Using Musical Instruments to Model Negative Feedback in the Hypothalamo-Pituitary-Target Gland Axes

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Abstract

Homeostasis and negative feedback are crucial, yet difficult, concepts for undergraduates, particularly in the context of the hypothalamo-pituitary axes. This interactive activity was designed to (1) reveal how negative feedback can restore homeostasis following transient disturbances and (2) help students predict the effect of over- or under-activity of one element on the other elements of the axis. Student volunteers use different musical instruments to represent the output of the hypothalamus, anterior pituitary (AP), and target gland (e.g., adrenal gland). The other students form support groups that provide advice about how many noises each instrument should produce. In the simulation, the hypothalamic output determines the AP output, which, in turn determines the target gland output. The hypothalamus compares its set point with the target gland output and modulates its output accordingly. After practicing the simulation under normal conditions, students work with their support groups to predict how the simulation would change in response to perturbations such as an altered set point, dysfunction of the target organ, or a tumor (an audience member playing an additional instrument). Students found the activity useful and enjoyable, and a subsequent exam question showed that 45/47 students were able to predict the effect of a perturbation in one element on the other axis elements. In summary, this simulation effectively promotes student understanding of negative feedback and homeostasis without consuming excessive lecture or laboratory time.

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Learning Goal(s)

Students will apply the principles of homeostasis and negative feedback to the hormones of the hypothalamic-pituitary axes.

This learning goal aligns with the following Scientific Society goals:

1. The American Physiological Society Medical Curriculum Objectives Project: Endocrinology and Metabolism (2011). EN 21: Understand negative feedback control of anterior pituitary hormone secretion at multiple levels.

2. Human Anatomy and Physiology Society (HAPS) A & P Learning Outcomes (2019). Module J (Endocrine System): (9) Predictions related to disruption of homeostasis:
   - Given a factor or situation (e.g., lack of iodine in the diet), predict the changes that could occur in the endocrine system and the consequences of those changes (i.e., given a cause, state a possible effect).
   - Given a disruption in the structure or function of the endocrine system (e.g., hypothyroidism), predict the possible factors or situations that might have caused that disruption (i.e., given an effect, predict possible causes).

Learning Objective(s)

Students will be able to:

1. Predict the physiological consequences of alterations in the hypothalamic-anterior pituitary axis and explain the rationale behind the prediction(s).

2. Predict how the hypothalamus, anterior pituitary, and target gland will alter their activity in response to a changing set point and explain the rationale behind the prediction(s).

3. Predict the site of dysfunction in the hypothalamic-anterior pituitary axis given a set of pathophysiological signs and symptoms and explain the rationale behind the prediction(s).

4. Use examples from the hypothalamic-pituitary axes to explain how negative feedback maintains the level of the regulated variable at the set point by altering signal strength and effector activity.

Learning objectives 1-3 are modified from those of Michael et al. (1)

INTRODUCTION

The landmark monograph *The Core Concepts of Physiology* describes 15 physiology core concepts, the best characterized of which explains homeostasis and negative feedback (2). Michael and colleagues (2) propose that the term "homeostasis" applies to a limited number of regulated variables, the values of which are kept within limits (a set point) by a negative feedback system. The level of each regulated variable is measured by sensors. The control center receives information from the sensor(s) and from other components that determine the set point (such as higher brain centers). It compares the level of the regulated variable with the set point and alters the production of signals (e.g., action potentials, hormones) in response to any error signal. Signals alter the activity of effectors, which are components that determine the value of the regulated variable.

Key physiologic variables such as blood glucose concentrations, basal metabolic rate, and tissue growth are directly or indirectly regulated by complex regulatory systems involving the hypothalamus and the anterior pituitary gland (often described as hypothalamo-pituitary axes). In these systems, hypothalamic releasing hormones control the release of specific anterior pituitary hormones, each of which controls the release of specific target gland hormones. Each target gland hormone (as well as growth hormone from the anterior pituitary) controls multiple physiologic variables for which we do not necessarily have identified sensors (e.g., basal metabolic rate). For these reasons, it can be helpful to treat the levels of the hormones themselves (rather than the physiologic variables they control) as if they were regulated variables (see the Discussion for more information). The hypothalamic secretory neurons can fulfill the roles of sensor and control center, since they detect the level of target gland hormone and alter their release of releasing hormones accordingly (3).

An excellent dry lab is available to help students deepen their understanding of the regulation of these hormones, in which students determine the identity of an administered hormone based on organ weights and hormone levels (3). However, my undergraduate students struggled to distinguish between cause (the actual perturbation) and effect (how the perturbation alters the output of the other glands), and exam results revealed the existence of multiple persistent misconceptions about feedback loops (discussed further below). Perhaps reflecting their frustration, students ranked this activity the lowest out of five lab activities in terms of perceived utility and enjoyment (data not shown). I developed the role-playing activity discussed in this article as an alternative to the dry lab. By using the output of musical instruments to represent the output of the hypothalamus and endocrine glands under normal and pathologic conditions, students can dynamically model how the perturbation affects the system, and then how the system reacts to the perturbation.

Intended Audience

This activity has been tested in classes of 30-55 students in the third or fourth year of a B.Sc. program (Biology, Neuroscience, or Biochemistry) at a 4-year primarily undergraduate university. The course is the second in a series of two Animal Physiology courses required of the Biology and Biochemistry students, but optional for Neuroscience students, and has two Cell Biology courses as prerequisites. The activity has been used in traditional lecture rooms and in active learning classrooms.

Required Learning Time

The entire endocrine role-play takes approximately 1 hour to complete; however, it can be shortened by omitting some of the scenarios. Instructors may want to provide a slightly longer time period the first time they implement this activity.

Prerequisite Student Knowledge

Students should have a working knowledge of the core concept of homeostasis, and should be able to:

- Identify the components of a negative feedback loop (regulated variable, sensors, control center, signals, effector);
- Explain how the components of a negative feedback loop maintain the level of a regulated variable with a given range (the set point);
- Explain that set points can change as a result of an external event.

Students should also have a working knowledge of the following concepts.

- The anatomic relationship between the hypothalamus and the anterior pituitary gland: The hypothalamus is neural tissue, but the anterior pituitary gland is endocrine tissue. Hypothalamic neurons terminate at capillaries in the infundibulum (pituitary stalk). The blood from these capillaries then enters a second capillary bed in the anterior pituitary gland (the hypothalamo-pituitary portal circulation).
- The functional relationship between the hypothalamus and the anterior pituitary gland: Hypothalamic neurons secrete releasing hormones into the portal circulation. Each releasing hormone binds receptors on a specific type of anterior pituitary cell, and thereby regulates the production of a specific anterior pituitary hormone.
- The functional relationship between the anterior pituitary gland and the target gland: Each anterior pituitary hormone travels through the circulatory system and regulates the production of a specific hormone from a target gland (e.g., the adrenal gland).

I cover these topics using a guided inquiry activity that is currently under consideration in a POGIL activity collection, but they can also be briefly covered in a mini-lecture using readily available images illustrating hypothalamo-pituitary anatomy and feedback relationships between the elements of a prototypical axis. Students can also be provided with an introductory reading from the Endocrinology chapter of a Physiology or Anatomy and Physiology textbook.

Students do not need to know the specific hormones involved in each axis.

Prerequisite Teacher Knowledge

Teachers should have a solid understanding of the core concept of homeostasis (2). This concept is summarized in the Introduction section, but teachers are also encouraged to read the article.

While not absolutely necessary, students may ask about specific axes. Ideally, teachers should know the names and abbreviations of the hormones involved in each axis (adrenal/

cortisol; liver/IGF-I; thyroid gland/thyroid hormone; gonads/gonadal steroids). Supporting File S1: Musical Feedback – Hormone Information provides a brief summary of each axis.

Instructors can choose the level of detail relevant to clinical topics. However, students usually find these topics very interesting, so it can be helpful to be familiar with the clinical aspects of at least one axis. Scenario 4 looks at the impact of therapeutic hormones, so it is helpful to know some examples (e.g., cortisol's role as an anti-inflammatory or the contraceptive use of gonadal steroids). It can also be helpful to know the most common endocrine diseases associated with at least one axis (e.g., Hashimoto thyroiditis (hypothyroidism), Graves disease (hyperthyroidism), Cushing syndrome (hypercorticolism), Addison disease (hypocorticolism)). Supporting File S1: Musical Feedback – Hormone Information provides a brief summary of diseases relevant to each axis.

SCIENTIFIC TEACHING THEMES

Active Learning

Role-playing simulations can be particularly effective at modelling dynamic physiologic processes, including muscle contraction (4), ventilation (5), protein synthesis (6), and the immune response (7). Experiential learning theory supports the use of this activity type, since it involves multiple learning environments (thinking, feeling, behaving (doing), and perceiving) (Kolb & Kolb, 2008). Role-plays are also highly motivating and they can provide immediate feedback (8). This activity uses student volunteers to act as the hypothalamus, anterior pituitary gland, and target gland, with the number of noises from different musical instruments representing the output of each gland. For each of the situations outlined in Table 1, students worked together to identify the perturbation (which instrument would "go first"), and then how the other instruments would modify their output as a result (see Supporting File S2. Musical Feedback – Student Handout). By subsequently applying the role play (and thus the underlying core concept) to different hormonal axes and under different situations, students construct knowledge by synthesizing new information with information that has already been learned. The activity provides opportunities to address numerous misconceptions targeted by the homeostasis conceptual framework (9). For instance, if students ceased making noises after homeostasis was restored, the instructor can mention that feedback mechanisms function even when the system is in balance (in other words, the music never stops). Other common misconceptions and errors are described in the Lesson Plan.

Assessment

The 2015 cohort completed a 4-question paper quiz after the mini-lecture based on the Homeostasis Concept Inventory, available in Supporting File S2. Musical Feedback – Assessment Questions (10). The questions addressed (1) the misconception that feedback loops only function when there is a problem, (2) how the negative feedback loop restores hormone levels following a transient perturbation, (3) how the system adapts to a hormone deficiency, and (4) how the system adapts to a tumor. The simulation was then used to model the latter three situations but was not used to explicitly examine the first misconception in either 2013 or 2015. Students completed a paper version of the post-test, which contained identical (question 1) or isomorphic (questions 2-4) questions. Students were not given the correct answer to the pre-quiz before completing the post-quiz. The final exam contained a question similar to question 3. With the exception of question 1, answers were arrayed in a grid format. The overall difference between the pre- and post-test scores for the four questions was analyzed by a paired *t*-test.

Inclusive Teaching

This role-play addresses issues of diversity and lack of participation by providing multiple means of representation (visual, auditory, and kinesthetic) (11) and allowing students to choose between multiple modes of involvement (6). Students volunteering to enact a particular role participate *physically*. The remainder of the class participates *cognitively*, by participating in support groups that predict how the simulation will proceed under various circumstances, and then provide advice to the actors as to who does what and when. The actors can, of course, participate both cognitively and physically, but the involvement of their support group can lessen performance anxiety. Visually and hearing-impaired students can fully participate in this activity, which uses noises generated by percussion instruments to represent output. All students will benefit by ensuring that the performers exaggerate the movements used to create the noises and are clearly visible. Moreover, support groups should be encouraged to provide their advice in an auditory, as well as visual, fashion.

LESSON PLAN

Materials Required

<u>Musical Instruments</u>

Three different instruments represent the hypothalamus, anterior pituitary gland, and target gland. The instruments should produce very distinct sounds and be relatively loud. I have used drums, bells, drumsticks (or any wooden sticks), and two tin cans. If instruments are not available, students can generate percussive sounds by clapping, foot stomping, whistling, vocalizing (e.g., "boom") or tapping the desk with a book. Instructors can ask students to suggest noises that are easily distinguishable from each other and provide visual cues for hearing-impaired students. Some parts of the activity use two of the same instrument.

<u>Signs</u>

Prepare a sign for each role. I write the role on a sheet of paper, punch holes in the upper corners, and tie a 1-foot piece of string to the two corners so that students can hang the sign around their neck. Completing the entire activity requires the following signs:

- hypothalamus
- anterior pituitary
- target gland
- exogenous hormone

Introducing the Role Play

If the pre- and post-tests are used, I either provide paper copies of the pre-test at the beginning of class or take 5 minutes to go through the four clicker questions (See Supporting File S3. Musical Feedback – Assessment Questions). I do not provide the answers or discuss the questions until the end of class.

In the instructions that follow, a drum represents the hypothalamus (H), drumsticks represent the anterior pituitary gland (AP), and bells represent the target gland (TG).

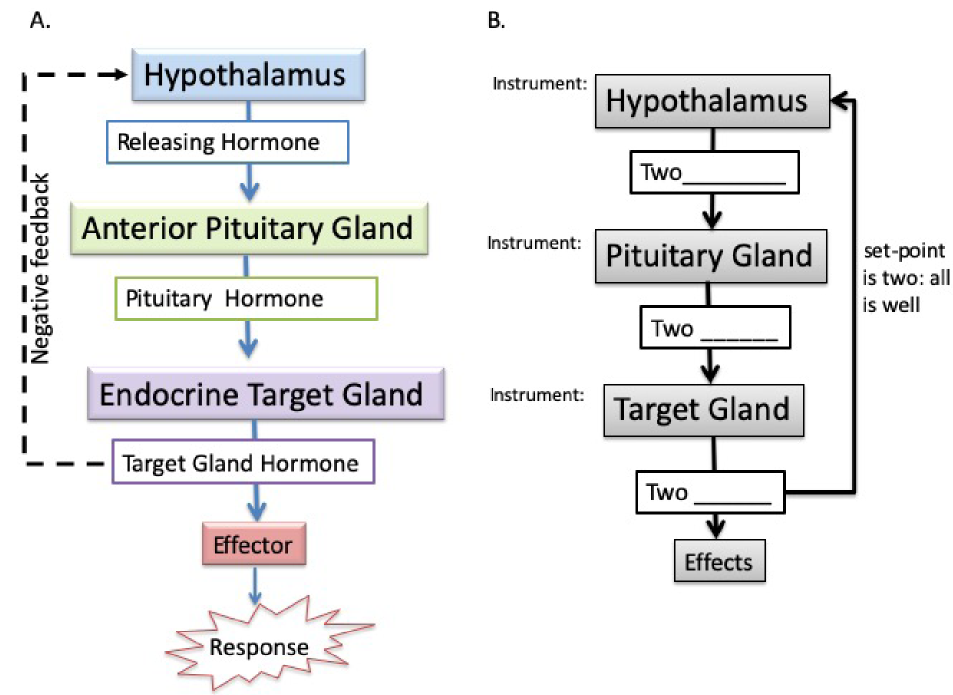

Figure 1. Negative feedback in the hypothalamo-pituitary axis. A. Feedback relationships between the hypothalamus, anterior pituitary, and target glands. Note that this figure does not illustrate feedback from the target gland to the anterior pituitary gland. B. The role-playing simulation under normal conditions. In this example, the target gland hormone setpoint is 2 noises.

Provide students with the handout (Supporting File S2. Musical Feedback – Student Handout) and, if desired, refer to Figure 1 as you introduce the role play as follows:

"We will be using noises to represent the output of the hypothalamus, anterior pituitary gland, and target gland. The number of noises made by each instrument represented the magnitude of the output. For instance, the output of the hypothalamus could be relatively small (make 2 noises) or relatively large (make 5 noises)."

"I need three volunteer actors to play these instruments. Each actor will have a support group to tell them how many noises to produce." (I incentivize volunteering using small chocolate bars or fruit.)

Ask the volunteers to come to a central area (or front of the class) and give each student an instrument and the relevant sign. The anterior pituitary gland student should be situated between the two others.

Divide the rest of the class into support groups for three actors. Ask students to fill in the blanks of the handout, indicating which instrument and noise is associated with each component.

Introduce the regulatory aspects of the role-play as follows:

- "The hypothalamus is the control center, so it controls the show. Let's say that it produces two noises (gesture to the hypothalamus to produce two drum taps). Which of our other two components will 'hear' these noises – the anterior pituitary or the target gland?" At this point, I ask support group students to vote, and may ask students what enables cells to "hear" the output of another cell (answer: receptors). "For convenience, let's say that that anterior pituitary produces the same number of noises as the hypothalamus. So, if the hypothalamus produces two drum taps, the anterior pituitary gland will produce... (pause for student input)... two thwacks."
- "The anterior pituitary gland output determines the target gland output. So, if the anterior pituitary produces two noises, the target gland will produce... (pause for student input)... two bell chimes."

Add negative feedback control as follows: "The output of the target gland is the regulated variable. The hypothalamus (drum) acts as the sensor and control center. The hypothalamic set point is a given number of target gland noises. The hypothalamus compares the target gland output with its set point and adjusts its output accordingly. For instance, if the hypothalamus hears two target gland noises (bell chimes) and its set point is two, then it will assume that all is well and maintain the same output."

If desired, run through two rounds of the simulation, with each instrument producing two noises.

Scenarios

The instructions that follow will assume an original set point of two bell chimes. For each scenario, students will run through at least three rounds of the simulation. Each round consists of the hypothalamus (H), anterior pituitary (AP), and target gland (TG) sequentially producing a given number of noises.

- Round 1: Normal conditions.
- Round 2: Change: One component changes its output.
- Round 3: Response: One or more components responds to the perturbation by changing its output. Note that the response to perturbations at the hypothalamic or pituitary level begins in round 2.
- Round 4: Compensation: The output of the components stabilizes.

At the beginning of each round, the support groups advise the actors how many noises to produce, ideally using both auditory and visual cues. Audience members can hold up the desired number of fingers; use hand gestures to indicate an increase (thumbs up), decrease (thumbs down), or no change (thumbs sideways); or write the number on a small whiteboard, and a group spokesperson can vocalize the advice. Instructors should also ask support groups to explain the reasoning. After each round, evaluate the success of the simulation, and instructors can provide guiding questions, if necessary, to help students arrive at the correct procedure, as outlined in the sections below.

Emphasize that, once the baseline level of secretion has been established, the anterior pituitary and target gland respond to changes in the amount of signal they receive rather than the absolute level of the signal. If desired, students can complete a row of the Table in the handout at the end of each scenario.

<u>Scenario 1: Change in Setpoint</u>

This part of the role-play addresses the following learning objective:

Predict how the hypothalamus, anterior pituitary, and target gland will alter their activity in response to a changing set point and explain the rationale behind the prediction(s).

It also targets an important concept relating to homeostasis, namely that feedback loops are always functioning, even when the system is in balance.

Procedure

Ask the target gland support group to choose a new set point and communicate their choice to the student representing the hypothalamus. For instance, they could increase the set point to three bell chimes. If desired, the instructor can provide an example, such as the increase in the cortisol set point in the early morning hours.

Follow the general procedure described above to work through three or four rounds of the simulation. If necessary, remind students that the actors will do one round under normal conditions, and that the perturbation (a new set point) will take effect in the second round. The correct procedure is shown below:

- R1 (normal): 2 H, 2 AP, 2 TG
- R2 (change): 3 H, 3 AP, 3 TG
- R3/4 (response/compensation): 3 H, 3 AP, 3 TG

If the class does not come up with the correct procedure for the second round, these guiding questions can help: "Now the hypothalamic set point changes to three chimes. Did the hypothalamus hear three chimes? (Answer: no. It only heard two.) What should the hypothalamus do to get its desired result? (Answer: increase its output to three.)

Students may predict that hypothalamic output should decrease in the third round, because the hypothalamus' "job is done." If so, these guiding questions can help: "Did the hypothalamus hear three chimes? (Answer: yes.) Will the hypothalamus change its output? (Answer: no, because it "hears" that the TG output is the same as the set point.)

The students may stop producing noises in the 4(th) round, claiming that the system is now in homeostasis, so no further noises are required. If so, ask the AP support group how the AP would respond to silence (it would stop producing noises). This step of the simulation addresses the common misconception that feedback loops only function when there is a perturbation.

<u>Scenario 2: Transient Disruptions to Homeostasis</u>

This part of the role-play addresses the following learning objective:

Predict the physiological consequences of alterations in the hypothalamic-anterior pituitary axis and explain the rationale behind the prediction(s).

It also helps students understand that negative feedback restores the level of the regulated variable to the setpoint by modifying the level of other variables.

Procedure

Explain that this scenario illustrates how the hypothalamo-pituitary axis can restore homeostasis when one of the components changes its output. If desired, the instructor can provide an example, such as growth of the adrenal gland or partial resistance of the adrenal gland to pituitary stimulation.

Ask the target gland support group to decide if their actor should increase or decrease the number of sounds (i.e., is target gland output increased or decreased?). If desired, ask students to predict how the output of each instrument will have changed (increased, decreased, or unchanged) once the system has compensated for the perturbation, and write their predictions on the handout.

Follow the general procedure described above to work through three or four rounds of the simulation, and see Table 2 for the desired procedure. Ask students to evaluate the accuracy of their predictions once they arrive at the correct outcome. Note that the anterior pituitary gland will echo the hypothalamus unless the anterior pituitary gland is the disruptive influence. Similarly, the target gland will echo the anterior pituitary gland unless the target gland is the disruptive influence.

If the class does not come up with the correct procedure for the third round, the instructor can ask guiding questions such as these:

- Does the hypothalamus hear the same number of noises as its setpoint? (Answer: no).
- What could the hypothalamus do to offset this change? (Answer: change its output in the opposite direction to the change.)

After round 4, students may question why the system is now in homeostasis when the levels of the H and AP output have changed. Guiding questions could include:

- Does negative feedback act to keep the level of all variables at the same level? (Answer: no. Negative feedback functions to keep the level of the regulated variable at the setpoint; it does so by altering the levels of other variables.)
- Does the hypothalamus respond to absolute levels of the regulated variable or changes in the level of the regulated variable? (Answer: changes.) Similarly, the AP and TG only modify their activity if the number of signals that they receive (hear) changes.

If desired, repeat the procedure for other perturbations shown in Table 2. Note that changes in hypothalamic output have been covered in Scenario 1, because they result from a change in the hypothalamic setpoint.

Scenario 3: Gland Failure

Scenarios 3 and 4 illustrate what happens when negative feedback cannot restore homeostasis, and address the following learning objective:

Predict the site of dysfunction in the hypothalamic-anterior pituitary axis given a set of pathophysiological signs and symptoms and explain the rationale behind the prediction(s).

Note that student mastery of this objective also requires that they learn about the individual axes and the clinical implications of over- and under-production of the different target gland hormones. I cover this information using lectures, short case studies, and peer instruction. See Supporting File S1: Hormone Information for a brief summary of the relevant details, and the Implementation Guide below.

Procedure

By this point, students may be able to autonomously run the simulation and come up with the desired procedure. It can be helpful to ask for a new set of volunteers.

Explain that the next scenario illustrates what happens a gland fails completely, or if it is removed by surgery. Ask the AP support group to select the failing gland. If desired, ask students to predict how the output of each instrument will have changed (increased, decreased, or unchanged) once the system has compensated for the perturbation, and write their predictions on the handout.

Follow the general procedure described above to work through at least four rounds of the simulation. Table 3 summarizes the desired procedures for each. Note that hypothalamic and/or anterior pituitary output continues to rise in subsequent rounds in the case of target gland or anterior pituitary failure.

Common student errors include the failed gland continuing to produce noises and the target gland responding to the hypothalamic noises in the case of AP failure. At this point in the simulation it can be helpful to ask the class at large to self-correct any errors without providing instructor input.

Scenario 4: Exogenous Hormones

This scenario addresses the same learning objective as the previous scenario. If desired, the instructor could mention specific examples of therapeutic hormones, such as the anti-inflammatory use of cortisol or the contraceptive use of gonadal steroids.

Procedure

Explain that the next scenario illustrates how the hypothalamo-pituitary axes respond to therapeutic hormones (such as cortisol or anabolic steroids) or to endocrine tumors. For convenience, I often use the word “exogenous” (relating to external factors) to describe the tumor-produced or therapeutic hormone, and “endogenous” to describe the hormone produced by the healthy gland. Emphasize that exogenous hormone production is not regulated by the body, and that body cells cannot distinguish between the normally produced hormone and the tumor-produced or therapeutic hormone.

Ask the AP support group to choose the instrument producing the exogenous hormone and give the corresponding instrument to a volunteer in the audience. Explain that the simulation will begin as in the other scenarios, and that the new volunteer will begin making a lot of noise at a moment of their choosing. If desired, ask students to predict how the output of each instrument will have changed (increased, decreased, or unchanged) once the system has compensated for the perturbation, and write their predictions on the handout.

When the audience member starts making the noise, pause the simulation. Ask the class to vote on which component will respond to the new noises and how. For instance, exogenous target gland hormone will be sensed by the hypothalamus, which will reduce its output. Then, continue to work through multiple rounds of the simulation. The desired procedures are summarized in Table 4.

The most common error is that the actors do not respond to the exogenous hormone as they would the endogenous hormone. If so, ask students to repeat the simulation with their eyes closed, and, if necessary, remind students that receptors allow cells to hear signals. This variation should highlight that receptors cannot determine the source of the signal.

Instructor Debrief and Post-quiz

After the class has successfully performed the desired number of scenarios, I leave at least 5 minutes for student questions. The class then completes the post-quiz (see Supporting File S3. Musical Feedback – Assessment Questions), and we review the answers. I often use the musical instruments to illustrate the answers for questions 2-4.

TEACHING DISCUSSION

Implementation Notes

This activity has undergone considerable modifications over successive years. As mentioned in the Methods section, providing signs for the actors indicating their roles in large enough print for the entire class to read helps the spectators follow the simulation. It also reduces the anxiety for the actors, who otherwise tended to forget which gland they were representing. The activity also benefits from a 5-minute instructor debrief, and from repeating the simulation during the coverage of specific hypothalamic-pituitary axes. While I have only used this approach in a conference presentation (not in the classroom), the simulation can also be introduced in the context of a specific axis. This modification would involve adding the name of the target gland (e.g., thyroid gland) to the relevant sign and potentially adding the name of the hormones to each sign (e.g., thyrotropin releasing hormone, thyroid stimulating hormone, thyroxine).

Case studies involving endocrine diseases or the impact of therapeutic hormone administration can help students apply the basic principles learned in this activity to the different hormonal axes. While many case studies are available on the internet (see, for instance, https://www.wikidoc.org/index.php/Hashimoto%27s_thyroiditis_case_study_one), instructors can also develop their own. "Supporting File S1. Musical Feedback – Hormone Information" provides the normal ranges for each hormone and clinical indications of representative endocrine diseases for each axis.

While the use of support groups attenuates the riskiness of volunteerism, students can still be reluctant to participate (12). Instructors may have to overcome student bias that role-plays are childish by directing students towards academic articles documenting their effectiveness (13). It can also be helpful to frequently and explicitly address the relationship of the role-play to the physiological situation it is designed to represent. Instructors can encourage role-play participation by assuming more risky roles themselves, by performing role plays early in the semester alone, and/or by involving all students in a role-playing simulation early in the course (14,15). Optimizing the physical environment by ensuring clear sight lines for spectators is equally important.

As with any analogy, instructors should explicitly discuss the limitations of the role-playing exercise. For instance, while the simulation uses a single value (e.g., 2 noises) as the set point, students should be reminded that the set point is actually a range of values (e.g., between 2 and 4 noises). For clarity, the actors representing the separate glands usually act sequentially, so it is useful to run the simulation at least once with all instruments playing at once. Moreover, the analogy models long-loop feedback pathways between the target gland and the hypothalamus but does not address short- loop feedback between the target gland and the pituitary gland or the pituitary gland and the hypothalamus. Advanced students could be asked to develop and potentially enact protocols that more accurately portray the complexities of feedback pathways. For instance, receptor downregulation could be modelled by using earplugs. Short-loop feedback could be incorporated by asking the anterior pituitary gland to behave in a similar way as the hypothalamus, modifying their output if there is a discrepancy between the set point and the target gland output. It should also be noted that the effectiveness of an analogy does not necessarily reflect its goodness of fit (16). Asking students to identify flaws in the analogy can effectively reveal student misunderstandings and provide starting points for the instructor debriefing.

The use of target gland hormone levels as the regulated variable allows students to make accurate predictions and follows the approach of common textbooks (17,18) and clinical endocrinology articles (19). However, Michaels et al. (1) propose that the physiologic response (e.g., blood glucose in the case of cortisol, or basal metabolic rate in the case of thyroid hormones) is the regulated variable rather than the hormone level. If desired, the simulation could be modified to reflect this understanding by adding an additional instrument. However, this additional level of complexity decreases the utility of the simulation. Consider, for instance, the hypothalamo-pituitary-thyroid axis. Thyroid hormones bind specific receptors in the hypothalamus, which responds by reducing the output of the relevant releasing hormone (19). The resulting reduction in thyroid hormone output decreases basal metabolic rate. The model of homeostasis and negative feedback presented in the introduction can explain this observation if the thyroid hormone concentration is the regulated variable. At least three considerations muddy the situation if we use basal metabolic rate as the regulated variable: (1) The existence of a basal metabolic rate sensor is unclear, (2) thyroid hormones do not affect BMR in the brain and actually inhibit it in the anterior pituitary (20), and (3) the key role of thyroid hormones in utero and in childhood is the regulation of central nervous system development (21). Since the situation is similarly complex for the other target gland hormones, I have found that using their levels as the regulated variable provides an "approximation simple enough to be computable, but not so simple that you lose the useful detail" (22).

Figure 2B maps the regulation of target gland hormones onto a conventional feedback loop diagram (Figure 2A). Note that the alignment is not perfect; as mentioned above, it is unusual to have a hormone (signal) as a regulated variable, and the anterior pituitary also senses the level of the target gland hormone and could thus be considered a secondary sensor/control center. While I have not yet tried this extension activity with my students, advanced students could be asked to create their own Figure 2B and discuss the limitations of the model. It should also be noted that the existence of a set point for any variable (even body temperature) is not universally accepted (see, for instance, (23)). Nevertheless, this construct provides a useful framework for many regulatory systems, including those controlling core body temperature and blood calcium concentrations, and is still in common use in most physiology textbooks.

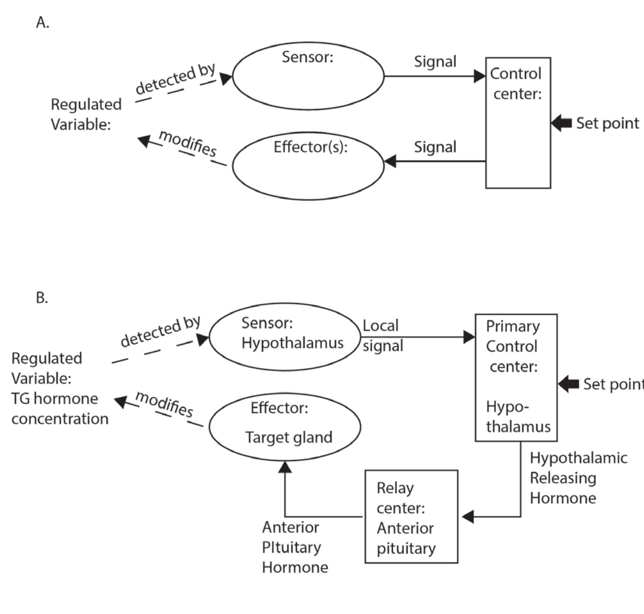

Figure 2. Negative feedback loops. A. In this prototypical negative feedback loop, sensors convey information about the level of a regulated variable to the control center, which compares the sensor input with the set point. If the level differs from the set point, the control center alters the activity of the effector in a way that returns the level of the regulated variable closer to the set point. B. If the target gland (TG) hormone is considered the regulated variable, the hypothalamus acts as the sensor and the control center. The hypothalamus alters the production of releasing hormone if the level differs from the set point, thereby altering the production of anterior pituitary hormone. The change in anterior pituitary hormone levels then modifies the activity of the target gland in a way that returns the level of the target gland hormone closer to the set point.

The music simulation is an effective analogy for the hypothalamo-pituitary-target gland axes because there is a single effector organ (the target gland) directly determining the level of the regulated variable. It would be difficult to use the analogy for other homeostatic systems, since the effector may alter the regulated variable indirectly and/or there may be multiple effectors. For instance, blood pressure regulation involves changes in the strength and frequency of heart muscle contractions as well as the diameter of blood vessels. In my experience, however, once students understand the relationship between set points, effector activity, and regulated variables in the context of the simulation, they can then transfer their conceptual understanding to other homeostatic systems.

Activity Evaluation

Classroom Observations

This activity has been used since 2013, and it consistently results in engaged students and lively discussions. There were always enough volunteers to repeat the simulation multiple times, and students asked to repeat the simulation in subsequent classes to help visualize changes in specific hypothalamo-pituitary axes. For instance, the simulation was used as described to distinguish between the different causes of hypercorticolism. It was also adapted to illustrate Graves disease, by inviting an audience member to produce the same sound as the anterior pituitary in an unregulated fashion to represent thyroid-activating autoantibodies.

Evidence of Student Learning

The 2015 student cohort completed a 4-question quiz before and after the simulation (Supporting File S3: Musical Feedback – Assessment Questions and Table 5). The percentage of correct answers was significantly higher for the post-test (mean = 87, SD = 13) than for the pre-test (mean = 64, SD = 13; paired t-test, $p = 0.015$). It should be noted that students were not given any feedback on the test questions until after the post-test. The final exam contained an alternate version of question 3 on the pretest. Forty-five out of forty-seven (96%) students selected the correct answer (final exam average: 62%).

Student Perceptions

I evaluated student perceptions of the case study activity using anonymous surveys in which they indicated their agreement with the statements "The activity helped me understand concepts in class" and "The activity was interesting and/or enjoyable" (with 1 indicating "Strongly disagree" and 5 indicating "Strongly agree") for each activity. For comparative purposes, students answered the same questions regarding peer instruction (24), which is well-validated in the literature. Students were also encouraged to provide written comments.

In 2013, a large majority of the students agreed or strongly agreed with the statements "The activity helped me understand concepts in class" (21/33) and "The activity was interesting and/or enjoyable." (25/33) (Figure 3). The activity engendered positive comments such as 'Best, really helped me understand how negative feedback worked." However, the effectiveness scores were significantly lower than those for peer instruction, and student comments mentioned that "students acting... were lost and could not keep up" and that "would help to have a background first." The activity was modified to more clearly indicate student roles using signs, and the pre-activity explanation was expanded somewhat. In 2015, the scores for peer instruction and the role-playing activity did not significantly differ, with 26 of 33 students agreeing or strongly agreeing with the effectiveness statement for the music activity. Positive comments included "This I believed was the most beneficial simulation we've had. It helped me really visualize it and answer it correctly (hopefully) on one midterm!" The only negative comment was that "There should be more discussion by the class about why."

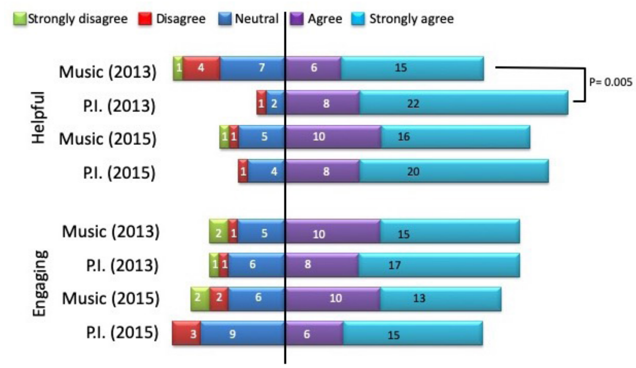

Figure 3. Student survey responses. For the music role-play and peer instruction (P.I.) activities in 2013 and 2015, students indicated how strongly they agreed with these two statements: (1) The activity helped me understand concepts discussed in class (helpful), (2) The activity was interesting/and or enjoyable (engaging). The numbers in each bar segment represent the number of students selecting each rating. The bar segments to the right of the vertical line indicate responses the met the goal (positive perceptions), while the bars to the right indicate responses that did not meet the goal (neutral or negative perceptions). Differences between the scores for the two activities were determined by Wilcoxon pairs test. Significant differences are indicated.

The project was approved by the Research Ethics Board of Bishop's University, File # R2014-08 and R2015-03.

SUPPORTING MATERIALS

- S1. Musical Feedback – Hormone Information
- S2. Musical Feedback – Student Handout
- S3. Musical Feedback – Assessment Questions

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Table 1. Activity Teaching Timeline.

Activity	Description	Estimated Time	Notes
Preparation for Class			
Prepare materials to hand out in class	1. Obtain or create three musical instruments that make distinct sounds. Scenario 4 requires two of each instrument. 2. Create signs for each role. I prepare signs on loose-leaf paper and use string to hang the signs around the student's neck. 3. Photocopy the Student Handout, if used.	5-10 minutes	The Student Handout is provided in Supporting File S2. Possible instruments include tin cans, sticks, drums, or bells.
Class Session			
Pre-test	If desired, administer a paper version of the pre-test or use clicker questions.	5 minutes	The assessment questions are provided in Supporting File S3.
Introduction	1. Explain the analogy. 2. Recruit three volunteers. 3. Organize the rest of the class into support groups. 4. Run through the role-play under normal conditions.	5-10 minutes	The article provides a detailed script.
Scenario 1: Setpoint change	1. The target gland (TG) support group chooses a new setpoint. 2. The class works through 3-4 rounds of the simulation.	5 minutes	See Table 2 for desired procedures.
Scenario 2: Transient disruption (Change in TG output)	1. The TG support group chooses between an increase and decrease in TG output. 2. The class works through 3-4 rounds of the simulation.	5 minutes	See Table 3 for desired procedures.
Scenario 3: Gland failure	1. The anterior pituitary (AP) support group selects the failing gland, which will stop producing noises. 2. The class works through 3-4 rounds of the simulation.	3 minutes	See Table 4 for desired procedures.
Scenario 4: Exogenous hormones	1. The AP support group selects one of the three hormones (instruments). A second copy of the chosen instrument is given to an audience member. 2. The simulation begins as in the other scenarios. 3. The audience member begins to produce noises at a high frequency at a random moment. 4. The class works through 3-4 additional rounds of the simulation.	3 minutes	See Table 5 for desired procedures.
Post-test and Debrief	1. Administer the post-test. 2.If desired, use the musical instruments (with or without student volunteers) to illustrate the answers to the questions.	10 min	The assessment questions are provided in Supporting File S3.

Table 2. Desired outcomes for Scenario 2.

Round	Increased TG output	Decreased TG output	Increased AP output	Decreased AP output
1 (normal)	2 H, 2 AP, 2 TG	2 H, 2 AP, 2 TG	2 H, 2 AP, 2 TG	2 H, 2 AP, 2 TG
2 (change)*	2 H, 2 AP, 3 TG	2 H, 2 AP, 1 TG	2 H, 3 AP, 3 TG	2 H, 1 AP, 1 TG
3 (response)	1 H, 1 AP, 2 TG	3 H, 3 AP, 2 TG	1 H, 2 AP, 2 TG	3 H, 2 AP, 2 TG
4 (compensation)	1 H, 1 AP, 2 TG	3 H, 3 AP, 2 TG	1 H, 2 AP, 2 TG	3 H, 2 AP, 2 TG

*Note that the system is already responding to perturbations at the pituitary level in round 2.

Table 3. Desired outcomes for Scenario 3.

Round	TG failure	AP failure	H failure
1 (normal)	2 H, 2 AP, 2 TG	2 H, 2 AP, 2 TG	2 H, 2 AP, 2 TG
2 (change)*	2 H, 2 AP, 0 TG	2 H, 0 AP, 0 TG	0 H, 0 AP, 0 TG
3 (response)	3 H, 3 AP, 0 TG	3 H, 0 AP, 0 TG	0 H, 0 AP, 0 TG
4 (compensation)	4 H, 4 AP, 0 TG	4 H, 0 AP, 0 TG	0 H, 0 AP, 0 TG

*Note that the system is already responding to perturbations at the hypothalamic or pituitary level in round 2.

Table 4. Desired outcomes for Scenario 4.

Round	Exogenous TG hormone (TGX)	Exogenous AP hormone (APX)	Exogenous H hormone (HX)*
1 (normal)	2 H, 2 AP, 2 TG	2 H, 2 AP, 2 TG	2 H, 2 AP, 2 TG
2 (change)*	2 H, 2 AP, 2 TG, many TGX	2 H, 2 AP, 2 TG, many APX	2 H, 2 AP, 2 TG, many HX
3 (response)	1 H, 1 AP, 1 TG, many TGX	1 H, 1 AP, many TG, many APX	1 H, many AP, many TG, many HX
4 (compensation)	0 H, 0 AP, 0 TG, many TGX	0 H, 0 AP, many TG, many APX	0 H, many AP, many TG, many HX

*The exogenous hormones in the final two columns can come from a tumor or can be therapeutically administered.

Table 5. Assessment questions results.

Question*	Correct Answer	Distractors	% correct (pre-test)	% correct (post-test)
1. A homeostatic control mechanism functions to maintain the concentration of X at a relatively constant level. When is the mechanism functioning?	At all concentrations of X.	When the concentration of X gets too high, too low, or either too high or low.	45	70
2. Hormone X, secreted from gland X, stimulates the production of hormone Y from gland Y. Hormone Y stimulates the production of hormone Z from gland Z. Imagine that gland Y suddenly increases its output. How will the activity of the other glands change, in order to restore homeostasis?	Decreased activity of gland X and Z.	Various combinations of increased and decreased output from gland X and gland Z.	70	85
3. The anterior pituitary secretes hormone R, the hypothalamus secretes hormone B and the target organ secretes hormone M. This system is regulated by negative feedback. If an individual has a target organ defect that significantly impairs hormone M production, which of these lab results would you expect?	Increased R and M, decreased B.	Various combinations of increased and decreased concentrations of the three hormones.	64	100
4. The anterior pituitary gland secretes GH, the hypothalamus secretes GHRH and the liver (target organ) secretes IGF-I. This system is regulated by negative feedback. Joanne is taking daily GH injections in an attempt to improve her marathon time. Which of these lab results are hers?	Increased GH and IGF-I, decreased GHRH.	Various combinations of increased and decreased concentrations of the three hormones.	76	94

*The post-test used slightly different questions for 2-4. See Supporting File S3. Musical Feedback – Assessment Questions for the list of questions.