Cell culture: complications due to mechanical release of ATP and activation of purinoceptors

Geoffrey Burnstock1,2 · Gillian E. Knight1

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Abstract There is abundant evidence that ATP (adenosine 5’-triphosphate) is released from a variety of cultured cells in response to mechanical stimulation. The release mechanism involved appears to be a combination of vesicular exocytosis and connexin and pannexin hemichannels. Purinergic receptors on cultured cells mediate both short-term purinergic signalling of secretion and long-term (trophic) signalling such as proliferation, migration, differentiation and apoptosis. We aim in this review to bring to the attention of non-purinergic researchers using tissue culture that the release of ATP in response to mechanical stress evoked by the unavoidable movement of the cells acting on functional purinergic receptors on the culture cells is likely to complicate the interpretation of their data.

Keywords P1 receptors · P2 receptors · Purinoceptor · Shear stress · Ectonucleotidases

Introduction

While it was recognised early that ATP (adenosine 5’-triphosphate) is released from damaged or dying cells, it was shown more recently that gentle mechanical perturbation, such as shear stress, membrane stretch and hypo-osmotic cell swelling, leads to release of ATP from most cell types (Bodin and Burnstock 2001; Bodin et al. 1991; Chaudry 1982; Dolovcak et al. 2011; Forrester 1972; Grygorczyk and Guyot 2001; Milner et al. 1990, 1992; Praetorius and Leipziger 2009, 2010; Sperlágh et al. 2007; Wang et al. 1996). In the outstanding review by Lazarowski et al. (2011), it was stated that “P2Y receptor expression-dependent formation of second messengers was noted in cultured cells subjected to mechanical stress, for example medium displacement or cell wash (Filtz et al. 1994; Lazarowski et al. 1995; Parr et al. 1994). A vast number of studies have followed, illustrating that nonlytic release of ATP occurred in practically every cell type subjected to physical stresses, such as flow resulting in shear stress, hydrostatic pressure, osmotic swelling or shrinking, compressive stress, mechanical loading, plasma membrane stretch, hypoxia and cell swelling” performed during routine experimental procedures, such as cell rinsing and medium changes. It is unlikely that ATP release caused by gentle mechanical stimulation arises from cell damage, for example mechanical stimulated ATP release occurs without associated membrane conductive changes (Hamill and Martinac 2001). Many novel assays (or sensors) have been developed.
to detect ATP release from cells, including luciferin–luciferase bioluminescence and atomic force microscopy (see Dale and Frenguelli 2012; Furuya et al. 2014; Khlyntseva et al. 2009; Praetorious and Leipziger 2009).

The mechanisms responsible for the transport of ATP from cells have been a matter of intense debate. For most cell types, it appears to be a combination of vesicular exocytosis and connexin or pannexin hemichannels (Dahl 2015; Dubyak 2007; Lazarski et al. 2011; Li et al. 2011; Lohman and Isakson 2014; Novak 2003; Scemes et al. 2009; Spray et al. 2006), although for some cells ATP-binding cassette transporters or maxi ion channels have been claimed (Sabirov and Okada 2005). It has also been proposed that P2X7 receptors may mediate ATP release (Pellegratti et al. 2005; Suadicani et al. 2006). A vesicular nucleotide transporter has been identified (Sawada et al. 2008).

ATP released from cells is rapidly broken down by ectonucleotidases to adenosine (see Cardoso et al. 2015; Yegutkin 2008; Zimmermann 2006) but both ATP and adenosine will have functional effects on the cells via P1, P2X and P2Y receptors (see Corriden and Insel 2010).

Two purinoceptor families were recognised in 1978, namely P1 (adenosine) and P2 (nucleotide) receptors (Burnstock 1978). Purinoceptor subtypes were cloned and characterised in the early 1990s, consisting in 4 P1 G protein-coupled receptor subtypes, 7 P2X ion channel receptor subtypes and 8 P2Y G protein-coupled receptor subtypes (see Burnstock 2007; Ralevic and Burnstock 1998).

Release of ATP from cultured cells in response to mechanical stimulation

A comprehensive summary is shown in Table 1.

Function of purinergic receptors on cultured cells in response to released ATP

A comprehensive review of the functional expression of P2 receptors on a wide range of cell types is available (Burnstock and Knight 2004). Some examples follow. ATP released from retinal epithelial cells acts via P2 receptors to increase the rate of fluid transport or decrease phagocytosis (Mitchell 2001) and regulate neural retinal progenitor cell proliferation (Pearson et al. 2005). ATP released by osteoblasts inhibits bone mineralisation (Orriss et al. 2013). Stretch-released ATP from fibroblasts results in cell proliferation (Wang et al. 2005). ATP released from astrocytes mediates glial calcium waves (Guthrie et al. 1999). ATP released from endothelial cells by shear stress acts on endothelial P2 receptors to release nitric oxide resulting in vasodilatation (Burnstock and Ralevic 2014).

Mechanically-induced Ca\textsuperscript{2+} waves have been observed in a variety of cells, including chondrocytes (D’Andrea and Vittur 1996), airways epithelial cells (Boitano et al. 1994; Hansen et al. 1993; Sanderson et al. 1990), glial cells, including Müller cells (Charles et al. 1991, 1992, 1993; Newman 2001), keratinocytes (Koizumi et al. 2004), endothelial cells (Demer et al. 1993), T cells (Wang et al. 2014), mast cells (Osipchuk and Cahalan 1992) and others (see Leybaert and Sanderson 2012). It is likely that they are due to the activation of purinergic receptors by ATP released from the mechanically stimulated cells, mainly via P2Y\textsubscript{1} and P2Y\textsubscript{4} receptors (Frame and de Feijter 1997; Gallagher and Salter 2003; Stamatakis and Mantzaris 2006). Calcium waves are a dynamic intracellular signalling mechanism that allows spatio-temporal information to be rapidly propagated in tissues. ATP released at sites of cell stress signals danger to the immune system.

Conclusion: need for re-interpretation of data derived from cell culture experiments

Release of ATP from cultured cells is unavoidable, due to gentle mechanical stimulation. The released ATP acts on purinoceptors expressed by these cells, which mediate both secretion and trophic events, such as cell proliferation, differentiation, death and migration. These events mean that interpreting results from experiments based on tissue culture need to take into account the effects of released ATP and its actions on purinoceptors.
| Cell type                    | Stimulus       | References                                                                 |
|-----------------------------|----------------|----------------------------------------------------------------------------|
| Vascular endothelial cells  | Shear stress   | Bodin et al. 1991, Li et al. 2015, Milner et al. 1990, 1992, Xiang et al. 2007, Yamamoto et al. 2011, Shinozuka et al. 2001, Hamada et al. 1998 |
|                              | Hypotonic stress| Hisadome et al. 2002, Oike et al. 2000, Shinozuka et al. 2001             |
| Airways                     |                |                                                                            |
| Lung epithelial cells       | Stretch        | Ramsingh et al. 2011, Zhang et al. 2014, Guyot and Hanrahan 2002, Homolya et al. 2000, Okada et al. 2006, Ransford et al. 2009, Seminario-Vidal et al. 2011 |
|                              | Mechanical stress| Hamada et al. 1998                                                        |
| Nasal epithelial cells      | Mechanical stimulation | Watt et al. 1998                                                          |
| Tracheal epithelial cells   | Hypotonic stress| Kawakami et al. 2004                                                      |
| Eye                         |                |                                                                            |
| Retinal ganglion cells      | Swelling       | Xia et al. 2012, Xi et al. 2012                                            |
| Retinal pigment cells       | Mechanical stretch | Eldred et al. 2003, Mitchell 2001, Reigada and Mitchell 2005             |
| Retinal glial (Müller) cells| Hypo-osmotic swelling | Brückner et al. 2012, Voigt et al. 2015, Li et al. 2010, Mitchell et al. 1998, Luna et al. 2009, Li et al. 2011, 2012, Gomes et al. 2005 |
| Lens                        | Hypertonic stress| Eldred et al. 2003                                                         |
| Ciliary epithelial cells    | Hypotonic stress| Li et al. 2010, Mitchell et al. 1998, Luna et al. 2009, Li et al. 2011, 2012, Gomes et al. 2005 |
| Trabecular meshwork cells   | Mechanical stress | Swelling                                                                      |
| Corneal endothelial cells   | Mechanical stimulation |                                                                  |
| Liver                       |                |                                                                            |
| Hepatocytes                 | Hypotonic cell swelling | Pafundo et al. 2008, Roman et al. 1999, Sathe et al. 2011, Woo et al. 2008, 2010, Darby et al. 2003 |
| Biliary epithelium (cholangiocytes) | Hypotonic cell swelling |                                                                 |
|                              | Shear stress    |                                                                 |
| Glial cells                 | Hypotonic cell swelling | Beckel et al. 2014, Darby et al. 2003                                     |

Table 1 (continued)

| Cell type                    | Stimulus       | References                                                                 |
|-----------------------------|----------------|----------------------------------------------------------------------------|
| Astrocytoma cells           | Hypotonic stress| Blum et al. 2010, Joseph et al. 2003, Bennett et al. 2008                 |
| Microglia                   | Mechanical stimulation |                                                                 |
| Bladder urothelial cells    | Stretch        | Mansfield and Hughes 2014, Sun and Chai 2002, Sun et al. 2001              |
| Eye                         |                |                                                                            |
| Retinal ganglion cells      |                |                                                                            |
| Retinal pigment cells       |                |                                                                            |
| Retinal glial (Müller) cells|                |                                                                            |
| Lens                        |                |                                                                            |
| Ciliary epithelial cells    |                |                                                                            |
| Trabecular meshwork cells   |                |                                                                            |
| Corneal endothelial cells   |                |                                                                            |
| Liver                       |                |                                                                            |
| Osteoblastic cells          | Mechanical stress | Hecht et al. 2013, Romanello et al. 2001, 2005, Gardinier et al. 2014, Genetos et al. 2005, Rumney et al. 2012, Xing et al. 2014 |

References:
- Bodin et al. 1991
- Li et al. 2015
- Milner et al. 1990, 1992
- Xiang et al. 2007
- Yamamoto et al. 2011
- Hisadome et al. 2002
- Oike et al. 2000
- Shinozuka et al. 2001
- Hamada et al. 1998
- Ramsingh et al. 2011
- Zhang et al. 2014
- Guyot and Hanrahan 2002
- Homolya et al. 2000
- Okada et al. 2006
- Ransford et al. 2009
- Seminario-Vidal et al. 2011
- Watt et al. 1998
- Wang et al. 1998
- Zhang et al. 2014
- Liu et al. 2008
- Beckel et al. 2014
- Lee et al. 2015
- Stout et al. 2002
- Zhang et al. 2008
- Blum et al. 2010
- Joseph et al. 2003
- Bennett et al. 2008
- Mansfield and Hughes 2014
- Sun and Chai 2002
- Sun et al. 2001
- McClatchie and Fry 2015
- Birder et al. 2003
- Hamada et al. 1998
- Takahara et al. 2014
- Kim and Woo 2015
- Oishi et al. 2012
- Dutta et al. 2004, 2008
- Grierson and Meldolesi 1995
- Funuya et al. 2005, 2014
- Murata et al. 2014
- Boudreault and Grygorczyk 2002, 2004
- Lu et al. 2012
- Riddle et al. 2007
- Ito et al. 2014
- Luckprome et al. 2010, 2011
- Wongkhanteew et al. 2008
- Hecht et al. 2013
- Romanello et al. 2001, 2005
- Gardinier et al. 2014
- Genetos et al. 2005
- Rumney et al. 2012
- Xing et al. 2014
| Cell type                  | Stimulus                          | References                        |
|---------------------------|-----------------------------------|-----------------------------------|
| Intervertebral disc       | Vibratory stimulation             | Yamazaki et al. 2003              |
| annulus cells             | Hypotonic challenge               | Rosenthal et al. 2013             |
| Chondrocytes              | Mechanical stress                 | Graff et al. 2000                 |
|                           |                                   | Kono et al. 2006                  |
|                           |                                   | Millward-Sadler et al. 2004       |
| MLO-Y4 osteocytes         | Mechanical loading by fluid flow   | Genetos et al. 2007               |
|                           | Focal-force stimulation           | Wu et al. 2013                    |
|                           | Mechanical stimulation            | Kringelbach et al. 2015           |
|                           | Membrane stretch                  | Thompson et al. 2011              |
| Immune cells              | Jurkat T lymphocytes              | Loomis et al. 2003                |
|                           | Hypertonic stress                 | Woehrle et al. 2010               |
|                           |                                   | Yip et al. 2007                   |
|                           | Mechanical stress                 | Loomis et al. 2003                |
|                           | Shockwaves                        | Weih et al. 2014                  |
|                           | Osmotic stress                    | Yu et al. 2010                    |
|                           | B lymphoblasts                    | Sakowicz-Burkiewicz et al. 2010   |
|                           | Slow motion                       |                                   |
| Neutrophils               | Hypertonic stress                 | Chen et al. 2004, 2015            |
| Mast cells                | Hypo-osmotic stress               | Wang et al. 2013                  |
| Macrophages               | Hypotonic stress                  | Burow et al. 2015                 |
| Tumour cells              | Prostate cancer cells             | Nandigama et al. 2006             |
|                           | Hypotonic stress                  | Sauer et al. 2000                 |
|                           | Mechanical stress                 | Dolovack et al. 2011              |
|                           |                                    | Espelt et al. 2013                |
|                           |                                    | Feranchak et al. 2010             |
|                           |                                    | Wang et al. 1996                  |
|                           |                                    | Gatof et al. 2004                 |
| Cholangiocarcinoma        | Hypotonic cell swelling           | Roman et al. 1999                 |
|                           |                                    |                                    |
| Lung epithelial carcinoma| Hypotonic shock                   | Seminario-Vidal et al. 2011       |
| (A549) cells             |                                    | Tatur et al. 2008                 |
|                           | Stretch                            | Ramsingh et al. 2011              |
| Mammary carcinoma (C127)  | Hypotonic challenge               | Grygorczyk et al. 2013            |
| cells                     | Mechanical stress                 | Hazama et al. 2000                |
| Ehrlich ascites tumour    | Mechanical stress                 | Sabirov et al. 2001               |
| cells                     |                                    | Pedersen et al. 1999              |
| Ovarian carcinoma (SKOV-3)| Mechanical stimulation            | Vázquez-Cuevas et al. 2014        |
| cells                     | Hypotonic challenge               | Islam et al. 2012                 |
| L929 fibrosarcoma cells   |                                    |                                    |

Table 1 (continued)

| Cell type                  | Stimulus                          | References                        |
|---------------------------|-----------------------------------|-----------------------------------|
| Skin                      | Adipose tissue-derived stem cells | Shock wave treatment             |
|                           | Keratinocyte cell lines           | Air stimulated                    |
| Pancreas                  | Acinar cells                      | Mechanical stimulation            |
|                           | Duct cells                        | Mechanical & hypotonic stress     |
| Gut                       | Epithelial cell lines             | Hypotonic challenge               |
|                           | Submandibular gland               | Mechanical stimulation            |
| Kidney                    | Collecting duct epithelial cells  | Mechanical stimulation            |
|                           | A6 distal nephron epithelial cells| Mechanical stretch               |
|                           | Hypotonic treatment               | Gheorghiu and Van Driessche 2004 |
|                           |                                    | Jans et al. 2002                  |
|                           |                                    | Silva and Garvin 2008             |
|                           |                                    | Prætortius et al. 2005            |
|                           |                                    | Rodat-Despoix et al. 2013         |
|                           | Epithelia from cysts of polycystic| Hypotonic challenge               |
| Blood cells               | Erythrocytes                      |                                    |
|                           | Platelets                         | Hypotonic stretch                 |
|                           | Leukocytes                        |                                    |
|                           |                                    |                                    |

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Table 2 Purinergic receptor expression in cultured cells (references in Table 1)

| Cell type                                | Receptors expressed                      |
|------------------------------------------|------------------------------------------|
| Vascular endothelial cells               | P2X4, P2X5, P2X7                        |
| Airways                                  |                                          |
| Lung epithelial cells                    | P2X4, P2X5                              |
| Nasal epithelial cells                   | P2X4, P2X7                              |
| Tracheal epithelial cells                | P2X4, P2X7                              |
| Eye                                      |                                          |
| Retinal ganglion cells                   | P2X2-7                                  |
| Retinal pigment cells                    | P2X2, P2X3, P2X7                        |
| Retinal glial (Müller) cells             | P2X7                                    |
| Lens                                     | P2X1, P2X4                              |
| Ciliary epithelial cells                 | P2X2, P2X3, P2X7                        |
| Trabecular meshwork cells                | P2X1, P2X7                              |
| Corneal endothelial cells                | P2X4-7                                  |
| Liver                                    |                                          |
| Hepatocytes                              | P2X4, P2X7                              |
| Biliary epithelium (cholangiocytes)      | P2X4                                    |
| Glial cells                              |                                          |
| Astrocytes                               | P2X4, P2X7                              |
| Astrocytoma cells                        | P2X7                                    |
| Microglia                                | P2X4, P2X7                              |
| Bladder urothelial cells                 | P2X2, P2X3, P2X4                        |
| Muscle                                   |                                          |
| Vascular smooth muscle                   | P2X1, P2X2, P2X4                        |
| Bladder smooth muscle                    | P2X1, P2X2                              |
| Cardiomyoctes                            | P2X1,3,4,5,6 and 7                      |
| Fibroblasts                              | P2X7                                    |
| Cardiac fibroblasts                      | P2X4, P2X7                              |
| Bone                                     |                                          |
| Bone marrow stromal cells                | P2X7                                    |
| Periodontal ligament                     | P2X1-7                                  |
| Osteoblastic cells                       | P2X4, P2X7                              |
| Intervertebral disc annulus cells        | P2X1,3,4,5,6 and 7                      |
| Chondrocytes                             | P2X1,3,4,5 and 7                        |
| MLO-Y4 osteocytes                        | P2X1,2,3,4 and 7                        |
| Immune cells                             |                                          |
| Jurkat T lymphocytes                     | P2X1,4,5 and 7                          |
| B lymphoblasts                           | P2X1, P2X4, P2X7                        |
| Neutrophils                              | P2X1, P2X4, P2X7                        |
| Mast cells                               | P2X7                                    |
| Macrophages                              | P2X7                                    |
| Tumour cells                             |                                          |
Table 2 (continued)

| Cell type                                | Receptors expressed |
|------------------------------------------|---------------------|
|                                          | P2X                | P2Y                | P1          |
| Prostate cancer cells                    | P2X4-7             | P2Y_{1,2,6} and 11 | A_{1,2A,2B, A3} |
| Hepatoma cells                           |                    | P2Y_{1,2,4,6} and 13 | A_{2A,2B, A3} |
| Cholangiocarcinoma                       |                    | P2Y_{5}            |             |
| Lung epithelial carcinoma (A549) cells   | P2X4-7             | P2Y_{2,4,6}, P2Y_{6} | A_{2A,2B, A3} |
| Mammary carcinoma cells                  | P2X7               | P2Y_{1}            | A_{1,2A, A3} |
| Ehrlich ascites tumour cells             | P2Y_{1,2}, P2Y_{5} |             |             |
| Ovarian carcinoma (SKOV-3) cells         | P2X7               | P2Y_{2,6}          |             |
| L929 fibrosarcoma cells                  | P2X7               |                  |             |
| Skin                                     |                    | P2X2,3,5 and 7     | P2Y_{1,2,4,6} and 11 |
| Keratinocyte cell lines                  |                    |                  |             |
| Pancreas                                 |                    |                  |             |
| Acinar cells                             | P2X12,3,4,6 and 7  | P2Y_{1,2,4,11,12,13} and 14 | A_{1,2A,2B, A3} |
| Duct cells                               | P2X1,2,4,5,6 and 7 | P2Y_{1,2,4,11,12,13} and 14 | A_{1,2A,2B, A3} |
| Xenopus oocytes                          | P2X4               | P2Y_{2-like}       | Atypical A_{1} |
| Stem cells                               |                    |                  |             |
| Mesenchymal stem cells                   | P2X4,5,6 and 7     | P2Y_{1,2,4,11,13} and 14 | A_{1,2A,2B} |
| Gut                                      |                    |                  |             |
| Epithelial cell lines                    | P2X7               | P2Y_{2,6}          | A_{2A,2B}   |
| Salivary glands                          |                    |                  |             |
| Submandibular gland                      | P2X1-7             | P2Y_{1,2}          |             |
| Kidney                                   |                    |                  |             |
| Collecting duct epithelial cells         | P2X4, P2X5, P2X6   | P2Y_{1,2,4,6}      | A_{1,2A,2B, A3} |
| A6 distal nephron epithelial cells       | P2X4               | P2Y_{1,2}          | A_{1,2}     |
| MDCK cells                               | P2X7               | P2Y_{1,2,6} and 11 | A_{1}       |
| Epithelia from cysts of polycystic kidneys | P2X4, P2X5       | P2Y_{1,2}, P2Y_{6} |             |
| Blood cells                              |                    |                  |             |
| Erythrocytes                             | P2X1, P2X4, P2X7   | P2Y_{1,2}          | A_{2B}      |
| Platelets                                | P2X1               | P2Y_{1,2,12}, P2Y_{14} | A_{2A,2B} |
| Leukocytes                               | P2X4, P2X7         | P2Y_{2,6}          | A_{1,2A,2B, A3} |

Compliance with ethical standards

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