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Cyclic AMP is both a pro-apoptotic and anti-apoptotic second messenger

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Abstract

The second messenger cyclic AMP (cAMP) can either stimulate or inhibit programmed cell death (apoptosis). Here, we review examples of cell types that show pro-apoptotic or anti-apoptotic responses to increases in cAMP. We also show that cells can have both such responses, although predominantly having one or the other. Protein kinase A (PKA)-promoted changes in phosphoylation and gene expression can mediate pro-apoptotic responses, such as in murine S49 lymphoma cells, based on evidence that mutants lacking PKA fail to undergo cAMP-promoted, mitochondria-dependent apoptosis. Mechanisms for the anti-apoptotic response to cAMP likely involve Epac (Exchange protein activated by cAMP), a cAMP-regulated effector that is a guanine nucleotide exchange factor (GEF) for the low molecular weight G-protein, Rap1. Therapeutic approaches that activate PKA-mediated pro-apoptosis or that block Epac-mediated anti-apoptotisis may provide a means to enhance cell killing, such as in certain cancers. By contrast, efforts to block PKA or stimulate Epac have the potential to be useful in diseases settings (such as heart failure) associated with cAMP-promoted apoptosis.

Keywords

apoptosis; protein kinase A; Epac; Rap1; S49 cell

Introduction

Cyclic AMP (cAMP) is a well-studied second messenger with >95,000 entries (as of December, 2010) in PubMed. Regulation of cell death is one of the actions of cAMP. Indeed, a PubMed search with the terms “cyclic AMP” and ”cell death” reveals >2000 published articles (including 160 reviews) over the past 40 years but none that review the stimulation or inhibition of cell death, in particular, apoptosis (programmed cell death) by cAMP. Moreover, components in the cAMP signaling pathway, including the cAMP effector protein kinase A (PKA), have been proposed as targets to enhance apoptosis, such as in the treatment of certain cancers (e.g., Cross, et al 2000;Lerner et al 2000). In this article we focus on publications in recent years and summarize pro-and anti-apoptotic responses to cAMP in various cell types, mechanisms for these actions and therapeutic implications of such findings.

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Conflict of interest
There is no conflict of interest.

cAMP as a regulator of cell death

Even though cAMP was discovered in the late 1950's, the role of cAMP in regulating cell death has been studied much less intensely than other actions, such as regulation of metabolism and various physiological responses. The ability of cAMP to promote cell death was first recognized in the early 1970's (e.g., Martorana 1971; Basile et al 1973; Pratt and Martin, 1975; Coffino et al 1975; Insel et al 1975) but the full range of cell types subject to this action is still being defined. The initial description of apoptosis occurred at about the same time (Kerr et al 1972) but only in recent years has the regulation of apoptotic cell death by cAMP been studied.

Apoptosis is one form of cell death, the two other major types being autophagy and necrosis, each of which has distinct morphological features and mechanisms. Considerable effort has been directed at distinguishing necrosis from apoptosis (e.g., Walker et al, 1988). Necrosis is a largely passive phenomenon that follows irreversible injury while apoptosis is an active process that requires numerous proteins and has two primary forms: intrinsic, mitochondrial-dependent and extrinsic, resulting from the action of membrane death receptors by extracellular agents such as Fas ligand. The intrinsic pathway involves B-cell lymphoma (Bcl)-related family proteins that have anti-apoptotic (e.g., Bcl-2, Bcl_{XL}) or pro-apoptotic (e.g., Bax, Bak, BAD, BIM, Bcl_{XS}) actions that can regulate mitochondrial release of cytochrome c and Smac (second mitochondria-derived activator of caspases/DIABLO (direct IAP-binding protein with low pI). Both intrinsic and extrinsic pathways involve the activation of caspases (cysteinyl aspartate-specific proteinases), enzymes that mediate cell killing. Apoptosis has physiological roles in regulating tissue size and remodeling but also occurs in pathological settings. Characteristic morphological features of apoptosis include condensation of nuclear chromatin and the cytoplasm, fragmentation of the nucleus (in association with internucleosomal cleavage of DNA) and cell budding with eversion of the plasma membrane and generation of membraneous bodies that are disposed of by adjacent cells. The distinctive internucleosomal cleavage of DNA in apoptosis generates electrophoretically observed DNA "ladders" that contrast with the random degradation of DNA that occurs with necrosis.

Few studies have assessed the impact of cAMP on necrosis (e.g., Journot et al, 1998) but there has been recent interest related to cAMP and autophagy--a mechanism by which cells deliver misfolded, ubiquinated proteins for degradation by lysosomes, in particular as a means to supply macromolecules in settings of nutrient deprivation. Its action in such settings has led to the proposal that autophagy is primarily a mechanism for cell survival rather than cell death (e.g., Levine and Yuan 2005). Numerous studies implicate cAMP in the regulation of autophagy in mammalian cells and lower eukaryotes and suggest that cellular components involved in autophagy can influence cAMP-mediated signal transduction (e.g., Holen et al, 1996; Budovskaya et al, 2005; Stephan et al, 2009; Houslay and Christian, 2010; Chin et al, 2010).

Cells that show pro-apoptotic responses to cAMP

Increases in cAMP are pro-apoptotic in numerous cell types (Table 1), including normal cells as well as malignant cells from virtually every tissue. In some cases, the apoptotic responses to cAMP analogs have been assessed whereas in other studies, endogenous cAMP concentrations have been raised by the use of hormones, neurotransmitters, the diterpene forskolin (which activates adenylyl cyclase) or cAMP phosphodiesterase (PDE) inhibitors. Cyclic AMP can also sensitize cells to the pro-apoptotic action of agents, such as DNA damage, that work via non-cAMP pathway components (e.g., Ugland et al 2008).

Some examples in Table 1 involve individual cell lines or cultured cells; for that reason, we use the term “certain” before several cell types. Of note are the substantial data indicating cAMP-promoted apoptosis in certain lymphoid cells, especially immature lymphoid cells, certain neuronal cells and cardiac myocytes (Table 1). The findings for cardiac myocytes, including the evidence that apoptosis occurs in response to the activation of β1-adrenoceptors (e.g., Singh et al 2001;Hasegawa et al 2001), are implicated in the progression of heart failure and provide a rationale for the use of β-blockers to treat patients with heart failure (McMurray 2010).

Cells that show anti-apoptotic responses to cAMP

Table 2 summarizes examples of settings in which cAMP is anti-apoptotic, including its blockade of spontaneous apoptosis and apoptosis induced by a variety of agents. Agents that elevate cAMP (e.g., endogenous hormones or neurotransmitters, forskolin, PDE inhibitors or cAMP analogs) blunt apoptosis in numerous types of neurons, epithelial cells, in pancreatic islet β-cells and many other cell types.

Can cAMP be pro-and anti-apoptotic in the same cell?

Certain cell types are listed in both Tables 1 and 2. In some cases, this reflects the use of different cell lines derived from the same tissue, perhaps reflecting differences in the capacity of particular cell types in a given tissue to undergo pro- or anti-apoptosis in response to cAMP or the use of different experimental approaches, for example, whether spontaneous apoptosis is assessed or if a pro-apoptotic agent is added prior to assessing the impact of endogenous cAMP or a cAMP analog. Cell permeable cAMP analogs that are resistant to PDE inhibition can lead to sustained PKA activation and regulation of downstream targets. Elevation of endogenous cAMP by receptor activation generally produces more transient PKA activation due to receptor desensitization and PDE-mediated degradation of cAMP. Thus, different responses, both qualitatively and quantitatively, may occur with these two means of increasing cAMP.

In other cases, though, investigators use similar cell types but obtain different results. Although technical differences may contribute (especially since different methods are sometimes used to assay apoptosis and isolate and grow cells or in some cases, different cell isolates are employed in different studies), we believe that there is another explanation: *Individual cells may undergo both pro-apoptotic and anti-apoptotic responses to cAMP*. Results in a given experiment may thus depend on the conditions under which it is conducted (e.g, Chen et al 2002). For example, murine S49 lymphoma cells, which undergo apoptosis in response to increased cAMP levels, in particular after 48–72 hr treatment (Yan et al 2000; Zhang and Insel 2001; Zhang and Insel 2004; Zambon et al 2005; Zhang et al 2008b), show a transient anti-apoptotic response to cAMP (in terms of annexin V binding to phosphatidylserine on plasma membrane and caspase 3 activity; Figure 1) if also treated with certain pro-apoptotic agents (e.g., anti-Fas in Figure 1 and ultraviolet light, data not shown). Data from other laboratories also implicate cAMP as having pro- or anti-apoptotic activity in the same cell (e.g., McEwan et al 2007; Loffler et al 2008).

Mechanisms for pro-and anti-apoptotic actions of cAMP

Different molecular mechanisms mediate cAMP-promoted pro-apoptosis and anti-apoptosis. Substantial evidence indicates that PKA is pro-apoptotic through the phosphorylation of protein targets (e.g., Zambon et al, 2005; Carie and Sebti 2007; Zhang et al 2008b; Benz et al 2008). Studies in S49 lymphoma cells have shown that this pro-apoptotic effect of PKA occurs by an intrinsic, mitochondria-dependent mechanism (Coffino et al 1975; Insel et al 1975; Yan et al 2000; Zhang and Insel 2004; Zambon et al 2005; Zhang et al 2008b). The

exact nature of the protein targets, in particular those that are necessary and sufficient to induce cAMP-promoted apoptosis, in wild-type S49 cells and other cell types has not yet been defined but is an area of active study.

Selective involvement of the two isozymes (I and II) of PKA may influence the role of cAMP in cell death. For example, cAMP analogs selective for the type I regulatory (R) subunit inhibit natural killer cell-mediated cytotoxicity (Torgresen et al 1997; Raskovalova et al, 2006) and expression of PKA type II R subunits can modulate apoptosis of fibroblasts (Porcellini et al 2003). An altered balance between PKARI and RII has been implicated in various cancers; manipulation of these isozymes may be a means to enhance cAMP-mediated apoptosis (Mantovani et al 2008; Bouizar et al 2010).

In addition to being pro-apoptotic, PKA can also be anti-apoptotic, perhaps via effects that alter the balance of serine/threone phosphorylation of Akt by other kinases, such as p38 kinase and phosphatidylinositol 3-kinase (PI3 kinase) (Kragsted et al 2004; Leone et al 2007; Torella et al 2009). Dynamin-related protein 1, a mitochondrial protein, is a PKA target that protects from apoptosis (Cribbs and Strack 2007). Inhibition of the PI3 kinase/Akt pathway can also occur in a PKA-independent manner (Smith et al 2005).

Epac (Exchange protein activated by cAMP) is a second effector of cAMP action that can mediate cAMP-promoted anti-apoptosis (Tiwari et al 2004; Kamrava et al 2005; Misra and Pizzo 2005; Grandoch et al 2010; Murray and Insel [unpublished]). Epac, a guanine nucleotide exchange factor (GEF) for the low-molecular weight GTP binding protein Rap1, produces PKA-independent responses (Gloerich and Bos 2010; Grandoch et al 2010). Epac-regulated targets for cAMP-promoted anti-apoptosis are not well defined. Limited data also implicate Epac in certain pro-apoptotic responses (e.g., Grandoch M, Lopez de Jesus M et al 2009).

Potential therapeutic applications of the pro-and anti-apoptotic actions of cAMP

Information related to the ability of increases in cAMP to promote or block apoptosis may provide opportunities for new therapeutic approaches. Apoptosis is desirable in some settings (e.g., killing of neoplastic cells) but harmful in others (e.g., loss of pancreatic β-cells that leads to diabetes mellitus or of neurons, cardiac myocytes or epithelial cells following injury). Thus, one would seek to enhance cAMP/PKA-promoted apoptosis in cancer but blunt such apoptosis or increase cAMP/Epac-promoted anti-apoptosis in settings to maintain tissue integrity. Agents that target PKA will likely have undesirable side effects because of its widespread expression. Alternative approaches to exploit the pro-apoptotic role of PKA are by seeking to achieve specificity in PKA signaling, for example by targeting selectively expressed or subcellularly localized PKA R or C (catalytic) subunits, A kinase anchoring proteins (AKAPs) or phosphorylation targets of PKA.

The development of Epac-directed drugs or agents directed at Epac targets is an alternative approach that may yield novel ways to alter cAMP-regulated apoptosis, especially if used together with increases in cAMP in particular cell types or cellular compartments or that would regulate partners of Epac and PKA (e.g., Gao et al 2010; Savai et al 2010; Perrino et al 2010; Patel et al 2010). Perhaps approaches that increase cAMP along with ones that inhibit Epac could provide combination therapies to supplement other types of anti-neoplastic agents (e.g., Desiniotis et al 2010), although one must be cautious since increased cAMP can blunt apoptosis by such agents in cancer cells (Naderi et al 2009; Safa et al 2010).

Conclusions

Cyclic AMP can either promote or block apoptosis in a large number of cell types. The pro-apoptotic response to cAMP occurs via PKA and its phosphoylation of target proteins while the anti-apoptotic response may occur through the actions of Epac. Increasing insight regarding the pro- and anti-apoptotic actions of cAMP has the potential to identify new therapeutic approaches that may impact on a number of clinically important disorders.

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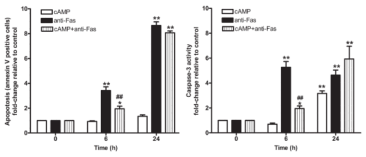

Figure 1. cAMP can both stimulate and blunt apoptosis in S49 lymphoma cells

Wild-type S49 cells were incubated with 100μM CPT-cAMP, 500ng Anti-Fas or the combination of CPT-cAMP and Anti-Fas for 6h and 24h and then assayed for apoptosis (Annexin-V binding; left panel) or caspase 3 activity (determined using a colorometric assay kit from EMD; right panel). The results shown are from 3 separate experiments. *$p<0.05$, ** $p<0.01$ compared to control (0h), ## $p<0.01$ compared to anti-Fas alone by t-test analysis. Note that CPT-cAMP blunts Annexin V binding and caspase 3 activity induced by anti-Fas treatment at 6 hr but this blunting is lost by 24h and that CPT-cAMP increases caspase 3 activity at 24 hr as a prelude to apoptosis (Zhang and Insel, 2004; Zhang et al, 2008b).

Table 1

Examples of cell types in which increases in cAMP are pro-apoptotic

Cell Type	References
Cardiac myocytes	Singh et al. (2001); Hasegawa et al. (2001); Xiao. (2001); Iwai-Kanai and Hasegawa. (2004); Ding et al. (2005); Zheng et al. (2005); Yan et al (2007); Suzuki et al (2010)
Certain adrenocortical cells	Liu et al. (2004); Mantovani et al. (2008); Bouizar et al. (2010)
Certain breast cells	Naviglio et al. (2009); Carie and Sebti. (2007)
Certain fibroblasts	Valente et al. (2003); Moghadam et al. (2005); Quinteros Villarruel E in press. (2010)
Certain leukocytes /lymphomas/leukemias	Thompson et al (1999); Lerner et al. (2000); Yan et al (2000); Zhang and Insel (2001); Zhang and Insel (2004); Altucci et al (2005); Smith et al (2005); Lerner and Epstein (2006); Closter et al.(2008); Zhang L et al. (2008a); Zhang L et al. (2008b); Ji et al. (2008); Jiang et al (2009); Kim et al (2009); Sousa et al. (2009); Dong et al (2010); Dou and Wang (2010); Sousa et al. (2010)
Certain neuronal/glial cells	Chen et al. (1998); Kumar et al (2004); Linden et al. (2005); Takadera and Ohyashiki. (2006a Takadera and Ohyashiki. (2006b); Chan et al. (2007); Svoboda et al (2007); Zhao et al. (2007); Suzuki et al (2010)
Lung carcinoma cells	Shafer et al. (1998); Adissu and Schuller (2004); Zhou et al. (2005); Al-Wadei and Schuller (2006); Choi et al (2009).
Melanoma cells	Mantovani et al. (2008)
Osteoblasts	Chen et al. (2002)
Ovarian cancer and granulosal cells	Slot et al. (2006); Amsterdam et al. (2003a and 2003b)
Renal mesangial cells	Muhl et al (1996); Zhu et al (2006)
Vascular endothelial and smooth muscle cells	Werstiuk and Lee. (2000); Koyama et al. (2001); Li et al. (2004); Growcott et al. (2006); Ohtsubo et al. (2007); Kumar et al. (2009);

Table 2

Examples of cell types in which increases in cAMP are anti-apoptotic

Cell type	References
Adrenal cortical cells	Gallo-Payet and Payet. (2003)
Cardiac myocytes (post-nitric oxide)	Kwak at al. (2008)
Certain breast cancer cells	Sastry et al. (2007)
Certain fibroblasts	Yusta et al. (2000); Uzan et al. (2006); Jasinska et al. (2006); Zhang J et al. (2008)
Certain prostate cancer cells	Sastry et al. (2007)
Corneal endothelial cells	Li et al. (in press, 2011)
Gastrointestinal epithelial cells	Nishihara et al. (2003; 2004); Brubaker and Drucker. (2004); Joseph et al. (2005); Holla et al. (2006); Hawcroft et al. (2007); Leone et al. (2007); Loffler et al. (2008)
Hepatocytes	Sinclair et al. (2008); Gates et al. (2009)
Keratinocytes/Melanocytes	Slominski et al. (2006); Passeron et al. (2009)
Leukocytes/macrophages (including malignant cells)	Kragsted et al. (2004); Tiwari et al. (2004); Misra and Pizzo (2005); Conran et al (2007); Vaughan et al (2007); Kostylina al. (2008); Parkkonen et al. (2008); Grandoch et al. (2009); Kottyan et al. (2009); Lee et al. (2010)
Neuronal cell types	Journot et al. (1998); Iwai-Kanai and Hasegawa (2004); Chai et al. (2006); Pugh and Margiotta (2006); Chen et al. (2006); Dai et al. (2006); Szatmari et al. (2007); Jiao et al. (2007); Qin et al. (2008); Wang and Yang (2009); Andrade da Costa et al (2009); Vaudry et al. (2009); Park et al. (2009); Counts and Mufson. (2010); Stetler et al. (2010); Kang et al (2010); Brown et al. (2010); Shao et al. (2010); Shao et al. in press (2011)
Oligodendrocytes/Oligodendroglial progenitor cells	Whitaker et al. (2008); Horiuchi et al (2010); Kim et al (2010)
Osteoblasts/osteocytes	Chen et al. (2002); Kitase et al. (2010)
Ovarian cells and cancers	Pon et al. (2005); Kamrava et al. (2005); Chen et al. (2010)
Pancreatic islet β-cells	Brubaker and Drucker (2004); Granata et al. (2008); Ferdaoussi et al. (2008); Yu and Gin. (2010); Balhuizen et al. (2010); Cornu et al. (2010); Shao et al. (2010); Soleimanpour et al. (2010)
Pituitary tumors	Tada et al. (1999); Yu and Melmed. (2001); Faglia and Spada (2001)
Pulmonary airway/epithelial cells	Zhou et al. (2005); Barlow et al. (2008)
Renal epithelial cells	Yano et al. (2005); Elberg et al. (2007); Steinert et al. (2009)
Salivary gland acinar cells	Calafat et al. (2009)
Vascular smooth muscle cells	Torella et al. (2009)
Vascular endothelial cells	Torella et al. (2009); Kim et al. (2010)