3.6: Inositol Trisphosphate and the Calcium Ion Messenger System

A "second" messenger is an entity that inside a cell mediates the action of some hormone at the plasma membrane, the hormone being considered the "first" messenger. The first such second messenger to be discovered—in fact, the very molecule that led to the formulation of the whole concept—was cyclic AMP.[69] During the decade following the discovery of cAMP, it was gradually realized that intracellular release of Ca^{2+} ions also accompanied hormonal stimuli, and the Ca^{2+} ion slowly became regarded as a second messenger. This idea was first clearly enunciated by Rasmussen[70] as early as 1970, and gained general acceptance when the ubiquitous intracellular Ca^{2+}-binding protein calmodulin (see Section V.A) was discovered. In the mid-1970s this protein was shown to be a Ca^{2+}-dependent regulator of a large number of Ca^{2+}-dependent enzymes, transport proteins, etc., establishing a molecular basis for Ca^{2+} action in cells.

There were some puzzling facts, however. Although a transitory increase in intracellular Ca^{2+} concentration in response to the binding of a hormone or transmitter substance to a surface receptor could result from extracellular Ca^{2+} being released into the cytoplasm, there was compelling evidence for muscle cells that the main Ca^{2+} source was the sarcoplasmic reticulum (SR). This result led to the hypothesis of "Ca^{2+}-induced Ca^{2+} release," i.e., that upon stimulation of the cell, a small amount of Ca^{2+} entered into the cytoplasm and triggered the release of greater amounts of Ca^{2+} from the SR. For some cell types it could, however, be shown that transient increases in intracellular Ca^{2+} could occur even when extracellular Ca^{2+} was removed, although *prolonged* responses required the presence of extracellular Ca^{2+}. Although some specialized cells have gated plasma-membrane Ca^{2+} channels, release of Ca^{2+} into the cytoplasm from intracellular stores appears to be of at least equal importance. Furthermore, there is now overwhelming evidence[63,70-72] that intracellular Ca^{2+} is released in response to the formation of a new type of intracellular messenger: 1,4,5-IP_3. Receptors for this messenger have recently been found in the membranes of intracellular organelles, and binding of 1,4,5-IP_3 to these receptors results in the release of Ca^{2+} ions.[73]

1,4,5-IP_3 is formed as a product in the hydrolysis of a special phospholipid present in the cell membrane: phosphatidyl-inositol-4,5-bisphosphate. This reaction, then, is the initial receptor-stimulated event. The newly formed 1,4,5-IP_3 is assumed to diffuse into the cytoplasm, and eventually reach intracellular 1,4,5-IP_3 receptors on the ER, thereby triggering the release of Ca^{2+}. A simplified reaction scheme is shown in Figure 3.15.

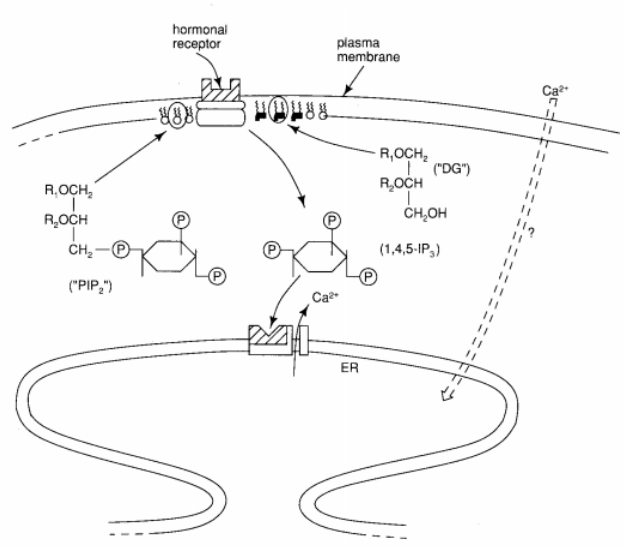

Figure 3.9) and also by a direct influx of Ca^{2+} from the extracellular medium.[70,81]

A diacylglycerol (DG) is also formed in the hydrolysis step. DG can also act as an intracellular messenger, and stimulates the activity of a membrane-bound protein kinase, known as *protein kinase C* (PKC). As a result, PKC may phosphorylate certain key proteins and influence their activity. Protein kinase C is also activated by Ca^{2+} ions, a fact that illustrates Nature's knack in designing regulatory networks! 1,4,5-IP_3 is either directly degraded in a series of enzymatic steps back to inositol, which is then used to resynthesize the phospholipid, or it may be further phosphorylated to inositol-1,3,4,5,-tetraphosphate (1,3,4,5-IP_4), which may undergo dephosphorylation to form inositol-1,3,4-trisphosphate (1,3,4-IP_3). The biological functions of the latter compounds are now being investigated.

The intracellular levels of Ca^{2+} are restored back to the normal low resting values (100 to 200 nM) via transport back into the SR, and/or into mitochondria, or out through the plasma membrane by the pumping mechanisms discussed in Section IV.B. As was briefly mentioned above, depriving a cell of extracellular Ca^{2+} will eventually make the cell incapable of prolonged responses to external stimuli. It appears that the intracellular Ca^{2+} stores may become depleted if not replenished. It has been suggested that the intracellular ER Ca^{2+} pool has a direct route of access to the extracellular pool, a route that is closed when the ER pool is full.[74]

In a sense, then, Ca^{2+} seems to have been downgraded by the inositolphosphates from a "second" to a "third" messenger; however, the pivotal role of Ca^{2+} as a regulator of cellular activities remains undisputed.
