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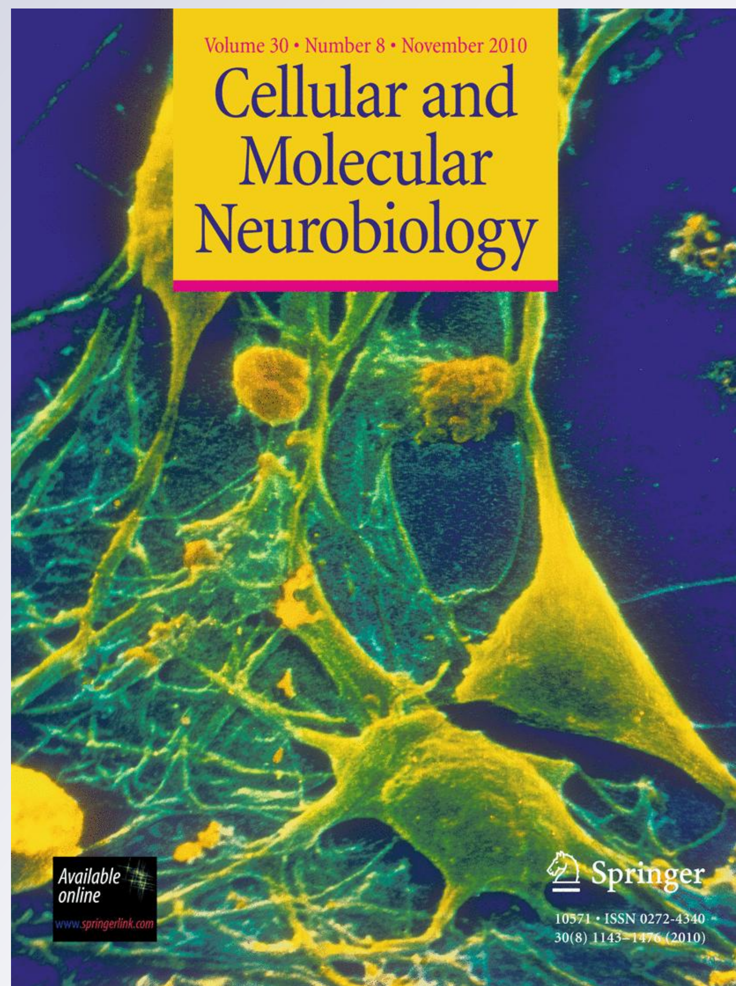

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REVIEW PAPER

Rapid Endocytosis and Vesicle Recycling in Neuroendocrine Cells

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Abstract Endocytosis is a crucial process for neuroendocrine cells that ensures membrane homeostasis, vesicle recycling, and hormone release reliability. Different endocytic mechanisms have been described in chromaffin cells, such as clathrin-dependent slow endocytosis and clathrin-independent rapid endocytosis. Rapid endocytosis, classically measured in terms of a fast decrease in membrane capacitance, exhibits two different forms, "rapid compensatory endocytosis" and "excess retrieval." While excess retrieval seems to be associated with formation of long-lasting endosomes, rapid compensatory endocytosis is well correlated with exocytotic activity, and it is regarded as a mechanism associated to rapid vesicle recycling during normal secretory activity. It has been suggested that rapid compensatory endocytosis may be related to the prevalence of a transient fusion mode of exo-endocytosis. In the latter mode, the fusion pore, a nanometric-sized channel formed at the onset of exocytosis, remains open for a few hundred milliseconds and later abruptly closes, releasing a small amount of transmitters. By this mechanism, endocrine cell selectively releases low molecular weight transmitters, and rapidly recycles the secretory vesicles. In this article, we discuss the cellular and molecular mechanisms that define the different forms of exocytosis and endocytosis and their impact on vesicle recycling pathways.

Keywords Exocytosis · Endocytosis · Secretory vesicle · Recycling · Kiss and run · Chromaffin cell

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In neuroendocrine cells and neurons, the transmitter release process generates an increase in plasma membrane surface and a depletion of releasable vesicle pools. In consequence, endocytosis and vesicular recycling are critical to maintain membrane homeostasis and secretion (Heuser and Reese 1973; von Grafenstein and Knight 1992; Smith and Neher 1997). In this article, we discuss the current models of endocytosis and vesicle recycling in neuroendocrine cells. These mechanisms are analyzed with regard to the maintenance of cellular secretion performance. Although this article is mainly focused on the chromaffin cell, we also discuss the aforementioned mechanisms observed in other endocrine and neuronal cells.

Endocytosis and the Cycle of Secretory Vesicles: Is There a Short-Cut?

After an increase in cytosolic Ca^{2+} concentration, vesicles storing neurotransmitters or hormones fuse with the plasma membrane, and release their vesicular content. The resultant excess plasma membrane must then be internalized via endocytosis to maintain a constant cell membrane area and allow the reutilization of vesicle components. Classically, endocytosis has been considered a clathrin-mediated process (Phillips et al. 1983; Murthy and De Camilli 2003). Indeed, endocytosis via clathrin-coated vesicles has been

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shown to participate in the recycling of synaptic vesicles in nerve terminals (Heuser and Reese 1973; Gad et al. 1998; Teng and Wilkinson 2005). Clathrin and their accessory factors act as molecular sorters that select the proteins to be internalized and in turn provide the driving force for membrane invagination. Afterward, the GTPase dynamin self-assembles forming a ring around the neck of a deeply invaginated pit, and catalyzes the fission of clathrin-coated vesicles (Koenig and Ikeda 1983; Murthy and De Camilli 2003). Fission of clathrin-coated vesicles is rapidly followed by calthrin uncoating (Maxfield and McGraw 2004), and the uncoated vesicles are then fused with early endosomes from where definitive synaptic vesicles supposedly emerge (Murthy and De Camilli 2003).

In nerve terminals, clathrin-mediated endocytosis is a fast phenomenon, with time constants of approximately 30 s (Miller and Heuser 1984; Ryan et al. 1996). However, in neuroendocrine cells, this endocytic mechanism has been shown to be remarkably slow (see Table 1), hence, insufficient to account for rapid recovery of plasma membrane and vesicle pools (Phillips et al. 1983; Artalejo et al. 2002). In addition to this slow kinetics for membrane internalization, the main limitation of this path in endocrine cells is associated with the assembly of new vesicles. While being in the presynaptic terminal, the internalized membrane is thought to mix with endosomal compartments from which new functional synaptic vesicles can emerge in a short period of time (Heuser and Reese 1973; Koenig and Ikeda 1996; Murthy and De Camilli 2003), the recycling of dense core vesicles in neuroendocrine cells must follow a longer path to recover the matrix proteins secreted during exocytosis (Fulop et al. 2005). When specific antibodies against vesicle membrane proteins were applied in chromaffin cells, the internalized membrane after clathrin-mediated endocytosis was found in organelles devoid of chromogranin A, and finally in lysosomes after periods in excess of 30 min (Benedeczky and Somogyi 1978; Phillips et al. 1983; Patzak et al. 1987). In addition, Patzak and Winkler (1986) described that 30 min after stimulation, part of the immunolabel localized in the Golgi region, and after 6 h, it was finally found in vesicles indistinguishable from mature chromaffin vesicles. These results suggest that, after clathrin-mediated endocytosis, new secretory vesicles must be synthesized "de novo" via the Golgi apparatus to keep the vesicle pools at a constant value.

From this prior information, we can conclude that the recovery of endocrine secretory vesicles is a slow process. However, von Grafenstein and Knight (1992), when studying the uptake of horseradish peroxidase after cholinergic stimulation, provided the first evidence that endocytic vesicles of chromaffin cells can re-enter the secretory cycle in 5 min after the end of endocytosis (approximately 15 min after exocytosis). More recently, one of our groups (Perez Bay et al. 2007), using FM1-43, a fluorescent styryl dye used to label membranes, demonstrated that this recycling period can be much shorter. We

Table 1 Time frames for the different type of endocytosis and exocytotic events in chromaffin cells

Type of process	Time frame	Technique used/reference
Clathrin-mediated endocytosis	$t_{1/2}$: 15–30 min	Immunofluorescence microscopy/Phillips (1983)[a]
	Duration: 10 min	Whole-cell Cm/Artalejo et al. (2002)
Rapid endocytosis		
Excess retrieval	τ_I: 0.67 s; τ_{II}: 6.3 s	Perforated-patch Cm/Engisch and Nowycky (1998)
Compensatory exocytosis	τ: 5–20 s	Perforated-patch Cm/Engisch and Nowycky (1998), Smith and Neher (1997)
Compensatory endocytosis after AP	τ: 560 ms	Perforated-patch Cm/Chan and Smith. (2001)
Transient fusion events		
Induced by APs (7 Hz)	Duration: 82 ± 6 ms	Cell-attached Cm/Elhamdani et al. (2006a)
Stand-alone foot events	Duration: 445 ms	Patch amperometry/Alés et al. (1999)
Fast kiss-and-run events at 90 mM Ca^{2+}	T: 41 ms	Patch amperometry/Alés et al. (1999)
Catecholamine release events		
Induced by 100 mM KCl	$t_{1/2}$: 14 ± 0.8 ms	Amperometry/González-Jamett et al. (2010)
Induced by 100 mM KCl + antidyn	$t_{1/2}$: 21 ± 1.5 ms	Amperometry/González-Jamett et al. (2010)
Induced by 20 mM caffeine	$t_{1/2}$: 7.1 ± 0.7 ms	Amperometry/Chen et al. (2005)
Induced by 20 mM caffeine + dynPRD	$t_{1/2}$: 21.3 ± 2.6 ms	Amperometry/Chen et al. (2005)

$t_{1/2}$ half time, τ time constant of exponential fitting, *T* mean pore open time, *Cm* membrane capacitance measurements, *AP* action potential; *antidyn* anti-dynamin antibody, *dynPRD* a peptide derived from the proline-rich domain of dynamin

[a] Internalization of the immunocomplex antibody-dopamine beta-hydroxylase, which is an antigenic determinant of the interior surface of the vesicle membrane. All the data represented in this table were obtained in isolated chromaffin cells

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have observed that after inducing stimulus dependent FM1-43 uptake, the application of a second stimulus 2 min after the first one provoked the release of 40–100% of previously internalized FM1-43. These studies strongly suggest that, in addition to clathrin-mediated endocytosis, other mechanisms participate in membrane retrieval and vesicle recycling in neuroendocrine cells.

Does Rapid Endocytosis Explain the Rapid Recycling of Secretory Vesicles?

In the last 20 years, several studies using patch clamp capacitance measurements have demonstrated the existence of a different type of endocytosis, highly coupled to exocytosis, with time constants between 0.2 and 20 s, which is in general regarded as rapid endocytosis (RE). RE was reported in chromaffin cells, pancreatic beta-cells, melanotrophs, posterior pituitary nerve terminals, PC12 cells, retinal bipolar cell presynaptic terminals, and dorsal root ganglion neurons (Neher and Zucker 1993; Thomas et al. 1994; von Gersdorff and Matthews 1994; Burgoyne 1995; Artalejo et al. 1995; Hsu and Jackson 1996; Smith and Neher 1997; Nucifora and Fox 1998; Chan and Smith 2001; Zhang et al. 2004; He et al. 2008).

Using melatotrophs, Thomas et al. (1994) showed that RE not only compensates for changes in plasma membrane surface, but that it can also retrieve much more membrane than that added by the preceding exocytosis. This phenomenon, called excess retrieval, has also been observed in chromaffin cells (Artalejo et al. 1995, 2002; Smith and Neher 1997; Engisch and Nowycky 1998), pancreatic beta cells (He et al. 2008) and in nerve terminals of the posterior pituitary (Hsu and Jackson 1996; He et al. 2008). Further, it has been associated to the presence of a very fast component of endocytosis, with time constant values of 0.2–1 s (Thomas et al. 1994; Artalejo et al. 1995; Engisch and Nowycky 1998; He et al. 2008; see Table 1 for chromaffin cells). It has been proposed that excess retrieval and compensatory endocytosis are produced by two different mechanisms with different purposes (Smith and Neher 1997; Engisch and Nowycky 1998). Excess retrieval is activated above a certain Ca^{2+} entry threshold, proceeds with at a very high rate, and its magnitude has no relationship to the amount of membrane added during preceding exocytosis (Smith and Neher 1997; Engisch and Nowycky 1998). On the other hand, rapid compensatory endocytosis is an order of magnitude slower than excess retrieval (Table 1) and correlates with previous stimulus-evoked exocytosis (Smith and Neher 1997; Engisch and Nowycky 1998). Compensatory endocytosis also shows Ca^{2+} dependency, but in a wider range of Ca^{2+} entries (Smith and Neher 1997; Engisch and Nowycky 1998).

Thomas et al. (1994) also showed that during excess retrieval in melanotrophs, the capacitance often decreased in steps larger than 20 fF, which represent vesicles with diameters of approximately 0.8 μm. Consistently, "in vivo" confocal imaging studies of the intracellular distribution of 70-kD fluorescent dextrans after the application of a stimulus (50 mM K^{+} during 30 s) that induce excess retrieval in mouse chromaffin cells, have shown the formation of 0.7-μm non-releasable endosomes (Perez Bay, Belingheri, Alvarez and Marengo, unpublished data). The formation of large endosomes during excess retrieval suggests the participation of bulk endocytosis (Richards et al. 2000; de Lange et al. 2003; Holt et al. 2003; Perez Bay et al. 2007; Clayton et al. 2008). Although it was previously believed that bulk endocytosis was a slow process (Richards et al. 2000), recent study indicates that it can indeed be very fast (Wu and Wu 2007; Clayton et al. 2008).

While excess retrieval is apparently not related with vesicle recycling, rapid compensatory endocytosis seems to be a likely candidate to initiate rapid vesicular recycling during normal secretory activity (Smith and Neher 1997; Engisch and Nowycky 1998). Chan and Smith (2001) described two types of compensatory endocytosis in chromaffin cells stimulated with action potential wave forms. Action potentials applied at low frequencies (single to 0.5 Hz) activated a very fast compensatory endocytosis (Table 1). As the stimulation frequency was increased, this fast endocytosis diminished markedly, and a second endocytic mechanism augmented in the range of 6–16 Hz. While this second mechanism was blocked by inhibitors of the calcium–calmodulin–calcineurin cascade, the former was clathrin-independent and regulated via a protein kinase C-dependent mechanism (Chan and Smith 2001, 2003). Later, the same group provided new evidence suggesting that low frequency action potentials favor a transient fusion mode of exo-endocytosis, which will be discussed below (Fulop et al. 2005; Fulop and Smith 2006).

Transient Fusion of Secretory Vesicles

During the exocytotic process, a narrow channel that connects the vesicular and extracellular compartments is formed (Breckenridge and Almers 1987). This channel, called "fusion pore," allows the slow release of transmitter molecules (Albillos et al. 1997). The classical model of exo-endocytosis proposes that the fusion pore expands to the point where the vesicle collapses into the plasma membrane (see F-F in Fig. 1), releasing the entire vesicular content (Rizzoli and Jahn 2007). Then, the vesicle membrane is recovered by clathrin-mediated endocytosis. However, in addition to this classical model known as

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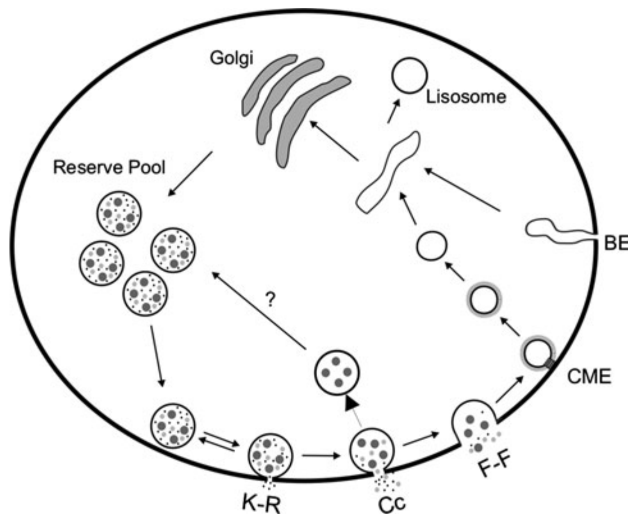

Fig. 1 Schematic model showing the different modes of exocytosis and endocytosis in endocrine cells: Kiss-and-run (K-R), cavicapture (Cc), full-fusion (F-F), clathrin mediated endocytosis (CME), and bulk endocytosis (BE)

"full-fusion," other modes of exo-endocytosis have been described in endocrine cells. One of these modes, known as kiss-and-run, corresponds to the transient opening of the fusion pore (K-R in Fig. 1). Cell-attached capacitance measurements, a technique that allows resolving single vesicle fusion events, showed the presence of transient events in chromaffin cells (Elhamdani et al. 2006a), lactotrophs (Vardjan et al. 2007), and pancreatic beta-cells (Hanna et al. 2009). Using patch-amperometry, a technique that combines cell-attached capacitance measurements with electrochemical detection of catecholamines, Alvarez de Toledo and Lindau demonstrated that transient events are accompanied by the release of catecholamines (Albillos et al. 1997; Alés et al. 1999). Those authors observed two types of transient events in chromaffin cells. The first, called fast kiss and-run, is characterized by a brief expansion of the fusion pore accompanied with the rapid release of catecholamines in a spike-like form. The quantal size of these events was similar to those observed during full-fusion events (Alés et al. 1999). The second type of transient event, known as "stand-alone foot," is characterized by the slow release of catecholamines through a narrow fusion pore, with conductance levels of 500–600 pS (Albillos et al. 1997; Alés et al. 1999).

Using carbon fiber amperometry, Elhamdani et al. (2001) and Fulop et al. (2005) observed that catecholamine release events with small quantal size were mainly observed during low-frequency electrical stimulation (0.25–1 Hz). Fulop et al. (2005) also showed that using 0.5-Hz frequency stimulation, neuropeptides were retained inside the secretory vesicles (Fulop et al. 2005). Conversely, elevated electrical stimulation, which mimics stress-activated firing, induced the full release of both catecholamines and neuropeptides (Fulop et al. 2005). Corey Smith and his coworkers (Fulop et al. 2005) proposed that adrenal chromaffin cells differentially release catecholamines and neuropeptides depending on sympathetic activity. Thus, under basal conditions, chromaffin cells selectively release small amounts of catecholamines through a narrow fusion pore that contributes to keep a "breed and feed" state, while sympathetic activation during acute stress favors the dilation of the fusion pore and the consequent massive release of the catecholamines and other vesicle constituents, setting our body into a "fight or flight" state.

Using evanescent wave microscopy, Wolf Almers and coworkers (Perrais et al. 2004) observed that chromaffin cells differentially released neuropeptide Y and tissue plasminogen activator. After stimulation, a small percentage of vesicles released small molecules but retained neuropeptide Y. These kinds of phenomena seem to correspond to transient events with incomplete release of catecholamines, where the fusion pore apparently fails to expand (Alés et al. 1999). However, the majority of the chromaffin vesicles released neuropeptide Y, and retained tissue plasminogen activator. This mode of exo-endocytosis that selectively releases peptides and proteins has been called "cavicapture" (Cc in Fig. 1), since the cavity of the vesicle is recovered intact (Taraska and Almers 2004). Cavicapture has also been demonstrated in insulin-secreting cells (Tsuboi et al. 2004) and anterior pituitary cells (Ferraro et al. 2005).

Are the Proteins of Endocytotic Machinery Involved in Kiss-and-Run and Cavicapture?

As mentioned previously, dynamin is a GTPase that participates in the final step of endocytosis, allowing the pinching-off of the clathrin-coated vesicle. Different findings have led to propose that dynamin is also involved in both kiss-and-run and cavicapture, thus promoting the closure of the fusion pore (Elhamdani et al. 2001; Graham et al. 2002; Holroyd et al. 2002; Tsuboi et al. 2004). According to this rationale, disruption of dynamin function would increase the amount of transmitter released per individual exocytotic event, as it has been demonstrated in chromaffin cells using specific antibodies or GTPγS to disrupt dynamin function (Graham et al. 2002; González-Jamett et al. 2010). Nevertheless, the molecular mechanism by which dynamin regulates the quantal release of transmitters is unknown. One possibility is that amphiphysin, an important dynamin-binding partner at the synapse, recruits dynamin to the exocytotic sites. However, contradictory results have been reported for the effects of

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disrupting dynamin/amphiphysin association: Graham et al. (2002) and Chen et al. (2005) have shown an increase in the quantal size of the exocytotic events, while Fulop et al. (2008) have observed a decrease. On the other hand, Elhamdani et al. (2006b) found no effect. In addition, Leon Lagnado and coworkers (Llobet et al. 2008) have proposed that amphiphysin, but not dynamin, controls the constriction of the mouth of fused vesicles.

Recent data from one of our labs show that synaptophysin, one of the most abundant proteins of synaptic vesicle, is a partner of dynamin in chromaffin vesicles, and that the association between these proteins modulates the quantal release of catecholamines (González-Jamett et al. 2010). Hence, although several findings support the idea that dynamin modulates the quantal release of hormones and peptides, further experimental study is required to learn more about the mechanism by which this GTPase controls exocytosis.

Are Transient Fusion Events Related with Rapid Endocytosis?

Using double patch-clamp technique to electrically stimulate the cells in whole cell configuration while individual fusion events were resolved by cell-attached capacitance measurements, Artalejo and Elhamdani observed that brief trains of depolarizations that induce RE, also promoted transient events (Elhamdani et al. 2006a). However, this conclusion should be regarded with caution, as the stimulation pattern used by Artalejo et al. (1995) triggers excess retrieval. On the other hand, as aforementioned, Corey Smith and coworkers (Chan and Smith 2001, 2003) found that action potentials at 0.5 Hz induced both a fast compensatory endocytotic process and catecholamine release events with small quantal size (Fulop et al. 2005; Fulop and Smith 2006), suggesting that RE may be related to transient fusion events. However, due to the complexity and variety of exocytotic–endocytotic processes described in chromaffin cells, more work is needed to precise the relationship between the different types of RE and transient fusion events.

Schematic Model for Chromaffin Cell Exo/Endocytosis

The information discussed along this review can be interpreted through the following model. Transient fusion mechanisms allow the selective release of active components of vesicle cargo in response to stimulation at different intensities. This property provides endocrine cells with a mechanism to adequately respond to external changes. In addition, the transient fusion mechanism allows the cells to conserve an important fraction of the vesicle matrix protein cargo, as well as all vesicle membrane components. Because the basic structure of the secretory vesicle is kept intact, the vesicle can be recovered after a short cycle (see K-R and Cc in Fig. 1). If, conversely, the vesicle fuses entirely with the plasma membrane (F-F in Fig. 1), then the vesicle components should follow a longer cycle that includes clathrin-mediated endocytosis (CME in Fig. 1) or alternatively bulk endocytosis (BE in Fig. 1), and the formation of new vesicles from the Golgi apparatus.

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