Study reveals new data on circadian rhythms

May 7 2009

Fluctuations in light intensity allow restoring the regularity of circadian rhythms. This is the main conclusion of the work carried out by Javier Buceta, group leader of The SiMBioSys Group (Theoretical and In Silico Modelling of Biological Systems) and Antoni Da ez-Noguera, dean at the Faculty of Pharmacy of the University of Barcelona. The study is published today in *Biophysical Journal*.

In higher organisms, such as mammals, biological or circadian rhythms are generated by a multicellular genetic clock which is located in two regions of the hypothalamus that are connected to each other known as suprachiasmatic nuclei (SCN), containing about 10,000 neurons each. In order to generate and regulate circadian rhythms, our biological clock needs to use the “cooperative cell behaviour” of SCN neurones. These neurons generate self-sustained, coherent oscillations and interact in a coupled manner -through a genetic circuit- forming a single unique rhythm (circadian rhythm) that is very efficiently modulated by the light-darkness alternance cycle in the 24 hours of a day.

Up until now, several studies had established that arrhythmia was associated with a lack of coordination among the periodic expression of SCN neurone proteins: in arrhythmic animals, the expression of SCN neurone proteins is desynchronised. It was also known that constant light is one of the triggers of arrhythmia. Neurons are only capable of generating self-sustained and coherent oscillations (biological rhythm) if the illumination is sufficiently low. However, when intensity is increased, this coherent behaviour is lost and the biological rhythm is distorted: animals become arrhythmic.

The researchers of the study looked at the possibility to restore rhythmicity in the animals under these conditions by means of fluctuations in light intensity and decided to use mathematical modelling techniques to simulate the genetic and cell interactions of the neuro-physiological system that regulates the biological clock. This *in silico* experiment is of extraordinary interest because it has enabled researchers to find out that light intensity fluctuations help restore rhythmicity and coherence of circadian rhythms, and not the contrary, that is, their distortion, as could be intuitively deduced.

“This research work has enabled us to explore a phenomenon known in physics as “coherence resonance”, which shows that noise (understood as irregular fluctuations) may be an order source. In other words, chance is not an order that induces disorder, but totally the opposite; for some biological processes, such as the circadian rhythm, it can be beneficial. Noise-induced coherence has previously been established in other systems. Our objective was to implement this coherence in the control of circadian rhythms”, explained Javier Buceta, group leader of The SiMBioSys.

In the work, researchers also worked on how interactions between light fluctuations and intercellular coupling affected the dynamics of the collective rhythm. The outcome of the research has helped gain further understanding of the genetic circuit of the approximately 20,000 neurons that control circadian rhythms and, to gain further insight into the influence exerted by the periodic expression of the involved proteins in the synchronisation process of this multicellular clock.

“Thanks to this computer-generated simulation we have been able to discover that light fluctuations play a constructive role by synchronising communication -via a neurotransmitter- between neurones The study constitutes a new example of how modelling has become a very useful tool to discover in silico new phenomena in biological processes that will be

subsequently corroborated in vivo", continued to explain Javier Buceta.

In support the hypothesis formulated by this *in silico* study, the authors are currently conducting *in vivo* trials with mice. The trials are headed by Antoni Díez-Noguera, current dean of the Faculty of Pharmacy at the University of Barcelona, and group leader of Chronobiology at the Department of Physiology of this faculty. Díez-Noguera has been studying for over 30 years the structure and functioning of the circadian rhythm in rodents.

More information: "Noise-Induced Coherence in Multicellular Circadian Clocks", Ekkehard Ullner,Javier Buceta,Antoni Díez-Noguera and and Jordi García-Ojalvo. *Biophysical Journal*, Volume 96, Issue 9, 3573-3581, 6 May 2009, doi:10.1016/j.bpj.2009.02.031

Source: Barcelona Science Park, Spain