UCM – course SCI2009
2017-2018

Human physiology

PHYSIOLOGY

The Chinese version of the word Physiology consists of 3 characters.
From top to bottom they mean: life, logic, study.
In other words: The study of the logic of life.

Introduction

This Physiology course is intended to increase your understanding of the general homeostatic mechanisms that control our body. The course is constructed as such that you will be stimulated to perform both individual as well as collaborative work. Almost all cases in this booklet are set in their historical context and illustrate that 'learning by doing' is one of the major strategies for mankind.

Organization

Each week, two tutorial meetings are scheduled and one lecture. In each tutorial meeting, a task will be discussed using the approach of problem-based learning. In addition to the tasks, you will prepare a paper on a particular domain within the field of Physiology.

Evaluation

We will evaluate your individual progress throughout this course in three ways:

1) By a written exam consisting of both open questions and multiple choice questions at the end of the block period. Time required: 2 hours maximum (70% of final grade). The personal feedback on the result is possible on request.

2) By a paper (2000 words) on a physiological topic of your own choice. We will discuss your individual proposal during the second week of the block period. Some research will be needed to find the necessary and relevant literature. Help will be provided if necessary (30% of final grade).

3) Attendance and participation (Pass or Fail) (85% rule applies with additional assignment). Notification in case of absence is compulsory!!!

UCM Rules and Regulations apply to all parts of the course.
Resit-exam is provided to students who comply with UCM Rules and Regulations. The resit consists of a written exam.

I wish you success in finishing this course and hope you will enjoy this trip.

The coordinator, Andries Gilde (a.gilde@maastrichtuniversity.nl)

Course objectives

Human Cells and functions
Functional organization of the body
Membrane Physiology
Cardiac function and blood pressure control
Red blood cell function and gas transport and exchange
Pulmonary ventilation and regulation
Kidney function, intra-and extracellular compartments
Neuronal control
Hormonal control
Gastrointestinal Physiology

Resources:

Multiple sources via Online library **UB**
https://library.maastrichtuniversity.nl/collections/databases/medicine-health-life-sciences/

Such as:

Medical Physiology: The Big Picture, Jonathan D. Kibble, PhD, Colby R. Halsey, MD
https://accessmedicine.mhmedical.com/book.aspx?bookid=1291

Guyton and Hall Textbook of Medical Physiology, Thirteenth Edition
https://www.clinicalkey.com/#!/browse/book/3-s2.0-C20120065131

General Physiology

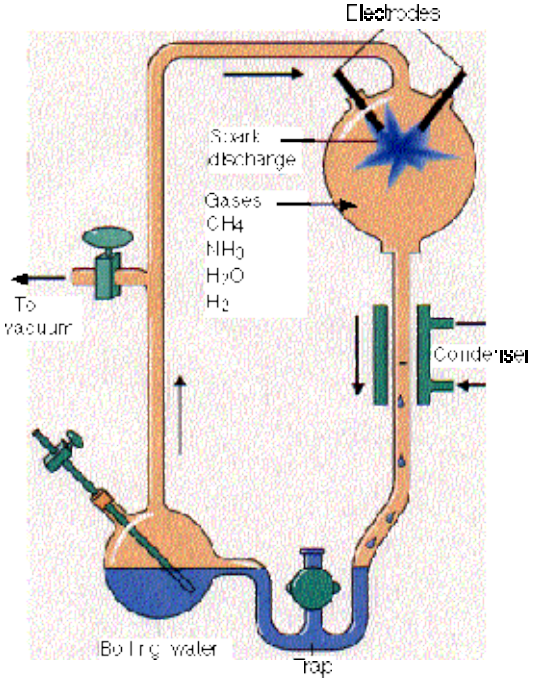
Task 1

Splendid isolation, role of the cell membrane

The human body is composed of billions of cells. The human brain, for instance, contains about 25 billion nerve cells only. Not only in quantity this represents an enormous structural complex, but also the variety of cell types and their function is impressive. We should try to imagine the human body to be a multi-cellular organism composed of colonies of individual cells that are very dependent of each other. A colony of unicellular organisms can be easily separated in two new colonies; both will continue their life undisturbed. This however is not the case in the human body.

But why has evolution led to a structure like the cell? And what identifies a cell as a cell? It has been shown that chemical reactions that normally occur within the cell can also take place in a very simple environment without the spatial limitation by membranes. So, why has evolution benefited the formation of cell membranes?

By closing up the cell with a cell membrane, it becomes isolated from its immediate environment. As such, the cell would be completely blind for the outer world, progressively accumulated waste products, and exhausted its own fuel stores. We know that this is not the case! How are essential substances taking up in the cells and how are waste products excreted? Is the cell able to communicate to other cells?



The Stanley Miller experiment:

Stanley Miller, a graduate student in biochemistry, built the apparatus shown in this picture. He filled it with

- Water
- Methane CH_4
- Ammonia NH_3
- Hydrogen H_2

But no oxygen

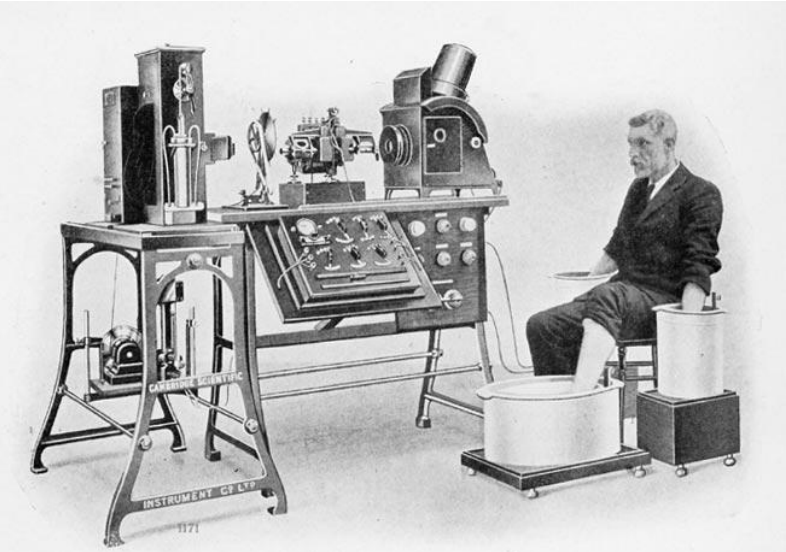
Stanley Miller Experiment (Youtube)

General Physiology

Task 2

Excitable cells

Some cells in our body are specialized in such a way, that they can generate electrical impulses. These impulses are used to activate cells and to transmit signals through tissues. The electrical impulses can even be measured on the outside of our bodies.



PHOTOGRAPH OF A COMPLETE ELECTROCARDIOGRAPH, SHOWING THE MANNER IN WHICH THE ELECTRODES ARE ATTACHED TO THE PATIENT, IN THIS CASE THE HANDS AND ONE FOOT BEING IMMERSED IN JARS OF SALT SOLUTION

Figure shows the first practical device to measure the electrocardiogram (ECG or EKG) invented by Willem Einthoven (1860 1927). He was a Dutch doctor and physiologist who received the Nobel Prize in Medicine in 1924 for his invention.

Thus, communication between cells can be based on electrical signalling. Nerve cells and muscle cells are examples of cells that use electrical impulses as a signal. Such a signal starts with a change in electrical charge across the membrane, or the so-called membrane potential. Electrical potentials exist across the membrane of almost all the cells in our body, however, only some cells are capable of rapidly changing their membrane potential. Such a rapid change is called the action potential.

- Try to imagine what could cause a membrane potential across the cell membrane.
- How can a sudden change in membrane potential arise?
- Can you think of the consequence of an action potential in nerve cells and in muscle cells?
- Will there be differences between skeletal muscle and heart muscle?

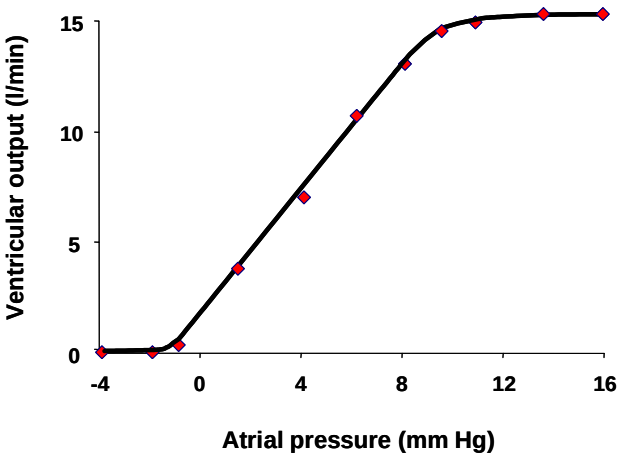
Cardiovascular Physiology

Task 3

Regulation of cardiac output

As all other organs the heart needs oxygen and substrates in order to perform contractile work. For this the heart is equipped with coronary arteries providing blood supply to its own tissue. It is now clear to us that the heart needs this supply in order to perform work. However, even at the end of the 19th century scientists believed that cardiac contractility could only be established when blood was flowing into the ventricles. In the 1890's Otto Langendorff (Germany) developed the hypothesis that the heart only needed perfusion into its coronary arteries in order to contract. In an extensive publication he described an experimental set-up in which he was able to proof his hypothesis. He showed that hearts remained contracting for up to 24 hours when only the coronary arteries were perfused while the heart chambers were artificially kept empty.

At the same time, Otto Frank (Germany, 1865-1944) described a fundamental characteristic of the contractility of the heart. He found that the peak pressure reached in the left heart chamber increased when the blood volume in the heart was raised. As this observation was done in isolated hearts of frogs, the direct meaning and implications for humans escaped the attention of clinical scientists. However, around 1910 Ernest Henry Starling (England, 1866-1927) described this phenomenon in another way. He and his colleagues stated that the cardiac output of the heart increased when the filling pressure in the chamber was enhanced. This was a crucial finding to understand the central role the heart plays in the general body homeostasis. Indeed, if we think in terms of demand and supply, then the heart reacts by increasing its output when the supply is increased. In turn this supply can be increased by forcing more blood to the heart through changing the diameter of the returning blood vessels (see figure).



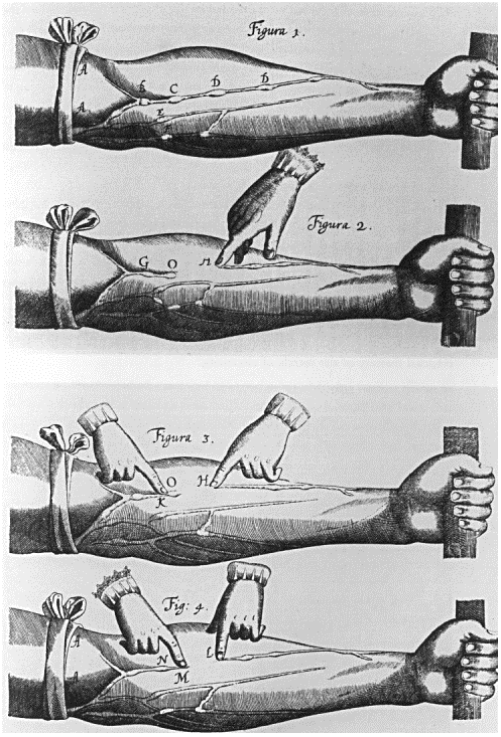
Cardiovascular Physiology

Task 4

Why does our heart pump?

In Claude Bernard's concept the heart is necessary to pump blood through our body so that all tissues can be provided with oxygen and substrates. Furthermore, the blood caries away carbon dioxide and waste products produced by the cell. Also fitting in his concept is that very active tissues should receive more blood, while others that are less active receive less.

In order to reach all the tissues the blood needs to be pressurized. Blood pressure can be measured. William Harvey (England, 1578-1657) studied Medicine in Cambridge, England and in Padua, Italy. He was fascinated by the way blood flows though the human body. Most people of the day believed that food was converted into blood by the liver and consecutively consumed as fuel by the body. In 1628 Harvey published 'An Anatomical Study of the Motion of the Heart and of the Blood in Animals' which explained how blood was pumped from the heart throughout the body, then returned to the heart and recirculated.



This illustration depicts one of William Harvey's experiments described in his manuscript:

On the Circulation of the Blood (1628).

Venal valves had already been discovered, but here Harvey shows that venal blood flows only toward the heart. He ligatured an arm to make obvious the veins and their valves, then pressed blood away from the heart and showed that the vein would remain empty because blocked by the valve.

Respiration Physiology

Task 5

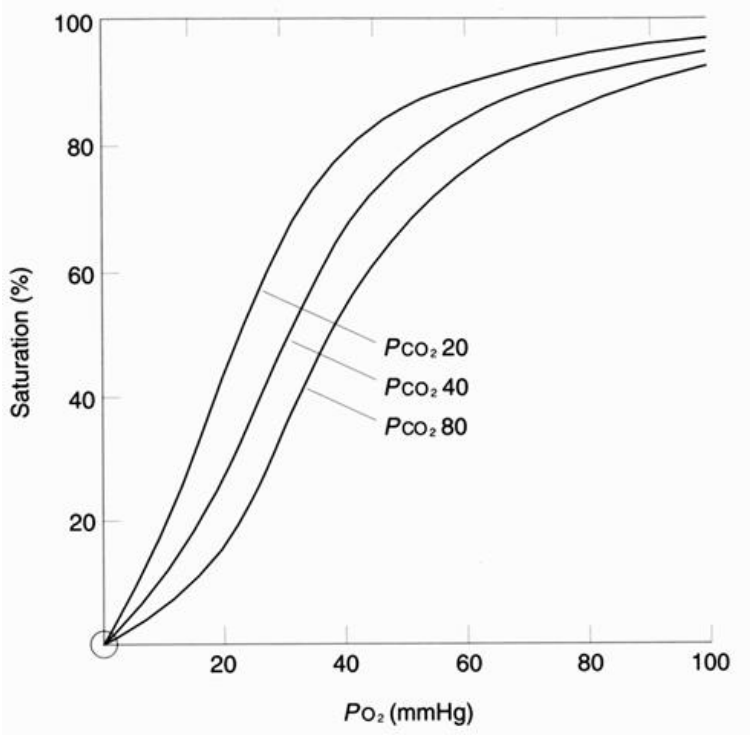
The Bohr family

We all probably know the famous atom scientist Niels Bohr (Danmark, 1885-1962) for his fundamental contribution to the understanding of the atomic structure. Less well known is that his father, Christian Bohr, was also a renowned scientist. Christian Bohr was a physiologist and professor of Physiology at the University of Copenhagen. He seemed to be a great source of inspiration for his son. His father inspired Niels also to work on a PhD thesis in his laboratory. After four years of study, Christian Bohr urged his son to write down his findings in his thesis and to provide him a draft. Christian read the thesis on a summer night in 1912 and died from a heart attack the following day.

Christian Bohr is known in the respiration physiology for the so-called 'Bohr effect'. This physiological principle is a key mechanism in the gas homeostasis in our body. In our body, gases like oxygen and carbon dioxide can be transported in different ways. Oxygen can be found physically dissolved, but the major part is transported, bound to haemoglobin in our red blood cells. Carbon dioxide transport is more complicated. The gas has also an affinity for haemoglobin, but can also be transported freely dissolved (bound to other proteins or not) or in the form of HCO_3^-.

Christian Bohr performed the following experiment: He took a solution of blood, in which several variables could be held constant. For instance, pH and temperature were held respectively at 7.4 and 37°C. Bohr was also able to control the partial pressure of CO_2 and held it at very low levels, as in open air. He then varied the partial pressure of O_2 above the solution and measured the change in colour of the haemoglobin. As we all know, the more oxygen is bound to haemoglobin, the redder this protein will turn. Finally Bohr was able to construct a diagram in which the haemoglobin oxygen saturation was plotted on the y-axis against the partial O_2 pressure level on the x-axis.

In the second part of his experiment, Christian Bohr performed the same experiment, but now he not only varied the partial O_2 pressure above the solution, but also that of CO_2. He found that the percentage of O_2 saturation decreased more pronounced upon lowering the partial O_2 pressure when the partial CO_2 pressure was higher than normal. This means that the new curve had shifted to the right compared to the original curve from the first experiment.



Three oxygen dissociation curves illustrating the Bohr effect.
Increased carbon dioxide in the blood causes a right-shift in the curves, such that the hemoglobin more easily unloads the oxygen it is carrying

What could Bohr conclude from this experiment?
And far more important, what could this mean for the homeostasis in the body?

Respiration Physiology

Task 6

Working on bridges

Several architectural art works have been built thanks to the use of caissons. The construction of the New York Brooklyn Bridge was started on January 2, 1870 with the sinking of two pine caissons (each 3000 tons) to a depth of about 30 meters below high water. The caissons were equipped with locked shafts for man and supply. The idea of a caisson is that it contains an open bottom that is put on the floor of a river or even the sea. Workers can freely move in these caissons because the constructions are pressurised from the surface with air under a pressure high enough to withhold water to enter the caisson from underneath. Such techniques have been used for the construction of the foundations of several architectural realizations, such as the Eiffeltower, the St. Louis Bridge, and the Antwerp quay-walls on the river Scheldt.

For the construction of the St. Louis Bridge a pressure of 4.5 atmospheres was needed to allow the men to work dry in the caissons. Out of the 600 men working in these caissons, 199 were affected by pain in the muscles and joints, deafness, embarrassed breathing, vomiting, paralysis, fainting and sometimes even death. In total 14 men died from these symptoms. This disease was called the ‘Caisson disease’ or 'compressed air illness'. Interestingly, the symptoms did not occur during the time the pressure on the workers bodies was raised or so long as it was continued, but only after it was removed.

What do we know about this disease? Caissons are not used anymore, and divers do the crucial interventions. These days we know that we have to act very rapidly when divers have complaints as mentioned above. They are immediately transferred to a so-called 'decompression chamber', in which the pressure is rapidly raised to levels as high as that where the divers worked under in the water. After reaching this level, the pressure is released very slowly, sometimes over a period of one day. Divers working on oil drill islands sometimes remain in decompression chambers for over a week. Can you come up with an understandable explanation for “Caisson disease”?

The Brooklyn Suspension Bridge at its opening ceremony in May 1883. Construction was started in 1870 with two caissons at the place where the towers had to be constructed.

Renal Physiology

Task 7

Living in the ' milieu intérieur'

Claude Bernard (France, 1813-1878) was the first to recognize the remarkable resemblance between the constituents and ion concentrations of plain seawater and those of the immediate environment of a cell. To describe the nature of this peri-cellular liquid, he introduced the concept of the ‘milieu intérieur’. He opposed this environment to that around our bodies, which he called – in analogy – the ‘milieu extérieur’. His remarkable theorem that an organism not really lives in the milieu extérieur but in the milieu intérieur was based on the observation that cells only can live, grow and perform their specialized function when the various characteristics of their immediate environment, such as pH, ion and gas concentrations, temperature, substrates are very constant.

Translated citation from C. Bernard (1878) ‘Leçons sur les phenomènes de la vie communs aux animaux et aux végétaux’. J.B. Ballière et Fils, Paris, France:

‘…….. The stability of the milieu intérieur is the primary condition for freedom and independence of existence…….’

and

‘ The necessary conditions for the life of the elements which must be brought together and kept up constantly in the milieu intérieur if freedom and independence of existence are to be maintained are already known to us: water, oxygen, heat, and reserve substances…….’.

To maintain the quality of the ‘milieu interieur’ (which is now mostly called the extracellular or interstitial fluid) in a relatively simple organism like a worm is not too difficult. In contrast, in humans several ingenious systems had to be developed to control the milieu intérieur in deep tissue layers. Almost all organs in the human body contribute to maintain the constant condition of the internal environment (homeostasis). What is the role of the kidneys in body fluid homeostasis? Which are the different compartments that contain our body fluids? What do you know about the composition of the body fluids?

Renal Physiology

Task 8

The kidney power

As we are organisms in equilibrium, our body needs a continuous supply of liquid and food, which is also regularly excreted. Under normal circumstances we drink about 2 litres of water per day. We loose this water via various ways: respiration, transpiration, and in faeces and urine. The balance between supply and loss is well regulated: various sensors continuously sense the volume state of our body, while other sensors control the concentrations of various products, like salts and sugars. If the supply is too low, the kidney will reduce the normal urine production. Otherwise, our kidneys will produce more urine when the supply of water is too high. The fact that both volume and salt concentrations have to be controlled complicates the kidney function.

Let us take an example to highlight the importance of the kidney. Some people produce 3 to 20 litres of urine per day. They also drink continuously. Question is what the real reason for this pathology is: is it that the person drinks too much, or is there something wrong in the kidney? If such people are deliberately held away from drinking, they will continue to produce high amounts of urine. Moreover, they will collapse very rapidly. This finding indicates that there must be something wrong within the kidney.

In the Greek and Roman world, physicians used the term ‘diabetes’ to refer to conditions in which the cardinal finding was a large urine volume. They distinguished two types: ‘diabetes mellitus’ in which the urine tasted sweet, and ‘diabetes insipidus’ in which the urine was tasteless.

Diabetes mellitus is characterised by polyuria (too much urine), polydipsia (high water intake), hyperglycemia (too high blood glucose concentrations) and glycosuria (glucose loss in urine). We now know that the disease ‘diabetes mellitus’ is caused by either insulin-deficiency (type 1 diabetes mellitus) or insulin-resistance (type 2 diabetes mellitus. Insulin is an important metabolic hormone that stimulates the glucose entry in cells.

But let us concentrate on the disease of diabetes insipidus. Since the urine is tasteless it is clear that too high glucose levels are not the cause of this excessive urine production. Scientists have found that the concentrations of ions in the urine of these patients were never higher than those found in blood. This triggered some of them to think that these patients were unable to concentrate their urine. Therefore, they infused the ‘anti-diuretic hormone’ (ADH) in these patients. Some of them reacted positively; i.e. they immediately reduced the amount of urine. Besides, the concentrations of ions in the urine increased.

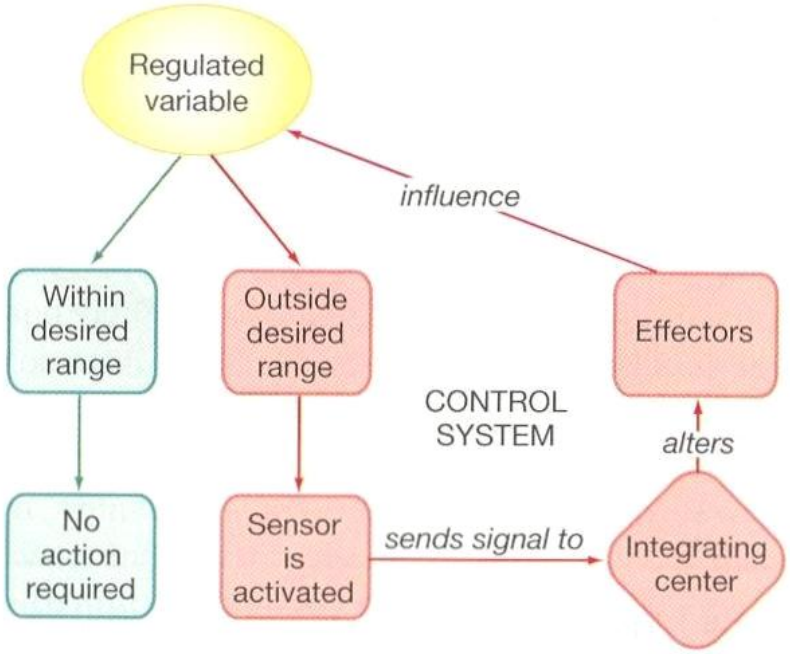
However, there were also patients that did not react upon ADH infusion. They remained producing high amounts of ‘diluted urine’. To differentiate between the two types of patients, the first class was called ‘central diabetes insipidus’, while the second class was called ‘nephrogenic diabetes insipidus’.

Autonomic nervous system

Task 9

Fast control of visceral functions

A special portion of our nervous system controls the functioning of the major organ systems in our body to maintain homeostasis. This portion of the nervous system is called the autonomic nervous system. The following figure shows a general scheme by which control of a regulated variable can occur. In this scheme, the autonomic nervous system is the integrating center.



Regulated variables might be:

- Body temperature
- Blood pressure
- Blood volume
- Blood osmolarity
- Concentration of specific molecules
- pH
- Etc.

The autonomic nervous system can be influenced by other parts of our nervous system. Try to imagine what happens if you are scared and you literally feel your heart ‘beat in your throat.

Endocrine Physiology

Task 10

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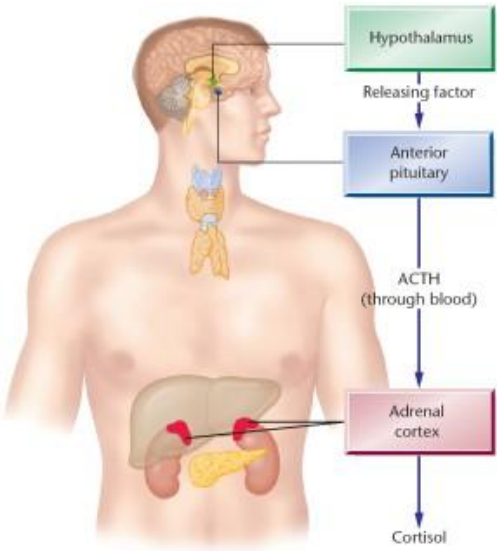
Stress, a human disease?

The brain in response to real or imagined stimuli creates biological stress. The many physiological responses associated with stress help protect the body and the brain from the dangers that triggered the stress in the first place. But stress in chronic doses can have serious harmful effects as well. Neuroscientists have only begun to sort out the relationship between stress, the brain, and brain damage.

Stress leads to the release of the steroid hormone cortisol from the adrenal cortex. Cortisol travels to the brain through the bloodstream and binds to (intracellular) receptors in the cytoplasm of many neurones. The activated receptors travel to the cell nucleus, where they stimulate gene transcription and ultimately protein synthesis. Steve Kerr and colleagues (1) have found that cortisol - among others - increases the influx of calcium into the neuronal cells. Presumable, this makes the brain better able to cope with the stress, perhaps by helping it figure out a way to avoid it!



But what about the effects of chronic, unavoidable stress? We know that too much calcium in a cell can be a bad thing. If neurones become overloaded with calcium, they die. The question arises: can cortisol kill? McEwen and colleagues at Rockefeller University, and Sapolski at Stanford University have investigated this question in the brain of the rat. They found that daily injections of rat cortisol for several weeks caused

dendrites to wither or many neurones with cortisol receptors. A few weeks later, these cells started to die. Sapolski's studies on baboons in Kenya further revealed the scourges of chronic stress. Baboons in the wild maintain a complex social hierarchy, and subordinate males stay away from dominant males if they can. During one year when the baboon population boomed, local villagers caged many of the animals to prevent them from destroying their crops. Unable to escape the caged 'top baboons', many subordinate baboons subsequently died – not from wounds or malnutrition, but apparently from severe and sustained stress-induced effects. They had gastric ulcers, colitis, enlarged adrenal glands, and extensive degeneration of hippocampal neurones. These effects of cortisol and stress resemble the effects of aging of the brain. Indeed, research has clearly shown that chronic stress causes premature aging of the brain.

It is not yet clear how the animal studies relate to humans, but we can consider them as a caution. Modern life leads to tremendous, sustained stress for many people. Some athletes recklessly, and illegally, take large doses of various steroids for long periods in an effort to bulk-up their bodies. Do these damage the brain? More research is needed to establish whether stress and steroids themselves can harm our brain, or if they facilitate the harmful effects of other disease processes. But in the mean time, it can't hurt to take it easy.

Excerpt from: Bear, Connors, and Paradiso (Eds): Neuroscience. Exploring the brain (1996). Ch. 15: Chemical control of brain and behavior, Williams and Wilkins. p.412

1. Kerr DS, Campbell LW, Applegate MD, Brodish A, Landsfield PW (1991) Chronic stress-induced acceleration of electrophysiological and morphometric biomarkers of hippocampal aging. Journal of Neuroscience 11: 1316-1324
2. McEwen BS, Schmeck HM (1994) The hostage brain. New York: Rockefeller University Press
3. Sapolski RM, Krey LC, McEwen BS (1986) The neuroendocrinology of aging: the glucocorticoid cascade hypothesis. Endocrine Reviews 7: 284-301

Gastrointestinal Physiology

Task 11

Diarrhea

A young Dutch man (age 23) returns very ill from his backpack vacation in India. He has extreme diarrhea and is taking up in a hospital, with severe dehydration. Research shows that his diarrhea is caused by the bacterium Vibrio cholerae.

The man that is mostly recognized to have discovered this bacterium is the German physician Robert Koch (1843 – 1910). He became famous for the discovery of the anthrax bacillus (1877), the tuberculosis bacillus (1882) and also the Vibrio cholerae bacterium (1883). In addition he is well-known for the so-called Koch's postulates. He was awarded the Nobel Prize in Physiology or Medicine for his tuberculosis findings in 1905.

Actually, it was the Italian anatomist Filippo Pacini who first discovered the Vibrio cholera bacterium already in 1854. His findings were ignored because the general believe at that time was that diseases such as cholera or the Black Death were caused by a miasma (Greek language: "pollution"), a noxious form of "bad air".

This picture shows a microscope slide prepared by Pacini in 1854 containing the Vibro cholerae bacteria which proved that he was the first to discover this bacterium

Could you try to imagine what happened in the digestive tract of the Dutch “Backpacker”? Do you know other causes of diarrhea?