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An inbuilt timekeeper

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We have been doing the same thing for almost thirty years now. Clocks are put forward one hour in the Spring and then back an hour in the Autumn. Daylight saving time was introduced as a means of saving electricity but, for a variety of reasons, this practise has now become a subject of controversy. In particular, this slight – and apparently harmless – shift in time is not without effect on our organism which needs several days to adjust to a new rhythm. Why? Because sleeping or eating are activities which are ruled by an internal clock – our biological rhythm – the complex workings of which are regulated by numerous proteins.

Summertime

In Switzerland, daylight saving time was made official in 1981. The concept goes back to the 18th c. when, in 1784, Benjamin Franklin (1706–1790) – an American famed for his invention of the lightening conductor – put forward the possibility of saving energy by synchronizing our timetables with the sun. The idea was not forgotten and was adopted in the beginning of the 20th c. in Germany and then spread to the rest of the European Union early in the 1980s. In an attempt to unify all European timetables, Switzerland had to comply in spite of an unfavourable vote in 1978. Since 1996, the change of hour for daylight saving time in Europe occurs on the last Sunday in March for the Summer, and on the last Sunday in October for the Winter.

You may think that a shift of one hour in a day is of little consequence and, for a long time, this was the general belief. However, children and elderly people are sensitive to the change and can develop sleeping disorders for a while after the changeover. In order to evaluate the effects such a time change can have on our organism, the European Union has just launched a vast study. Researchers have already come to the conclusion that putting clocks forward for daylight saving time is a far more delicate operation than putting them back in the Autumn. In particular, it disturbs the rhythm of "late nighters" who tend to retire to bed even later than usual in the Summer although their social and professional obligations don't permit them to make up for the lost sleep the next morning.

The "tick-tock" of our organism

Our day follows a rigorous beat. We wake with the daylight, rise and get ready for the day. Then we go about our daily business, pausing for meals at regular intervals. At the end of the day, we retire to our beds and fall asleep. And the following morning is the beginning of a new day. In between time, 24 hours have just slipped by. This is no coincidence. Twenty-four hours marks the time it takes the Earth to rotate 360° around its axis. So it is the alternation of night and day which results from the earth's rotation, that synchronizes the pattern of our sleeping and waking hours.

The sequence of light and darkness has undoubtedly played a crucial role in the evolution of all forms of life, from the simplest of organisms to more complex ones such as human beings. Environment is paramount for the survival of species. Plants need daylight to generate energy whereas animals adapt their quest for food depending on its availability during daytime. A few centuries ago, it was thought that this circadian behaviour – from the Latin circa diem meaning 'about one day' – was dictated by some external electromagnetic force. The likelihood of internal dynamics was broached much later, in 1729, by Jean-Jacques d'Ortous de Mairan, a French astronomer. He noted that the leaves of a mimosa tree he was keeping in his cellar – and hence deprived of light – folded and unfolded every day. He concluded that living beings, or at least plants, have an internal clock which does not depend on the sun yet works on an approximate 24 hour cycle.

What about human beings? Do they also have an internal tick? A number of volunteers agreed to be subjected to experiments termed 'timeless'. One of them, the speleologist Michel Siffre, spent a few weeks and then a few months in the depths of a cave without light, without sound and with no indication of the time. Thanks to the information transmitted to scientists –such as mealtimes or sleeping periods –a remarkable observation was made: the sleeping/waking rhythms of isolated people gradually move out of sync with the day/night cycle. It is hardly a surprise. Indeed, our interior metronome spontaneously beats to a cycle of something between 24.2 and 25.5 hours and not the 24 hour cycle, as we had always believed. This apparently insignificant difference means that a rhythm of 24 hours and 30 minutes would propel the daily activities of an individual into nocturnal activities inn the space of only 3 weeks!

Ups and downs

In 24 hours, our organism carries out many tasks which are beyond our control. It governs our temperature, stimulates hunger and regulates our digestion. The function of our internal clock – or biological clock – is to synchronize our body's major physiological processes with the different times of the day. Indeed, body temperature, hormone release, sleep, metabolism, cardiovascular activity and intestinal transit all undergo fluctuations in the course of one day (fig.1).

As an example, our body temperature is at its lowest – about 36°C – when we sleep, during the night. And for those of you who like your afternoon nap, your temperature also goes down – though to a lesser extent – which may account for the physical and mental drowsiness some of us feel at that time of day.

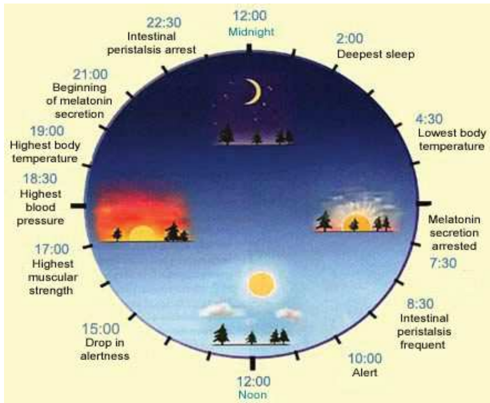

Fig.1 *Fluctuations of our biological functions in the course of a day.*

Even more amazing is the ebb and flow of the levels of certain hormones in the blood. This is the case for melatonin and growth hormone. Melatonin is often referred to as the sleep-inducing hormone because it is secreted while we sleep. Synthesized in a small cerebral structure – the pineal gland – melatonin is released into our blood stream at dusk and disappears at dawn when our organism gets under way again. Growth hormone is essential for the growth of bones and muscles in children; in adults, its role is mainly a healing one. Surprisingly, growth hormone is only secreted in the early hours of the night when sleep is deep.

A symphony of clocks

How can our biological clock be so precise? Scientists have found that there is not only one clock but hundreds ticking away in our bodies. In fact our biological clock resides in each of our cells which beat in unison. In the same way as musicians are guided by the conductor, cells take the tempo from two minuscule cerebral structures: the suprachiasmatic (NSC) nuclei. These nuclei are located in the lower part of the hypothalamus, above the two optical nerves where they cross. The zone is known as the optical chiasma, from which the nuclei get their name (fig.2).

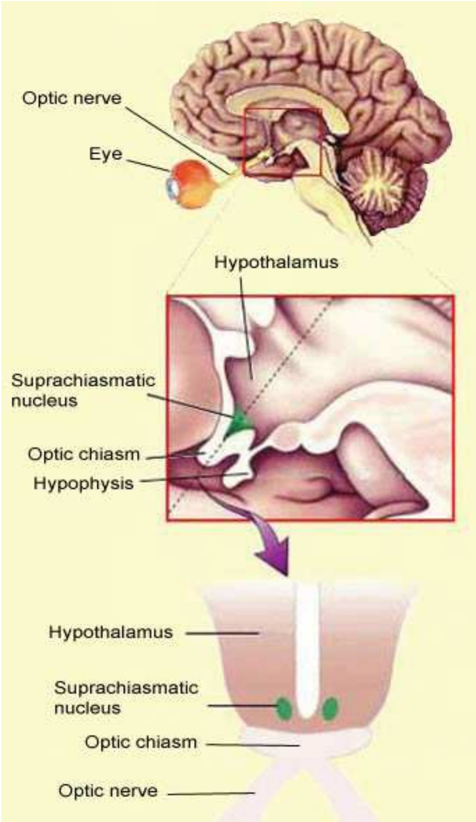

Fig.2 *The suprachiasmatic nuclei are the biological clock's conductor.*

Day after day, the NSC or the central biological clock, keeps remarkable time. But no clock is perfect and the NSC have to be readjusted daily to keep the high level precision. How? The clocks consist of neurons which re-synchronize their activity by way of the retina which continuously informs them of the ambient luminosity. Hence our biological clock goes round the clock, so to speak, in 24 hours, and not in 25 as would be dictated by its natural rhythm.

24 hours in the life of a cell

What are the molecular mechanisms that motivate our biological clock? The answer is far from simple. Its works are made up of a complex network of interrelating proteins. The first proteins to be identified were found in flies in 1970. In humans, similar proteins were isolated from the neurons of the suprachiasmatic nuclei in the late 1990s. Once the mechanisms had been understood, significant variations were found between different species. However, in all species, the biological clock seemed to be regulated by a loop system, termed the negative retro control loop. This particular loop allows the fine-tuning of cellular activity whereby proteins control their own activity by slowing down their own synthesis.

The loop starts in the cell's nucleus, prompted by a protein known as the Clock protein (fig.3). Clock protein acts as an on/off switch. By rearranging the structure of DNA, in particular by modifying the histones – which are proteins that associate with DNA - Clock protein enables certain genes which are involved in biological rhythms to be read. To do this, Clock protein binds to another protein, bmal1, which it modifies as well. Together the two proteins "activate" various other genes amongst which those that hold the recipe for two key families of proteins: the per proteins (per1, per2 and per3) and the cry proteins (cry1 and cry2).

Synthesized outside the nucleus, the per and cry proteins assemble by way of their PAS domains. Thus stabilized, they return to the nucleus where their role is to interact with the clock protein and its partner which they neutralize. As a result, the decoding of the per and cry genes is immediately inhibited. In short, the per and cry proteins inhibit their own synthesis; this is termed a negative retro control loop. Then, progressively and like any other protein, the per/cry couples are degraded with the difference that they will never be replaced. In the long run, their numbers become so few that they lose the ability to block clock and bmal1 altogether. Consequently, the inhibition to produce per and cry is lifted and their production is resumed. A new loop begins. Characteristically, the whole process takes about 24 hours. Which is all the more amazing when you consider that loops of this type are usually completed in one minute, if not a split second.

Time variations

Protein "pulses" inside the suprachiasmatic nuclei beat the time for our whole organism. How does this central clock synchronize all the other clocks found in the peripheral organs? Very little is known on this subject. What we do know, however, is that synchronization is done rapidly via the nervous pathway, and more slowly via hormones. Is this enough to explain the effects of jetlag for instance? Yes, partly. Since the central clock is guided by light, it will respond fairly quickly to the time of day in the new time zone. However, the signals it transmits reaches the peripheral clocks with a delay. This difference in phase could account for the characteristic sleeping and digestive disorders. But it only takes a few days before all the clocks are synchronized again and the symptoms vanish.

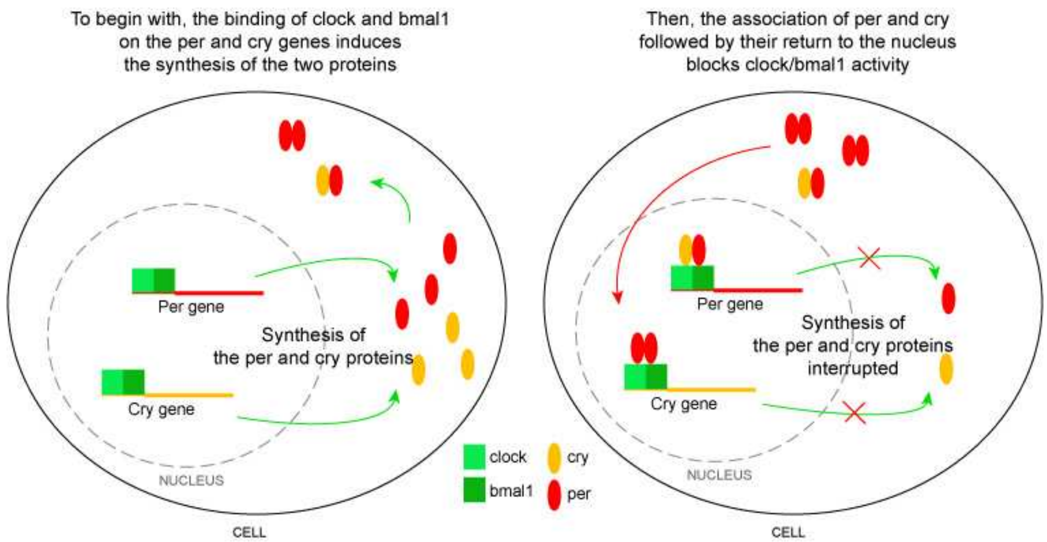

Fig.3 *The molecular mechanism of the biological clock.*

Intercontinental flights are not solely responsible for sleeping disorders. A number of very rare molecular dysfunctions in the internal clock can disrupt the sleeping rhythm in such a way that the whole day/night cycle is completely perturbed – which has its consequences from a social point of view. "Familial advanced sleep phase syndrome" is caused by a mutation in the per2 gene. People afflicted with this syndrome are dead tired around 7 p.m. and then wide awake at 4 a.m. "Delayed sleep phase syndrome" is caused by a mutation in the per3 gene and causes an illness which predisposes to the opposite symptoms. Patients with this affliction are unable to wake in the mornings at the usual time since they only fall asleep between 6 a.m. and midday.

Cancer specialists are very attentive to the mechanisms of our internal clock. In our modern society, the treatment of cancer is a matter of great concern. One of the many difficulties is to choose the right moment for the administration of anti-cancer treatments. Indeed, their effectiveness coupled with their toxicity towards healthy cells varies according to the time of day. Some are more effective in the morning, whilst others are better tolerated in the evening. And the degree of malignancy of cells also has an effect on the biological clock. As an example, it has been noted that in some types of cancer the malignant cells do not proliferate at the same time of day as the healthy ones. Since the object of chemotherapy is to stop the proliferation of cancerous cells, this new understanding can help determine the moment when medication is both most effective but also the least harmful to the rest of the organism.

The list of processes which are influenced by the state of our biological clock is long. It can affect our ability to memorize, our mental health – manic depression has been associated with a mutation in the clock protein – and our humour which can sometimes fluctuate drastically with the changing of the seasons. And old-age? Our biological clock sets the rhythm of everyday life. What if we could set it? So that our rhythm is speeded up or slowed down? Would it have an effect on life expectancy? Some researchers have already tried to "shorten" time by making small rodents believe that there are only five months in a year as opposed to twelve. Much to their amazement, the animals aged prematurely! The obvious question is then: is it possible to reverse the experiment? Perhaps. Checking the ageing process by slowing down the biological clock's tempo could be one of the secrets of eternal youth which humanity has never ceased to flirt with.

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For further information

On the Internet:

- About the circadian clock (in French) : http://lecerveau.mcgill.ca/flash/d/d_11/d_11_m/d_11_m_hor/d_11_m_hor.html
- An other website (in French) : http://savoirs.essonne.fr/dossiers/la-vie/medecine-sante/article/type/0/intro/cette-horloge-qui-rythme-l-organisme/
- The European project Euclock : http://www.euclock.org

Illustrations:

- Heading illustration, Source : Gerrit Gerritsen, http://timeandtubes.blogspot.com
- Fig.1, Source : http://lecerveau.mcgill.ca/flash/i/i_11/i_11_p/i_11_p_hor/i_11_p_hor.html
- Fig.2, Source : http://lecerveau.mcgill.ca/flash/d/d_11/d_11_cr/d_11_cr_hor/d_11_cr_hor.html

At UniProtKB/Swiss-Prot:

- Clock, Homo sapiens (humain) : O15516
- Cryptochrome-1 (cry1), Homo sapiens (humain) : Q16526
- Cryptochrome-2 (cry2), Homo sapiens (humain) : Q49AN0
- Period circadian protein homolog 1 (per1), Homo sapiens (humain) : O15534
- Period circadian protein homolog 2 (per2), Homo sapiens (humain) : O15055
- Period circadian protein homolog 3 (per3), Homo sapiens (humain) : P56645

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