

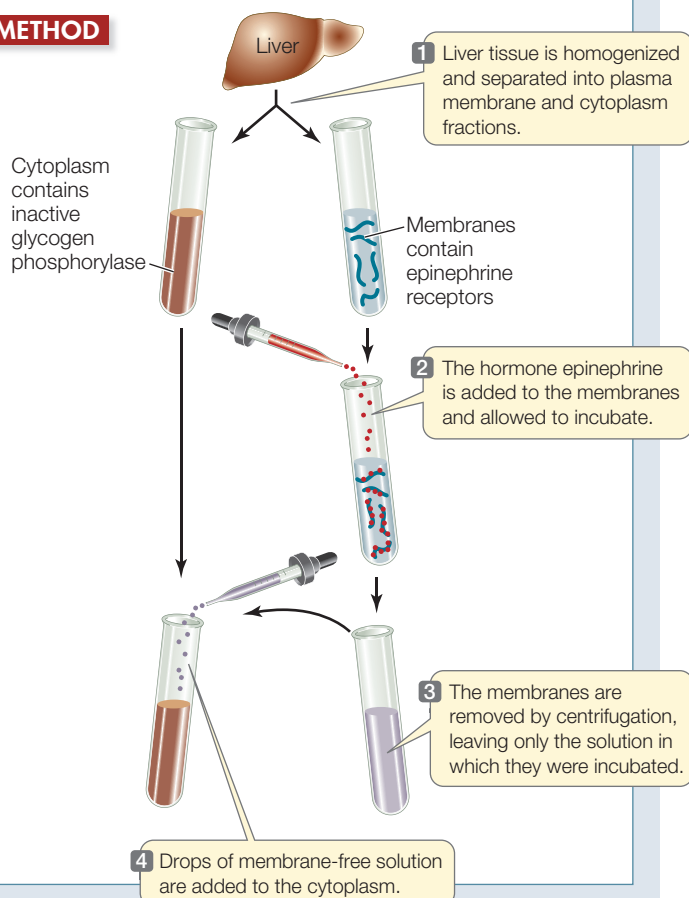
INVESTIGATING LIFE

7.13 The Discovery of a Second Messenger

Glycogen phosphorylase is activated in liver cells after epinephrine binds to a membrane receptor. Sutherland and his colleagues observed that this activation could occur *in vivo* only if fragments of the plasma membrane were present. They designed experiments to show that a second messenger caused the activation of glycogen phosphorylase.

HYPOTHESIS A second messenger mediates between receptor activation at the plasma membrane and enzyme activation in the cytoplasm.

METHOD



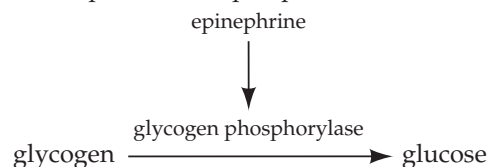
RESULTS Active glycogen phosphorylase is present in the cytoplasm.

CONCLUSION A soluble second messenger, produced by hormone-activated membranes, is present in the solution and activates enzymes in the cytoplasm.

FURTHER INVESTIGATION: The soluble molecule produced in this experiment was later identified as cAMP. How would you show that cAMP, and not ATP, is the second messenger in this system?

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ble chemical messenger mediates the cytoplasmic events initiated by a plasma membrane receptor. These researchers were investigating the activation of the liver enzyme glycogen phosphorylase by the hormone epinephrine. The enzyme is released when an animal faces life-threatening conditions and needs energy fast for the fight-or-flight response. Glycogen phosphorylase catalyzes the breakdown of glycogen stored in the liver so that the resulting glucose molecules can be released to the blood. The enzyme is present in the liver cell cytoplasm, but is inactive except in the presence of epinephrine.



The researchers found that epinephrine could activate glycogen phosphorylase in liver cells that had been broken open, but only if the entire cell contents, including plasma membrane fragments, were present. Under these circumstances epinephrine bound to the plasma membranes, but the active phosphorylase was present in the solution. The researchers hypothesized that there must be a second “messenger” that transmits the signal of epinephrine (the “first messenger,” which binds to a receptor at the plasma membrane) to the phosphorylase (in the cytoplasm). To investigate the production of this messenger, they separated plasma membrane fragments from the cytoplasms of broken liver cells and followed the sequence of steps described in **Figure 7.13**. This experiment confirmed their hypothesis that hormone binding to the membrane receptor causes the production of a small, water-soluble molecule that diffuses into the cytoplasm and activates the enzyme. Later, this second messenger was identified as **cyclic AMP (cAMP)**. (We will describe the signal transduction pathway leading to the fight-or-flight response in more detail in Section 7.4.) Second messengers do not have enzymatic activity; rather, they act to regulate target enzymes (see Chapter 8).

A second messenger is a small molecule that mediates later steps in a signal transduction pathway after the first messenger—the signal or ligand—binds to its receptor. In contrast to the specificity of receptor binding, second messengers allow a cell to respond to a single event at the plasma membrane with *many events inside the cell*. Thus, second messengers serve to amplify the signal—for example, binding of a single epinephrine molecule leads to the production of many molecules of cAMP, which then activate many enzyme targets by binding to them noncovalently. In the case of epinephrine and the liver cell, glycogen phosphorylase is just one of several enzymes that are activated.

Cyclic AMP is a second messenger in a wide variety of signal transduction pathways. An effector protein, adenylyl cyclase, catalyzes the formation of cAMP from ATP. Adenylyl cyclase is located on the cytoplasmic surface of the plasma membrane of target cells (**Figure 7.14**). Usually a G protein activates the enzyme after it has itself been activated by a receptor.

Cyclic AMP has two major kinds of targets—ion channels and protein kinases. In many sensory cells, cAMP binds to ion channels and thus opens them. Cyclic AMP may also bind to a