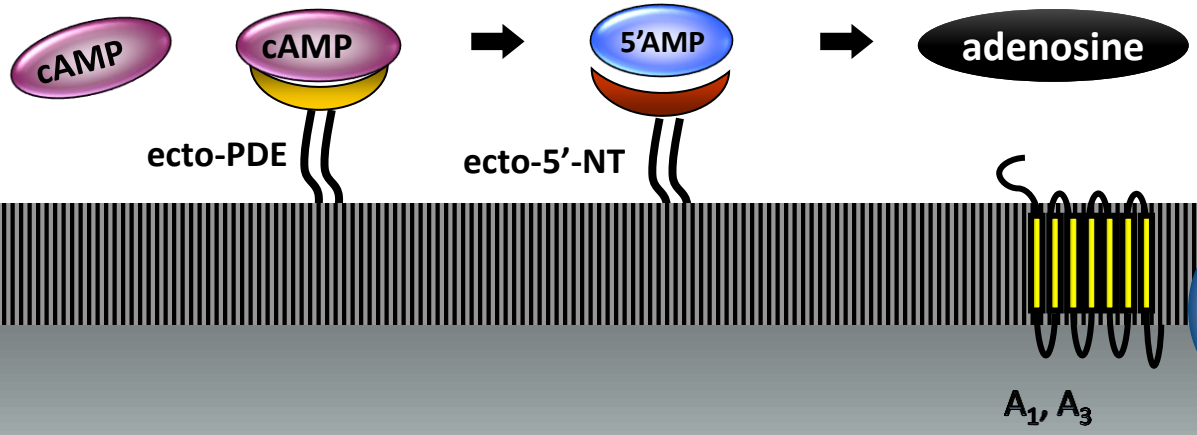
intracelullar

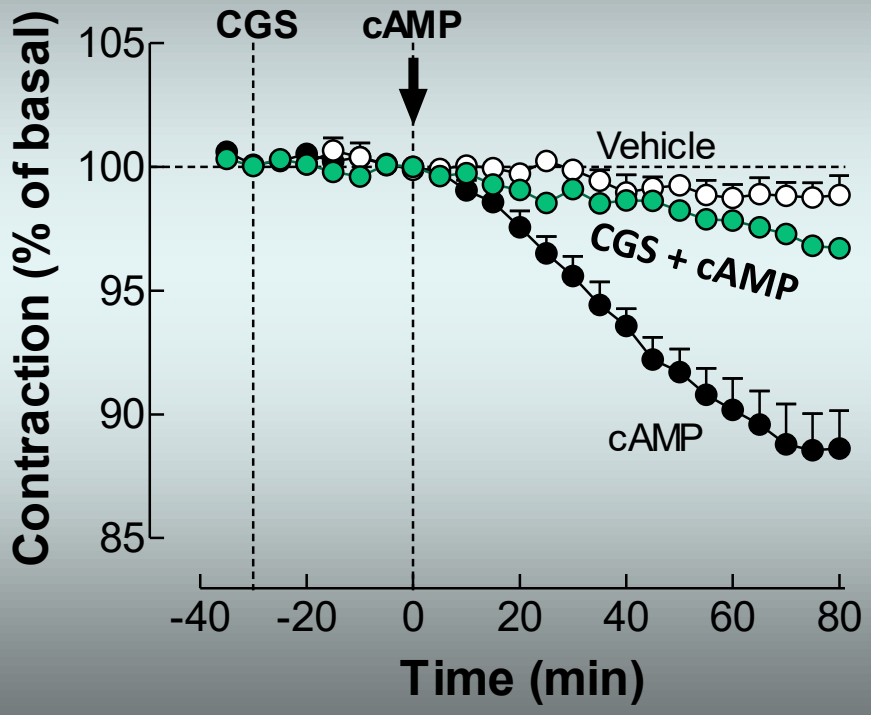
8-Br cAMP — cell permeable, PDE-resistant cAMP analog



Mouse diaphragm (direct electrical stimulation)
Duarte et al., J Pharmacol Exp Ther, 341:820–828, 2012

Extracellular cAMP-adenosine pathway in skeletal muscle

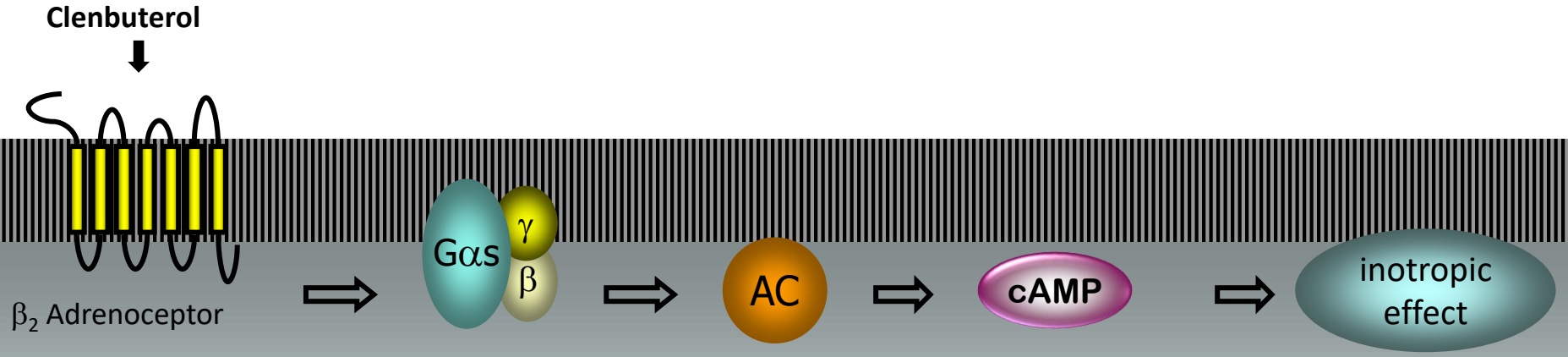


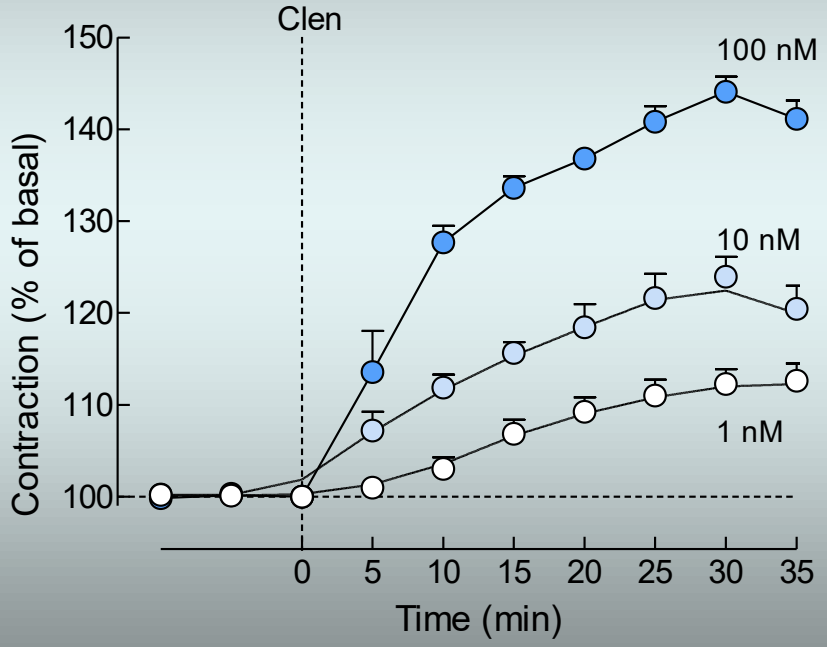


CGS 15943 = non-selective adenosine receptor antagonist

Mouse diaphragm (direct electrical stimulation)
Duarte et al., J Pharmacol Exp Ther, 341:820–828, 2012

Activation of β_2 adrenoceptor increases skeletal muscle contraction





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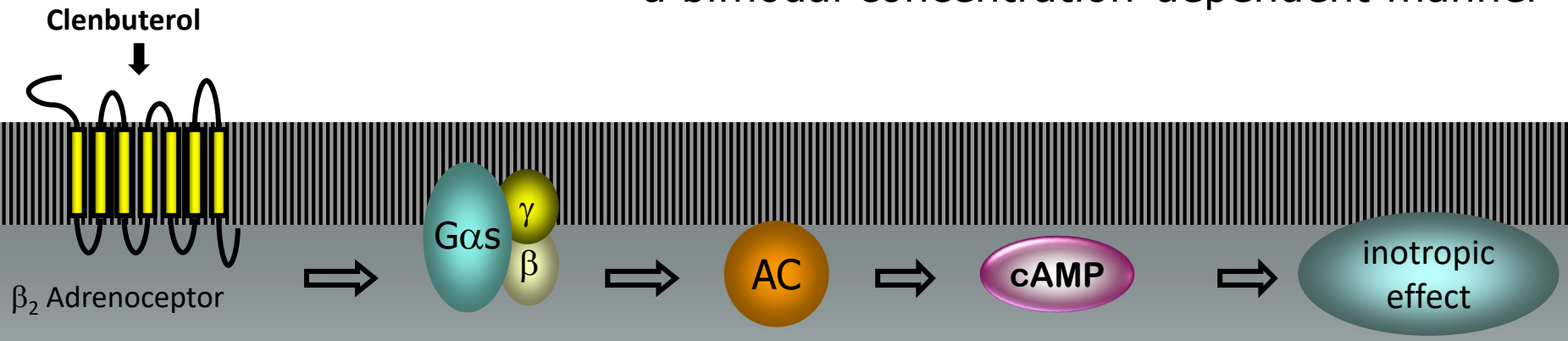
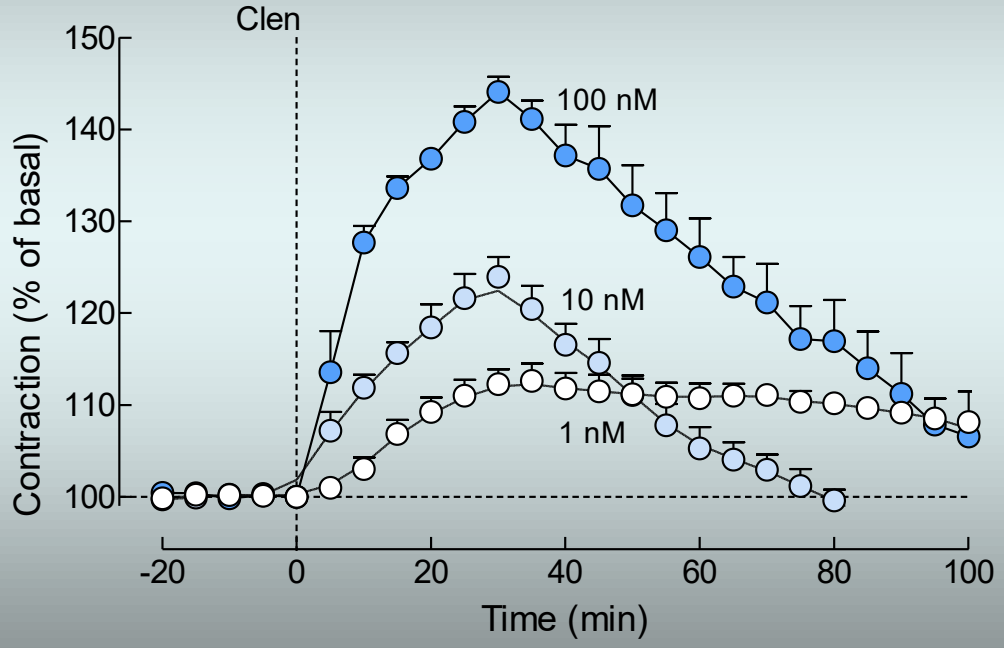
β_2-adrenoceptor agonists potentiate skeletal muscle contraction force in a bimodal concentration-dependent manner





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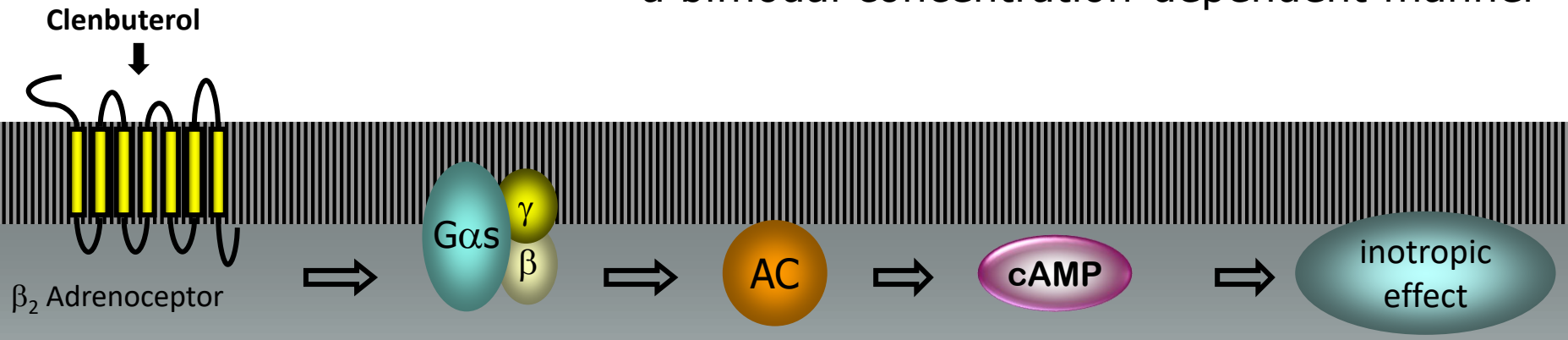

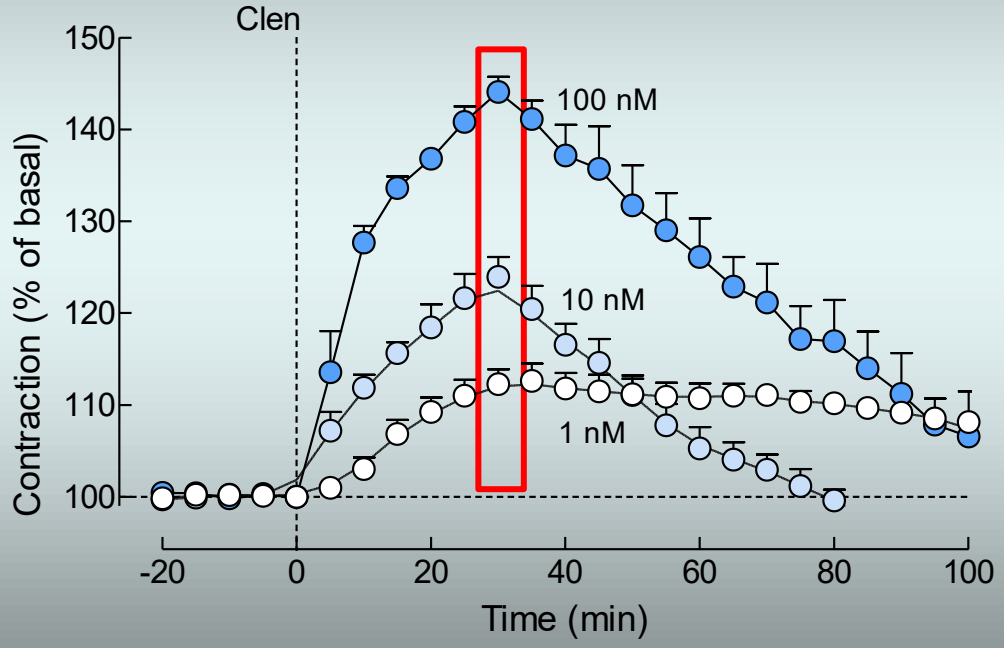

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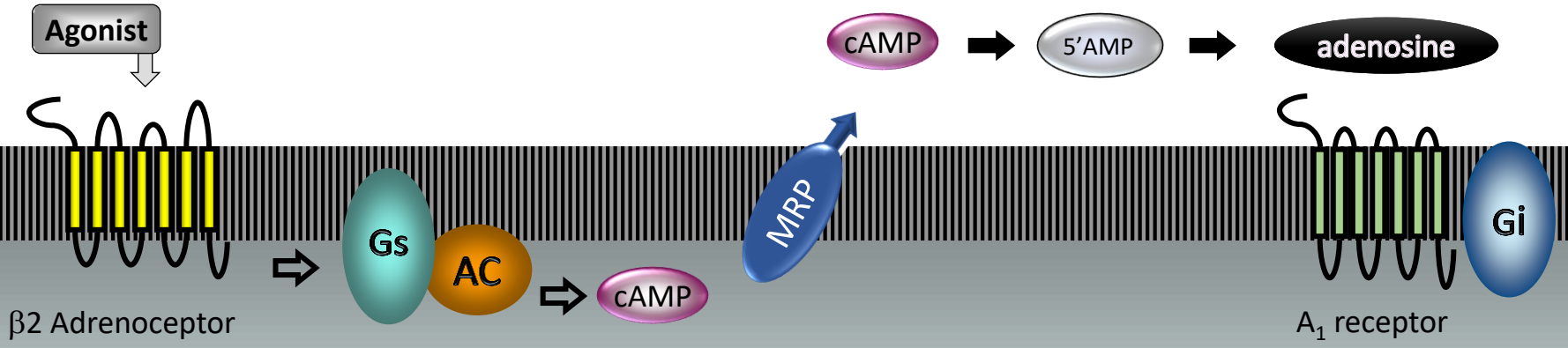
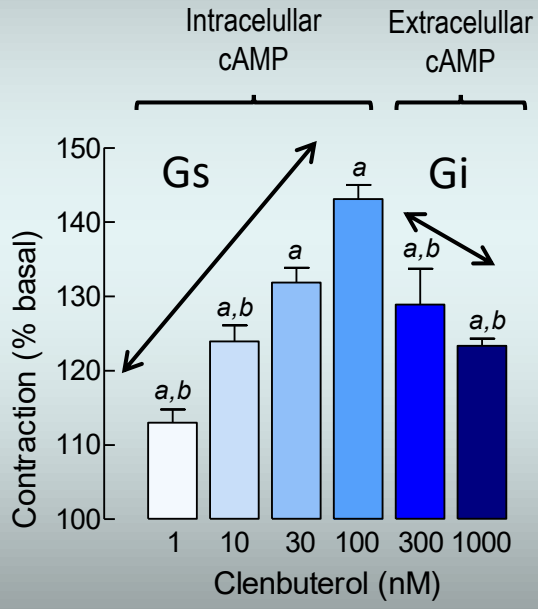
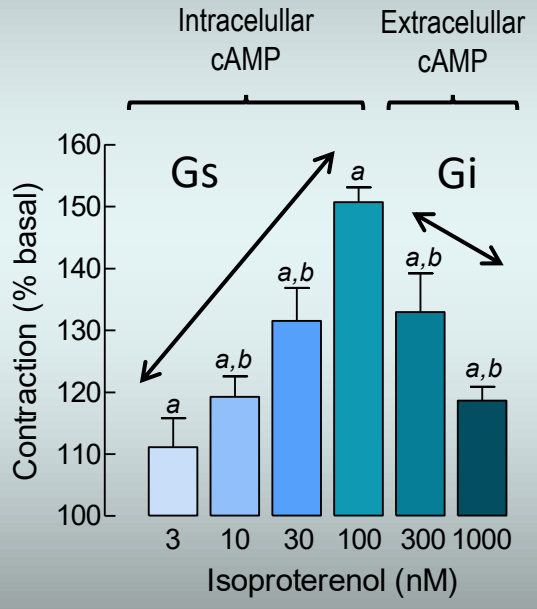
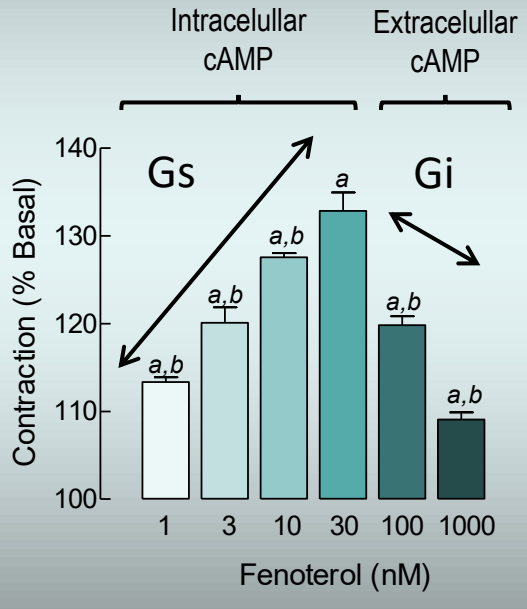


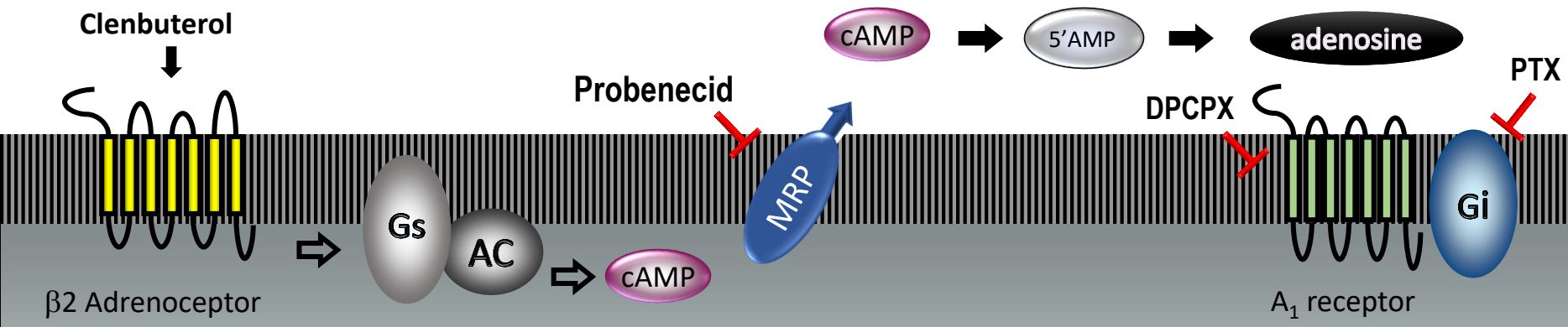


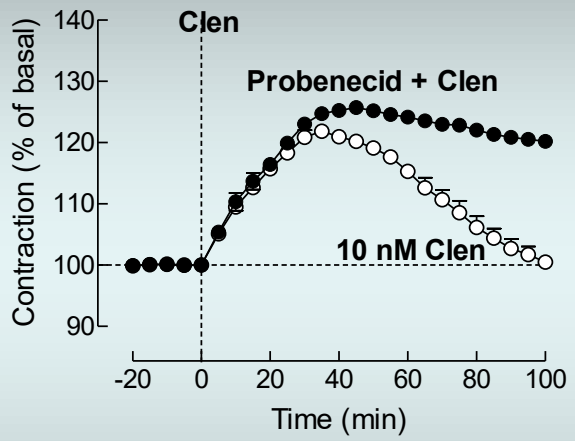


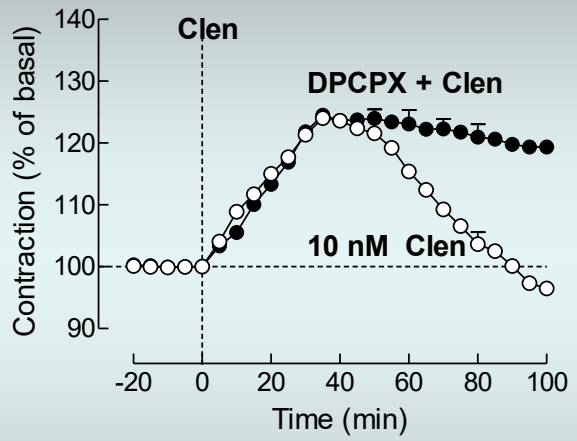


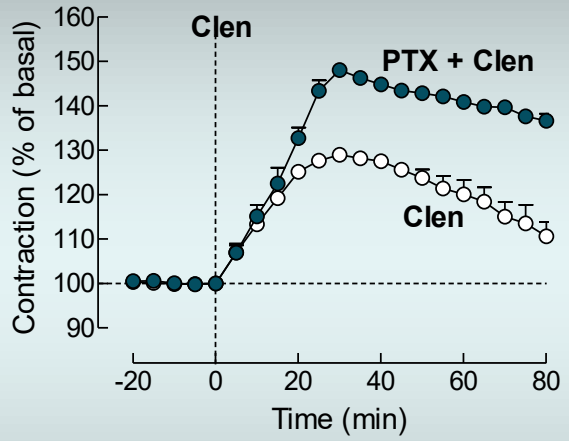
Duarte et al., J Pharmacol Exp Ther, 341:820–828, 2012

The late descending phase of clenbuterol inotropic effect depends on extracellular cAMP–adenosine pathway







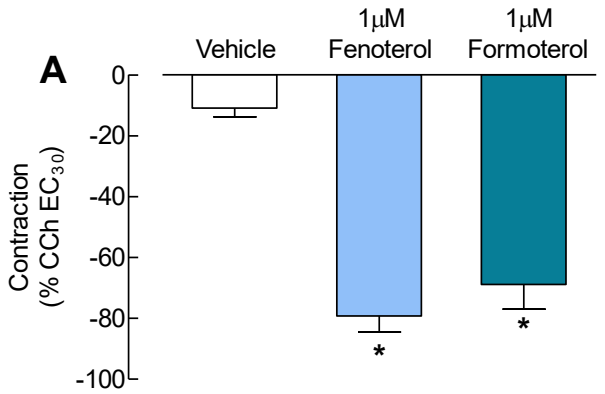


Probenecid = MRP inhibitor
DPCPX = A1 receptor antagonist
PTX = G1 protein inhibitor

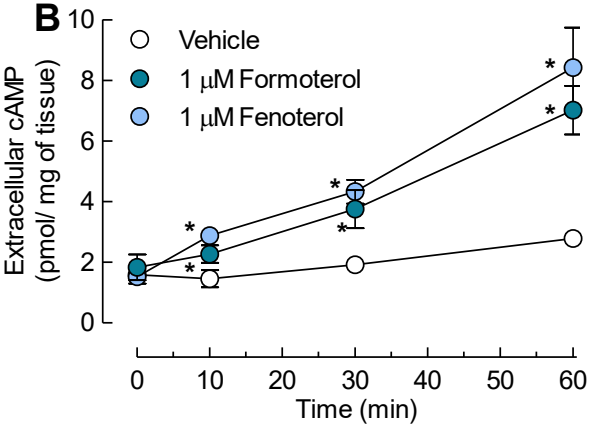
Mouse diaphragm (direct electrical stimulation)
Duarte et al., J Pharmacol Exp Ther, 341:820–828, 2012

Rat Tracheal Rings

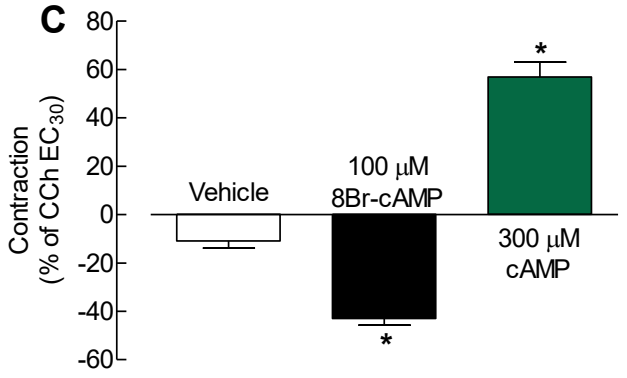
β_2 adrenoceptor agonists induce relaxation of smooth muscle



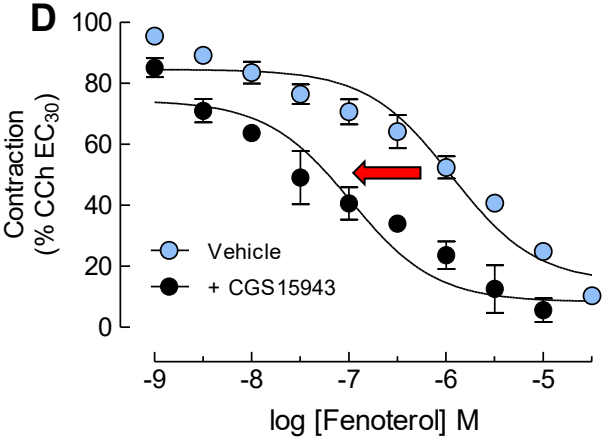
β_2-adrenoceptor agonists increase extracellular accumulation of cAMP



8Br-cAMP induce relaxation whereas cAMP induces contraction of smooth muscle

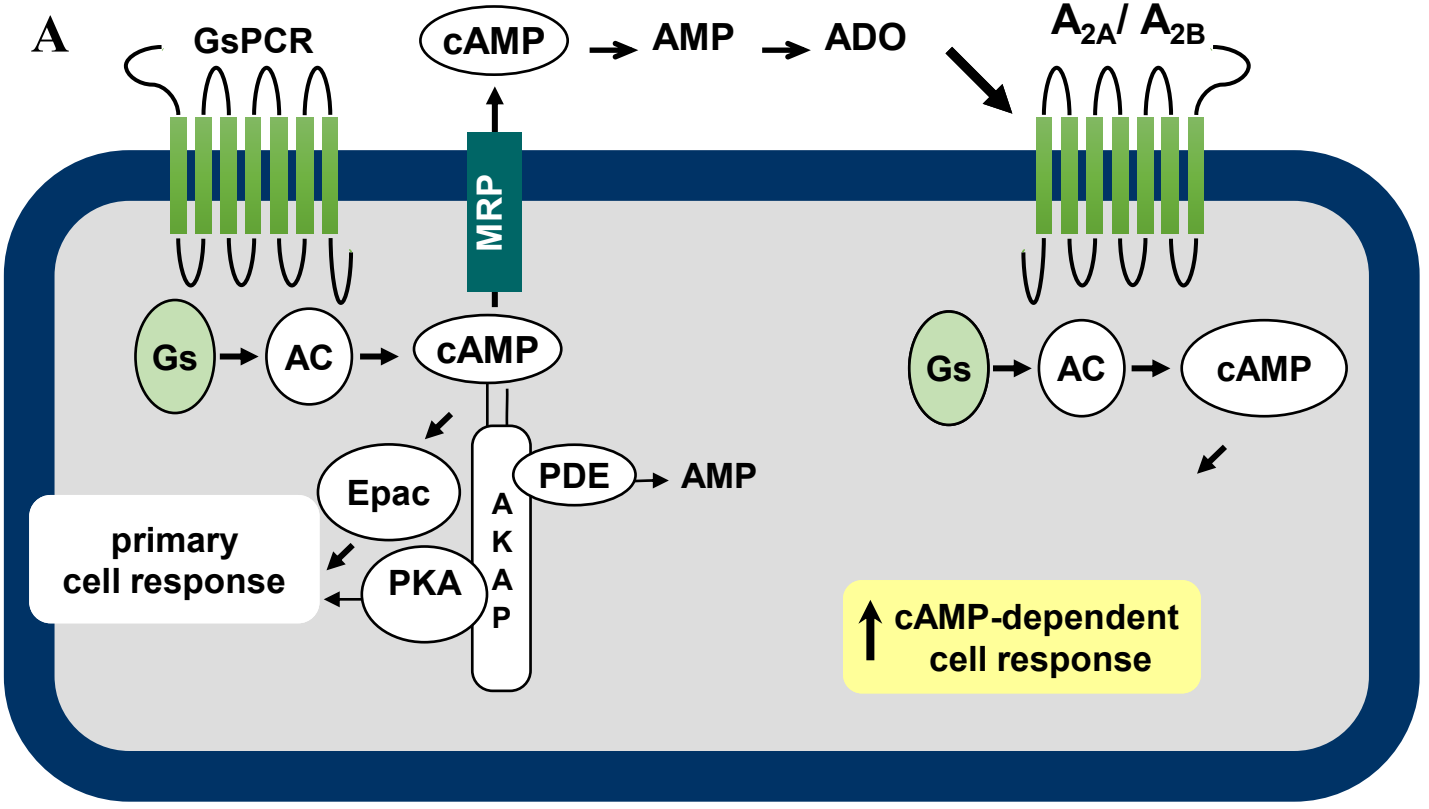


Nonselective adenosine receptor antagonist potentiates the relaxation effect of Fenoterol



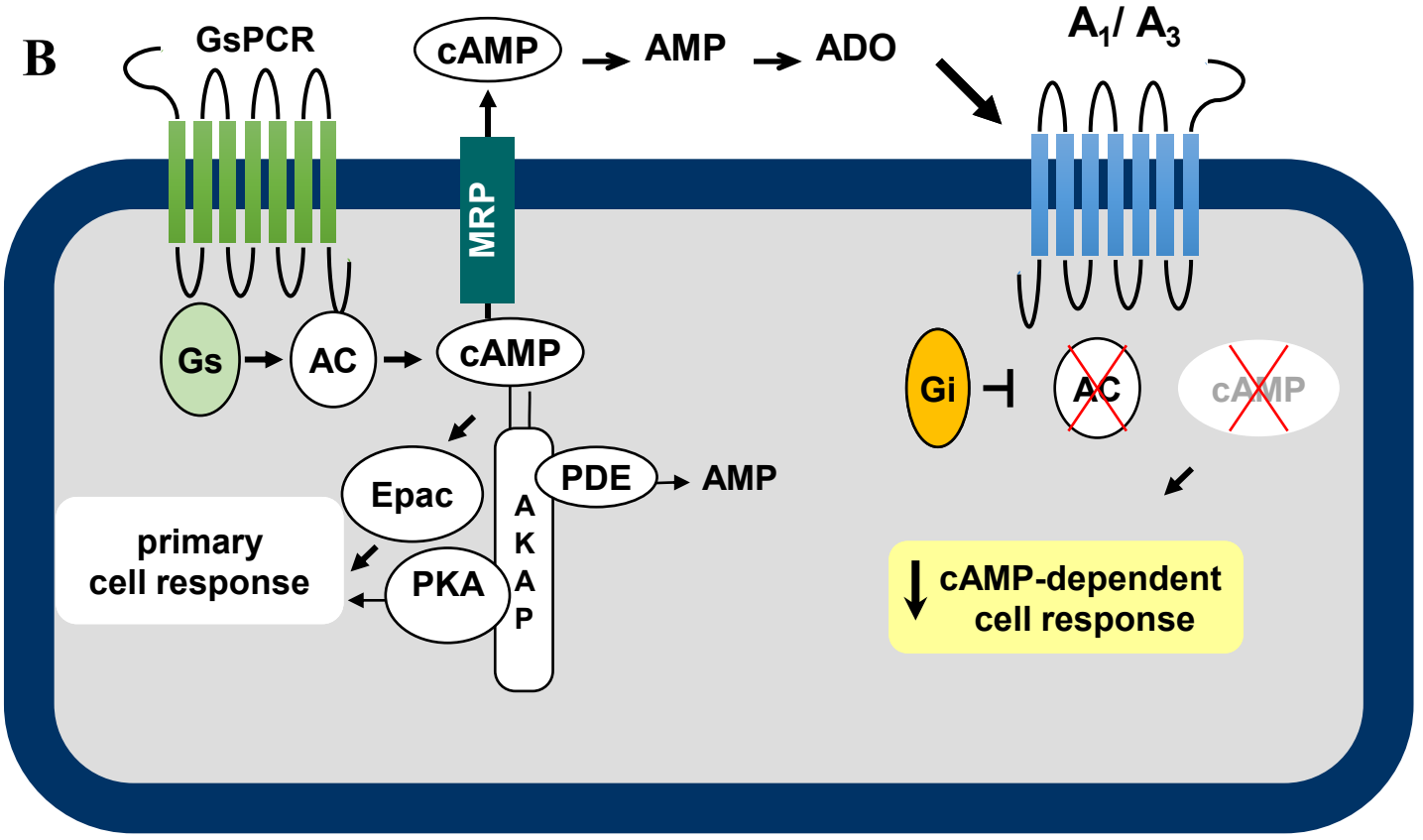
Pacini *et al.*, J Pharmacol Exp Ther 366:75–83, 2018 https://doi.org/10.1124/jpet.118.247734

Feedback Function of the Extracellular 3',5'-cAMP-Adenosine Pathway



Godinho *et al.*, Frontiers in Pharmacology, 6:58, 2015

Negative Feedback Functions of the Extracellular 3',5'-cAMP-Adenosine Pathway



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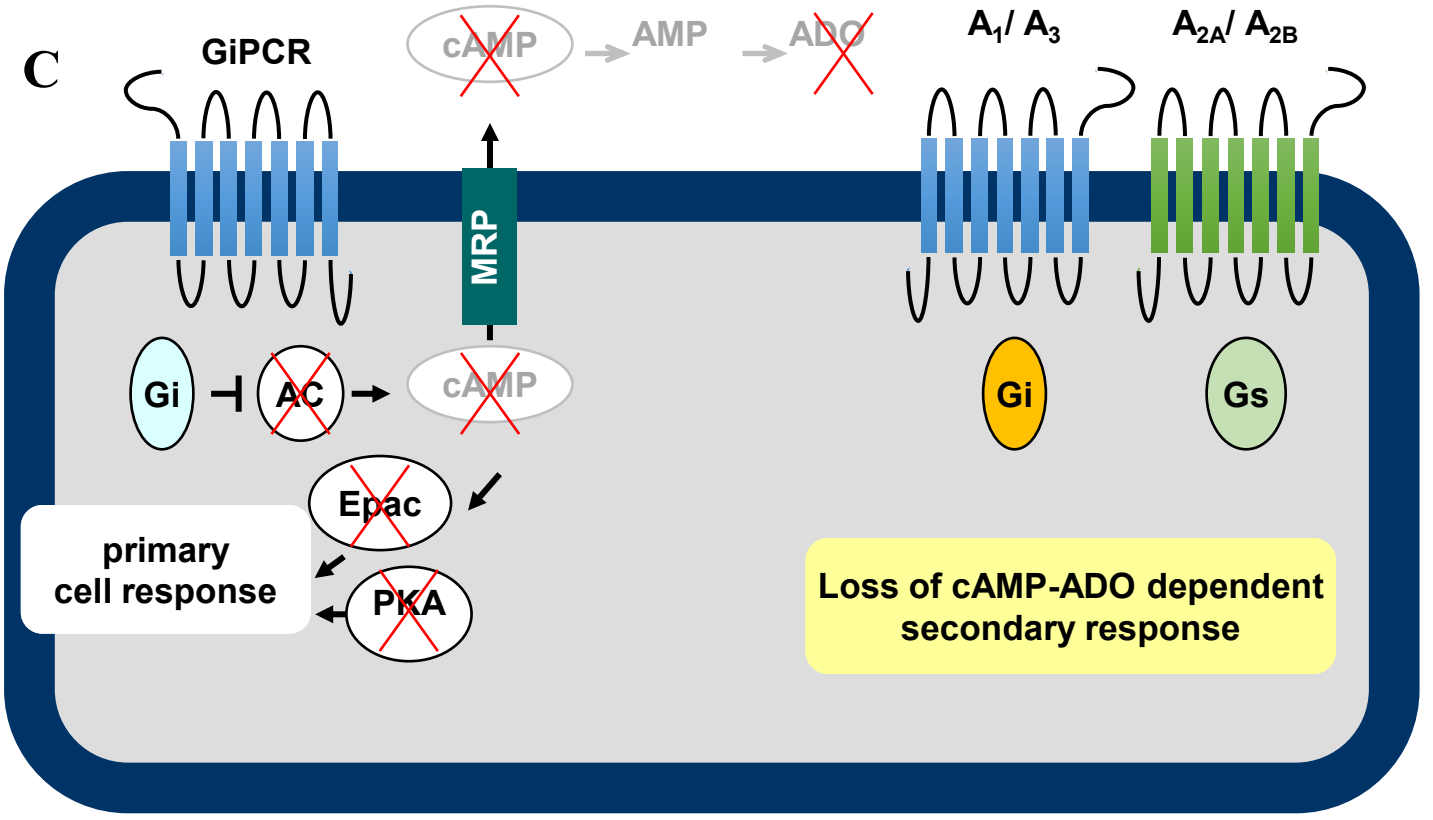
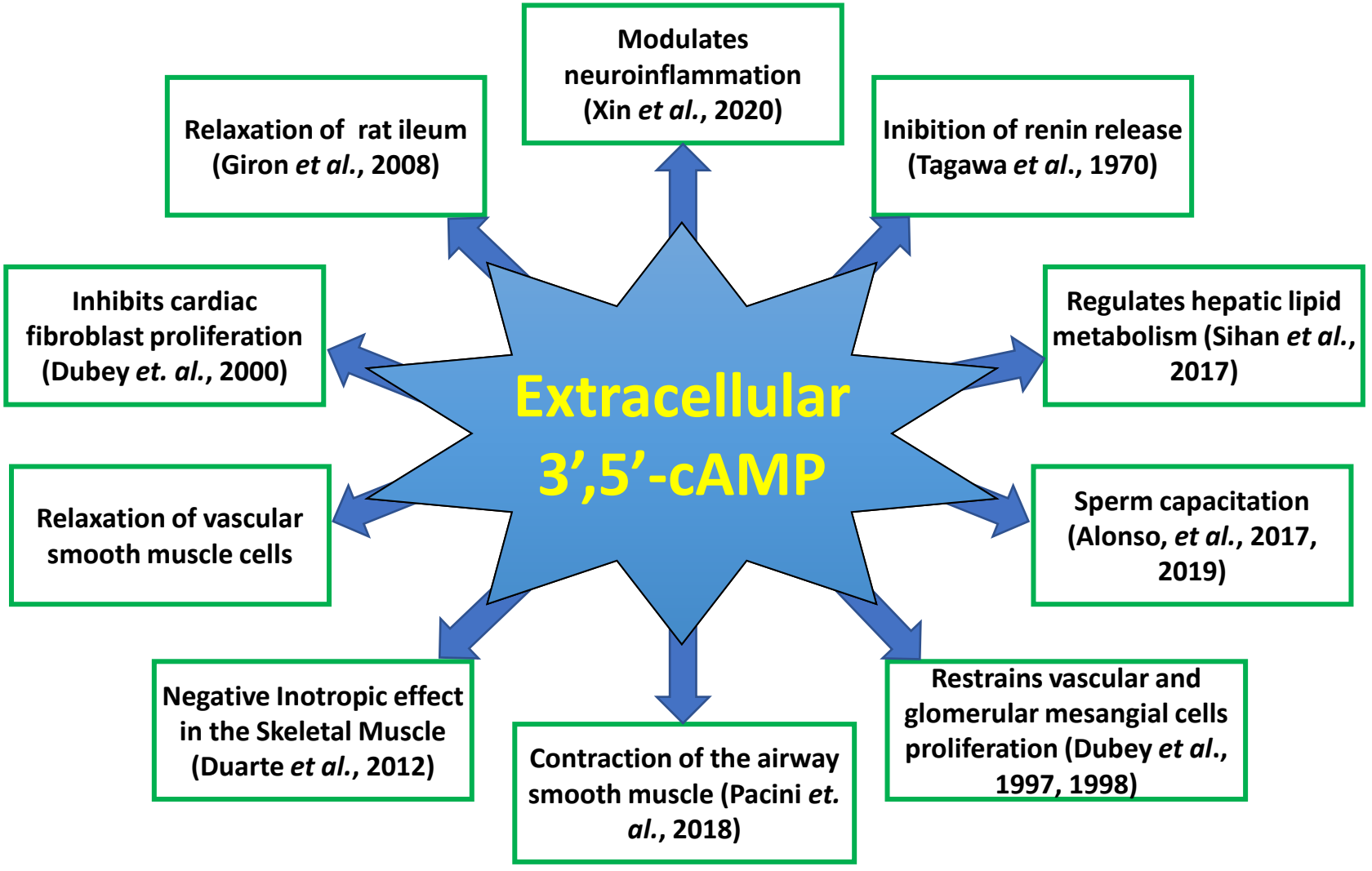


Godinho *et al.*, Frontiers in Pharmacology, 6:58, 2015

3’,5’- cAMP Function



The extracellular 2’,3’-cAMP – adenosine pathway:

0022-3565/09/3283-855–865$20.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
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JPET 328:855–865, 2009

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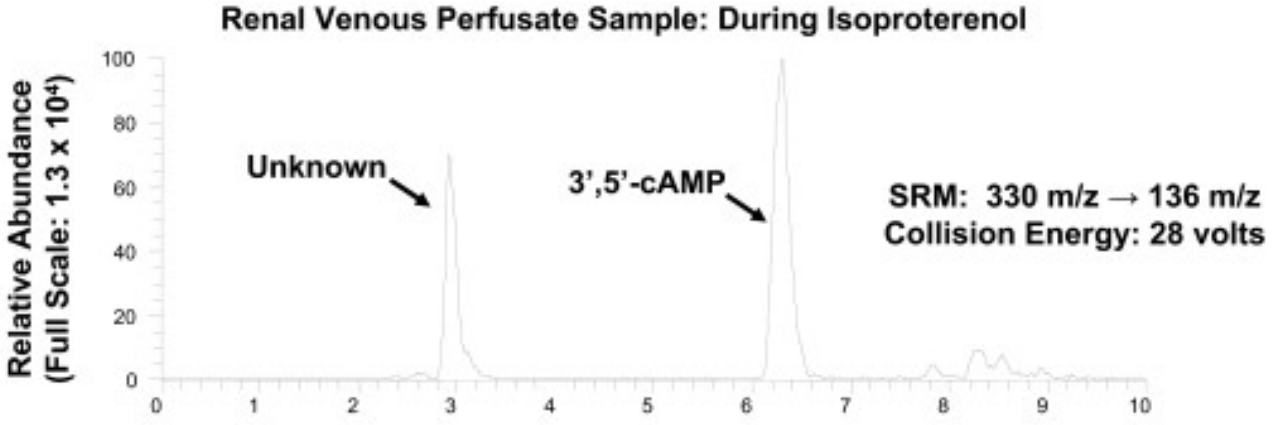
Identification and Quantification of 2′,3′-cAMP Release by the Kidney

Jin Ren, Zaichuan Mi, Nicolas A. Stewart, and Edwin K. Jackson



Liquid chromatography-tandem mass spectrometry (LC-MS/MS)

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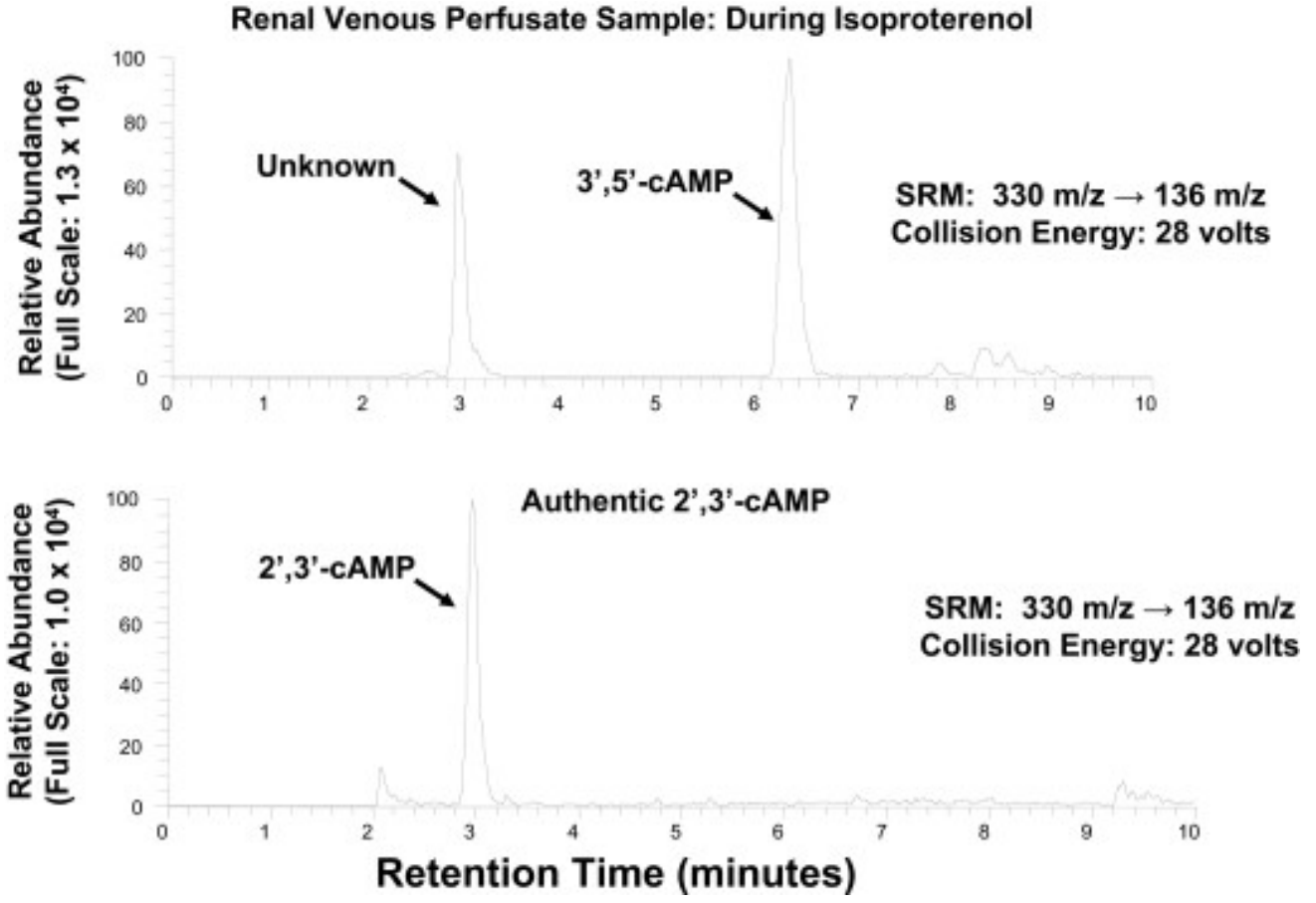
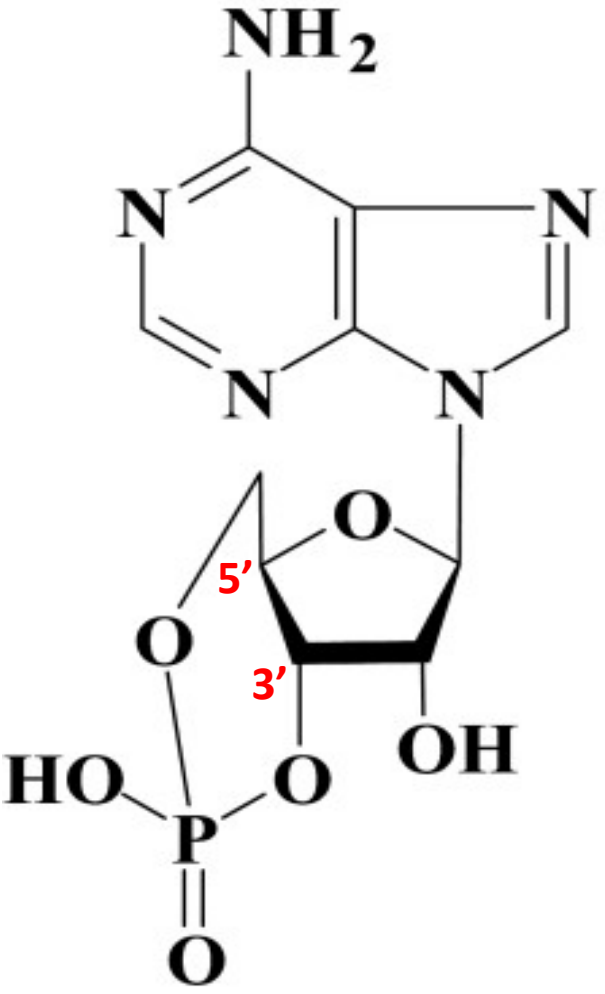
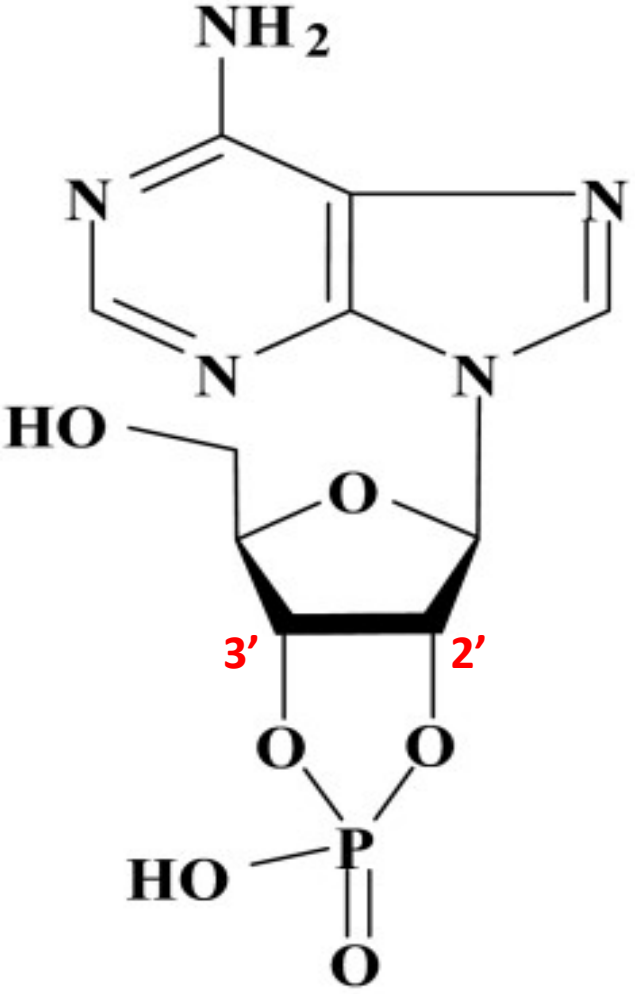
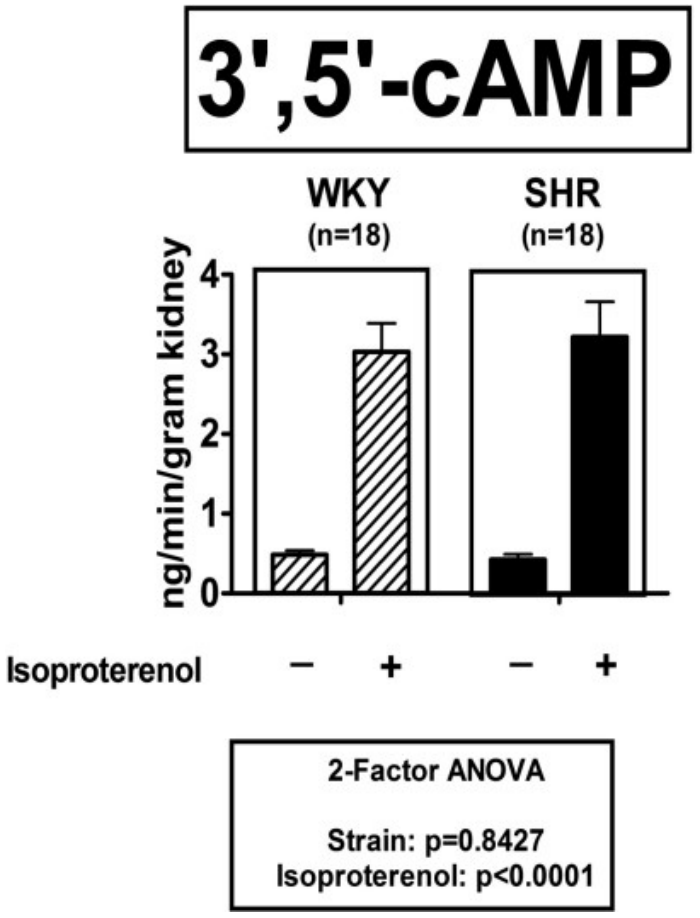


3’,5’-cAMP



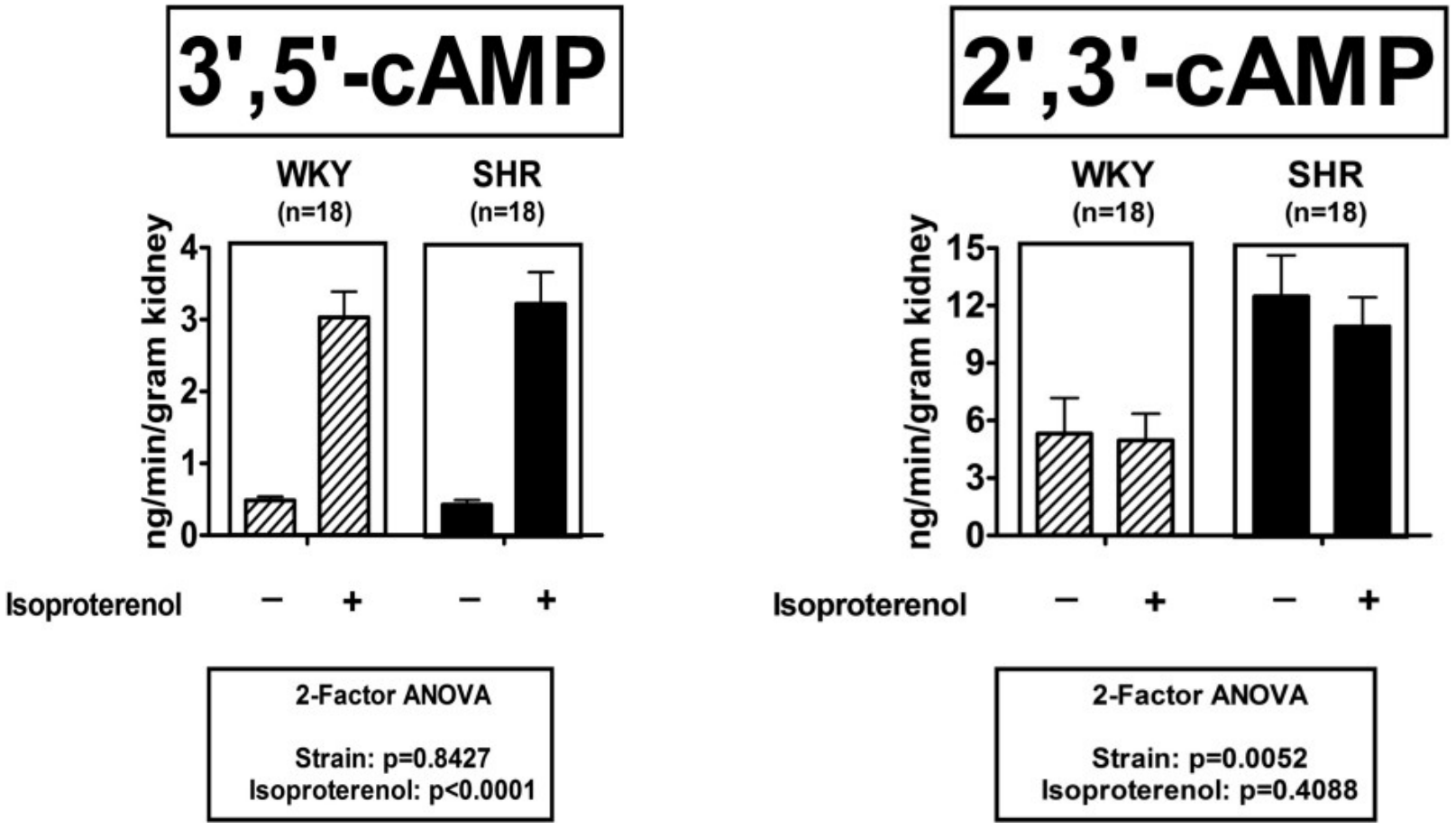
2’,3’-cAMP





Renal venous secretion rate of 3',5'-cAMP in kidneys from SHRs and WKY rats both under basal conditions and with the addition of isoproterenol (1μM) to stimulate adenylyl cyclase via β-adrenoceptors.

Ren Et al., J Pharmacol Exp Ther. 2009 328(3): 855-865.
doi: 10.1124/jpet.108.146712



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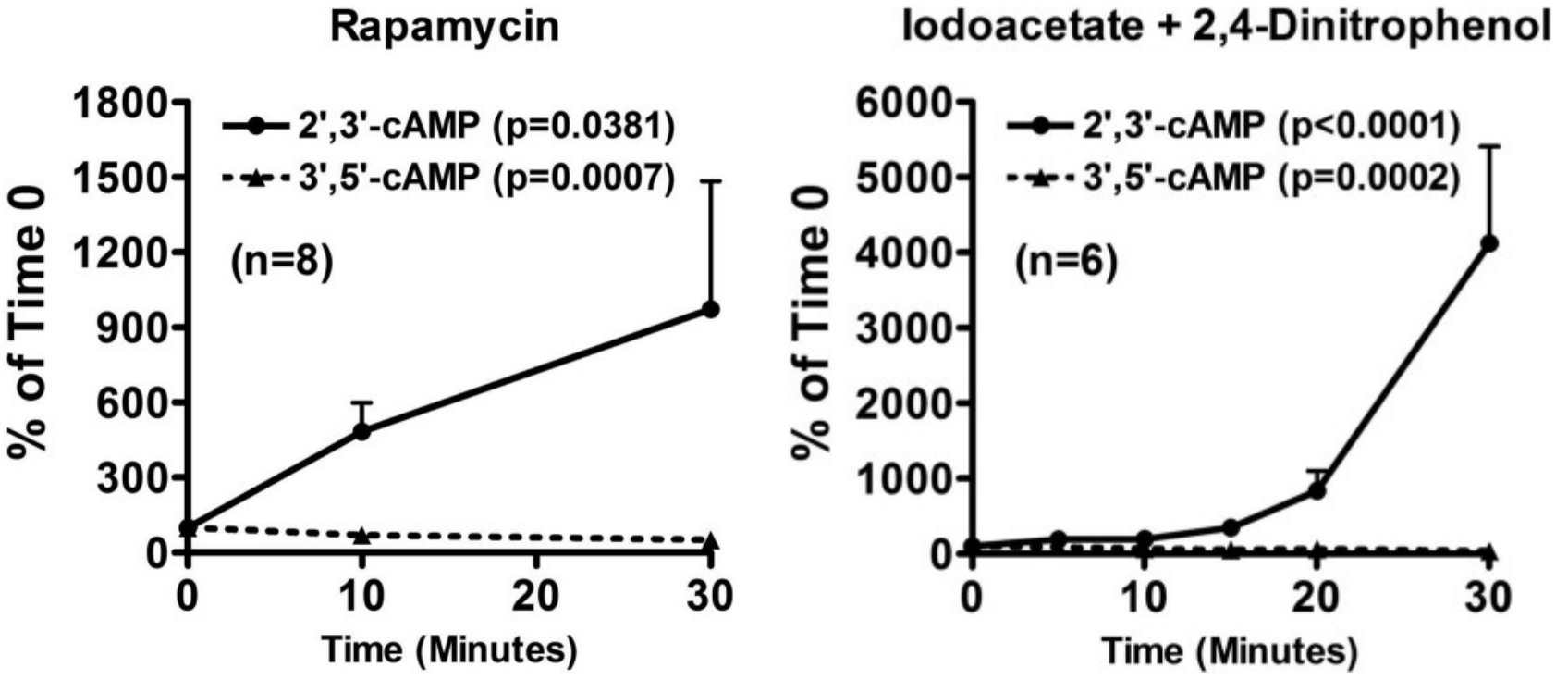

Rapamycin (0.2 μM; activator of mRNA turnover) and iodoacetate 2,4-dinitrophenol (50 μM; metabolic inhibitors) increased the renal venous secretion of 2,3-cAMP (~1000 and 4100% of control, respectively).

Ren Et al., J Pharmacol Exp Ther. 2009 328(3): 855-865.
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2',3'-cAMP is:

- ✓ a naturally occurring endogenous isomer of 3',5'-cAMP;
- ✓ **not made by adenylyl cyclase;**
- ✓ released from kidneys into the extracellular compartment;
- ✓ released more by kidneys from rats with long-standing hypertension (SHR);

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- ✓ **derived from mRNA turnover;**

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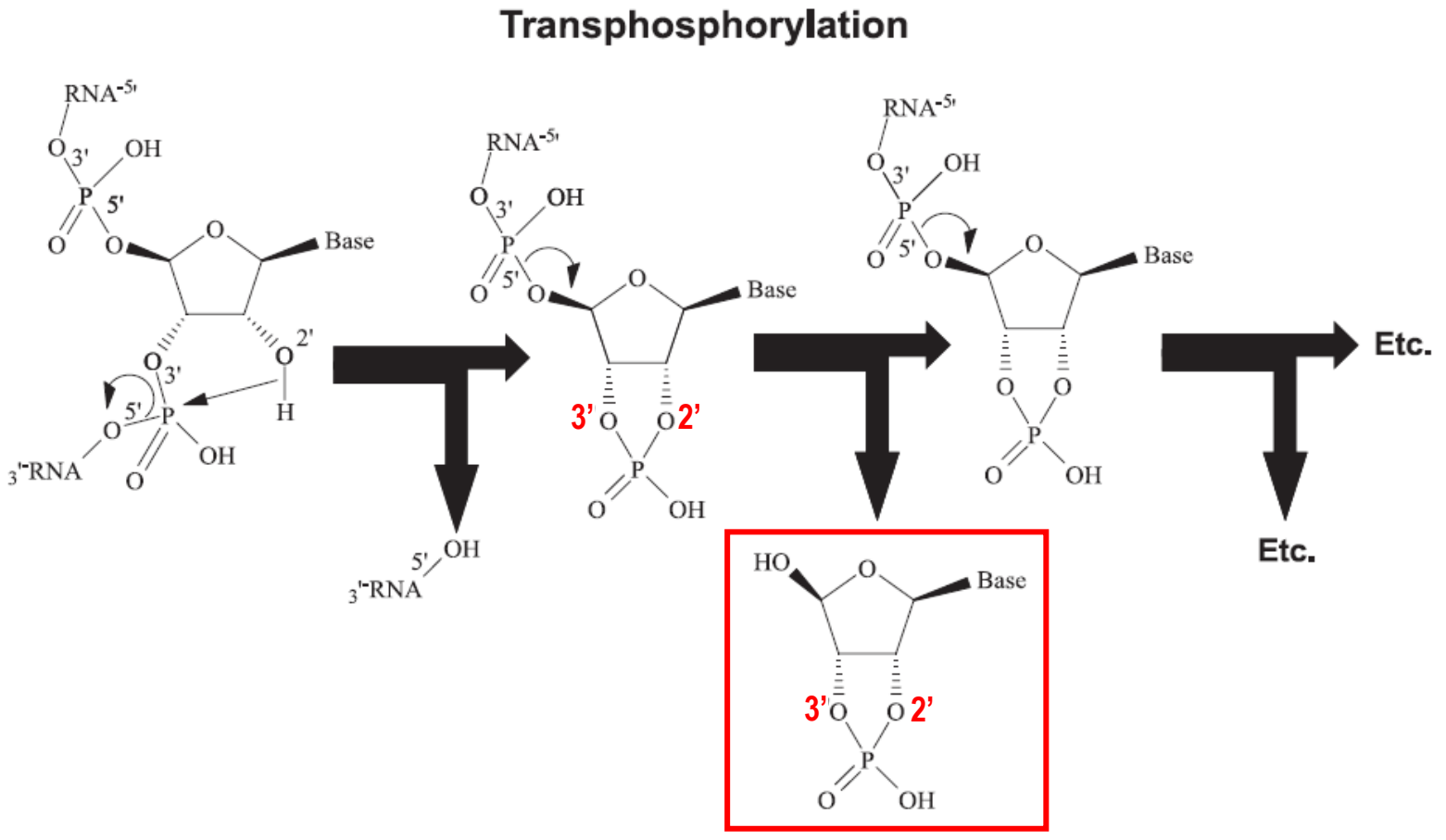
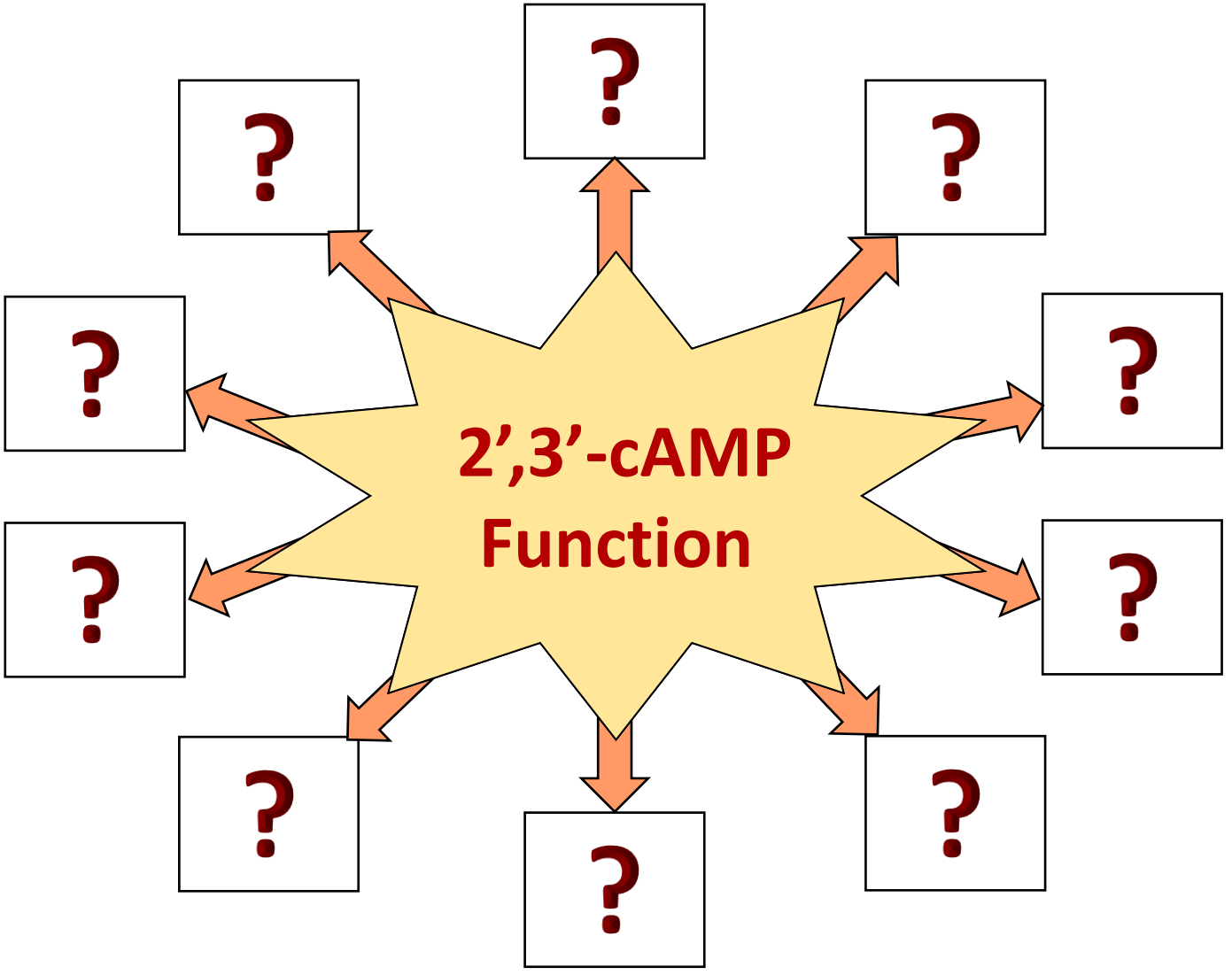
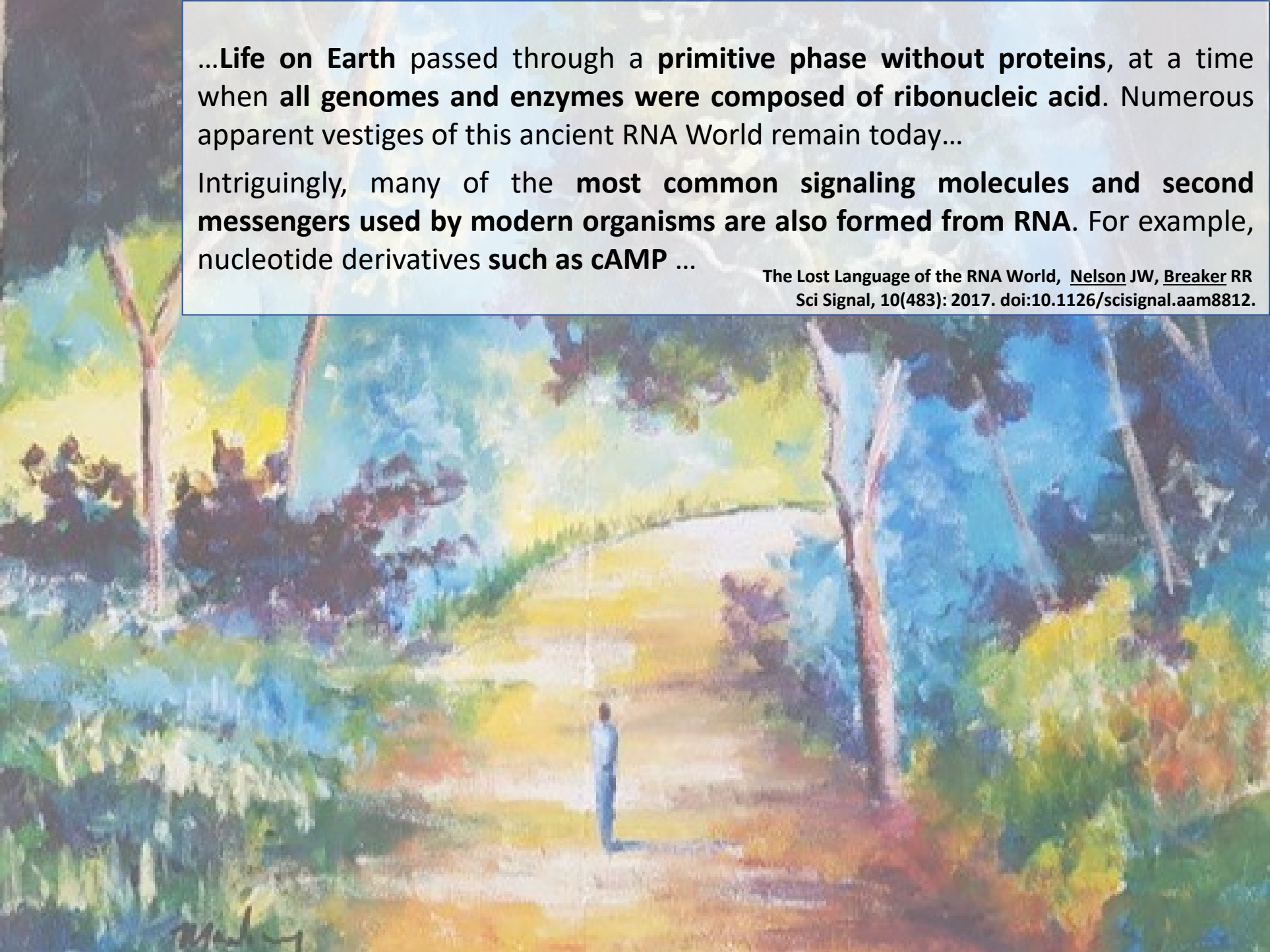
Proposed biochemical mechanism for the production of 2',3'-cAMP by RNase-mediated transphosphorylation of mRNA.



Jackson EK, Am J Physiol Renal Physiol **301: F1160, 2011.**
doi:10.1152/ajprenal.00450.2011.

Extracellular 2’,3’-cAMP – Adenosine Pathway





…**Life on Earth** passed through a **primitive phase without proteins**, at a time when **all genomes and enzymes were composed of ribonucleic acid**. Numerous apparent vestiges of this ancient RNA World remain today…

Intriguingly, many of the **most common signaling molecules and second messengers used by modern organisms are also formed from RNA**. For example, nucleotide derivatives **such as cAMP** …

The Lost Language of the RNA World, Nelson JW, Breaker RR
Sci Signal, 10(483): 2017. doi:10.1126/scisignal.aam8812.

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sigfarmaco@gmail.com

2020	TEMA	COORDENADOR LOCAL/ APRESENTADOR
15/07	Conceitos em Farmacologia: "Sinalização intra- e extracelular do cAMP: papeis complementares ou diferenciais? (pesquisa)	**Coordenador Local – UNIFESP -** Maria Christina W. Avellar **Palestrante -** Rosely Godinho/UNIFESP-EPM
19/08	Ligas acadêmicas de Farmacologia: como podem ser aliados na formação acadêmica de fato? (ensino)	**Coordenador Local – UFAM -** José Wilson N. Correa **Palestrante -** Cinthya Iamile – UFAM
16/09	Influência do Oua-Na,K-ATPase na sinalização inflamatória (pesquisa)	**Coordenador Local – UFG -** Paulo César Ghedini **Palestrante -** Jacqueline Alves Leite-UFG
21/10	Metabolômica e/ou proteômica aplicada a descoberta de fármacos (pesquisa)	**Coordenador Local – UFRJ -** Francois Noel **Palestrante -** CCS-UFRJ
18/11	Influência dos hormônios sexuais femininos no processo inflamatório e estudo das alterações e dos métodos de preservação dos enxertos empregados nos transplantes cardiotorácicos (pesquisa)	**Coordenador Local – USP -** Wothan Tavares de Lima **Palestrante** - Ana Cristina Breithaupt-Faloppa INCOR/USP
16/12	Avaliação e Agenda 2021	**Palestrantes -** Emiliano Barreto (UFAL) Maria Christina W. Avellar (UNIFESP-EPM)

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1) Do navegador do seu smartphone, tablet ou notebook, acesse:
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2) Informe seu CPF, E-mail e clique em “Registrar Presença”
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4) A SENHA DA SESSÃO do SIG é: 50504
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- Avalie a sessão após registrar sua presença
- O registro deve ser feito no mesmo dia (até 23h59) da sessão
- Em caso de dúvidas ou suporte, contate o e-mail: sig@rute.rnp.br