

P2Y₁ and P2Y₂ receptors are coupled to the NO/cGMP pathway to vasodilate the rat arterial mesenteric bed

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Abstract

- To assess the role of nucleotide receptors in endothelial-smooth muscle signalling, changes in perfusion pressure of the rat arterial mesenteric bed, the luminal output of nitric oxide (NO) and guanosine 3',5' cyclic monophosphate (cGMP) accumulation were measured after the perfusion of nucleotides.
- The rank order of potency of ATP and analogues in causing relaxation of precontracted mesenteries was: 2-MeSADP=2-MeSATP>ADP>ATP=UDP=UTP>adenosine. The vasodilatation was coupled to a concentration-dependent rise in NO and cGMP production. MRS 2179 selectively blocked the 2-MeSATP-induced vasodilatation, the NO surge and the cGMP accumulation, but not the UTP or ATP vasorelaxation.
- mRNA encoding for P2Y₁, P2Y₂ and P2Y₆ receptors, but not the P2Y₄ receptor, was detected in intact mesenteries by RT-PCR. After endothelium removal, only P2Y₆mRNA was found.
- Endothelium removal or blockade of NO synthase obliterated the nucleotides-induced dilatation, the NO rise and cGMP accumulation. Furthermore, 2-MeSATP, ATP, UTP and UDP contracted endothelium-denuded mesenteries, revealing additional muscular P2Y and P2X receptors.
- Blockade of soluble guanylyl cyclase reduced the 2-MeSATP and UTP-induced vasodilatation and the accumulation of cGMP without interfering with NO production.
- Blockade of phosphodiesterases with IBMX increased 15–20 fold the 2-MeSATP and UTP-induced rise in cGMP; sildenafil only doubled the cGMP accumulation. A linear correlation between the rise in NO and cGMP was found.
- Endothelial P2Y₁ and P2Y₂ receptors coupled to the NO/cGMP cascade suggest that extracellular nucleotides are involved in endothelial-smooth muscle signalling. Additional muscular P2Y and P2X receptors highlight the physiology of nucleotides in vascular regulation.

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Abbreviations:

□ ACh

□ acetylcholine

- ☐ **CD31**
 - ☐ platelet-endothelial cell adhesion molecule
- ☐ **cGMP**
 - ☐ guanosine 3',5'-cyclic monophosphate
- ☐ **IBMX**
 - ☐ 3-isobutyl-1-methylxanthine
- ☐ **L-NNA**
 - ☐ N^ω-Nitro-L-arginine
- ☐ **MALC**
 - ☐ myosin alkali light chain
- ☐ **2-MeSADP**
 - ☐ 2 methylthioADP
- ☐ **2-MeSATP**
 - ☐ 2 methylthioATP
- ☐ **MRS 2179**
 - ☐ N6-methyl-2'-deoxyadenosine-3',5'-bisphosphate
- ☐ **NA**
 - ☐ noradrenaline
- ☐ **NO**
 - ☐ nitric oxide
- ☐ **NOS**
 - ☐ nitric oxide synthase
- ☐ **ODQ**
 - ☐ 1H-[1,2,4]Oxadiazolo[4,3-a]quinoxalin-1-one
- ☐ **UDP**
 - ☐ uridine 5' diphosphate
- ☐ **UTP**
 - ☐ uridine 5' triphosphate