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An Emerging New Paradigm of the Control Mechanism of Cellular Functions

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The control mechanism of cellular functions has been classified into two modes: one rapid mechanism occurring within minutes by kinetic alterations of effector proteins without changing the number of effector molecules and another slow mechanism occurring over hours and days by changes in the number of effector molecules without kinetic alterations. The latter mechanism has been thought to be due to changes in the rate of synthesis or degradation of effector proteins. The first exception to this generalization observed in 1977 was that stimulation of gastric H^+ secretion in response to histamine was by fusion of H^+,K^+-ATPase-containing intracellular vesicles with apical membrane, resulting in insertion of the H^+-pump into the apical membrane with 5~10 fold increase in the membrane surface area. Since then this new type of control mechanism involving exocytic insertion and endocytic retrieval of effector proteins into or out of the plasma membrane was reported in a wide variety of cellular functions mediated by channels, carriers as well as pumps, and has established as a widespread common mechanism in response to stimuli.

The stimulus-dependent recycling or shuttling of effector-containing vesicle between the cytoplasm and plasma membrane is currently thought to involve microtubules and microfilaments with their associated motors such as kinesin, dynein

and myosin. The translocated vesicles to the vicinity of the plasma membrane are then fused with the plasma membrane, thereby increasing the number of effector proteins in plasma membrane. The inserted or resident effector protein in the plasma membrane are retrieved by endocytosis via clathrin-coated pits and vesicles. Thus, the control of cellular functions in response to neurohormonal stimuli can be achieved by changing the net number of effector proteins in the plasma membrane either by increasing exocytic insertion or endocytic retrieval or in combination of both. The underlying molecular mechanism(s) of how the intracellular signals generated in response to neurohormonal stimuli regulates the vesicular trafficking in opposite direction is unknown and under active investigation. The SNARE and an alternative hypothesis(actin and myosin) will be presented.