P2Y₁₁ Receptors Activate Adenylyl Cyclase and Contribute to Nucleotide-promoted cAMP Formation in MDCK-D₁ Cells

A MECHANISM FOR NUCLEOTIDE-MEDIATED AUTOCRINE-PARACRINE REGULATION*

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Extracellular nucleotides activate P2Y receptors, thereby increasing cAMP formation in Madin-Darby canine kidney (MDCK-D₁) cells, which express P2Y₁, P2Y₂, and P2Y₁₁ receptors (Post, S. R., Rump, L. C., Zambon, A., Hughes, R. J., Buda, M. D., Jacobson, J. P., Kao, C. C., and Insel, P. A. (1998) J. Biol. Chem. 273, 23093–23097). The cyclooxygenase inhibitor indomethacin (indo) eliminates UTP-promoted cAMP formation (i.e. via P2Y₁ receptors) but only partially blocks ATP-promoted cAMP formation. The latter response is completely blocked by the nonselective P2Y receptor antagonist suramin. We have sought to identify the mechanism for this P2Y receptor-mediated, indo-resistant cAMP formation. The agonist rank order potencies for cAMP formation were: ADP*S ≥ MT-ADP > 2-MT-ATP > ADP, ATP, ATP*PS > UTP, AMP, adenosine. We found a similar rank order in MDCK-D₁ cells overexpressing cloned green fluorescent protein-tagged P2Y₁ receptors, but the potency of the agonists was enhanced, consistent with a P2Y₁₁ receptor-mediated effect. cAMP generation by the P2Y₁ and P2Y₁₁ receptor agonist ADP*PS was not inhibited by several P2Y₁-selective antagonists (PPADS, A2P5P, and MRS 2179). Forskolin synergistically enhanced cAMP generation in response to ADP*PS or PGE₂, implying that, like PGE₂, ADP*PS activates adenylyl cyclase via Gₛ, a conclusion supported by results showing ADP*PS and MT-ADP promoted activation of adenylyl cyclase activity in MDCK-D₁ membranes. We conclude that nucleotide-promoted, indo-resistant cAMP formation in MDCK-D₁ cells occurs via Gₛ-linked P2Y₁₁ receptors. These data describing adenylyl cyclase activity via endogenous P2Y₁₁ receptors define a mechanism by which released nucleotides can increase cAMP in MDCK-D₁ and other P2Y₁₁-containing cells.

Cells commonly co-express multiple receptor subtypes that recognize the same physiological agonist, but it is difficult to define which among such receptor subtypes mediates a particular response. This can be a particularly vexing problem if subtype-selective agonists and antagonists are not available. One such example is P2Y receptors, which respond to ATP and other nucleotides, are expressed in a variety of tissues and cell types, and for which few subtype-selective antagonists exist (2–4). Our laboratory has undertaken a series of studies related to signal transduction by P2Y receptors in the renal epithelial cell line, MDCK*-D₁ (reviewed in Refs. 5 and 6). P2Y receptors in MDCK-D₁ cells modulate membrane potential and short circuit current, and the receptors regulate phospholipases, intracellular [Ca²⁺], prostaglandin E₂ (PGE₂) formation, and cAMP accumulation (1, 7–14).

Cyclooxygenase (COX) inhibitors, such as indomethacin (indo), have proven useful for studying P2Y receptors in MDCK-D₁ cells (1, 12). Agonist-stimulated cAMP accumulation in MDCK-D₁ cells occurs via both indo-sensitive and -insensitive pathways. Response to the P2Y₂ agonist UTP is entirely indo-sensitive, whereas response to ATP is partially sensitive and to 2-methylthio-ATP (MT-ATP) is insensitive (1). These findings suggest that UTP, and ATP in part, stimulate P2Y₂ receptors to cause COX-mediated (perhaps by both COX1 and COX2, see Ref. 15) formation of arachidonic acid metabolites (e.g. PGE₂), which activate EP receptors to stimulate cAMP formation, while ATP and MT-ATP can also enhance cAMP formation via an indo-insensitive P2Y₂ receptor pathway (1).

The present studies were designed to characterize more fully the nature of the latter pathway. Our working hypothesis, based in part on initial results obtained with MDCK-D₁ cells (12), was that the indo-resistant response might represent a P2Y₁ receptor effect. The current data show results not consistent with this hypothesis but instead suggest a key role for another receptor, the P2Y₁₁ receptor, in indo-resistant cAMP formation. The findings directly document a role for P2Y₁₁ receptors in stimulation of adenylyl cyclase activity and in potentially contributing to autocrine-paracrine regulation by nucleotides.

EXPERIMENTAL PROCEDURES

Cell Culture—MDCK-D₁ cells were maintained in Dulbecco’s modified Eagle’s medium supplemented with 10% mixed serum (85% horse serum, 15% fetal bovine serum). Cells were used in assays at 60–80% confluency. GFP-tagged P2Y₁₁ receptor-overexpressing MDCK-D₁ cells were cultured from the stable cell line prepared by Zambon et al. (14).

Measurement of cAMP Accumulation in Normal and GFP-tagged P2Y₁₁ Receptor-overexpressing MDCK-D₁ Cells—Prior to the treatment of the cells, the growth medium was removed, and cells were equilibrated for 30 min at 37 °C in serum-free 20 mM HEPES-buffered Dulbecco’s modified Eagle’s medium (DMEM, pH 7.4). Subsequently, cells were incubated in fresh DMEM and various agents as shown in the figures. Incubations with the agonists ADP*PS, MT-ADP, ATP*PS, ATP,

* The abbreviations used are: MDCK, Madin-Darby canine kidney cells; COX, cyclooxygenase; indo, indomethacin; ATP*PS, adenosine 5′-O-(thio)triphosphate; MT-ATP, 2-methylthio-ATP; MT-ADP, 2-methylthio-ADP; PPADS, pyridoxal-phosphate-6-azophenyl-2′,4′-disulfonic acid 4 sodium; AMP-PNP, adenosine 5′-(β,y-imino)triphosphate; IBMX, isobutylmethylxanthine; GFP, green fluorescent protein; PGE₂, prostaglandin E₂; A2P5P, adenosine 2′,5′-diphosphate; ADP*PS, adenosine 5′-O-2(thio)diphosphate; ATP*S, adenosine 5′-O-3(thio)triphosphate; MAP, mitogen-activated protein.

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MT-ATP, ADP, AMP, adenosine, UTP, PGE₂, and forskolin and the antagonists PPADS, A2P5P, and MRS 2179 were conducted for 7 min at 37°C in the presence of 200 μM IBMX, a phosphodiesterase inhibitor, and terminated by placing on ice and replacing the medium with 7.5% trichloroacetic acid. Trichloroacetic acid extracts were frozen (-20°C) until assay. Intracellular AMP levels were determined by radiomunnoassay (Calbiochem) of trichloroacetic acid extracts following acetylation according to the manufacturer’s protocol. Production of cAMP was normalized to the amount of acid-insoluble protein (Lowry and Bradford methods).

Preparation of Membranes—Membranes were prepared from MDCK-D₁ cells as follows: cells were grown to confluency on 15-cm plates and washed twice with phosphate-buffered saline, the second wash containing 0.01% EDTA. Cells were then incubated for 15 min at 37°C in phosphate-buffered saline containing 0.01% EDTA. Detached cells were centrifuged at 1,000 rpm, and the resulting pellet was suspended in 10 ml of 4°C lysis buffer (20 mM Tris-HCl, pH 7.4, 10 mM MgCl₂, 2 mM EDTA, 1 mM dithiothreitol) containing protease inhibitors (10 μg leupeptin, 500 nM pepstatin, 200 μM benzamidine, 200 μM 4-(2-aminoethyl) benzenesulfonylfluoride-HCl (AEBSF). Suspended cells were then placed under 450 p.s.i for 10 min to lyse the cells. The resulting lysed cell mixture was centrifuged at 2,000 rpm for 15 min at 4°C to remove cell nuclei. The supernatant was separated from the nuclear pellet and centrifuged for 90 min at 15,000 rpm. The resulting supernatant in buffer was used to assay for cAMP. ATP, ADP, AMP, adenosine, UTP, PGE₂, and forskolin and the diterpene forskolin enhance coupling of the P2Y₁₁ receptor in MDCK-D₁ cells (12), showing an even greater enhancement in apparent potency in the P2Y₁₁-overexpressing cells (Table 1). UTP treatment gave no response; thus overexpression of P2Y₁₁ receptors did not alter P2Y₂ response (data not shown). Taken together with data in the native cells (Figs. 1 and 2), this enhancement of the indo-resistant cAMP formation in P2Y₁₁-overexpressing MDCK-D₁ cells is consistent with the notion that P2Y₁₁, and not P2Y₂, receptors mediate this response.

As a first step toward investigating the basis for indo-resistant cAMP formation in MDCK-D₁ cells, we determined the ability of different P2 agonists to elicit this response. Stimulation of cells with UTP was maximally able to increase cAMP levels—3-fold over basal levels, but consistent with previous results (1, 12), pretreatment with 1 μM indo abolished this response (Fig. 1A). Treatment of cells with indo also partially decreased ATP-stimulated cAMP accumulation but was less effective than the inhibition of the response to UTP, particularly at higher concentrations of ATP (Fig. 1B). The methylthio- derivative of ATP, MT-ATP, produced a largely indo-resistant increase in cAMP levels (Fig. 1C). ATP can be sequentially dephosphorylated to ADP, AMP, and adenosine by ecto-ATPases and nucleotidases (16, 17). To assess whether the ATPs contribute to the observed increase in cAMP levels or whether an ATP metabolite might be responsible, we treated cells with ATPase-resistant analogs of ATP, ATP₂S (16), and obtained results comparable with those observed with ATP (Fig. 1D), suggesting that ATP need not be metabolized to raise cAMP levels.

Like ATP, ADP elevated indo-resistant cAMP levels in a concentration-dependent manner (Fig. 1E). ADP₂S, a nonhydrolyzable analog of ADP, and MT-ADP both increased indo-resistant cAMP levels as much or more than did ADP, ATP, or ATP₂S (Fig. 1, F and G). The ADP₂S-stimulated cAMP increase was entirely indo-resistant. Stimulation of MDCK-D₁ cells with AMP and adenosine, both metabolic breakdown products of ADP, did not elevate cAMP (Ref. 12 and data not shown).

The observed pattern of response for the different agonists, in particular with reference to ATP, ADP, ADP₂S, and MT-ATP, suggested that indo-resistant cAMP accumulation might be the result of an action at the P2Y₁ receptor (2–4). We thus tested several P2Y₁ antagonists to determine whether this receptor might mediate indo-resistant cAMP accumulation. The P2Y-nonselective antagonist suramin blocked this response to 10 μM ADP₂S in MDCK-D₁ cells (Fig. 2), but several other putative P2Y₁-selective antagonists proved ineffective, including PPADS and A2P5P (2, 18, 19). Additionally, the highly selective P2Y₁ antagonist MRS 2179 failed to inhibit indo-resistant cAMP accumulation in MDCK-D₁ cells even though in parallel control studies MRS 2179 inhibited canine P2Y₁-mediated inositol trisphosphate formation in P2Y₁-transfected 1231N1 cells (Ref. 20 and data not shown). These findings suggested that the receptor responsible for the indo-insensitive effect is not the P2Y₁ receptor but instead is another receptor, perhaps the P2Y₁₁ receptor, which in MDCK-D₁ cells also responds to adenosine bisphosphates (14, 21).

Investigation into whether the P2Y₁₁ receptor can cause indo-resistant cAMP elevation in MDCK-D₁ cells is hampered by the lack of antagonists to this receptor. Therefore, as an alternative strategy, we used P2Y₁₁ receptors that we had cloned from MDCK-D₁ cells expressed as P2Y₁₁-GFP receptors in MDCK-D₁ cells (14) and assessed cAMP accumulation. In the cells overexpressing P2Y₁₁-GFP receptors, we found a 5- to 10-fold increase in sensitivity of indo-resistant cAMP formation in response to several nucleotides, compared with responses observed with native MDCK-D₁ cells (Table I and Fig. 3). The relative potency of the different nucleotides in P2Y₁₁-GFP-overexpressing MDCK-D₁ cells was similar to that for native MDCK-D₁ cells, although compared with other agonists, ADP had a somewhat greater enhancement in apparent potency in the P2Y₁₁-overexpressing cells (Table 1). UTP treatment gave no response; thus overexpression of P2Y₁₁ receptors did not alter P2Y₂ response (data not shown). Taken together with data in the native cells (Figs. 1 and 2), this enhancement of the indo-resistant cAMP formation in P2Y₁₁-overexpressing MDCK-D₁ cells is consistent with the notion that P2Y₁₁, and not P2Y₂, receptors mediate this response.

To define the molecular mechanism underlying the indo-resistant cAMP elevation in MDCK-D₁ cells, we assessed whether this response results from the coupling of a P2Y receptor, presumably the P2Y₁₁ receptor, to an increase in adenyl cyclase activity. In previous studies it has been difficult to ascertain whether P2Y₁₁ receptors increase cAMP via a receptor/G₂-mediated activation of adenyl cyclase activity or indirectly via alterations in calcium or other regulators of cAMP formation (14, 22–24). We used two approaches to assess this possibility. The diterpene forskolin enhances coupling of G₂-linked receptors to adenyl cyclase, thereby enhancing the ability of G₂ receptors to raise cellular cAMP levels (12, 25–27). Co-incubation of indo-treated MDCK-D₁ cells with 10 μM ADP₂S and 0.1 μM forskolin led to a cAMP elevation that was greater than the sum of the individual responses for forskolin and ADP₂S. Co-incubation of forskolin and PGE₂, a known G₁ activator in MDCK-D₁ cells (12), showed an even greater enhancement of cAMP levels than was caused by co-incubation with ADP₂S and forskolin (Fig. 4). Nevertheless, the synergistic effect obtained with forskolin and agonists, when expressed
as-fold increase over the sum of separate forskolin- and agonist-stimulated cAMP accumulations, was similar or even greater for ADP/H9252S-stimulated cAMP generation than for PGE2 response (Fig. 4, inset). These results suggest that ADP/H9252S, like PGE2, activates Gs to promote cAMP formation in MDCK-D1 cells.

As a more direct test for the ability of a P2Y receptor to couple to an increase in adenylyl cyclase activity, we sought to assay enzyme activity, but we reasoned that such an assay would require use of a nucleotide as a substrate, which unlike ATP was not active at the P2Y receptors that increase cAMP levels in MDCK-D1 cells. We chose as an alternate substrate AMP-PNP, which has previously been used as a substrate for adenylyl cyclase assays (28) and which we found in preliminary studies did not promote indo-resistant cAMP accumulation (following 30 min of treatment of cells with 30 μM AMP-PNP, data not shown). We also found that AMP-PNP yielded linear time- and protein-dependent cAMP generation in MDCK-D1 membranes, whereas MT-ADP and ADP/H9252S, nucleotides that promoted cAMP accumulation in intact cells, did not (data not shown).

MT-ADP, ADP/H9252S, and PGE2 all elevated cAMP levels in the presence of AMP-PNP, whereas UTP had no effect (Fig. 5). Thus, while MT-ADP and ADP/H9252S lack the ability to serve as substrates for adenylyl cyclase, in combination with AMP-PNP they, like PGE2, are agonists that can increase adenylyl cyclase activity, consistent with activation of P2Y11 receptors linked to Gs. In contrast, UTP, which stimulates Gq-coupled P2Y2 receptors (2, 3, 13), did not lead to increased adenylyl cyclase activity. Taken together with other data shown here, these findings provide direct evidence for P2Y11 receptor-mediated activation of adenylyl cyclase activity.

**DISCUSSION**

P2Y receptors are increasingly recognized as providing an important means by which extracellular nucleotides regulate a

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**Fig. 1.** The effect of indo on ADPβS cAMP generation is minimal compared with its effect on cAMP generation by nucleotides in MDCK-D1 cells. Cells were treated as described under “Experimental Procedures.” Cells were incubated for 30 min with or without indomethacin (1 μM), then for 7 min with IBMX (200 μM) and the indicated agonist. Cells were then assayed for cAMP. Data are mean ± S.E. of triplicate determinations and are representative of results obtained in at least three separate experiments.
The P2Y antagonist suramin, but not the P2Y agonists PPADS, A2P5P, and MRS 2179, inhibits indo-insensitive cAMP generation in ADPβS (10 μM)-stimulated MDCK-D1 cells. Cells were incubated with indomethacin (1 μM, 30 min) and antagonist (PPADS, 10 min; suramin, 5 min; A2P5P, 5 min; MRS 2179, 5 min) prior to incubation with IBMX (200 μM) and ADPβS for 7 min. Data are normalized to cAMP levels obtained with ADPβS (10 μM) without antagonist and are mean ± S.E. of triplicate determinations representative of values obtained in at least two separate experiments.

**Table I**

Rank order potency of various adenine nucleotides as agonists of cAMP production in native and P2Y11 receptor-transfected MDCK-D1 cells

| Nucleotide | EC50 (MDCK) | EC50 (P2Y11-GFP MDCK) |
|------------|-------------|------------------------|
| ADPβS      | 1.43        | 0.15                   |
| MT-ATP     | 7.76        | 1.30                   |
| ADP        | 9.19        | 0.73                   |
| MD-ATP     | 10.9        | 1.90                   |
| ATP        | 66.4        | 7.94                   |

Wide variety of cell types (2–4). Of the seven unique P2Y receptor subtypes (P2Y1, P2Y2, P2Y6, P2Y11, P2Y12, and P2Y13) all, with the exception of P2Y12 and P2Y13 subtypes, couple via G12/13-dependent mechanisms to the activation of phospholipase C and increases in cellular [Ca2+]i, but the various receptor subtypes have quite different abilities to regulate formation of cAMP. Certain of the receptors (e.g. P2Y12, P2Y13) are known to utilize Gi-dependent mechanisms to inhibit cAMP formation (29, 30), whereas other P2Y receptors may regulate adenylyl cyclase activity via effects on regulators of adenylyl cyclase, such as [Ca2+]i or protein kinase C.

MDCK-D1 cells, in common with several other cell types, express several different P2Y receptor subtypes (1, 6, 12, 31, 32). Early work on MDCK-D1 cells, prior to the molecular cloning and precise identification of the different P2Y receptor subtypes, emphasized the ability of added nucleotides to alter membrane potential, ion flux, or short circuit current (7, 8). Recent studies have indicated that MDCK-D1 cells release ATP and that this released nucleotide helps contribute to basal activity of signal transduction pathways (15, 33). Of the three different P2Y receptors that we have thus far detected on MDCK-D1 cells (P2Y1, P2Y2, and P2Y11, see Ref. 1), our previous work documented that P2Y2 receptors mediate the indosensitive (i.e. COX-dependent) cAMP accumulation via the ability of the receptors to increase formation of PGE2 and the subsequent activation of EP receptors linked to Gs and adenylyl cyclase activity (1, 12, 13).

Several lines of evidence from the current studies, designed to identify alternative mechanisms by which ATP might increase cellular cAMP levels, are consistent with the conclusion that MDCK-D1 P2Y11 receptors are responsible for the COX-independent (indo-resistant) increases in cAMP formation promoted by ATP and other nucleotides: 1) the rank order of potency of agonists in promoting this response; 2) the insensitivity to blockade by several P2Y1-selective antagonists; 3) the increased potency of several agonists in P2Y11-overexpressing MDCK-D1 cells; 4) the synergistic enhancement in response by coin incubation of cells with nucleotides plus forskolin; and 5) the ability of two P2Y11 agonists, MT-ADP and ADPβS, to enhance adenylyl cyclase activity in MDCK-D1 cell membranes. Taken together, we believe these results provide strong evidence for P2Y11 receptor-promoted stimulation of adenylyl cyclase activity, presumably secondary to enhanced enzyme activity by receptor-mediated activation of Gs.

This is the first data of which we are aware to document that P2Y11 receptors directly activate adenylyl cyclase activity. At the time of the initial cloning of P2Y11 receptors, Communi et al. (22, 23) utilized two different cell types to heterologously express the cloned P2Y11 receptors and to conclude that these receptors couple to both Gs and Gi. However, this conclusion was open to alternative interpretations, given the use of differ-
addition to activation of P2Y2 or adenosine receptors, by which exogenous or endogenously released nucleotides can increase cellular levels of this important cyclic nucleotide. Given the evidence that MDCK-D1 and a number of types of cells both release ATP and possess P2Y11 receptors, nucleotide-mediated activation of P2Y11 receptors provides a means for autocrine-paracrine regulation of epithelial and other cell types.

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