Coupling G protein-coupled receptors to exocytosis

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The primary driving force for regulated exocytosis is the elevation of cytosolic Ca^{2+}. In excitable cells, this is normally achieved by extracellular Ca^{2+} entering the cell through Ca^{2+}-permeable channels in the plasma membrane. Ionotropic receptors evoke exocytosis either by being themselves permeable to Ca^{2+} or by being non-selective cation channels that depolarise the cell, so activating voltage-sensitive Ca^{2+} channels (VOCCs). In contrast, the mechanisms by which G protein-coupled receptors (GPCRs) cause extracellular Ca^{2+} entry are much less clear. Possible mechanisms have been exploring using the secretion of catecholamines evoked by histamine H1 receptors from adrenal chromaffin cells (Marley, 2003).

Adrenal chromaffin cells express one of the highest densities of H1 receptor of any tissue and these are of critical importance in protecting against anaphylactic shock. The chromaffin cell H1 receptors are coupled through *Pertussis* toxin-resistant G proteins to the hydrolysis of membrane phosphatidylinositol 4,5-bisphosphate and the generation of inositol 1,4,5-trisphophate (IP3), which mobilises Ca^{2+} from intracellular stores. Of the GPCRs expressed by chromaffin cells, histamine H1 receptors are particularly effective at evoking exocytosis, having almost half the efficacy of powerful nicotinic receptor agonists. The great majority of this secretory response is inhibited by antagonists to L, N and P/Q-type VOCCs, indicating histamine recruits VOCCs, however histamine has complex effects on the membrane potential of these cells (Wallace *et al.,* 2002). Initially there is a transient hyperpolarisation that is abolished if intracellular Ca^{2+} stores are depleted and which is due to activation of small conductance Ca^{2+}-activated K^+ (SK) channels by store Ca^{2+} released by IP3. The hyperpolarisation is followed after 10-20 s by a slow depolarisation and an increase in frequency of spontaneous action potentials. The latter two effects persist after store depletion and after block of SK channels, and are accompanied by an increase in membrane resistance and by a small inward current. The latter are in part the result of the closure of a K^+ channel responsible for a novel M current that helps set the resting membrane potential. How the H1 receptors cause the closure of these channels is presently unknown, however the secretory response to histamine is not prevented by inhibitors of IP3 receptors or ryanodine receptors, by depletion of intracellular Ca^{2+} stores, or by protein kinase C inhibitors (Donald *et al.,* 2002). The identity of the cause of the rest of the depolarisation also remains unknown. H1 receptors regulate the activity of at least five classes of K^+ channels in chromaffin cells, however the secretory response is not prevented by blocking SK channels, intermediate- or large-conductance Ca^{2+}-activated K^+ (IK or BK) channels, K_{ATP} channels, delayed rectifier channels or A type channels, and inward rectifier K^+ channels are not expressed in these cells.

The results from such studies raise a number of important questions, including (i) what is the molecular mechanism by which GPCRs inhibit K^+ channels, (ii) through what other channels can GPCRs depolarise cells, and (iii) why do some GPCRs evoke large secretory responses, while others have very low efficacy, while apparently activating similar signaling pathways in the same cells?

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