IBMS1 Tutorial 2.7.2

FDG: Negative feedback and rhythms in the HPA axis

Wed 12.4.2017 13:00/14:00

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Aim

The aim of this tutorial is to explore the concepts of negative feedback and how it can affect pulsatile hormone release. Although we will use the stress (hypothalamic-pituitary-adrenal, or HPA) axis as an example in this tutorial, the same principles can be applied to the other hypothalamic-pituitary axes.

Learning outcomes

1. To describe the temporal relationships between the various hormones of the HPA axis

2. To describe how pulses of hormone release are generated by these interactions (especially negative feedback).

3. To outline how an acute stress can change the temporal relationship between different stress hormones.

Before the class

No specific preparation is required for this class, although thinking back of what we have discussed in lecture 2.7.2 about pulsatility and about feedback will be helpful.

In the class

Part 1

We will use a house heating system as an example of negative feedback. It may sound strange, but the basic principles that allow a heater to correctly heat your house are the same as those regulating hormone release!

You will be divided in two groups, and each group will be given a different set of "rules" through which the system works. You will have to work together to produce a (rough) graph of how the temperature in the house will change over time. It should take about 10 minutes to prepare the graph, and 5 minutes to discuss it.

Each group will then describe their results to the other group, and we will discuss and try to understand the differences between them.

Part 2

We will then use a computer model of the HPA axis to show how changing equivalent parameter in the biological system will produce similar results. This is a bit more complex because we will consider two outputs: the amount of ACTH and the amount of cortisol produced.

Do not worry about the exact functions of these hormones at this stage, we are interested in **basic principles** in this tutorial. Lecture 2.7.3 will outline the functions of ACTH and cortisol in more detail.

You will be able to change some of the parameters in the system and see the response.

Some points you may want to consider:

- What is the temporal relationship between the two hormones?
- What aspect of pulsatility is modified when the amount of CRH in the system increases too much? What if it is too low? (try decreasing it to 5 or increasing to 80)
- What happens if the adrenal gland takes too long to respond to ACTH? What if it is too fast? (after resetting CRH to 20, set the adrenal delay to 0.5 min, 20 min or 60 min)

Part 3

Finally, we will see what happens if we impose a stressor.

The model assumes a constant level of CRH input, we will simulate an acute stressor by giving a large CRH stimulus for a short time.

a) Let's start by giving a 30 min "stressor" at time 2.8h, when CORT is rising. What happens?

b) Now let's give a stressor of the same length at time 2.1h, when CORT is falling. What happens now? What is the difference?

c) What happens if you give a very long stressor (for example at 2h give a 600 min stressor, and increase simulation length to 10h to see long-term effects)?

Some points you may want to consider:

- The strength of the response to stress depends on the phase of CORT (that means if it's in the rising or the falling part of the pulse). Can you think of situations for which this may be important?
- What real-life situation is c) similar to?

TIP: when imposing a stressor, the model shows the "unstressed" output of CORT as a grey line. Use that to compare the "stressed" and "unstressed" profiles.

NOTE: the model is also available online at the following address:

https://nicolaromano.shinyapps.io/hpamodel/

Part 1 – Group 1

Rules for house heating system #1

1. Start temperature = **21°C**
2. Set-point = **25°C**
3. If the temperature goes **>1°C** below the set-point the heater will start
4. The heater increases temperature of **6°C** per minute
5. If the temperature goes **>1°C** above the set-point the heater will stop
6. When the heater is off, the temperature goes down **3°C** per minute

Draw a graph with time on the x-axis and temperature on the y-axis.

Calculate the temperature at 1 minute intervals, from 0 to 30 minutes

Example of how to proceed:

We start at 0 min, with a temperature of 21°C

We are >1°C below the set-point, so the heater starts, and in a minute it will heat 6°C

At 1 min the temperature will then be 27°C

We are now >1°C above the set-point…

Part 1 – Group 2

Rules for house heating system #2

1. Start temperature = **25°C**
2. Set-point = **30°C**
3. If the temperature goes >**2°C** below the set-point the heater will start
4. The heater increases temperature of **1°C** per minute
5. If the temperature goes >**2°C** above the set-point the heater will stop
6. When the heater is off, the temperature goes down **0.5°C** per minute

Draw a graph with time on the x-axis and temperature on the y-axis.

Calculate the temperature at 1 minute intervals, from 0 to 30 minutes

Example of how to proceed:

We start at 0 min, with a temperature of 25°C

We are >2°C below the set-point, so the heater starts, and in a minute it will heat 1°C

At 1 min the temperature will then be 26°C

We are still below the set-point, so we will continue to heat

At 2 min the temperature will be …