CELL SWELLING-INDUCED PEPTIDE HORMONE SECRETION

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ABSTRACT

Cell volume changes induced in various ways (anisomotic environment, hormones, oxidative stress, substrate uptake) are an integral part of a signal transduction network regulating cell function.\textsuperscript{1, 2, 3} Cell swelling has received increasing attention as a stimulus for a variety of intracellular phenomena.\textsuperscript{4} One of the most remarkable effects of cell swelling is its powerful effect in inducing exocytosis of material in intracellular secretory vesicles. Secretion of essentially all so-packaged hormones\textsuperscript{5-24} including those from hypothalamus (thyrotropin-releasing hormone, TRH; gonadotropin-releasing hormone, GnRH), pituitary (LH, FSH, ACTH, MSH, TSH, prolactin, beta endorphin), pancreas (insulin, somatostatin, glucagon), heart (atrial natriuretic hormone) and kidney (renin) are stimulated in a concentration-related manner by medium hyposmolarity or isosmolar medium containing permeant molecules such as ethanol or urea (reviewed in Ref. 21). Cell swelling-induced exocytosis is not restricted to endocrine cells and hormones; medium hyposmolarity also induces secretion of exocrine pancreatic enzymes\textsuperscript{5} and myeloperoxidase from human polymorphonuclear leukocytes.\textsuperscript{25}
1. EXPERIMENTAL

Dynamics of secretion induced by cell swelling closely resembles that induced by specific secretagogues.\(^9\), \(^10\), \(^26\) Perifusion of pituitary cells with 10 nM TRH (prolactin natural secretagogue) as well as cell swelling induced by hypotonic solution (medium dilution with 30% H\(_2\)O) or depolarizing 30 mM KCl stimulates an immediate dose-related high-amplitude prolactin secretory burst, reaching a peak at 1-2 minutes followed by a decline to a low plateau within 5-10 minutes during continuous exposure to the same stimulus (Figure 1A). Repeated stimuli with 30 sec. interstimulus interval produce the same secretory response as continuous stimulation (Figure 1B). For all three types of stimuli, the secretory response to continuous exposure and refractory periods to repeated stimulation (less than 1 minute) were essentially identical (1A, 1B and 1C). An identical high-amplitude secretory burst was induced by exposure to TRH for times varying from 6 to 600 sec. In contrast, for 30% H\(_2\)O and high KCl, the secretory amplitude was proportional to the exposure time between 6 and 60 sec (Figure 1D). While the TRH response was triggered by rapid specific receptor binding, a very short pulse would not have time to produce sufficient transmembrane osmotic gradient or K\(^+\) difference. It is concluded that hyposmotic medium does not trigger peptide release by the specific receptor-ligand binding.\(^26\)

The most striking and unusual feature of cell swelling-induced secretion is that it stimulates regulated secretion independent of intracellular Ca\(^{2+}\) concentration,\(^5\), \(^7\), \(^8\), \(^12\), \(^13\), \(^17\)-\(^24\) in contrast to most types of regulated secretion. When Ca\(^{2+}\) influx is prevented by removing extracellular Ca\(^{2+}\) or by adding Ca\(^{2+}\) channel blockers, cell swelling does not induce a rise in intracellular Ca\(^{2+}\), but hormone release is present and even enhanced. These peculiar features indicate a specific signal transduction pathway for cell swelling-induced peptide secretion. However, in clonal tumor-derived rat pituitary cells (GH\(_4\)C\(_1\) and MMQ), the situation was different. In contrast to normal freshly isolated pituitary cells, Sato et al.\(^13\) found that hyposmolarity induced hormone secretion in clonal cells only in the presence of extracellular Ca\(^{2+}\). It was suggested that this is a possible important hallmark for tumor cells.\(^13\) It is of interest that Straub et al. found two distinct mechanisms in the presence and absence of extracellular Ca\(^{2+}\) in clonal cells secreting insulin (\(\beta\)Hc9).\(^27\) While we did not see this dichotomy in isolated rat pancreatic islets,\(^28\) we believe that at least some tumor cells have special requirements for extracellular Ca\(^{2+}\) in cell swelling-induced hormone release.

Inhibition of stretch-activated channels by 10 \(\mu\)M GdCl\(_3\) did not affect cell swelling-induced TRH secretion from the posterior pituitary, hypothalamic paraventricular nucleus (Figure 2) or isolated pancreatic islets.\(^29\) It is of interest, however, that this stimulus did not induce release of oxytocin from the same tissue explants (Figure 2).\(^29\) It was therefore concluded that cell swelling-induced exocytosis possesses limited selectivity; cells specifically involved in water and salt metabolism retain their specific response to osmotic stimuli.\(^29\) However, our recent unpublished results suggest that inhibition of a specific response also unmasks general exocytotic response in these cells.

Swelling-induced secretion can be triggered in different parts of neurons – similar TRH release was evoked from the hypothalamic paraventricular nucleus (mostly perikarya) and the median eminence and posterior pituitary (exclusively axon terminals).\(^17\), \(^19\), \(^24\), \(^29\)