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ORIGINAL ARTICLE

MRP transporters as membrane machinery in the bradykinin-inducible export of ATP

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Abstract Adenosine triphosphate (ATP) plays the role of an autocrine/paracrine signal molecule in a variety of cells. So far, however, the membrane machinery in the export of intracellular ATP remains poorly understood. Activation of B2-receptor with bradykinin-induced massive release of ATP from cultured taenia coli smooth muscle cells. The evoked release of ATP was unaffected by gap junction hemichannel blockers, such as 18α-glycyrrhetinic acid and Gap 26. Furthermore, the cystic fibrosis transmembrane regulator (CFTR) coupled Cl^- channel blockers, CFTR(inh) 172, 5-nitro-2-(3-phenylpropylamino)-benzoic acid, $Gd3^+$ and glibenclamide, failed to suppress the export of ATP by bradykinin. On the other, the evoked release of ATP was greatly reduced by multidrug resistance protein (MRP) transporter inhibitors, MK-571, indomethacin, and benzbromarone. From western blotting analysis, blots of MRP 1 protein only, but not MRP 2 and MRP 3 protein, appeared at 190 kD. However, the MRP 1 protein expression was not enhanced after loading with 1 μM bradykinin for 5 min. Likewise, niflumic acid and fulfenamic acid, $Ca2^+$-activated Cl^- channel blockers, largely abated the evoked release of ATP. The possibility that the MRP transporter system couples with $Ca2^+$-activated Cl^- channel activities is discussed here. These findings suggest that MRP transporters, probably MRP 1, unlike CFTR-Cl^- channels and gap junction hemichannels, may contribute as membrane machinery to the export of ATP induced by G-protein-coupled receptor stimulation.

Keywords ATP export · Bradykinin B_2 receptor stimulation · MRP-1 protein expression · CFTR-Cl^- channels · Cultured taenia coli smooth muscle cells

Abbreviations

ABC	ATP-binding cassette
α-GA	18-α-glycyrrhetinic acid
CFTR	cystic fibrosis transmembrane regulator
CFTR(inh) 172	4-[[4-Oxo-2-thioxo-3-(3-trifluoromethyl) phenyl]-5-thiazo lidinylidene]methyl]benzoic acid
Gap 26	Val-Cys-Tyr-Asp-Lys-Ser-Phe- Pro-Ile-Ser-His-Val-Arg
MK-571	3-[[[3-[(1E)-2-(7-chloro-2-quinolinyl)ethenyl] phenyl] [[3-(dimethylamino)-3oxopropyl] thio]methyl]thio]propanoic acid

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MRP	multidrug resistance protein
NPPB	5-nitro-2-(3-phenylpropylamino)-benzoic acid
SMCs	smooth muscle cells

Introduction

It has been well-accepted that, in addition to an intracellular energy supplier, adenosine triphosphate (ATP) acts as an extracellular signal molecule via P2X and P2Y purinoceptors in modulating cellular functions (Ralevic and Burnstock 1998). Our studies with rodent smooth muscle cells (SMCs) have revealed that various agonists for G-protein coupled receptors, including ATP per se, are capable of releasing ATP from vas deferens and ileal SMCs (Katsuragi et al. 1996, 2008; Matsuo et al. 1997; Tamesue et al. 1998). Furthermore, we provided evidence that adenosine, a metabolite of ATP, also releases ATP from Madin-Darby canine kidney epithelial cells through a process regulated by a type of positive feedback system (Migita et al. 2005, 2007) and that the angiotensin AT_1 receptor-mediated ATP secretion is triggered by Ins(1,4.5)P_3-signaling (Katsuragi et al. 2002; Zhao et al. 2007). Aside from the SMCs, it has been shown that cardiac endothelial cells and glial cells release ATP in response to the stimulation of drug receptors with peptide and glutamate (Queiroz et al. 1997). So far, however, the mechanism underlying the autocrine/paracrine type of ATP release by receptor stimulation remains unknown. Recent studies have showed findings that ATP is released extracellularly by mechanical and hypotonic stress from epithelial (Hazama et al. 1999; Walsh et al. 2000), hepatic (Schlosser et al. 1996; Feranchak et al. 2000), and red blood cells (Sprague et al. 2001). In cultured epithelial cells, it has been revealed that the release of ATP induced by hypotonic stress is suppressed by 5-nitro-2-(3-phenylpropylamino)-benzoic acid (NPPB) and 4,4'-diisothiocyanatostilbene-2,2'-disulphonic acid (DIDS), Cl^- channel blockers, and Gd^{3+}, a blocker of stretch-activated channel (Hazama et al. 1999; Mitchell, 2001; Braunstein et al. 2001). Therefore, it is presumed that ATP moves out of the cells through a type of anionic channels after ionization to ATP^{4-} or $[Mg\ ATP]^{2-}$ (Roman and Fitz 1999; Dutta et al. 2004). There seems to be some candidates for the membrane machinery in ATP transport across the cell membrane. ATP binding cassette family, P-glycoprotein, multidrug resistance protein (MRP) and cystic fibrosis transmembrane regulator (CFTR) as well as gap junction hemichannels have been considered as ATP carriers. Accordingly, the present study was designed to clarify the membrane machinery that is responsible for the bradykinin-inducible release of ATP from cultured guinea-pig taenia coli (T. coli) SMCs.

Materials and methods

Materials

Alpha-GA, indomethacin and benzbromarone were purchased from Wako Pure Chemical (Osaka, Japan). MK-571, Gap 26, and CFTR(inh)172 were obtained from Tocris (Ellisville, MO, USA). All other reagents were obtained from Sigma (St. Louis, MO, USA).

Cell culture

The study protocols were approved by Fukuoka University, Animal Care Committee. For a successful cell culture, neonatal, immature male guinea pigs within one day of birth were purchased from KBT-Oriental (Tosu, Japan) and used here. The guinea pigs were stunned and bled. Then, taenia coli was removed and cut into segments in phosphate buffered saline (PBS) supplemented with 0.25 mg/mL of collagenase. The segments were then moved to a CO_2 incubator (37°C) and maintained there for 40 min. Under a microscope, the longitudinal muscle layer was separated from the circular muscles and plexus with a pair of fine tweezers. After mincing, the small pieces were transferred to a PBS dish supplemented with 0.125% trypsin and placed in the incubator. Following trituration, the content was moved to a tube with 10% fetal bovine serum (FBS) and centrifuged at 180×*g* for 5 min. The resulting pellet was dispersed in a culture medium, M-199 (Life Technologies, Rockville, MD, USA) with 10% FBS and culturing in the incubator was started. On the third day, the cells were rinsed with a fresh medium. After 4 days of culturing, the cells were used for the release experiment. The purity of SMCs cultured in this manner was checked by staining them with anti-α-actin (mouse monoclonar anti-actin α-smooth muscle antibody, Sigma) under fluorescence microscopy (data not shown).

ATP release and luciferase assay

The cells collected from two dishes were trapped in a Millipore filter (pore size 3 μm) and superfused at 0.5 mL/min using a peristaltic pump with oxygenated Krebs solution (37°C) of the following composition (mM): NaCl 122, KCl 5.2, $CaCl_2$ 2.4, $MgSO_4$ 1.2, $NaHCO_3$ 25.6, D-glucose 11, EDTA 0.03, and ascorbic acid 0.1. After 20 min of equilibration, the superfusate was collected every 90 s for 15 min. The agonist was applied to the medium from the fifth to the seventh fractions and antagonists were present in the superfusion medium throughout the experiment. Superfusate (200 μL in each fraction) was transferred into microtubes and ATP measured with 100 μL of ATP reagent solution (Lucifel-LU; Kikkoman, Noda, Japan).

The cells' protein content was determined using Bio-Rad protein assay kit II following cell lysis after overnight incubation (4°C) in deionized water containing 0.1% Triton X-100. Values for ATP released are expressed as pmol/mL/mg protein in the cultured cells.

Western blotting

SMCs treated with and without bradykinin were collected in a sample tube containing an ice cold buffer [50 mM Tris-HCl (pH 7.5) containing a protease-inhibitor cocktail after being washed with PBS. Cells were then centrifuged at 3,000×*g* for 10 min at 4°C. Pellets were homogenized by a lysis buffer (50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 5 mM EGTA, 1% Triton X-100) supplemented with a protease-inhibitor cocktail on ice. Then, the crude membrane proteins were obtained by centrifugation at 20,000×*g* for 1 h at 4°C. Total protein was determined by the Bio-Rad protein assay kit II. Protein samples (10 and 20 μg per lane) were resolved by 7% sodium dodecyl sulfate polyacrylamide gel electrophoresis and transferred to nitrocellulose membrane (Millipore, Bedford, MA, USA) using 25 mM Tris base, 192 mM glycine, and 20% methanol buffer. Blocking was performed with 5% skim milk in 150 mM NaCl, 10 mM Tris, pH 7.5, 0.1% Tween 20 (TBST) buffer for 1 h. The membrane was then incubated for 1 h with the rat anti-MRP1 antibody at 1:500 (clone MRPr1, Alexis Biochemicals, CA, USA), anti-MRP2 monoclonal antibody at 1:100 (clone M2III-6 Chemicon), anti-MRP3 monoclonal antibody at 1:100 (clone M3II-9, Alexis Biochemicals, CA, USA) and anti-β-actin monoclonal antibody at 1:10,000 (Sigma) dilution with 1% skim milk in TBST. The blot was then incubated for 1 h with horseradish peroxidase conjugated goat anti-rat IgG and anti-mouse IgG (Jackson Immunoresearch, West Grove, PA, USA) diluted 1:4,000 in 1% skim milk-TBST, and developed using an ECL system (Amersham Biosciences, Piscataway, NJ, USA) and then exposed to Kodak films.

Statistics

Differences between multiple means were tested for statistical significance by one-way analysis of variance followed by Dunnett's test. A value of $P<0.05$ was considered to be significant.

Results

In the superfusing experiment with cultured taenia coli SMCs, 1 μM bradykinin caused a sizable release of ATP. The evoked release of ATP was clearly diminished by HOE 140, a B_2 receptor antagonist, however, not by [des-Arg^{10}] HOE 140, a B_1 receptor antagonist. The basal and the peak releases of ATP with and without 1 μM bradykinin were 54.48±5.60 pmol ml^{-1} mg protein^{-1} (n=5) and 295.71±40.55 pmol ml^{-1} mg protein^{-1} (n=5), respectively.

In the presence of 3 μM HOE 140, these releases became 43.89±10.34 pmol ml^{-1} mg protein^{-1} (N=6) and 88.67±16.19 pmol ml^{-1} mg protein^{-1} (*p<0.01, N=6), respectively. In the presence of 3 μM [des-Arg^{10}] HOE 140, however, these releases amounted to 77.07±7.91 pmol ml^{-1} mg protein^{-1} (N=4) and 308.31±8.91 pmol mg^{-1} mg protein^{-1} (N=4), indicating no prevention of ATP release. Further experiments were arranged to reveal the membrane machinery underlying the export of ATP.

First, the role of the MRP transporters in the release of ATP were assessed by using MRP inhibitors. The bradykinin-induced release of ATP was markedly inhibited by MK-571, indomethacin, and benzbromarone, thus, suggesting that the activation of MRP transporters contributes to the outflux of ATP (Fig. 1). MRP transporter proteins in human consist of nine superfamilies (MRP 1-MRP 9). In the present western blot study, three superfamilies (MRP 1, MRP 2, and MRP 3), which have been reported to distribute to intestinal smooth muscles, were examined. Blots of MRP 1 protein only, but not MRP 2 and MRP 3 proteins, with and without bradykinin, appeared at 190 kD from the crude membrane proteins of guinea pig taenia coli SMCs (Fig. 2a). However, the enhancement in the protein level of the MRP 1 transporter in the presence of bradykinin was not shown after the 5-min loading with 1 μM bradykinin (Fig. 2b,c).

Second, the involvement of gap junction hemichannels in the bradykinin-inducible release of ATP was evaluated. The release of ATP was unaffected by 18α-glycyrrhetinic acid (α-GA) and Gap-26, both being hemichannel blockers.

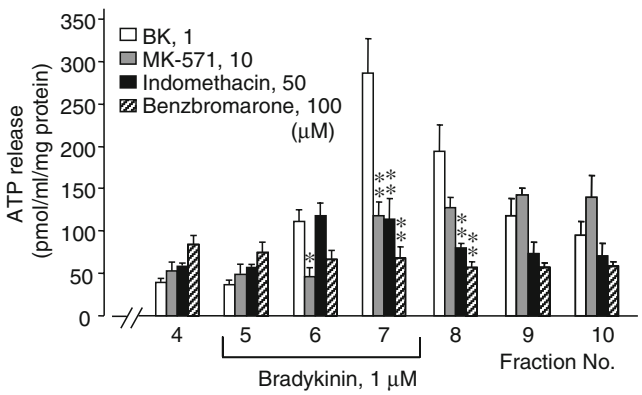

Fig. 1 Effects of MRP tranporter inhibitors on the release of ATP evoked by 1 μM bradykinin. Cells were exposed to bradykinin during the fifth, sixth, and seventh fractions and to antagonist 15 min before bradykinin. The time interval of one fraction is 90 s. Values are expressed as mean ± SEM of pmol^{-1} ml^{-1} mg protein^{-1} of ATP (n=3-5). *p<0.05, **p<0.01 compared with the corresponding evoked control

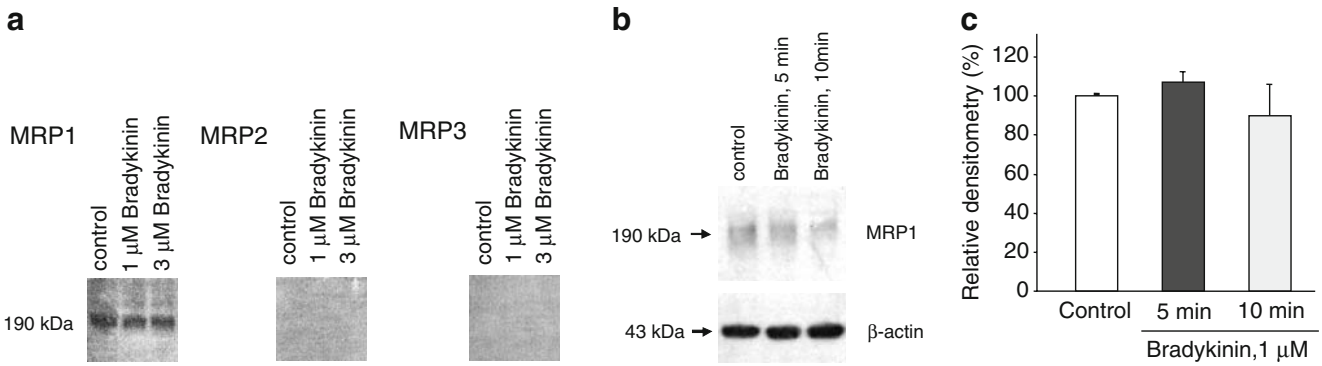

Fig. 2 Western blot analysis for MRP protein expression. **a** Effects of bradykinin (1-3 μM) on expressions of MRP 1, MRP 2 and MRP 3 (protein: 20 μg/lane). **b** The effects of exposures (5 and 10 min) to 1 μM bradykinin on MRP1 protein expression. **c** Mean density relative to MRP1 protein expression after a 5 and 10 min- exposure to 1 μM of the peptide (n=5)

Gap-26 was likely to increase rather than decrease the release (Fig. 3a).

Third, the contribution of the CFTR coupled Cl^- channels to the evoked release of ATP was elucidated. CFTR (inh) 172, NPPB, Gd^{3+} and glibenclamide failed to prevent the release of ATP (Fig. 3b). This casts doubt on the possibility that the transport of ATP is mediated by CFTR-Cl^- channels.

Finally, however, niflumic acid and flufenamic acid, Ca^{2+}-activated Cl^- channel blockers, largely abolished the release of ATP (Fig. 3c).

The concentrations of all antagonists were used in a range of effective concentrations confirmed in a pile of studies.

Discussion

Bradykinin is capable of releasing the intracellular ATP via the activation of G-protein coupled B_2 receptor and then, via the Ins(1,4,5)P_3 sensitive- Ca^{2+}-signaling as shown previously (Zhao et al. 2007). Similarly, a G-protein coupled NK-2 receptor agonist, neurokinin-A induced ATP release via Ins(1,4,5)P_3-sensitive Ca^{2+} release from the endoplasmic reticulum, then as further signals, via activations of protein kinase C and Ca^{2+}/calmodulin. The neurokinin A-inducible ATP release was also mediated by MRP transporters (unpubished observation). Accordingly, it is assumed that the bradykinin-inducible ATP release may also be mediated by activations of protein kinase C and Ca^{2+}/calumodulin. However, so far, there is no information how ATP is transported across the cell membrane following the signal pathway. Therefore, the present work aims to clarify the membrane machinery involved in the bradykinin-inducible transport of ATP. Recent investigations provide much evidence that the activities of gap junction hemi-channels enhance the release of ATP from rat brain endothelial cell lines (Braet et al. 2003a, b), rodent cultured astrocytes (Cotrina et al. 1998; Stout et al. 2002; Coco et al. 2003), and retinal pigment epithelium

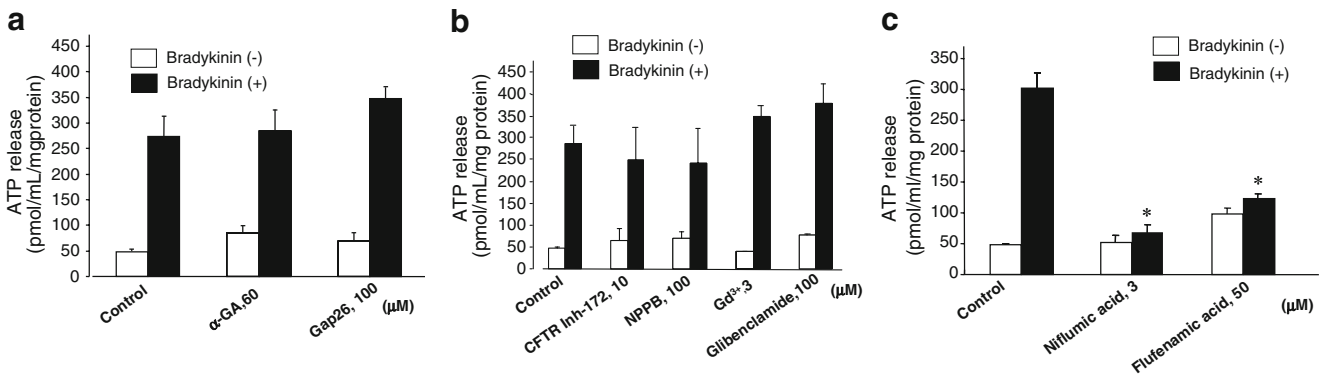

Fig. 3 Effects of hemichannel blockers (**a**), CFTR-Cl^- channel blockers (**b**) and Ca^{2+} activated Cl^- channel blockers (**c**) on the release of ATP evoked by 1 μM bradykinin. In the fractional experiment as shown in Fig. 1, the forth fraction (*empty square*, basal ATP release) and the seventh fraction (*filled square*, evoked peak ATP release with and without antagonists) were extracted and illustrated here. The cells were exposed to antagonists 30 min before bradykinin. Values are expressed as mean ± SEM of $pmol^{-1}$ ml^{-1} mg $protein^{-1}$ of ATP (n=3-10). *p<0.05 compared with the evoked control

from chicken embryos (Pearson et al. 2005). In the present study, however, the bradykinin-evoked release of ATP was unaffected by the typical hemichannel blockers, α-GA and Gap 26, indicating a lesser role of gap junction hemichannels in the membrane transport of ATP. The relevance of CFTR as another ABC (ATP-binding cassette) transporter in ATP transport is a matter of dispute (Abraham et al. 1997). Cantiello et al. (1998), on the basis of their patch-clamp study, postulated that CFTR is a dual ATP and Cl^- channel (Reisin et al. 1994; Lader et al. 2000). In wild-type CFTR-expressing cells, the basal and hypotonic stress-evoked release of ATP was attenuated by CFTR-Cl^- channel blockers, Ga^{3+}, and DIDS (Braunstein et al. 2001). Sprague et al. (2001) reported a deformation-induced, glibenclamide-sensitive release of ATP from the red blood cells of healthy humans but not from patients with cystic fibrosis. On the other hand, a number of objections to the hypothesis of the CFTR-related ATP release have been raised (Reddy et al. 1996; Grygorczyk and Hanrahan 1997; Watt et al. 1998). Besides, our current study showed that a series of CFTR-Cl^- channel blockers, Gd^{3+}, glibenclamide, CFTR (inh)-172, and NPPB failed to attenuate the bradykinin-induced outflow of ATP from the cells, thus, strongly indicating that the evoked release of ATP is not mediated by a CFTR-channel. As to the other ABC superfamilies, there is the possibility that the P-glycoprotein (P-gp) and MRP are able to regulate ATP release induced by hypotonic stress from hepatoma cells (Roman et al. 2001) and cultured astrocyte cells (Darby et al. 2003). Our study found that the extracellular release of ATP with bradykinin was markedly suppressed by MRP inhibitors, MK-571 (Prime-Chapman et al. 2004; Ji and Morris 2005), indomethacin (Darby et al., 2003), and benzbromarone (Hooijberg et al. 2004; Prime-Chapman et al. 2004). We failed to obtain antibodies for MRPs against guinea pig. Thus, in the present study, all antibodies were applied to against rat. As in western blot analysis, a clear band from MRP 1 protein appeared at 190 kD, MRP 1 protein was defined, at least, to exist on the smooth muscle cells in spite of the species mismatch. However, it is necessary to be considered that the negative expressions of MRP 2 and MRP 3 proteins may be due to a matter of specificity of antibodies. The release of ATP with bradykinin is a transient and instantaneous because the peak release occurred around 3 min after the addition. Nevertheless, the 5-min loading with bradykinin did not enhance the expression of MRP 1 protein. At present, the reason remains uncertain whether it comes from a transient response to the peptide or from the species mismatch of antibodies.

Our study provided evidence that niflumic acid and flufenamic acid, Ca^{2+}-activated Cl^- channel blockers, strongly suppressed the evoked release of ATP. There are several findings indicating that activities for MRP transporters and Ca^{2+}-activated Cl^- channels are involved in facilitating the outflux of ATP. Niflumic acid and flufenamic acid blocked the release of the nucleotide triggered by zero calcium from brain endothelial cells (Braet et al. 2003a, b). Similarly, niflumic acid significantly inhibited the release of ATP from multicellular tumor spheroids evoked by electrical field stimulation (Sauer et al. 2002). ATP release and Cl^--current induced by hypotonic stress was reversibly prevented by MRP transporter inhibitors, MK-571 and indomethacin in rat cultured astrocytes (Darby et al. 2003). These findings suggest that the MRP transport system may also couple with the Ca^{2+}-activated Cl^- channel activities in the release of ATP, by analogy that the CFTR transport is mediated by coupling with Cl^- channels. Supportingly, it has been postulated that MRP and CFTR are closely related ABC proteins and both transporters may share a structurally similar binding site on the cytoplasmic membrane (Linsdell and Hanrahan 1999). The release of ATP was blocked by Ca^{2+}-activated Cl^- channel blockers such as niflumic acid, whereas a volume-sensitive outwardly rectifying (VSOR) Cl^-channel blocker, NPPB, and a Maxi Cl^- channel blocker, Gd^{3+} were incapable to inhibit the release. There may be a different nature in ATP release between G-protein-coupled receptor stimulation and hypotonic or mechanical stimulation. The meaning of the dissimilar effects shown with these Cl^- channel blockers might be clarified by a patch-clamp analysis in future studies.

In conclusion, the membrane transport of ATP induced by B2 receptor-stimulation with bradykinin is enhanced by the activation of MRP, presumably MRP 1 transporter, in coupling with Cl^- channels, and not by the activations of CFTR-Cl^-channels and jap junction hemichannels, However, the possibility that P-gp as the member of MDR group, similar to MRP, may be involved in operating the membrane transport of ATP via receptor- stimulation remains to be clarified (Roman et al. 2001)

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