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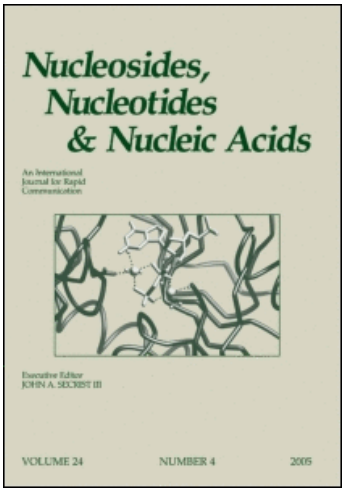

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TRANSDUCTION MECHANISMS OF P_2 PURINERGIC RECEPTORS : ROLE OF PHOSPHOLIPASE C AND CALCIUM

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ABSTRACT

The transduction mechanisms of P_2 receptors have remained uncharacterized until recently. Data accumulated in the last few years demonstrate that, in many cell types, ATP induces a rise of cytoplasmic Ca^{2+}, which often results from the direct coupling between P_2 receptors and phospholipase C.

P_2 purinergic receptors are widely distributed and extracellular ATP modulates the activity of many cell types. For example, it induces the release of nitric oxide and prostacyclin from vascular endothelial cells, contracts various smooth muscles, enhances the secretion of insulin from β cells and of surfactant from alveolar pneumocytes... Most of these actions of ATP are mediated by a rise in cytoplasmic Ca^{2+}. In most cases, this rise is the consequence of phospholipase C activation and inositol(1,4,5) trisphosphate generation. It is now well established that P_{2Y} receptors, as well as other subtypes of P_2 receptors, are coupled to phospholipase C via a G protein. In some instances, ATP induces an influx of

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Table 1. List of cell types in which ATP increases inositol phosphates formation and/or $[Ca^{2+}]_i$

Cell type	Receptor				Second messenger		Biological response	Ref.
	P_{2y}	ATP versus ADP	ATP^{4-}	UTP/ITP	IP_3	Ca^{2+}		
Hepatocytes	+	≈			+	+	Glycogenolysis	6-9
Turkey erythrocytes	+	<			+	+		10-15
Vascular endothelial cells	+	≈			+	+	EDRF and PGI_2 release	1-5
HL60		>		+	+	+	Glucuronidase secretion	18
Neutrophils		>		+	+	+	O^-_2 formation-glucuronidase lysosyme secretion	18-20
FRTL-5 (rat) thyroid cells		>			+	+	Efflux of iodide	21
Human thyroid cells		>			+	•		23
Rat aortic myocytes		>			+	+	Contraction	24,25
Cardiomyocytes					+	+	Positive inotropy	27
Human skin fibroblasts		>		+	+	+		
Mouse 3T6 fibroblasts		>	+	+		+	Mitogenesis Membrane permeability	29-31
Erhlich Ascites tumor cells		>		+	+	+	Membrane permeability	32-33
A431 cells		>		+	+	+	Mitogenesis	34-35
Alveolar type II pneumocytes	?	>			+	+	Surfactant release	36-39
Pancreatic islets		≈			+	+	Insulin secretion	40
β cell line						+	Insulin secretion	41-43
Human amnion cells		>		+	+	+		44

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Sheep pituitary cells		>	+	+	+	+		45-46
Rat renal cortex	?				+		? Antinatriuretic effect ?	47
Rat mesangial cells	?	>			+		? Regulation of glomerular filtration ?	48
Mouse peritoneal macrophages	?	>			+		↓ Cytotoxicity	49
Rat parotid		?	+			+	Amylase release ?	53
Mouse lacrimal cells		?				+		
Mouse thymocytes		>				+	Mitogenesis - Blastogenesis	57-58
J774 mouse macrophages		>	+	+		+	Membrane permeability-phagocytosis	59-63
Snail neurones						+	Opening of a Ca^{2+} channel	64
Ear artery smooth muscle cells		>	+			+	Opening of a Ca^{2+} channel	65

ATP^{4-} : + indicates that the action of ATP is mediated by its tetraanionic form; UTP/ITP : + indicates that the action of ATP is mimicked by UTP and ITP; ? : controversial result.

extracellular Ca^{2+} and P_2 receptor-operated Ca^{2+} channels have been characterized. Table 1 provides a list of cell types in which ATP increases inositol phosphates formation and/or $[Ca^{2+}]_i$.

Coupling of P_{2y} receptors and phospholipase C

The coupling between typical P_{2y} receptors and phospholipase C has been demonstrated in hepatocytes, turkey erythrocytes and vascular endothelial cells. In endothelial cells, ATP and ADP induce the release of prostacyclin and nitric oxide, which synergize to inhibit platelet activation (1). These actions are likely to play a major role in the interaction between platelets, a rich source of adenine nucleotides, and the vessel wall. ATP induces a rapid accumulation of inositol 1,4,5-trisphosphate in endothelial cells from bovine aorta (2) and from adrenal medullary capillaries (3). This is accompanied by a rapid and transient rise of cytoplasmic Ca^{2+}, resulting from the mobilization of intracellular stores, followed by a more sustained elevation, which involves an influx of extracellular Ca^{2+} (4, 5). The P_{2y} receptors, which are present on endothelial cells, are also expressed in hepatocytes (6, 7) where a stimulatory effect of ATP on the hydrolysis of phosphatidylinositol 4,5 bisphosphate could also be detected (8, 9). While they were studying the control of phospholipase C in turkey erythrocytes membranes, Harden et al serendipitously observed a stimulation by ATP (10), which appeared to be mediated by P_{2y} receptors (11). Although the physiological significance of P_{2y} receptors on turkey erythrocytes remains unclear, this model was extremely useful for molecular studies of the coupling between P_{2y} receptors and phospholipase C (12-15). The rank order of potency of various nucleotides for either activation of phospholipase or for competition with $[^{35}S]$ ADPβS was typical of P_{2y} receptors. Indeed K_i (binding) or $K_{0.5}$ (activation) were around 10 nM for 2-methylthio ATP, 100 nM for ADPβS, ADP

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and ATP, 400 nM for β,γ -adenylylimidodiphosphate, 4 μM for α, β-methylene ATP and 16 μM for β,γ -methylene ATP (13).

Coupling of phospholipase C and other P_2 receptors subtypes

In a variety of cells, the activation of phosphoinositide turnover does not involve typical P_{2Y} receptors. The major feature of these non-P_{2Y} responses is that ATP is much more potent than ADP. In HL60 promyelocytic leukemia cells and in human neutrophils, ATP induces an accumulation of inositol phosphates (16-18) and a mobilization of intracellular Ca^{2+} (19, 20). Similar responses have been observed in rat FRTL-5 (21, 22) and human (23) thyroid cells, in rat aortic myocytes (24, 25), in cardiomyocytes (26, 27), in human skin (28) and mouse 3T6 (29-31) fibroblasts, in Ehrlich ascite tumor cells (32, 33) and in human epidermoid carcinoma cells (34, 35).

In rat alveolar type II pneumocytes, ATP induces an accumulation of inositol phosphates and the mobilization of intracellular Ca^{2+} : however, it seems that it is protein kinase C activation rather than the rise of cytosolic Ca^{2+} which is responsible for the enhanced secretion of surfactant (36-39). In rat pancreatic islets and β cell lines, ATP stimulates insulin secretion, but the role of phospholipase C activation in this response remains controversial (40-43). Finally, an increased polyphosphoinositide turnover in response to ATP has been observed in human amnion cells (44), in cultured pituitary cells (45, 46), in rat renal cortex and mesangial cells (47, 48) and in mouse peritoneal macrophages (49).

Role of G proteins in the coupling between P_2 receptors and phospholipase C.

The role of a GTP-binding protein in the coupling between P_2 receptors and phospholipase C is supported by the action of $GTP_\gamma S$ on permeabilized cells (50), by the absolute requirement for GTP in order to demonstrate a stimulatory

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effect of ATP on phospholipase C activity in membranes (10, 12, 22) and by the decreased binding of [^{35}S] ADPβS to the P_{2Y} receptors in the presence of GTPγS (13). In turkey erythrocytes, there is evidence that the G protein would possess an αβγ heterotrimeric structure (14). The accumulation of inositol phosphates in response to ATP was partially inhibited by pertussis toxin in the following cell types : aortic endothelial cells (51), FRTL-5 thyroid cells (21), HL60 cells and human neutrophils (16, 17) and rat mesangial cells (48). However, in other cells, including turkey erythrocytes, the activation of phospholipase C by ATP was insensitive to pertussis toxin (46, 47), suggesting an heterogeneity of the G proteins coupling P_2 receptors to phospholipase C.

P_2-receptor-mediated increases incytosolic Ca^{2+} without phospholipase C activation.

In many cells, such as endothelial cells (4, 5), the rise of cytoplasmic Ca^{2+} induced by ATP is biphasic: the mobilization of intracellular Ca^{2+} by inositol (1,4,5) trisphosphate is followed by a lasting influx of extracellular Ca^{2+}. In some cells, ATP acts exclusively on Ca^{2+} influx. In rat parotid acinar cells, ATP induces a greater rise of $[Ca^{2+}]_i$ than carbachol, but a smaller increase in amylase release. In contrast to carbachol, it has little effect on the formation of inositol phosphates and its sole action is to increase the influx of Ca^{2+} (52-54). Similar observations have been made in mouse lacrimal cells (55). In thymocytes also, the rise in cytosolic free Ca^{2+} triggered by ATP results from an increased influx and does not involve the hydrolysis of polyphosphoinositides (56-58).

In the J774 mouse macrophage cell line (59-63), as well as in Swiss 3T6 mouse fibroblasts (30, 31), ATP produces a generalized increase of the cell membrane permeability, which results, among other consequences, in an increased

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cytosolic free Ca^{2+} concentration. In the presence of Mg^{2+}, mM concentrations of ATP are required to induce this action, which is mediated by the minor form ATP^{4-} instead of the major component $ATPMg^{2-}$. Desensitization experiments suggest that the permeabilizing effect of ATP on 3T6 cells involves a receptor, distinct from the phospholipase C-coupled receptor which is also present on these cells (29-31).

In neurones from snail digestive ganglia, ATP induces the opening of Ca^{2+} channels (64). A more detailed characterization of a P_2-receptor-operated Ca^{2+} channel has been performed in isolated smooth muscle cells from the rabbit ear artery (65). This channel is not voltage-dependent and is insensitive to nifedipine; it has a 5 pS conductance and only a partial selectivity for Ca^{2+} (3 to 1 preference for Ca^{2+} over Na^{+}). It is likely, although not definitely proven, that this channel plays a role in the contraction of smooth muscle triggered by the activation of P_{2x} receptors : both the direct entry of Ca^{2+} through this channel and the influx of Ca^{2+} via voltage-dependent channels, opened in response to the depolarization resulting from Na^{+} inflow, might contribute to contraction.

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