Signal Transduction Timed Simulation

Resource Type: Curriculum: Classroom

Publication Date: 4/7/2004

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Abstract

This simulated exercise is intended to familiarize students with the flow of steps involved in signal transduction. Students divide into two teams of 15 or more students, and each student in the team is assigned to be a component of a signal transduction pathway within the classroom “cell.” The two teams compete for the fastest signal transduction time, starting with a signal molecule contacting a cell receptor and ending with the transcription of a gene. Students then make modifications to make the steps more efficient, thereby decreasing the signal transduction time. This activity can easily be designed for any signal transduction pathway for any cell.

Activity

Invitation for User Feedback. If you have used the activity and would like to provide feedback, please send an e-mail to MicrobeLibrary@asmusa.org. Feedback can include ideas which complement the activity and new approaches for implementing the activity. Your comments will be added to the activity under a separate section labeled "Feedback." Comments may be edited.

INTRODUCTION

Learning Objectives.
At the completion of this activity, students will be familiar with all components of a specific signal transduction pathway, how these components work together, and how they are most efficiently distributed within a cell. Students will also become familiar with the use of energy molecules such as ATP and GTP and the role of phosphorylation in molecular function.

Background.
Before starting this activity, students should be introduced to the process and components of signal transduction. This particular exercise is designed for a eukaryotic cell pathway involving a G-protein-linked receptor and a hormone signal (Appendix 1, diagrams A and B), but other pathways can easily be enacted (Appendix 2). The instructor may either draw this pathway on the board for students to copy, or photocopy this diagram. This exercise emphasizes specific components in the pathway, cellular distribution, and adherence to a specific sequence of events. This exercise also emphasizes the amplification of a signal, although the amplification step incorporates only a few students; to be accurate it should incorporate hundreds.

PROCEDURE

Materials.
1. Colored paper and markers. Colored paper cut into various shapes and labeled to represent each component of a signal transduction pathway (see suggested shapes in Appendix 1). These papers and labels should be large enough to be seen by the entire class. Some shapes may be labeled on both sides to represent the conversion of a molecule from one form to another, for example, inactive A-kinase to active A-kinase or ATP to cyclic AMP (cAMP). The following is an example of possible components of a signal transduction pathway initiated by a G-protein-linked receptor, involving a G protein and adenylate cyclase. The numbers of each component can be modified to include more students. Instructor prep time is approximately 30 minutes to 1 hour to draw the components of the pathway.

There should be one set of components for each team:

- 1 signal molecule, e.g., a hormone
- 1 cell membrane
- 1 G-protein-linked receptor that converts from an inactive state to an active state when the signal molecule binds to it
- 3 G-protein subunits consisting of an alpha subunit, a beta-gamma subunit, and a GDP. Initially these three students must assemble together before the process starts because these subunits form the inactive G protein.
- 1 GTP that switches to GDP (this student is different from the GDP student who starts out with the G protein)
- 1 adenylate cyclase enzyme that switches from an inactive to an active state
- Several ATPs that switch from ATP to cAMP. Students should see that this part of the pathway represents an amplification of the signal.
- Several A-kinases that switch from an inactive to an active state
- 1 to 2 nuclear pores

- 1 DNA
- 1 to several gene regulatory proteins that switch from an inactive to an active, phosphorylated state
- 1 to several RNA polymerases
- 1 to several RNA transcripts
- 1 timekeeper with a watch that has a second hand or a stop watch for timing each team's signal transduction. The timer should not be a member of either team to avoid bias and cheating.

2. General diagram of a signal transduction pathway (Appendix 1 or 2)

Student Version.

1. This exercise is designed for participation of 30 to 40 students, divided into two teams. While remaining in your seat, count off by "1's" and "2's" to divide the class into two teams.
2. Team 1 will be first to receive colored paper representing components of a signal transduction pathway.
3. Team 2 will then receive colored paper representing components of a signal transduction pathway.
4. One student will serve as an unbiased timekeeper for the class.
5. Follow your instructor's directions in setting up your classroom "cell." If you convert from one state to another, for example from GTP to GDP, you must show that change in your colored paper before the next step can proceed.
6. This is a contest to see which team has the fastest signal transduction process starting from contact of a cell receptor with a signal, to the completion of an RNA transcript. Use the signal transduction diagram you have been given as a guide to what your function is and where your cellular destination is. Don't let your team down.

Instructor Version.

1. This exercise is designed for participation of 30 to 40 students, divided into two teams. This works best if students on each team are distributed throughout the classroom "cell," rather than dividing the classroom in half where students on each team will be "bunched." Therefore, have students count off by "1's" and "2's." You want to give the impression that a cell environment is vast compared to each cellular component, and components may have to travel some distance around obstacles to get to their destination.
2. Depending on whether your classroom "cell" is eukaryotic or prokaryotic, you will need to establish one part of the room that is the nucleus and one part that is a portion of the plasma membrane.
3. Randomly hand out the colored paper representing components of a signal transduction pathway to Team 1. You want the cytoplasmic components to be scattered throughout the classroom, so you will first need to shuffle the colored papers. Repeat with Team 2.
4. Instruct the students that this is a timed contest between the two teams. The team with the shortest time from contact of the signal to transcription of a gene will receive a reward (extra credit points, cookies, etc.). Team 1 goes first while Team 2 observes. The students in Team 1 will complain that Team 2 will have a chance to watch the process carried out by Team 1 and will therefore have a shorter signal transduction time. Encourage the discontent.
5. Students in Team 1 representing nuclear pores should move to the nuclear region of the classroom, and the cell membrane component should move to its designated area, but the rest of the cellular components must remain **near their seats.** You want this first attempt at signal transduction to be chaotic and disorganized. When the process begins, students should move around the room to their particular destinations in accordance with the signal transduction diagram they have been given.
6. Start the timer when the signal molecule contacts the G-protein-linked receptor. All students in a team should perform their task, even if another student with the same component has completed their task first. Stop the timer when the first RNA transcript is made. Record the time and then repeat this process with Team 2. Team 1 will invariably have the slower signal transduction time and will complain, and Team 2 will feel smug.
7. After this first contest is completed, instruct Team 1 that they will have a chance to redeem themselves by repeating the signal transduction process, but they are free to distribute themselves anywhere in the cell **before** the signal transduction process starts. Students will have figured out that they can cluster near each other in different portions of the cell for most efficient contact. Team 1's new time will be significantly faster than Team 2's time (there is no need for Team 2 to repeat the modified process, unless they want to).
8. All students who participate receive the reward.
9. Possible questions for discussion after the activity:
   - Why did students modify the process by clustering in various parts of the cell? Does this occur in a real cell?
   - How do cellular components "know" where to go to carry out their function? What are some signals that guide them?
   - How do these cellular components actually move toward their destination? Is this process random?
   - Why does amplification of the signal occur and what components of this pathway are critical for the amplification?
   - What happens to the signal transduction process if one or more components are defective or inhibited in their activity? Are some components more critical than others?
10. At the end of this exercise, students will have had a signal transduction pathway described to them once by the instructor in lecture format, will have seen it enacted three times, including improvements to the organization of the cell and distribution of cell components, and will have discussed it.

Safety Issues.
None, other than students tripping over desks and backpacks as they move quickly through the classroom "cell" trying to get to their destination in the pathway.

ASSESSMENT and OUTCOMES

Suggestions for Assessment.

Students can be quizzed on all or parts of the pathway to assess their grasp of signal transduction. Each student receives credit for participating in the activity.

Field Testing.
This activity has been used three times in a Cell Biology course (class size ~30) at the freshman level. The students enjoyed acting out this complex and abstract process and were willing to discuss the complexities of the process.

Student Data.
Students who were present for the lecture and signal transduction game performed about 10% better on the signal transduction questions on an exam in a freshman-level cell biology class.

SUPPLEMENTARY MATERIALS

Possible Modifications.

1. After completing this activity, the instructor may give each team an array of signal transduction components of an unknown pathway and ask each team to come up with a logical sequence of steps. Many pathways use the same or similar components, and students will find that the cell makes efficient use of a small number of components in different combinations.
2. This game can also be taken beyond the point of RNA transcription (after processing in the case of a eukaryotic cell) to translation of a protein product (or multiple products from a single transcript in a prokaryotic cell). The RNA transcript would have to leave the nucleus and find a ribosome and the appropriate tRNAs to make the protein.

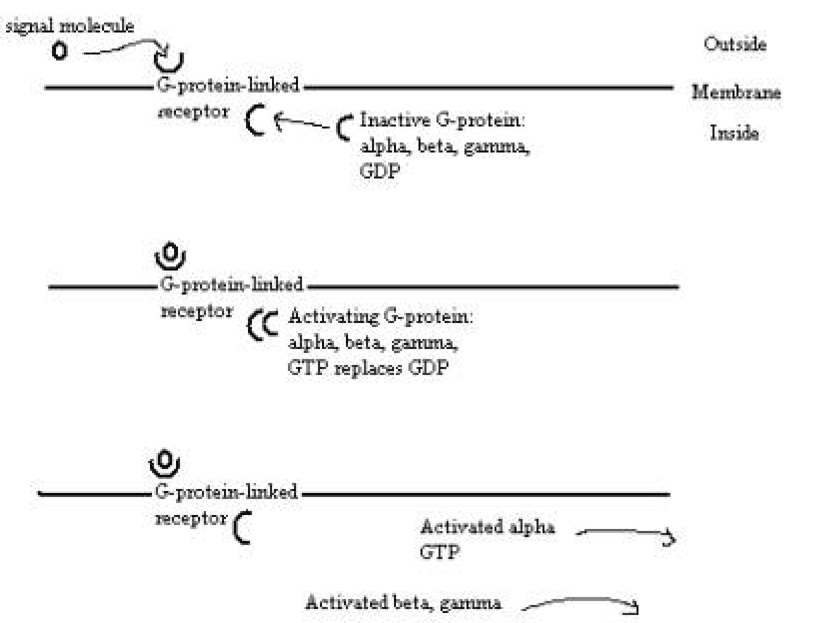
References.

1. **Alberts, B., D. Bray, A. Johnson, J. Lewis, M. Raff, K. Roberts, and P. Walter.** 1998. Essential cell biology: an introduction to the molecular biology of the cell. Garland Publishing, Inc., New York, N.Y.
2. **Madigan, M. T., J. M. Martinko, and J. Parker.** 2003. Brock biology of microorganisms, 10th ed. Prentice Hall, Upper Saddle River, N.J.

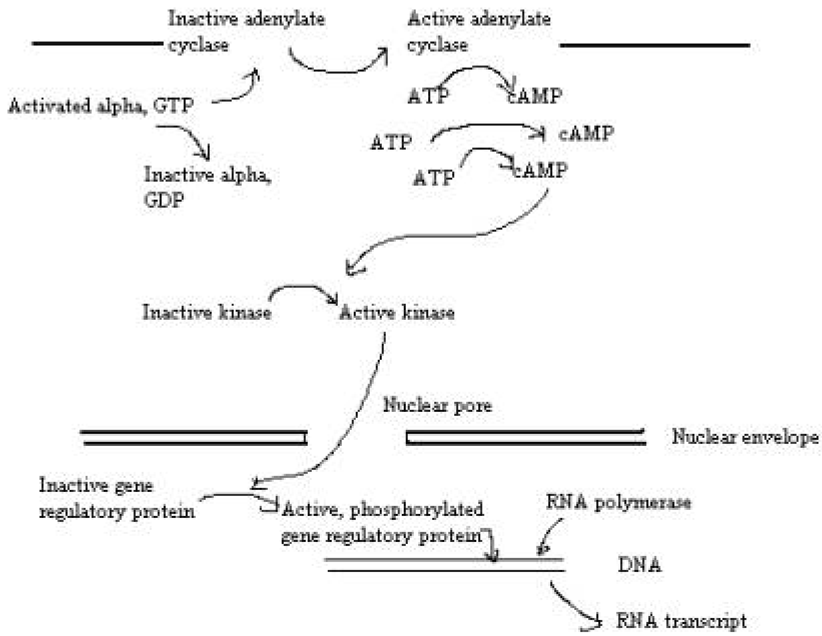
Appendices.

Appendix 1. Example of G-protein-linked signal transduction with adenylate cyclase in eukaryotic cells (1)
The hormone signal molecule contacts a G-protein-linked receptor and activates it (step A; activation is depicted with an asterisk). An inactive G protein is activated by contact with the activated receptor. Activation of the G protein involves contact with the receptor, a separation of the alpha subunit from the beta-gamma subunit, and a replacement of GDP with GTP. The activated alpha subunit contacts adenylate cyclase and activates it. The GTP converts to GDP and the G protein is no longer activated. The activated adenylate cyclase converts many ATPs to cAMPs, thus amplifying the signal. Cyclic AMP activates A-kinase which then travels through a nuclear pore and phosphorylates a gene regulatory protein. This phosphorylated regulatory protein promotes transcription by RNA polymerase, resulting in RNA transcripts of a specific gene.

A. Activation of the G-linked protein receptor



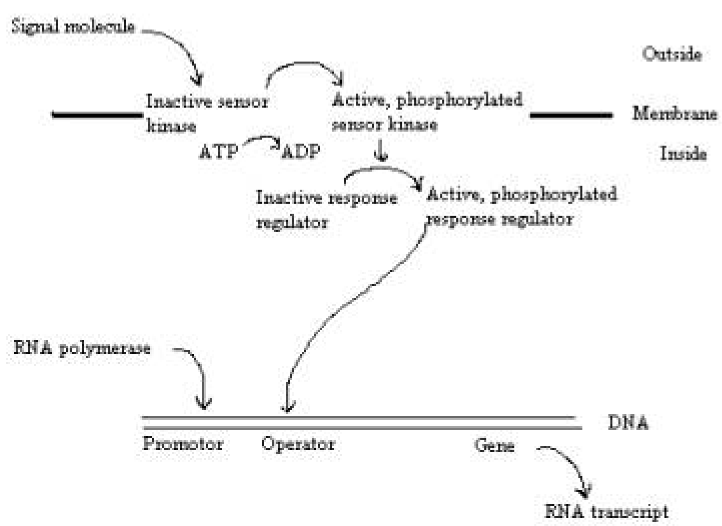
B. Signal transduction pathway involving a G protein and adenylate cyclase



Appendix 2. Example of a two-component system of signal transduction in prokaryotic cells (2)
Microorganisms use this system for sensing fluctuating conditions in the environment so that they can make an appropriate response. It is called a two-component system because it involves a specific sensor protein and a response regulator protein, although other cellular components are also involved in the process. A signal molecule interacts with a sensor kinase in the membrane, along with an ATP, and the kinase becomes phosphorylated (activated). The activated kinase phosphorylates a response regulator and activates it. The activated response regulator then binds to an operator and acts as a repressor, blocking transcription by the RNA polymerase.

Components: signal molecule, sensor kinase (inactive and active), ATP/ADP, response regulator (inactive and phosphorylated), DNA, RNA polymerase, and RNA transcript

Two-component system of signal transduction



Appendix 3. Example quiz questions on signal transduction

1. Which of the following statements is true for signal transduction?
   a. It is a single-step process of relaying outside signals to the nucleus of the cell.
   b. It begins with the binding of cellular receptors to a signaling molecule.
   c. It occurs only in the nucleus and involves control of transcription.
   d. It is driven by a proton gradient across the membrane.

2. What role does phosphorylation play in signal transduction?
   a. It generates ATP to give the cell energy.
   b. It causes a change in conformation of molecules and allows their activity to be switched on or off.

c. Phosphorylation of RNA polymerase is necessary before it can transcribe the gene that is the final product of the transduction pathway.
d. When the signal molecule is phosphorylated, it is recognized by more cell components and the cell can respond more quickly.

3. In the signal transduction pathway involving the G-linked protein receptor, what would be the consequence of the kinase not being able pass through a nuclear pore?
   a. ATP could not be generated from ADP.
   b. The signal could not be amplified.
   c. The regulatory protein would not be phosphorylated and activated.
   d. ATP could not be converted to cAMP.

4. What steps are necessary for the activation of a G protein in signal transduction?
   a. The a subunit of the G protein must interact with a G-linked protein receptor, then join with a b subunit.
   b. An ATP must phosphorylate the a subunit of the G protein after the subunit contacts the G-linked protein receptor.
   c. The b-g subunits of the G protein must interact with adenylate cyclase.
   d. The entire G protein must first interact with the signal molecule.

5. Cells receive many types of signals and cells can respond to individual signals or combinations of signals. Often, the result is the expression of specific genes. Provide an example of a signal transduction event in a cell that begins with an external messenger that comes in contact with the cell in some way and ends with the transcription of a gene. Provide as much detail as possible.