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Cells at Work: Using Role Play to Model Biomolecular Processes

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Cells are in a constant state of flux, taking in "supplies" then modifying them into metabolites and necessary biomolecules as they perform energy transformations to build products for intracellular and extracellular use. This article describes ways to design props and perform skits and other physical demonstrations to model a variety of biomolecular processes. The open-ended style of these activities is intended to encourage discussion, incorporate student suggestions, and involve invention of variations to model regulatory complexities, to incorporate student suggestions, and to maximize meaningful engagement for all students. These activities may be adapted to small scale (partner, <5 min) or medium to large scale (whole class, 20 minutes+) applications.

Keywords: active learning, metabolic pathways, metabolic regulation, role play

Introduction

Collaborative, active learning activities are applicable to multiple educational contexts and in a variety of content areas in the university classroom. Role play, a highly adaptable form of active learning, allows students to take on an identity and behave in a manner consistent with that identity while interacting with other students playing related roles, in order to meet specified learning goals (Barkley *et al*, 2005). There is a body of pedagogical research supporting its effectiveness that reaches back to the 1970's and 80's (Rao and Stupans, 2012). Role play supports learning across many disciplines and at many levels (Rao and Stupans, 2012). I have found role play to be a useful immersive way for biology and biochemistry students to learn the fundamentals of intracellular processes including metabolic pathways, with great potential for students to explore nuances of regulation mechanisms. In this paper I will discuss aspects of preparation for the activity, both student and teacher, as well as execution tips for maximizing student engagement, exploration of regulatory components, and follow-up analysis of student learning. Specific examples outlined herein include operation of the mitochondrial ATP synthase complex and functioning of a G-protein coupled signaling pathway. These specific role-play exercises have been used and refined in biochemistry and cell biology classes over several years.

Characteristics of Successful Role-Play

Successful role-play activities are designed to be imaginative, interactive and exploratory – much more than simply walking through a sequence of stereotyped actions. They promote affective, social and psychomotor reinforcement of learning goals through personal emotional investment in "being" a molecule, cooperative interaction with other learners, and physical performance of the tasks and responses inherent to one's role in the activity. Otherwise passive learners are encouraged to participate, and the focused playfulness of a well-designed activity promotes retention of information. As the director your level of authority and control can vary greatly according to the characteristics of the student group, and you may find yourself shifting from being the authority figure to filling an advisory role to simply becoming an amused observer enjoying the action as the role-play progresses.

While scholars of teaching and learning recognize role-play to be a highly effective strategy, some caveats exist, particularly for weak and unprepared students. The exercise's preparatory phase must build basic comprehension of the process in all participants. During the role-play activity itself, participation needs to be accompanied by appropriate support including prompts to accurately reinforce concepts. Because each student is in a sense on display while participating, maintaining a light-hearted yet purposeful classroom atmosphere will help reduce anxiety. Leaving a less-than-confident student unsupported may result in a counterproductive experience

for the entire class, so preparatory and follow-up experiences require as much careful crafting as does the role-play itself. (Stevens, 2015).

Props are useful to highlight features of the mechanisms being simulated, and their creative selection and implementation will go a long way toward furthering the playful atmosphere. In addition to the props in the exercises that follow, I have found toy tractors to nicely represent RNA polymerase at an operon, a hula-hoop with multicolored streamers can simulate a nuclear pore for modeling protein sorting, a star-shaped sticky note can easily be added to a "molecule" to "phosphorylate" it, and peppermint candies strewn down a classroom aisle aptly represent glucose in the bloodstream moving toward an available GLUT4 channel under insulin regulation. Commercial molecular models, while they are excellent learning tools, are not necessary for successful role-play.

Two examples of role-play simulations developed for use in biochemistry and cell biology classes respectively are given herein. Many other metabolic processes may also be explored by such activities.

Student Outline
A. Mitochondrial ATP Synthase in Action

Objectives

- Model the structure and activity of the FoF1 ATP synthase
- Evaluate the relationship between electron transport chain operation and ATP production
- Demonstrate substrate and product exchanges via membrane transporters in the cristae
- Explore responses of the system to fluctuations in substrate availability, hypoxia, and/or loss of membrane integrity

Introduction

What is the mechanism whereby a protein gradient across the inner mitochondrial membrane drives the highly unfavorable reaction ADP + Pi → ATP? It took decades of research and exploration of a variety of options before the mechanics of this process were satisfactorily worked out, and nuances of its details are still being explored.

Methods

Part A: Your assigned textbook readings (*Lehninger's Principles of Biochemistry*, Chapter 19.2 ATP Synthesis) and viewing of an animation of the Fo-F1 ATP synthase complex in action should prepare you to discuss and answer questions on the system's basic structure and functioning. These activities will introduce you to

- major subunits of the complex
- subunits' organization in relationship to one another and the inner mitochondrial membrane
- location of the basic reaction (ADP + Pi → ATP)
- the sequential chemiosmotic process from entry of protons into the first ½ channel of Fo to the ultimate sequential synthesis and release of ATP from the surface of F1
- transport processes for substrates and product through the inner mitochondrial membrane.

Part B: After the discussion, as a group we will role-play the operation of this macromolecular complex. Each of you will be provided with a prop/props to help you in your role, simulating one of the subunits or other components of the system, and we will be interacting with one another to "produce ATP". Once we get the basics down, we'll explore how this system is regulated as oxygen or substrate availability varies, and how diseases may affect its operation. Some variations to consider and model include:

1. Different species have different numbers of c subunits in the c ring – what is the effect of having fewer or more binder clips on the sombrero?
2. Discuss conditions that may reduce oxygen levels within the cell. What will the synthase complex do if the proton gradient runs down or is reversed? What will happen to the ATP within the matrix if this happens?
3. How does the regulatory IF1 protein do its job? What activates and inactivates it?
4. Describe other regulatory mechanisms and simulate their action

Your understanding will be evaluated by quiz or other means following this simulation.

Part C: We'll conclude this study of ATP synthase by reading and discussing the Nobel Laureate Lecture from 1998 (*Energy, Life and ATP* by Paul Boyer; accessible at https://www.nobelprize.org/prizes/chemistry/1997/boyer/lecture/). Notice how Dr. Boyer describes the progression of scientific discovery – its non-linear path to answers, alternative hypotheses proposed and investigated, and the wide ranging contributions made by numerous "behind the scenes" researchers. Below is a set of reading questions to help you identify key points made in the lecture.

Questions on *Energy, Life, and ATP* (Nobel Lecture), Paul D. Boyer (1998)

1. Read through the entire overview. At the end you'll find the problem that Boyer and his fellow recipient, John Walker, were able to solve. Write it here.
2. Notice the recognition Boyer gives to the large number of researchers who contributed to discovery of ATP synthase's mechanism of action. He will name many of these research groups throughout the paper. This is a reminder that scientific discovery is a community effort, and that no one stands alone without drawing upon the work of others (*no question here*).
3. List the three unusual features of ATP synthase catalysis, all of them energy-linked changes in binding.

4. Boyer and others' first attempts to learn more about ATP formation came about after revelation of how step 6, followed by step 7, of glycolysis work. Refer to figure 14-8 in your textbook (step 6) and the step 7 reaction diagram to summarize these processes. Was this a useful model for understanding ATP synthesis in general?
5. List several uses of radioactive isotopes of oxygen and phosphorus that were helpful in determining specific aspects of the ATP synthesis process.
6. Figure 3 demonstrates Boyer's surprising observation that an uncoupler of oxidative phosphorylation (such as the uncoupling protein thermogenin or the alternate oxidase, or the S-13 uncoupler used by Boyer) can inhibit exchanges between Pi and ATP, and between ATP and water, but NOT exchanges between Pi and water. This was linked to his earlier observation that enzyme-bound Pi can tumble freely in the catalytic site of ATP synthase. Based on thoughts while letting his mind wander during a seminar lecture, what did he conclude was the best explanation of this phenomenon? How was this concept received by the NAS? How did myosin studies help support his idea?
7. Peter Mitchell, another giant in the study of oxidative phosphorylation, had a different idea about how proton-motive force contributed to ATP synthesis. What did he think?
8. What were the key contributions made by graduate students Celik Kayalar and Jan Rosing to an understanding of catalytic site activity on the synthase? Why must there be at least two catalytic sites on the synthase for this to work?
9. What is meant by the phrase "very tight preferential binding of ATP" on page 2301 (second column, halfway down the page)?
10. What kinds of F1-ATPases were quantified stoichiometrically to favor the subunit combination of 3 alpha, 3 beta and one gamma?
11. At the time of this speech, had it been unequivocally confirmed which subunit type(s) for sure is/are the actual sites of catalysis? How did they determine all the catalytic sites are identical?
12. Boyer struggled with the mechanism whereby all three catalytic beta sites could operate identically, especially with the understanding that one of the minor subunits must be involved by interaction with them all. This is how he came up with the idea of rotational catalysis. Explain his cam shaft idea and several similar ideas proposed by others.
13. Is there a stage of tightly bound ADP + Pi in the catalysis sequence? Why/why not?
14. On page 2305 Boyer discusses inhibition of the synthase (or reversal to hydrolysis) in the presence of high [ATP]. How does he think "nature" has avoided the problem of freshly manufactured/released ATP molecules inhibiting further activity on the synthase?
15. Generally, what does the tone and flow of Boyer's lecture tell you about scientific progress?

Student Outline
B. G-Protein Signaling at GPCRs

Objectives

- Model the structure and pathway of a common trimeric G protein signaling pathway
- Evaluate potential points of signal amplification along the pathway
- Demonstrate signal termination mechanisms
- Explore effects of selected diseases and/or pharmaceutical treatments that target GPCR signaling pathways

Introduction

Cells are constantly in communication with their environments, and in multicellular organisms they work to serve the organism as a whole. We know that hormones, paracrine, and neurotransmitter signaling molecules must interact with receptor proteins either on or inside their target cells to initiate an appropriate response. Today we will be exploring one of the most common signaling pathway types, where the receptor protein is a membrane bound G-protein coupled receptor. While all the GPCRs and their pathways have distinctive differences, we will gain a sense of how they all work by modeling the pathway initiated by adrenalin – a fight or flight response that reflects rapid intracellular metabolic adjustments under stressful circumstances.

Methods

Part A: You will need to complete assigned readings in the textbook (Albert's Essential Cell Biology, Cell Signaling – G Protein-Coupled Receptors) paying careful attention to the figures and their captions. Notice those that activate cAMP production inside the cell, which is a second messenger that directly modifies metabolism in a variety of ways. Be prepared to discuss this system in class prior to our activity. You should be able to

- identify major components of the generalized GPCR signaling cascade
- order the cascade properly, including signal termination
- recognize that there are numerous variations of this basic pattern – details differ in the cascade's format and in specific components involved
- appreciate the power a GPCR-targeting infectious agent or pharmaceutical intervention could have over this system.

Part B: After the discussion, as a group we will role-play the operation of the GPCR signaling pathway when the hormone adrenaline (epinephrine) serves as the signaling molecule. You will be provided with a prop/props to help you in your specific role, simulating one of the components of the system, and will be interacting with each other to accomplish the signaling task. Once we get the basics down, we'll explore various aspects of how this signal is deactivated and/or regulated to avoid overstimulation, and how diseases or drugs may affect its operation.

Part C: We'll conclude this study by collectively recapping the sequential process including how and where amplification or suppression of the signal takes place. We will specifically review the effects of cholera toxin and beta blockers on the pathway. Expect a quiz afterwards.

Materials

Exercise A.

Props:

The props listed below will supply one complete simulation. Exact items to be used may easily be modified according to individual circumstances, but these work well in the context of the Biochemistry II class at Lenoir-Rhyne:

1. A sombrero with 10 binder clips attached to its brim, evenly spaced (represents the c-ring of Fo)
2. A knee pad, to be worn on the knee on the rotating γ subunit (represents asymmetric region that interacts with αβ subunits)
3. At least 15 index cards with "H+" written on them (protons)
4. Six or so paper plates prominently labeled "ADP" (ADP)
5. Six or so star shaped post-it notes with "P" or "-PO_4" written on them (phosphate groups)
6. Three chairs (αβ subunits of F1)

Participants:

The exact number of student participants per simulation is variable according to class/group size, but the tasks to be accomplished include:

1. C ring + γ shaft – wears sombrero and knee pad (one per simulation)
2. A subunit's entry half-channel – clips H+ index cards onto sombrero (one per simulation)
3. A subunit's exit half-channel – unclips H+ index cards from sombrero and drops them (one per simulation)
4. F1 αβ subunit pair – sits in one of three chairs arranged symmetrically facing γ shaft's legs (three per simulation)
5. ATP/ADP translocase – antiporter for ATP/ADP plates through the (invisible) plane of the inner mitochondrial membrane, to be received/given from/to the αβ subunit pairs in turn (one per simulation)
6. Phosphate channel – cotransports H+ and Pi cards through the plane of the membrane into the matrix (one per simulation)
7. IF_1 monomers – use no props, but restrict rotation of two adjacent C ring + γ shaft units by physical contact - simulate regulatory mechanism activated when the proton gradient is too small (two per simulation)
8. Proton managers and ATP/ADP handlers may be useful additions to ease diffusion logistics for protons and ATP/ADP within the matrix or intermembrane space.

Exercise B.

Props:

The props listed below will supply one complete simulation. Exact items to be used may easily be modified according to individual circumstances, but these work well in the context of the Cell Biology class at Lenoir-Rhyne:

1. Tie down strap, 10-15 feet in length (represents the plasma membrane)
2. Foam tube cut to 4-6" length from pipe insulation, with cutout at one end to receive "signal" molecule. Duct-tape this tube across the tie down strap near the midpoint of its length. Ensure the cutout end is on the membrane's extracellular face (represents the GPCR)
3. A small object that fits snugly within the GPCR foam tube that will protrude from one end when pushed in from the other. I use items from a molecular model kit - a "bond" stick with two "atom" balls, one at each end, that will be hidden from view in the inactive state (demonstrates the activity status of the GPCR)
4. A cardstock cutout of the epinephrine molecule OR a visually appealing small object with a distinctively shaped protrusion that fits into the foam tube's cutout (represents the signaling molecule)
5. One cardstock cutout each of the α, β, and γ components of the trimeric G protein – each is a different color, and they are cut to the same shapes as in the textbook illustrations.
6. Binder clips or carabiner hooks to link trimeric G protein to the membrane. Tape is used to link β and γ to each other.
7. Two post-it notes, one labeled GTP and the other GDP, to be exchanged on the alpha subunit.
8. One cardstock cutout representing adenylyl cyclase, with a carabiner/binder clip attachment to the membrane.
9. A collection of paper plates marked ADP with an extended slip of cardstock taped off one end, so it looks like a banjo (cardstock illustrates the tri-phosphate chain of ATP – it will be cut and the "stump" looped/taped back onto the plate to represent cAMP).
10. One cardstock cutout representing a phosphodiesterase enzyme.

Participants:

The exact number of student participants per simulation is variable according to class/group size, but the tasks to be accomplished include:

1. Two students will hold the plasma membrane

strap stretched across the front of the room.
2. Adrenaline molecule in blood circulation, eventually to the vicinity of the GPCR (one per simulation)
3. GPCR operator, activating it by pushing its insert to make it "appear" on its intracellular face upon signal binding (one per simulation).
4. Trimeric G protein operators, working as a unit to slide toward to the activated GPCR then separating for the activated alpha subunit to work effectively alone (two per simulation).
5. Activator/inactivator of the G protein by tagging it with the GTP/GDP post-it notes respectively (one per simulation).
6. Adenylyl cyclase operator, converting ATP to cAMP on the inner face of the membrane (one per simulation).
7. Molecular responses to cAMP production (glycogen breakdown/ PKA activation/etc.) (several per simulation – variable props or simply describe in words)
8. Phosphodiesterase operator untapes the cAMP molecules' "loops" to inactivate them (one per simulation).

Notes for the Instructor

These role-play exercises may involve the whole class as a group or may be conducted in several small groups simultaneously, but ideally will include active participation of all students in some way. It is possible to assign individual roles to pairs of students, with one person "doing" the role while the other directs and/or advises. The activity may be conducted several times so that participants may switch roles. Operate the system slowly with lots of discussion along the way, particularly at first!

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