Cell Calcium 51 (2012) 207–211

Contents lists available at SciVerse ScienceDirect

Cell Calcium

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

Editorial

Neuroendocrine signalling: Natural variations on a Ca^{2+} theme

ARTICLE INFO

Keywords:
Neuroendocrinology
Anterior pituitary
Neurohypophysis
Hypothalamus
Supraoptic nucleus
Oxytocin
Vasopressin
Neurotransmitter/peptide release
Ca^{2+} homeostasis
Ca^{2+} clearance
Ca^{2+} stores
Stimulus–secretion coupling
Electrical activity
Endocrine cells
Chromaffin cells
Pancreatic islets
Exocytosis
cAMP
Second messengers
Transgenic rat model for AVP and OT
Gonadotropes
Lactotropes
Corticotropes
Opioids
ATP
Puriniceptors
Chromaffin cell biology and Ca^{2+} signalling

ABSTRACT

This special issue on Ca^{2+} signalling in neuroendocrine cells is an opportunity to assess, through a range of first-class review articles, the complex world of endocrine signalling, a complexity that is probably best captured by calling it "diversity in unity". The unity comes from the fact that all the endocrine cells are excitable cells, able to generate action potentials and are using Ca^{2+} as an essential informational molecule, coupling cell stimulation with the activation of secretion, through the exocytotic process. The 'diversity' element, illustrated by almost all the reviews, stems from the modalities employed to achieve the increase in cytosolic Ca^{2+} signal, the balance between the participation of Ca^{2+} entry through the plasma membrane voltage-operated Ca^{2+} channels and the release of Ca^{2+} from intracellular Ca^{2+} stores, and the cross-talk between the Ca^{2+} and cyclic AMP signalling pathways.

It is now a little bit more than half a century from the publication of one of the cornerstone books in the history of neuroendocrinology, the *Neural Control of the Pituitary Gland* (1955), written by one of the founding fathers of the field, Geoffrey W. Harris (1913–1971) [1]. The fundamental contribution of Harris was the establishment, through experimentation, demonstration and persuasion of the neurovascular concept in endocrinology. The advances in electronic technologies that resulted from the wartime efforts in the development of radar equipment allowed, in the mid to late 1940s, sophisticated electrophysiological protocols that recorded from stereotaxically implanted chronic electrodes in freely moving animals. These experiments showed that, in the absence of anaesthesia, stimulation of various small, localised regions in the basal brain determined the release into circulation of various hormones, the process taking place in a manner that could not be reproduced by direct stimulation of the anterior pituitary gland [2].

The initial hypothesis was for a neuronal control of such secretory activity, similar to that taking place in the posterior pituitary; however, the search for a diffuse innervation of the anterior pituitary gland proved fruitless and the nature of the communication between hypothalamus and the pituitary gland remained much of a mystery. And it is here that the fundamental concept of neurovascular link proposed by Harris came into play with full force. In proposing such a link, Harris took full advantage of his earlier meetings, in the early stages of his career in Cambridge, with Prof. Grigore T. Popa (1892–1948), then head of the Anatomy Department at Iasi University, in Romania. In the early 1930s, Popa, on a Rockefeller bursary in London, and Una Fielding, an Australian researcher working in the Anatomy Department in University

Abbreviations: AVP, arginine vasopressin; OT, oxytocin; SON, supraoptic nucleus; $[Ca^{2+}]_i$, cytosolic Ca^{2+} transients/increase; CPA, cyclopiazonic acid; TG, thapsigargin; CCCP, carbonyl cyanide 3-chlorophenylhydrazone; ER, endoplasmic reticulum; SERCA, sarcoendoplasmic reticulum Ca^{2+}-ATPase; PMCA, plasma membrane Ca^{2+} ATPase; NCX, Na^+/Ca^{2+} exchanger; $InsP_3$, inositol trisphosphate; VDCC, voltage-dependent Ca^{2+} channels; RyR, ryanodine receptors; VOCCs, voltage-operated Ca^{2+} channels; PLC, phospholipase C; PIP_2, that cleaves the plasma membrane phosphatidyl inositol to IP_3, inositol trisphospate and DAG, diacylglycerol; GPCR, G-protein-coupled receptor; CAPS, Ca^{2+}-dependent activator proteins for secretion; APUD, amine precursor uptake and decarboxylation; DNES, diffuse neuroendocrine system; GH, growth hormone; ACTH, adrenocorticotropic hormone; GnRH, gonadotropin-releasing hormone; TRPC, transient receptor potential currents.

0143-4160/$ – see front matter © 2012 Published by Elsevier Ltd.
doi:10.1016/j.ceca.2012.01.010

College London (UCL), demonstrated, by extensive dissection of a large number of cadavers (human but also animal), that the pituitary stalk is covered with a fine network of blood vessels, linking hypothalamus with the anterior pituitary gland, a network that they called the hypothalamo-hypophyseal portal system, since, like the liver portal circulation, the system is initiated and terminates in a capillary bed [3,4]. But Harris had a hugely important additional contribution. The initial proposal put forward, on their experimental evidence, by Popa and Fielding was that the flow of blood in this portal circulation is from the hypophysis to the hypothalamus, a view accepted in an early publication by Harris and Popa. At the same time with Harris and Popa paper, George Wislocki, working in the Anatomy Department at Harvard, submitted evidence to show that the blood flow in the portal system is from the hypothalamus to hypophysis [5,6], and this point of view was eventually proved conclusively by Harris [1].

The neuroendocrine system was also the central point for the development of another crucial concept in cellular physiology, central to most of endocrinology and, to a very good extent, central to this special issue: the role of Ca^{2+} in mediating the link between the arrival of the extracellular signal and the release of the secretory product (hormones) into the extracellular space and, ultimately, in the blood stream. The granular nature of the secretory cells evidenced by the early electron microscopy images [2], as well as the demonstration of the quantal nature of the neurotransmitter release through which action potentials release discrete packets of the neurotransmitter (in effect, the synaptic vesicles identified also by electron microscopy) [3], generated by the early 1960s the concept of a coupling between the stimulation of a secretory cell and the activation of secretion, through exocytosis, see ref. [7].

The nature of the coupling element became clear from the experiments, in the early 1960s, by William W. Douglas (1922–1998), who, using $^{45}Ca^{2+}$ as a marker, showed that stimulation of the adrenals, leading to an increase of catecholamine secretion, was always accompanied by an uptake of Ca^{2+} by the chromaffin cells. The studies also showed that depolarising the chromaffin cell with excess potassium also markedly increases secretion, but only if Ca^{2+} is present in the medium [8,9], a set of findings that led to the conclusion that entry of Ca^{2+} has some function critical to the secretory response and the release process. Like many experiments in the field of stimulus–secretion coupling, the main model has been a neuroendocrine cell: the chromaffin cell. Subsequently, Douglas confirmed these observations in other neuroendocrine cells, such as the magnocellular neurones that project to the posterior hypophysis ([10,11], in this issue) as well as in other secretory cells, such as the exocrine salivary cells in the submandibular gland.

From those relatively simple and straightforward beginnings, this special issue illustrates an incredibly complex world of endocrine signalling; if there would be a single phrase that could encapsulate this complexity, probably “diversity in unity” would be a fitful description. The unity elements are coming from the fact that all endocrine cells are excitable cells, all generate action potentials, and all are using Ca^{2+} as an essential coupler of stimulation with secretion (except for few isolated instances of reports of Ca^{2+}-independent secretion [12]). Upon this unity, a plethora of options of implementation of the basic exocytotic event are displayed by the endocrine cells.

In biological terms, there are two fundamental ways of activating the secretory process. One is represented by neuronal model (neurocrine mode) in which Ca^{2+} entry through a variety of plasma membrane channels with Ca^{2+} permeability, but in particular through the voltage-operated Ca^{2+} channels (VOCCs) that are opened by the plasma membrane depolarisation induced by the incoming action potential, triggers the fusion of microvesicles that contain principally neurotransmitters, with the plasma membrane [13]. This process involves the generation of small high Ca^{2+} microdomains (defined as such for the chromaffin cells by Garcia [14], and for the pancreatic β-cells by Rorsman et al. [15]), in which Ca^{2+} can reach values of tens to hundreds micromolar and will activate the synaptic vesicles clustered at such hot spots (or active zones) to fuse with the plasma membrane, open to the extracellular medium and release the vesicular content via an exocytotic process.

The other secretory modality is exemplified by the large group of non-excitable cells that secrete: not only the exocrine cells (e.g., pancreas, salivary gland) but also epithelial cells (in gut, respiratory tract) or blood cells (e.g., mast cell or platelets). In this exocrine mode of secretion, the Ca^{2+} signal is generated, ultimately, by the release of Ca^{2+} from intracellular stores represented principally by the endoplasmic reticulum [16]; although evidence continues to emerge supporting the involvement of a rather elusive and potentially important player: the secretory granules themselves, a topic reviewed here by Alvarez [17], Borges et al. [18] and Yoo and Hur [19]. This release of Ca^{2+} is the result of activation of a plasma membrane G-protein-coupled receptor, with subsequent activation of the phospholipase C (PLC) that cleaves the plasma membrane phosphatidyl inositol (PIP_2) to inositol trisphospate (IP_3) and diacylglycerol (DAG) [20]. Some of the major differences in terms of Ca^{2+} signalling between the two modalities are that, for the “exocrine” modality, the overall increases in cytosolic Ca^{2+} are much smaller (only low micromolar range) and the time course of the $[Ca^{2+}]_i$ increase and the resultant secretion is longer, as it involves several metabolic steps and diffusion pathways (in the range of seconds rather than milliseconds). It is also worth pointing out that in this exocrine pathway of secretion, in addition to the classical Ca^{2+}-dependent proteins that are involved in the docking and release of the secretory granules, such as synaptobrevins, synaptotagmins or generally SNARE proteins or CAPS (Ca^{2+}-dependent activator proteins for secretion) [21], there is a large and important set of proteins that can regulate the recruiting, docking, priming and fusion of secretory granules in a Ca^{2+}-independent fashion: the Rab small GTPases [22].

The endocrine secretion sits, in mechanistic terms, somewhere between these two poles, and most of the endocrine cells are excitable, and display a large complement of voltage-operated Ca^{2+} channels (see three reviews in this special issue: Stojilkovic [23], Lemos et al. [10] and Carbone and co-workers [24], each dealing with the Ca^{2+} channels in, respectively, anterior pituitary cells, the specific neuroendocrine terminals of the posterior pituitary and the chromaffin cells). However, in many endocrine cells, the secretion of specific peptides (hormones) is either supported or modulated by the release of Ca^{2+} from the intracellular stores. The attempts to provide a unique scheme that will integrate all these elements into a single, flat map is difficult, if not dangerous, and the “diversity” element can be illustrated from various perspectives.

Firstly, there is the difficulty of providing a tight and comprehensive definition of the category “neuroendocrine”. In a decade-old essay, the history of this concept is amply reviewed [25], starting from the 1897 initial observations of a chromaffin cell in an intestinal epithelium, leading much later to the concept of APUD (amine precursor uptake and decarboxylation) system of Pearse [26], who tried to produce a synthesis of observations concerning the histochemistry and function of peptide-secreting endocrine cells that shared with the neurones an ability to take up precursors of biologically active amines, to produce active amine through subsequent intracellular decarboxylation and then store the amine product in secretory vesicles. The concept was later refined to describe a whole ‘diffuse neuroendocrine system’ (DNES) supposed to share a similar set of functional and ultrastructural similarities and to stem from a common embryological origin (neuronal) (see ref. [27]). Whilst the functional and ultrastructural similarities have stood the test of time, it is clear that the neuroendocrine cells do not all stem from