17 | June 2018

MICE TIMES

The rhythm of life – Nobel Prize in Medicine for the inner clock

Day and night, summer and winter, ebb and flow – it's an eternal coming and going and, in the rhythm of nature, all creatures on this planet move in synchrony. The basis for this "synchrony", for the alternating rest and activity of the living world, is formed by molecular clocks that probably reside within each and every cell on this Earth. For their research into these tiniest of timepieces, three US American researchers were awarded the Nobel Prize in Medicine last autumn[1].

Jeffrey Hall, Michael Rosbash (both from Brandeis University in Waltham, Massachusetts) and Michael Young from the Rockefeller University in New York City tracked down the ticking of this biological clock around the mid-1980s with the aid of the common fruit fly (Drosophila melanogaster). The researchers first isolated a gene in the fly that controls the circadian biorhythm. The product of this gene, the protein PER, accumulates overnight in cells and is degraded during the day[2].

On the basis of these experiments, more and more individual parts of the clock were discovered. A fascinating mechanism came to light whose funda-

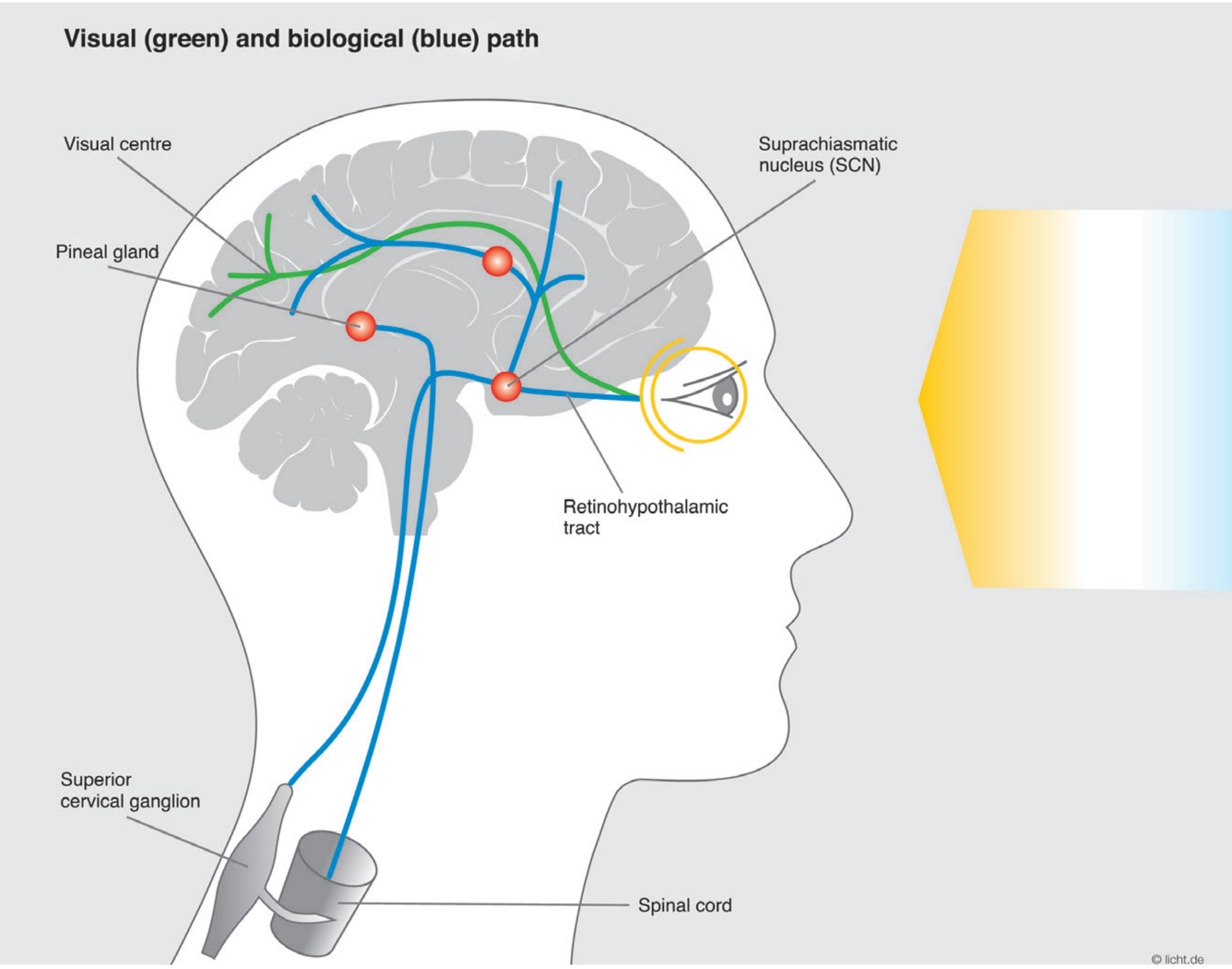

Figure 1: Photoreception via the suprachiasmatic nucleus (SCN) Source: www.licht.de

mental components operate identically – whether in plants, fungi, animals or humans – and essentially determine life. "There is no part of our highly complex body in which the inner clock does not play a role," says Till Roenneberg, chronobiologist from the Institute of Medical Psychology at the Ludwig Maximilian University in Munich[3].

Since the end of the 1990s, our understanding of the components which make up the inner clock in mammals has steadily improved, leading to huge progress in the field of chronobiology. It is becoming ever clearer just how much the inner clock influences human and animal behaviour, all physiological processes, and also the development of diseases and responses to treatment[4]. When the researchers started their work on the fruit fly, they never imagined what "a beautiful mechanism would emerge," as Nobel laureate Michael Young put it[5].

Tiny, completely autonomous inner clocks reside in every cell of the body. But these are synchronized and coordinated by a central pacemaker in the brain. This is located in the hypothalamus, directly above the optic nerve. This conductor, also known as the suprachiasmatic nucleus (SCN), is made up of around 100,000 neurons and occupies less than a millimetre of space (Figure 1).

Certainty as to the importance of the central clock in the brain was originally obtained from experiments with hamsters. In 1990, researchers from the University of Virginia succeeded in transferring the circadian rhythm specific to a group of hamsters (20 hours instead of 24 hours) to animals with a normal biorhythm by transplanting the SCN[6].

If a human lived without any external stimuli whatsoever, for example in permanent darkness, a day for that person would last not 24 hours, but 24.3 hours. To remain in synchrony with the actual length of the day, therefore, the inner clock would have to be adjusted slightly. This fine tuning takes place through light signals, amongst other things, which are captured not only by photoreceptors but also by light-sensitive neurons on or behind the retina.

"We on this planet are slaves of the sun," says Paul Nurse, director of the Francis Crick Institute in London[7]. It always becomes problematic when external circumstances, the day and night rhythm, change either suddenly (e.g. on a long-distance trip) or repeatedly (e.g. in people who work alternating shifts). In such cases, a synchronization of the inner clock with external time is difficult if not impossible, and jet lag or chronic disorders can occur as a result.

Inner clock and cancer

It is known from experiments in rodents that chronic jet lag accelerates the growth of tumour cells. However, in an experiment involving mice with pancreatic cancer, the restoration of a daily routine that brought the inner and external rhythm into line through regular feeding led to a reduction of tumour growth in these animals by about 40 %[8].

Nurses who have worked shifts involving night duty for 15 years or more have a 28 % higher risk of lung cancer than women who do not have to work nights. This was observed by Eva Schernhammer and other researchers from Harvard Medical School in an epidemiological study that gathered data from 78,612 women. But the increased risk for lung cancer was only seen in nurses who smoked. In non-smokers who work night shifts, the prevalence of lung cancer is no higher than in non-smokers who have regular sleeping times[9].

There is no question that smoking is the main risk factor for lung cancer, but the observations from the Nurses' Health Study suggest that shift work acts as a "second hit", providing an added boost to tumour growth. Clues to the underlying mechanism are offered by studies in mice. Aryl hydrocarbon (AhR) receptors boost production of detoxifying enzymes, and studies in mice show that the number of AhR receptors on lung tissue cells fluctuate depending on the time of day. It is therefore possible that there are times of day in both mouse and human when the body is more sensitive to the toxic substances in cigarette smoke[10].

Knowledge of the differing ability to cope with toxic substance according to the time of day could also alter cancer therapy. Initial studies have been performed to administer chemotherapy taking into consideration the rhythmic activities of the body. In studies on animal models, for example, it had become clear that chemotherapeutic agents are better tolerated and more effective when account is taken of differences in the bioavailability of the medicine, the detoxifying functions of the body and the cell cycle/cell division activities of the tumour cells and healthy cells of the body. In the study, therapy that was attuned to the biorhythm for the classical variant of colon cancer proved superior, at least in male patients[11].

Inner clock and nutrition

“Breakfast like an emperor, lunch like a king and dine like a pauper”. In one respect at least, this advice by Jewish philosopher Maimonides (1135-1204) would meet with the approval of today’s nutrition scientists, whose work is focused on chronobiology: namely, that it is not a question of what and how much you eat, but when you eat. Mice fed a high-fat diet, for example, are protected against overweight, fatty liver and elevated inflammation values when the food intake is restricted to eight hours a day. But if the mice have constant access to the feeding bowl, they get fat on the same calorie intake[12].

In another experiment, mice that were fed at the beginning and end of their active phase showed much better blood values than conspecifics that were fed the same quantity of calories in a single meal during the day[13]. These studies cannot be extrapolated 1 to 1 to humans for various reasons: rodents are nocturnally active, for example, unlike humans. But they definitely provide an indication of what to focus on in the healthy nutrition of humans.

Inner clock and vaccination

Body temperature, blood pressure, release of hormones and renal activity – they all follow the inner clock (Figure 2). It is known from studies in mice that the activity of the immune system is determined by the circadian rhythm. A group of alarm bells in the congenital immune defence system, for example, can be found in particular on somatic cells and can trigger defensive reactions when animals are at their most active[14]. Certain immunological messenger substances, such as tumour necrosis factor, are released towards the end of the night in humans. In patients with rheumatic diseases, this manifests itself in joint pain and stiffness, especially in the morning. In the treatment of rheumatoid arthritis, good results have already been achieved with a specially developed tablet that is taken in the evening, but does not release its active ingredient until around 2 in the morning. Patients had fewer symptoms, even at low concentrations of the active substance used[15].

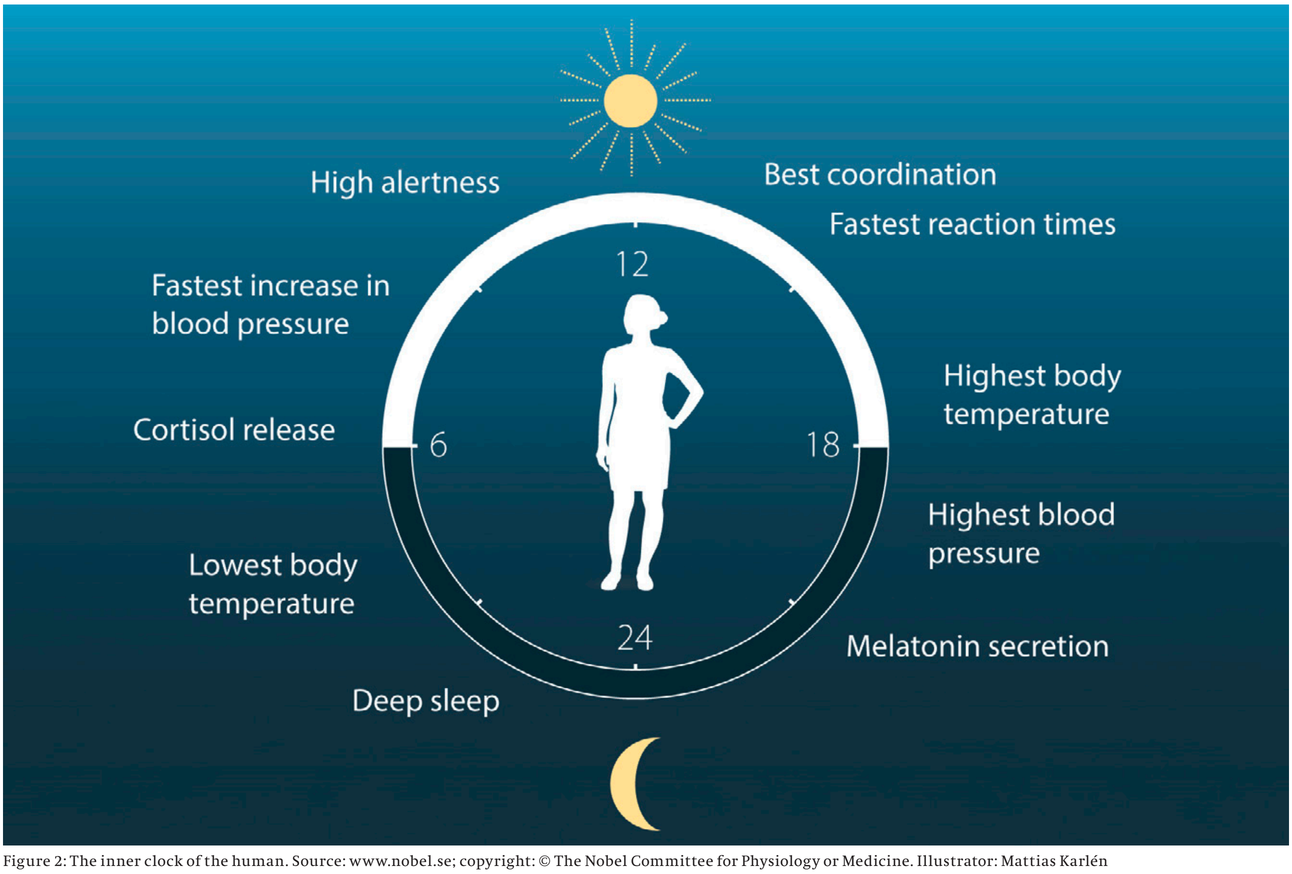

Figure 2: The inner clock of the human. Source: www.nobel.se; copyright: © The Nobel Committee for Physiology or Medicine. Illustrator: Mattias Karlén

In a clinical trial at the University of Birmingham with 276 older adults (65+) influenza vaccinations administered in the morning elicited a more marked antibody response than afternoon vaccinations[16]. The authors of the UK study therefore suggest that, especially in older subjects, the results of vaccination could be enhanced by means of a simple manipulation in the timing of the vaccination.

The hope of chronobiologists like Till Roenneberg from Munich is that the Nobel Prize for the inner clock will raise awareness of the issue. Society and decision makers are challenged to bring about change. "Medical practice, diagnostics and treatment should be attuned to the individual's inner timepiece and not to the clock on the church tower," says Roenneberg. The first steps have been taken, modest though they are. Of the clinical trials registered in 2016, only 348 worldwide (or 0.16 % of all registered clinical trials) were concerned with a treatment to be adjusted to the biorhythm of the patient[17].

1 http://www.sciencemag.org/news/2017/10/timing-everything-us-trio-earns-nobel-work-body-s-biological-clock

2 https://www.nobelprize.org/nobel_prizes/medicine/laureates/2017/

3 http://www.zeit.de/2017/41/innere-uhr-nobelpreis-medizin-faulheit-muedigkeit

4 https://smw.ch/article/doi/smw.2014.13984

5 https://www.nytimes.com/2017/10/02/health/nobel-prize-medicine.html

6 https://www.ncbi.nlm.nih.gov/pubmed/2305266

7 https://www.theguardian.com/science/2017/oct/02/nobel-prize-for-medicine-awarded-for-insights-into-internal-biological-clock

8 http://cancerres.aacrjournals.org/content/70/8/3351.long

9 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3813313/

10 https://www.ncbi.nlm.nih.gov/pubmed/?term=aryl+hydrocarbon+ohdo+kusunose

11 https://academic.oup.com/annonc/article/23/12/3110/175871

12 https://www.ncbi.nlm.nih.gov/pubmed/22608008

13 https://www.ncbi.nlm.nih.gov/pubmed/?term=differential+bigger+tahara+lipid

14 https://www.ncbi.nlm.nih.gov/pubmed/?term=circadian+clock+toll-like+fikring

15 http://ard.bmj.com/content/72/2/204.long

16 https://www.sciencedirect.com/science/article/pii/S0264410X16301736

17 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5082589/

It would be ideal if we could understand the complex mechanisms in living organisms without animal experiments. Unfortunately this is not possible yet. The dilemma will remain for quite some time: basic research without animal experiments would mean abandoning medical progress. «Mice times» reports on success stories in medical research that were only possible due to animal experiments.

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