Molecular and Cellular Endocrinology 463 (2018) 72–86

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

Cyclic 3′,5′-adenosine monophosphate (cAMP) signaling in the anterior pituitary gland in health and disease

Laura C. Hernández-Ramírez, Giampaolo Trivellin, Constantine A. Stratakis*

Section on Endocrinology and Genetics, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH), 10 Center Drive, CRC, Room 1E-3216, Bethesda, MD 20892-1862, USA

ARTICLE INFO

Article history:
Received 26 June 2017
Received in revised form
11 August 2017
Accepted 14 August 2017
Available online 16 August 2017

Keywords:
cAMP
PKA
Pituitary gland
Second messenger
Somatotropinoma
Pituitary adenoma

ABSTRACT

The cyclic 3′,5′-adenosine monophosphate (cAMP) was the first among the so-called "second messengers" to be described. It is conserved in most organisms and functions as a signal transducer by mediating the intracellular effects of multiple hormones and neurotransmitters. In this review, we first delineate how different members of the cAMP pathway ensure its correct compartmentalization and activity, mediate the terminal intracellular effects, and allow the crosstalk with other signaling pathways. We then focus on the pituitary gland, where cAMP exerts a crucial function by controlling the responsiveness of the cells to hypothalamic hormones, neurotransmitters and peripheral factors. We discuss the most relevant physiological functions mediated by cAMP in the different pituitary cell types, and summarize the defects affecting this pathway that have been reported in the literature. We finally discuss how a deregulated cAMP pathway is involved in the pathogenesis of pituitary disorders and how it affects the response to therapy.

Contents

* Corresponding author.
E-mail address: stratakc@cc1.nichd.nih.gov (C.A. Stratakis).

http://dx.doi.org/10.1016/j.mce.2017.08.006
0303-7207/

Abbreviations

α-GSU	α-glycoprotein subunit
AC	adenylyl cyclase
AHR	aryl hydrocarbon receptor
AIP	aryl hydrocarbon receptor interacting protein
AKAP	A-kinase anchoring protein
AKT	RAC-α serine/threonine-protein kinase
ATP	adenosine triphosphate
AVP	vasopressin
cAMP	cyclic 3′,5′-adenosine monophosphate
cGMP	cyclic 3′,5′- guanosine monophosphate
CBP	CREB-binding protein
CNB	cyclic nucleotide-binding
CNC	Carney complex
CNG	cyclic nucleotide-gated channel
CRE	cAMP response element
CREB	cAMP response element-binding protein
CRH	corticotrophin-releasing hormone
CRHR	corticotrophin-releasing hormone receptor
CRIS	cyclic nucleotide receptor involved in sperm function
D2R	D2 receptors
EGFR	epidermal growth factor receptor
EPAC	exchange protein directly activated by cAMP
FD	fibrous dysplasia
FIPA	familial isolated pituitary adenoma
FLNA	filamin A
GABA	gamma-amino butyric acid
GDP	guanosine diphosphate
GH	growth hormone
GHRH	growth hormone-releasing hormone
GHRHR	growth hormone-releasing hormone receptor
GIP	glucose-dependent insulinotropic polypeptide
GIPR	glucose-dependent insulinotropic polypeptide receptor
GnRH	gonadotropin-releasing hormone
GnRHR	gonadotropin-releasing hormone receptor
GPCR	G protein–coupled receptor
GRK	GPCR kinase
GTP	guanosine triphosphate
GTPase	guanidine triphosphatase
HCN	hyperpolarization-activated cyclic nucleotide-gated channel
ICER	inducible cAMP early repressor
LOF	loss-of-function
LOH	loss of heterozygosity
MAPK1	mitogen-activated protein kinase 1
MAS	McCune-Albright syndrome
NFPA	non-functioning pituitary adenoma
NO	nitric oxide
OGTT	oral glucose tolerance test
PACAP	pituitary adenylyl cyclase-activating peptide
PBC	phosphate-binding cassette
PDE	phosphodiesterase
PI3K	phosphatidylinositol 3-kinase
PKA	protein kinase A
PKC	protein kinase C
PKG	protein kinase G
PLC	phospholipase C
POMC	proopiomelanocortin
POPDC	popeye domain-containing protein
PP	precocious puberty
PRL	prolactin
SIRT1	sirtuin 1
SNP	single-nucleotide polymorphism
SS	somatostatin
SSA	somatostatin analog
SSTR	somatostatin receptor
TRH	thyrotropin-releasing hormone
TSH	thyrotropin
VIP	vasoactive intestinal polypeptide

1. Introduction

The so-called “second messengers” link extracellular stimuli with intracellular responses, and the cyclic 3′,5′-adenosine monophosphate (cAMP) was the first of such molecules to be described (Sutherland and Rall, 1958). This signal transducer is an essential mediator of the effects of multiple hormones and neurotransmitters and is conserved among most organisms (Danchin, 1993). Despite being a practically ubiquitous and almost generic intracellular response, cAMP signaling is deftly specific thanks to its temporally, spatially, and functionally regulated compartmentalization, assisted by a complex network of cell- and tissue-specific downstream effectors and regulators. Moreover, the cAMP pathway does not operate independently, but crosstalks with other signaling cascades, allowing the cell to finely-tune its responses by integrating different extracellular signals.

In the pituitary, cAMP has long since been established as a key signaling molecule that controls responsiveness to mitogens and secretagogues, such as hypothalamic hormones, neurotransmitters and other peripheral factors (Peverelli et al., 2014a). In this review, we discuss the most relevant physiological functions of cAMP signaling in the normal pituitary, emphasizing the specificity of the responses among different cell types. We also review the implications of deregulated function of this molecular pathway in the pathogenesis of pituitary disorders and the relevant search for novel therapeutic targets.

2. General roadmap of the cAMP signaling pathway

The cAMP pathway is intimately linked to the function of the seven-transmembrane (also referred as heptahelical) G protein–coupled receptors (GPCRs), as ligand binding to such