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http://www.sf-chronobiologie.org

Sommaire

Éditorial

La mélatonine complément alimentaire ou médicament ?

Enfin la mélatonine est disponible en France comme complément alimentaire dans les magasins de diététique et sur Internet. En effet, la Direction Générale de la Concurrence, de la Consommation, et de la Répression des Fraudes (DGCCRF) a donné son accord fin 2011, dans la mesure où la teneur en produit conduit, en fonctions des utilisations préconisées, à une prise journalière inférieure à 2 mg de mélatonine. Il se trouve que 2 mg est la dose contenue dans le Circadin®, spécialité à libération prolongée (et non immédiate de mélatonine) vendue en pharmacie sur prescription médicale pour corriger l'insomnie primaire des patients âgés de plus de 55 ans .

Nul doute que la DGCCRF a consulté l'AFSSAPS avant de donner cette autorisation, autorisation qui nous a été confirmée par la Direction Départementale de la Protection des Populations du Rhône, dans un mail adressé à une de nos étudiantes en pharmacie, soucieuse de faire le point sur la question.

Nous nous sommes donc renseignés sur Internet auprès des laboratoires susceptibles de nous fournir la mélatonine, complément alimentaire.

L'un d'entre eux, le Labo Solgar fournit des comprimés dosés à 1 mg, mais préconise d'absorber 1 à 2 comprimés, soit 2 mg dans le second cas, c'est à dire une dose qui soumet la mélatonine à la réglementation pharmaceutique !

L'autre fournisseur potentiel, Labo Diet Horizon propose un mélange renfermant des extraits de plantes, un précurseur de la mélatonine, le tryptophane dosé à 20mg (on n'est jamais trop prudent !) et la mélatonine dosée à 1,95 mg par comprimé ! La question est de savoir si les 20mg de tryptophane ne vont pas apporter les 0,05mg manquants pour atteindre les 2 mg, contribuant ainsi au changement de statut de mélatonine, auquel cas le laboratoire serait dans l'illégalité ? Par ailleurs ce laboratoire rapporte l'absence d'effets indésirables.

Notons aussi que ces préparations conviennent aux végétariens puisque la mélatonine est contenue dans des végétaux aussi banals que les tomates, pommes de terre, etc.…, mais à notre connaissance à des quantités inférieures à un ng/kg de végétal.

La connaissance de la table de multiplication de un (1 fois 1=1, 2 fois 1=2, 3 fois 1=3….) et des habitudes des utilisateurs de compléments alimentaires nous conduit à penser que la dose journalière absorbée rejoindra, voire même dépassera dans beau-

(Suite page 59)

(Suite de la page 58)

coup de cas, la dose réputée thérapeutique de 2 mg.

Cette situation, générée en partie par les propriétés de la mélatonine (substance naturelle simple à activités multiples, de faible toxicité….) et la complexité des réglementations (qui sont faites pour être contournées!), nous apparaît susceptible d'évoluer. Pour notre part, nous restons sur les positions que nous avons déjà développées. Nous considérons la mélatonine comme un médicament dont la forme galénique (libération immédiate ou prolongée) et la dose doivent être choisies en fonction des indications thérapeutiques (2mg n'est pas toujours la dose optimale, en particulier chez l'enfant). Des effets secondaires significatifs ou des interactions médicamenteuses existent et peuvent apparaître lors d'une utilisation prolongée, en particulier comme complément alimentaire.

Bruno Claustrat
Président de la Société Francophone de Chronobiologie

Les inscriptions sont ouvertes depuis le 1er mars 2012

les 26, 27 & 28 septembre 2012
Moulin des Cordeliers, 37600 Loches

Le prochain Congrès de la Société Francophone de Chronobiologie se déroulera à Loches, cité Royale, du 26 au 28 septembre 2012.

Cité Royale - © Inra

Bienvenue sur le site du 43ème Congrès de la Société Francophone de Chronobiologie.

C'est sous l'égide de la SFC que l'Unité Mixte de Recherche Physiologie de la Reproduction et des Comportements du centre de recherches de l'INRA de Tours et l'Unité de Psychologie des Ages de la Vie de l'Université François Rabelais de Tours, organisent le congrès 2012.

Pour ce congrès, nous serons heureux de vous accueillir dans la Cité Royale de Loches (Indre et Loire) du 26 au 28 Septembre 2012. En attendant cet évènement, vous trouverez sur ce site les informations concernant le programme, le lieu et les modalités d'inscription.

Pour plus d'informations consultez le site web du congrès : http://colloque4.inra.fr/tourschronobiologie2012 et le site de la SFC http://www.sf-chronobiologie.org

Visitez régulièrement le site Web de la SFC

Le site de la Société Francophone de Chronobiologie est consultable à l'adresse

http://www.sf-chronobiologie.org

Tout comme l'ancien site, il comporte une présentation de la société et de ses activités ainsi qu'un annuaire de ses membres. Chaque membre recevra un courrier avec un nom de login et un mot de passe personnel qui lui donnera un accès personnel pour notamment modifier sa fiche. Le site constitue aussi une riche source d'informations sur la recherche et l'enseignement qui portent sur la chronobiologie, ainsi que sur l'actualité de cette discipline. Je vous laisse explorer le site de manière plus approfondie et compte sur vous tous pour l'alimenter régulièrement et le faire vivre longtemps !

Sophie LUMINEAU

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Résumés des communications des membres de la SFC au 12ème Congrès de l'European Biological Rhythms Society

20-26 Août 2011, Oxford, Royaume-Uni

Résumés des communications

ebrs

RFRP-3 in the Syrian hamster: the exception proves the rule

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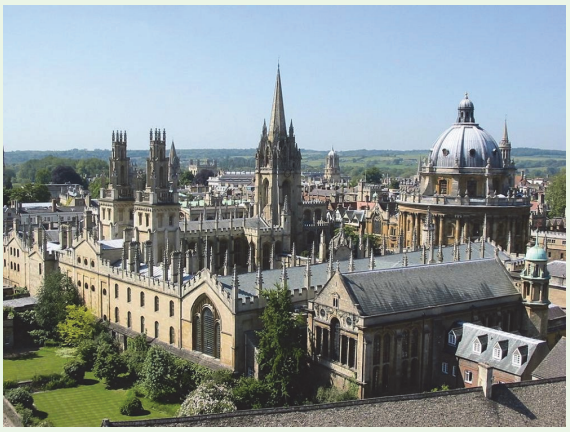

In 2000, gonadotrophin-inhibitory hormone (GnIH) was identified in the quail and shown to inhibit gonadotrophin release. Soon after, novel RFamide peptides structurally similar to GnIH were identified in mammals, and the mammalian orthologue of avian *gnih* was termed RFamide-related peptide (*rfrp*). The mammalian *rfrp* gene encodes two peptides, RFRP-1 and RFRP-3 and a large body of evidence now indicates that RFRP-3 plays a role as as a negative regulator of reproduction in various species. The Syrian hamster is a seasonal model in which sexual activity is promoted by exposure to long summer days (LD) and inhibited by short winter days (SD). Because we have previously demonstrated that the level of *rfrp* mRNA and the number of RFRP-immunoreactive cell bodies were reduced in sexually quiescent Syrian hamsters acclimated to SD compared with sexually active animals maintained under LD, we hypothesised that *rfrp* and its product RFRP-3 might play a role in the regulation of seasonal reproduction in this species.

To determine the physiological effects of RFRP-3 on the reproductive axis, plasma LH and FSH concentrations were measured after an intracerebroventricular (i.c.v.) injection in LD animals and testicular activity of SD hamsters was analysed after 5 weeks of central administration of RFRP-3. In order to determine RFRP-3 sites of action, c-fos expression in the brain was analysed following an i.c.v. injection of the peptide. A possible hypophysiotrophic effect was investigated using peripheral injections of RFRP-3 on one hand, and cultured pituitary cells on the other hand, to determine the effect of the peptide on LH secretion *in vivo* and *in vitro*.

The acute central administration of RFRP-3 induced a significant dose-dependent increase in LH and FSH plasma concentrations. Furthermore, the chronic central administration of RFRP-3 fully reactivated the reproductive axis, as manifested by increased paired testes weight and plasma testosterone concentrations in RFRP-3-treated hamsters compared to vehicle-treated animals. The i.c.v. injection of RFRP-3 induced a significant increase of c-fos in the GnRH neurons and in c-fos expression in the arcuate nucleus. Peripheral injections of RFRP-3 had no effect on LH secretion, nor did the peptide increase LH secretion in cultured pituitary cells.

Taken together, these results indicate that in the Syrian hamster, RFRP-3 has a stimulatory effect on the reproductive axis. This effect is most likely mediated via central targets, namely the GnRH neurons in the preoptic area, or the Kiss1 neurons in the arcuate nucleus, and probably not via peripheral tar-

gets.

A *Kiss* for the seasonal control of reproduction

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In seasonal rodents, melatonin tightly restricts reproductive activity to the most favourable period of the year. However, its precise sites of action on the reproductive axis remain uncertain. We recently identified several genes involved in the reproductive function that are regulated by photoperiod. One of these genes is *Kiss1* and encodes several peptides named kisspeptins. We studied the role of kisspeptins in the seasonal control of reproduction in the Syrian hamster. We identified two populations of neurons expressing *Kiss1* in the arcuate (ARC) and the anteroventral periventricular (AVPV) nuclei. Exposure to inhibitory short days or daily melatonin injections mimicking a short-day like nocturnal peak of the hormone drastically reduces *Kiss1* expression in both nuclei, but with different mechanisms. While melatonin inhibits *Kiss1* expression via a steroid-independent effect in the ARC, melatonin-induced *Kiss1* reduction in the AVPV is mediated by the decrease in testosterone levels. In short days, kisspeptins release is also decreased and the peripheral administration of exogenous kisspeptins to photo-inhibited sexually inactive hamsters reactivates the reproductive function. Kisspeptins stimulating effect is mediated by GnRH neurones and GnRH neurones' response to exogenous kisspeptins varies with the photoperiod. To summarise, we demonstrated that the kisspeptinergic system is tightly regulated by melatonin and that *Kiss1* expressing neurons convey the photoperiodic information to the reproductive axis, more specifically on GnRH neurons.

Role of the circadian clock on translation of ribosomal proteins (RP) and ribosome biogenesis in mouse liver

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Previous results showed clear biological evidences that the circadian clock coordinates mTOR (mammalian Target of Rapamycin), ERK (Extracellular signal-Regulated Kinase), and AKT signaling pathways. These pathways are known to modulate the translational process through phosphorylation cascades which activate the pre-initiation complex. On one hand this initiation requires that the eIF4F complex (eIF4E-eIF4G-eIF4A-eIF4B) unwinds the mRNAs 5'-terminal secondary structures, and on the other hand the 43S complex scans the 5'-untranslated region (UTR). The eIF4F complex binds the m^7GTP 5'-terminal 'cap' structure of mRNAs through the interaction of eIF4E. This step requires the phosphorylation of 4E-BP (eukaryotic initiation factor 4E binding protein) by mTOR, triggering the separation of 4E-BP from eIF4E, and then allows the formation of the eIF4F complex. We hypothesized that the circadian clock regulation of the mTOR pathway could modulate this pre-initiation step. Through 'cap' affinity proteins purification of mice liver extracts from Wild type, *Bmal1* KO and *Cry1*/*Cry2* KO mice, we will determine the role of the circadian clock on the translational initiation process.

Moreover, mTOR has been shown to regulate also different steps of the ribosomal proteins biogenesis such as the 5'-TOP (terminal oligopyrimidine tract) mRNAs translation. 5'-TOP motifs are predominantly found in the 5'-UTR of mRNAs that encode RP. Studies on various vertebrates have amply demonstrated that the 5'-TOP sequence represents the major cis-acting element involved in the translation of these mRNA. However, the trans-acting factors that mediate this translation are still unknown. Through mRNA affinity chromatography, we will try to identify proteins that bind 5'-TOP motifs on these RP mRNA on a rhythmic fashion and determine whether they act like transacting factors promoting RP mRNAs translation. Once characterized, we will study how the circadian clock influences their activity and characterize the role of the circadian clock on ribosome biogenesis.

Endogenous rhythm of *Talitrus saltator* from two geomrphologically different Tunisian beaches

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The locomotor activity rhythm of the supralittoral sandhopper Talitrus saltator was investigated over four seasons. To reveal the impact of environmental variation on the endogenous rhythm of this species, two populations were collected from two gemor-

phologically different beaches: Gabes gulf (N 33° 52'; E 10° 07') and Barkoukech (N 36° 36'; E 10° 52'). For each season, thirty adult individuals were collected by hand. These individuals were transferred individually in actographs, equipped with an infra-red recording system. These actographs are placed under two simultaneous experimental regimens (LD and DD) in a controlled environment cabinet.

Periodogram analysis and waveform of the rhythm have been investigated, as well as the incidence of rhythmic animals in each population. Whatever the season or the photoperiodic regimen imposed, the animals were found to exhibit a nocturnal circadian rhythm, close to 24h, of locomotor activity, with an ultradian component around 12h. This latter was only recorded for the population of Talitrus saltator individuals collected from Gabes gulf beach. In addition, for the two populations, the stability of the circadian rhythm was better defined in spring under the two photoperiodic regimens.

The variation of rhythm parameter's populations is considered according to changes in environmental conditions prevailing at the sites of collection.

Role of the circadian clock regulated ATF5 transcription factor

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By regulating the metabolism of fatty acids, carbohydrates and xenobiotic the mammalian circadian clock plays a fundamental role in the liver. Impairment of this rhythm has been shown to lead to diverse pathologies, including metabolic syndrome. At present, it is supposed that the circadian clock regulates metabolism mostly by regulating the expression of liver enzymes at the transcriptional level. However, we have now accumulated evidence that post-transcriptional mechanisms also play an important role in this regulation. In particular, recent results from our laboratory show that the circadian clock can regulates the posttranslational regulation of liver enzymes through a circadian clock-coordinated 12-hours period rhythmic activation of the IRE1 pathway of the unfolded protein response (UPR). In this context, the ATF5 transcription factor attracts our attention. ATF5 is a protein belonging to the family of bZip Transcription Factors whom mRNA is rhythmically expressed with a 24 hours cycle peaking during the end of the night period. Interestingly, translation of *Atf5* mRNA is also regulated by the UPR. As activation of UPR has often been linked to tumors growth and resistance to chemotherapeutics treatments, and ATF5 has been shown as a mediator of cell survival, we will try to characterize the potential role of ATF5 in liver metabolism and detoxification after activation of the UPR. To study this role, we have developed a mouse model with a conditional knockout of the *Atf5* allele. Through the determination of the yet unknown ATF5 target genes by transcriptome profiling and Chip-seq comparison of wild-type and knockout mice after pharmacological activation of the UPR, we planned to characterize the in vivo role of ATF5 in mouse liver circadian metabolism and detoxification.

Impact of mild hypobaric hypoxia on clinical tolerance and 24-h patterns in iron metabolism markers during simulated flights

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Long-distance flights can cause a number of clinical problems due to mild hypoxia resulting from cabin pressurization. Using an original chronobiological approach, the aim of this work was to assess the clinical tolerance and biological impact of daytime exposure to mild hypobaric hypoxia on markers of iron metabolism and plasma proteins. Since iron plays indeed a major in the control of oxygen carrying capacity, we hypothesized that a link could exist between the clinical tolerance and the ability of iron mobilization in response to hypobaric hypoxia.

Fourteen healthy, male volunteers, ages 23 to 39 yrs, spent 8.5 h in a hypobaric chamber (from 07:45 to 16:15 h) simulating an altitude of 8000 ft. This was followed by another 8.5-h session 4 wks later simulating conditions at an altitude of 12,000 ft. Biological variables were assayed every 2 h over two 24-h spans (control and hypoxia spans, respectively) per simulated altitude.

Whereas most of the subjects tolerated the 8000 ft exposure well, eight subjects (57%) presented clear clinical signs of hypoxic intolerance at 12,000 ft. The 24-h blood iron profile showed a biphasic pattern at both altitude simulations, with a significant (~40%) increase during hypoxia, followed by a (~25%) decrease during the first hours of recovery. The iron circadian rhythm showed a significant phase delay during the hypoxic exposure at 8000 ft

vs. reference. Mean 24-h ferritin levels decreased at both altitudes, but mainly during the nighttime after the 12,000 ft exposure in accordance with Cosinor analysis. The transferrin and total plasma proteins 24-h profiles did not show significant change. Moreover, significant differences, mainly in iron, ferritin, and transferrin, were found at 12,000 ft according to the clinical tolerance to hypoxia, and significant correlations were found between the midrange crossing times, i.e., here half-descent times (d-T50), for ferritin and total plasma proteins and the reported level of clinical discomfort under hypoxia.

This study shows that an 8.5-h exposure to mild hypoxia is able to alter very quickly the 24-h pattern of iron and ferritin. These alterations seem to depend, at least in part, on the clinical tolerance to hypoxia and may help explain the interindividual differences observed in the tolerance to hypoxia.

The deletion of *Rev-erbα* in mice alters glucose homeostasis and triggers risk factors for obesity

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Mutations of clock genes can lead to metabolic alterations such as diabetes and obesity. Conversely, metabolic diseases are associated with circadian disturbances at both central and peripheral levels. *Rev-erbα*, a nuclear receptor involved in the mechanism underlying circadian oscillations, has been shown to play a role in lipid and glucose metabolism in particular *in vitro*. In order to explore further the role of *Rev-erbα* in metabolic regulations *in vivo*, *Rev-erbα* mutant mice (-/-: homozygous) and their control littermates (+/+: wild-type) were fed either with chow (CD) or high-fat diet (HFD). Both genotypes fed with HFD showed an attenuated diurnal feeding rhythm and developed hyperlipidemia, hyperleptinemia and hypercholesteronemia. Interestingly, -/- mice on HFD gained significantly more body mass than control animals and became obese more rapidly. To determine whether the defective energy homeostasis was the consequence of altered liver clockwork, we analysed the day-night expression of clock and metabolic genes in both genotypes. The hepatic expression of major metabolic actors of lipolysis and lipogenesis was altered, indicating that the obese phenotype in *Rev-erbα* -/- mice implies a primary alteration in the liver. In addition, we observed that the blood glucose in -/- mice, regardless of the feeding conditions (CD or HFD), showed higher values than those in the +/+ group across the whole 24h cycle and after a fasting period as well. When challenged with a glucose tolerance test (GTT), a pyruvate tolerance test (PTT) and during a hyperinsulinemic euglycemic clamp, -/- mice showed responses not significantly different from +/+ animals. Despite these findings, the expression of key regulators of glucose metabolism was modified in the liver of -/- mice and the gluconeogenic response to fasting was disrupted. These results demonstrate that the absence of *Rev-erbα in vivo* leads to abnormal lipid and glucose homeostasis. Therefore, considering its role in the molecular clockwork, our findings and related studies show that *Rev-erbα* is a key actor of the crosstalk between the circadian system and metabolism.

Functional genomics identify *Birc5/Survivin* as a potential determinant of Seliciclib® chronopharmacology

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Circadian clocks orchestrate the timing of physiology and behaviour in most organisms. In mammals this control is achieved via a hierarchically organized system with a light sensitive central clock in the hypothalamus coordinating a plethora of clocks in the periphery. Central and peripheral clocks share the same transcriptional/posttranslational feedback mechanism and, they co,ntrol transcriptionally the circadian oscillation of key cellular processes such as signalling, metabolism, transport, and cell division. In line with this, it has long been recognized that the efficacy and toxicity of drugs is depending on the time of administration and for instance most chemotherapeutic agents display a chronopharmacological profile in mice. This has led to the concept of chronotherapy which aims at treating patients at a

time of the day that optimises the therapeutic index. Despite the considerable amount of knowledge regarding the molecular makeup of circadian clocks, the mechanisms underlying the chronopharmacology of drugs remain poorly understood. Here using the colon epithelial cells as a model system and functional genomics we investigated the putative molecular determinants of the pharmacology of Seliciclib®, a cyclin dependent kinase inhibitor currently under clinical trials for the treatment of lung and nasopharyngeal cancers. Results show that the mouse colon mucosa contains a *bona fide* molecular clock and mRNA profiling using microarrays indicates that a large proportion of rhythmic genes in this tissue regulate the cell cycle. Notably, mitosis appears to be restricted to the early resting phase. Using siRNA targeting these rhythmic mitotic genes we show that the expression level of *Birc5/survivin* determines the sensitivity of colon epithelial cells to Seliciclib. This may provide a mechanism contributing to the chronotoxicity of this candidate anticancer drug.

Circadian disturbances in an MPTP treated non-human primate model of Parkinson disease

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The clinical diagnosis of Parkinson disease (PD) rests mainly on the identification of the hallmark motor symptoms related to dopamine deficiency that are a consequence of degeneration of the Substantia nigra pars compacta. Although the major emphasis in research has focused on motor-related problems, there is increasing evidence that non-motor and perhaps non-dopaminergic related symptoms are sometimes present before diagnosis and inevitably emerge and worsen with disease advance.

Assessment of the alterations of circadian rhythmicity in relation to the appearance and progression of motor deficits and to the decrease in brain dopamine levels in a non-human primate model of PD.

A Parkinsonian state was induced in monkeys by treatment with MPTP. Clinical state was evaluated using Parkinsonian Monkey Rating scale (PMRS), cognitive performance using an Object Retrieval Detour Task (ORDT), circadian rest-activity rhythms were monitored by recording locomotor activity and hormonal rhythms (cortisol, melatonin) assessed from urinary samples. DA function was followed using PET scans (C-PE2I, DAT) and post mortem control of TH neurons in the brain and retina.

Before MPTP treatment, the animals showed robust daily rest-activity rhythms under a light dark (LD) cycle, with precise onsets and offsets of locomotor activity. In a continuous light cycle (LL), monkeys expressed clear circadian rest-activity rhythms with periods slightly different from 24hrs. Following MPTP treatment, daily rest-activity rhythms were similar to pre-treatment, although the level of motor activity generally decreased. In contrast, monkeys showed a significant alteration of the circadian rhythmicity in constant conditions (LL) characterized by a decrease in the amplitude of the rhythm and imprecise onset and offsets. The deterioration of the rhythms was inversely correlated with the clinical motor score with, in extreme cases a loss of rhythmicity. Cortisol and melatonin rhythms appeared to persist in MPTPO treated monkeys. PET scan and TH immunohistochemistry showed a 70-80% reduction of the dopaminergic system.

Our study shows that severe disturbances of circadian functions occur after MPTP treatment and stress the importance of non-motor symptoms in PD.

Support: Fondation de France (FdF), Rhône-Alpes Cible, FP6-EUCLOCK, Université de Lyon,

Beneficial effects of morning light on cognitive performance, mood, melatonin and cortisol during sleep restriction

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Light exposure elicits numerous effects on human physiology and behaviour. However, it remains inconclusive whether morning light exposure has beneficial effects on cognitive performance, mood and circadian physiology following sleep restriction (SR). Here we investigated the role of morning light exposure as a countermeasure for impaired cognitive performance and mood during SR.

Seventeen participants were studied in a balanced cross-over design, with light exposure in the morning after SR (8 h of a sleep episode curtailed to 6 h). The entire protocol comprised 42h in the laboratory. Three different light settings were administered each morning: 1. blue light (BL) (20 min expo-

sure 2h after wake-up; 200 lux of light at 470nm), 2. dawn simulating light (DsL) (blue-enriched polychromatic light gradually increasing from 0 to 250 lux during 30 min before wake-up time, with light around 250 lux for 20 min after wake-up time) and 3. Dim light (DL) (<8 lux). Cognitive tests were performed every 2 h during the wake episode and questionnaires were hourly completed to assess subjective mood and well-being. Salivary melatonin and cortisol were collected during wake episode in regular intervals.

Analysis of cognitive performance yielded a significant main effect of "light condition" ($p<0.01$), such that during the first day following SR, performance was significantly deteriorated during DL, while it maintained stable during BL and significantly improved with DsL. After the second SR night, these differences on cognitive performance did not further reveal significances between DsL and DL. Analysis of well-being revealed a significant main effect of "light condition", such that morning DsL improves levels of well-being, and even more after the second SR night, as compared to DL and BL ($p<0.001$). Exposure to morning DsL did not significantly affect circadian melatonin phase, while, after morning BL, melatonin onset was significantly earlier as compared to DsL and DL. Furthermore, after DsL, salivary cortisol levels were significantly higher at waketime as compared to BL and DL.

Our data indicate that exposure to morning light after the first and second day of SR alleviate decrements in cognitive performance under conditions of mild SR. This effect was more pronounced after dawn simulation, since the DsL was able to maintain higher well-being levels and did not affect circadian melatonin phase, whereas morning blue-light induced a phase advance of melatonin, and therefore impacted on the circadian system. In a broader context, these light conditions may provide an effective rationale for enhancing performance and mood in individuals who experience mild sleep restriction.

Bioluminescence analysis reveals presence of autonomous circadian oscillators in all cellular layers of the retina

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The retinal circadian clock is known to control many rhythmic processes involved in adapting retina physiology to the light/dark cycle. Localization of the circadian clock within the mammalian retina has been under debate for several years. Although clock gene expression has been described in all cellular layers, the functional organization of the clockwork within the whole retina has not been characterized. By using bioluminescence recording from retina layers isolated by vibratome sectioning, we show here that autonomous circadian oscillators are located in all three layers and display specific rhythmic patterns.

Retinas were dissected from either *Per2-luc* knock-in mice or *Per1-luc* transgenic rats housed under 12h/12h light/dark cycle, mounted on gelatin blocks, and tangentially sectioned by vibratome to isolate individual cell layers. Respective *Per2* or *Per1* clock gene expression was recorded from layer explants cultured on Millicell inserts in the Lumicycle for several days. Data analysis was performed by Lumicycle Analysis software or by evaluating non-linear least-square fitting to sinewave regressions.

We observed that each individual layer exhibited bioluminescent oscillations during several days in culture, with a period around 25 hours. Whole retinas also displayed rhythmic bioluminescence, but with a shorter period of about 23 hours. Sections comprising ganglion cell and inner nuclear layers oscillated with a period intermediate between individual layers and the whole retina. These results suggest a complex organization of the retinal clock, composed of three autonomous but interconnected oscillators driving together rhythmic retinal functions.

Systems chronopharmacology approaches for the personalization of cancer chronotherapeutics.

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Chronotherapeutics aim at improving treatment outcomes through the delivery of medicines according to the Circadian Timing System (CTS), a complex hierarchical and dynamic network system involving all cells in the body. As a result, circadian timing modifies up to 10-fold the tolerability of anticancer medications in experimental models and in cancer patients *(Lévi et al. Annu Rev*

Pharm Toxicol 2010). However, sex, circadian disruption and tumor protein expressions are independent determinants of the optimal chronotherapeutic schedule, in international studies involving large number of patients with metastatic colorectal cancer. Such clinical data have driven experimental confirmation studies in mice. Moreover, human cancer chronotherapeutics constitute a unique paradigm for cancer therapy, where "the lesser the toxicity, the better the efficacy", based on several landmark analyses of a randomized clinical trial involving 564 patients. Stochastic and deterministic mathematical models help analyze the dynamic interactions between circadian clocks, cell cycle and drug pharmacodynamics from single cell to whole organism. Biosimulation leads to the design of model-based optimal chronotherapeutic schedules, through the exploration of a wide range of parameter values, as shown for irinotecan. Systems chronopharmacology further reveals that optimal chronotherapeutics require circadian entrainment to be robust in healthy cells and disrupted in cancer cells. In practice, non invasive reliable circadian biomarkers are critical for modeling CTS dynamics, for increasing CTS robustness through intervention measures, and for effectively personalizing circadian drug delivery schedules.

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Circatidal and circadian rhythms interaction in the oyster *Crassostrea gigas*

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The marine habitat constitutes a highly complex biotope, where organisms are exposed to both daily solar and lunar cycles. In situ studies held in the Arcachon bay (France) indicated that the rhythm of valve activity in permanently immersed oyster Crassostrea gigas is mainly driven by the circatidal cycle, modulated by complex association of the sun-earth-moon orbital positions and the daily cycle (Tran et al., 2011). In the present work performed under laboratory conditions, we tested the water current as a potential circatidal zeitgeber and investigated the interaction between the circatidal and circadian cycles on oyster's rhythm.

Oysters (n = 31) collected in Arcachon bay were maintained in constant conditions of temperature (18.3 ± 0.5°C) and food ([chla] = 0.16 ± 0.05 µg/l). They were exposed in a flume to varying photoperiods (irradiance 26 µE.m-2.s-1) with or without water current regime mimicking natural tidal cycles (± 30 cm/s, constant water level). The valve activity was measured using light-weight electromagnetic electrodes glued on both valves at 0.6 Hz in each oyster.

Under L:D (12:12) conditions with current, the 1st significant period at the population level was circadian, and the 2nd was circatidal. At the individual level, it was as follow: 1st significant period, circadian (75-94 % of the animals), circatidal (0-12 %), infradian periods (0-13 %) or arrhythmic (0-6 %); 31 % exhibited both a circadian and a circatidal period. Under D:D conditions with current, the population exhibited only a tidal rhythm (12.4 h). At the individual level, the distribution of the periods was: circatidal (38 %), circadian (19 %), ultra- or infradian (31 %) and arrhythmic (12 %). Again, 31 % of the oysters exhibited both a circadian and a circatidal period. Under free-running conditions (D:D, no current), the individual periods were highly variable (7-83h) although the most frequently observed period was 20-28 hours.

To conclude, we showed that the water current is a zeitgeber of the circatidal rhythm in the oyster C. gigas. However, circatidal rhythm under our laboratory conditions is not prevailing. Water current by itself should not be the only zeitgeber of the circatidal rhythm in situ. Furthermore, if at population level the cyclic activity of C. gigas is robust, rhythms are very labile when considering individuals. Under free-running conditions, the circadian rhythm constitutes the main one, suggesting that the circatidal rhythm could be managed by the circadian clock. The different hypothesis put forward to explain endogenous rhythms in marine organisms will be discussed.

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Activation of glycine receptor phase-shifts the circadian rhythm in neuronal activity in the mouse suprachiasmatic nucleus

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In mammals, the suprachiasmatic nucleus (SCN) of the hypothalamus contains the primary endogenous oscillator that controls daily rhythmicity of numerous physiological, endocrine and behavioral processes. Although circadian rhythmicity is an intrinsic feature of SCN neurons, the master clock is constantly reset by diverse entrainment pathways involv-

ing different neuropeptides and neurotransmitters. The major inhibitory neurotransmitter GABA plays an important role in the intrinsic modulation of SCN clock cells and can possibly mediate the synchrony between dorsal and ventral SCN oscillators. However, the involvement of glycine, the second major inhibitory neurotransmitter in the brain, in the resetting of circadian clock mechanisms has until now not been investigated, despite some electrophysiological evidence of the presence of glycine receptors in the SCN.

In the present work, we performed whole-cell patch-clamp recordings as well as multi-microelectrode arrays (MEA) recordings to examine short- and long-term electrophysiological effects of glycine in acute and organotypic SCN slices of C57Bl/6 mice, respectively. Voltage-clamp recordings demonstrated the existence of glycine-induced, chloride-sensitive currents in SCN neurons. This glycine-induced current was partially blocked by specific blockers of glycine receptor, like strychnine, PMBA and ginkgolide B, showing that glycine acts through the activation of its specific receptor. Moreover, MEA recordings on organotypic SCN slices showed that glycine could act excitatory as well as inhibitory in SCN neurons. Interestingly, the proportions of cells showing an increase or a decrease of their firing rates following glycine application was varying depending on the phase of the circadian cycle. Additionally, we tested the long-term effect of glycine on the rhythmic firing of SCN neurons performing long-term extracellular recordings from organotypic slices cultivated on MEA. Glycine induced phase shifts of the cyclic neuronal activity in the SCN: phase advances during the subjective day, and phase delays during the early subjective night. These effects were blocked by co-application of glycine together with strychnine. In conclusion, we demonstrate for the first time that activation of glycine receptor belongs to an entrainment pathway which is able to reset the master circadian clock.

Relevance of *per2* mutation for diethylnitrosamine-induced liver carcinogenesis

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The disruption of the circadian timing system with chronic jet lag accelerated both experimental cancer progression and liver carcinogenesis (Filipski et al, JNCI, 2005; Mut Res, 2009). The mutation of clock gene Per2 promoted γ radiation induced carcinogenesis. (Fu and al, Cell, 2002). Both chronic jet lag and Per2 mutation enhanced genomic instability and down regulated apoptosis pathways in liver.

Purpose: To identify the role of Per2 in the liver carcinogenesis induced with diethylnitrosamine (DEN).

Methods: 26 male C57bl6/129 mice (13 wt and 13 $Per2^{m/m}$ kindly provided by U. Albrecht, Freiburg, Switzerland) were synchronized with LD 12:12 and received daily i.p DEN at ZT11 for 7 weeks (cumulative dose, 402 mg/kg). They were implanted i.p with a rest-activity and body temperature sensor and radio transmitter (Data Sciences). Body weight and physiological rhythms were assessed for 5.5 and 4 months respectively. Serum ALAT and ASAT were determined on weeks 10, 15, 19, and 22. Time series were analyzed with spectral analysis (Mathematica v.8) and Cosinor (SPSS v.18). Parameters were compared with ANOVA and paired t-test (SPSS v.18).

Results: Body weight loss was largest in $Per2^{m/m}$ mice as compared to wt ($p< 0.001$) with maximum loss being 8.9 ± 1.2 % in wt and 12.3 ± 2.2 % in $Per2^{m/m}$. ALAT and ASAT were elevated following DEN exposure without any significant difference between groups. Baseline circadian rhythms in body temperature displayed a lower mean amplitude (±SEM) in $Per2^{m/m}$ as compared with wt (0.7 ± 0.02 °C vs 0.9 ± 0.05, $p= 0.003$). DEN exposure further reduced the circadian temperature amplitude ~ four-fold in Per2m/m while it only halved it in wt mice (0.2 ± 0.03 °C vs 0.5 ± 0.07 °C, $p= 0.001$). Conversely, no significant difference was found for the circadian amplitude of activity between both groups. Four $Per2^{m/m}$ mice died on weeks 8-20. Pathology revealed severe dysmorphic precancerous liver in all the mice. One Per2m/m mouse dead on week 20 also had both cholangiocarcinoma and hepatocarcinoma. Final results on liver cancer incidence according to Per2 mutation will be presented.

Conclusions: Per2 mutation worsened both DEN-induced body weight loss and circadian temperature rhythm disruption, possibly resulting in accelerated liver carcinogenesis.

Aging of non-visual sensitivity to light: compensatory mechanisms?

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Sleep and circadian rhythm disturbances are prevalent in the elderly. These alterations may result from an inappropriate entrainment of the circadian clock. A decreased sensitivity of the circadian system to white light (Duffy et al. 2007) and to a short-wavelength light (456 nm) has been found in the elderly (Herljevic et al. 2005; Sletten et al. 2009). These findings, however, remain insufficient to characterize the origin of the diminished non-visual response in the elderly. The aim of our study is to investigate the effects of aging on the non-visual sensitivity over the visible light spectrum, and to determine whether these alterations are related to an increase in ocular lens density.

Eight aged (55-63 yrs old) and five young (24-27 yrs old) participants underwent 60-min of monochromatic light exposure sessions at nine different wavelengths (420–620 nm, $3.16x10^{13}$ photons/cm²/sec) from 00:30-01:30. Plasma melatonin suppression was calculated for each light session and used to derive individual sensitivity spectra. Lens density was assessed using a validated psychophysical heterochromatic flicker photometry technique, developed in our laboratory.

Compared to young subjects, our results show an altered spectral sensitivity of melatonin suppression in the aged. Sensitivity to light is similar in the short wavelength region of the spectrum (<500 nm), and higher in the 530-560 nm range, resulting in a shift of peak sensitivity from 484 nm in the young to 494 nm in the aged. Lens density measurements (17 young, 13 old) show an increased lens yellowing in the aged, leading to a relative decrease in transmittance of the crystalline lens, mainly in the short wavelengths range of the light spectrum (<500 nm).

As we expected, our results show a modified non-visual sensitivity to light in the elderly, characterized by a shift in peak sensitivity to longer wavelengths (484 to 494 nm). The lack of difference in the short wavelength range and the higher sensitivity in the mid-long wavelength range (530-560 nm) is, however, unexpected. Therefore, our hypothetical link between an increased lens filtering and a decreased non-visual sensitivity to short wavelength light in the elderly is not supported by our results. Changes in non-visual sensitivity to light in the aged subject may involve compensatory or adaptive mechanisms, as they take place in visual sensitivity (color perception).

Chemotherapy-induced circadian disruption in cancer patients

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Introduction. The robustness of the circadian timing system before chemotherapy (chemo) is associated with a better survival in cancer patients (pts) (Innominato et al. Cancer Res 2009). However, chemo itself disrupts circadian rhythms in mice (Li et al J Biol Rhythms 2007; Ahowesso et al. Chronobiology Int 2011).

Purpose. To evaluate the effect of chemo on the circadian timing system of cancer pts, using rest-activity as a circadian biomarker.

Methods. 49 pts (25 males and 24 females) with advanced gastro-intestinal cancers volunteered for the study. Rest-activity rhythm was monitored (Actigraph®, Ambulatory Monitoring) during 4 consecutive time spans: 'prechemo', at baseline (3 days, d), 'during chemo' (4-5 d of chemo delivery), and two subsequent 3-d spans corresponding to 'earlypostchemo' and 'latepostchemo'. Chemo usually involved 5-fluorouracil, irinotecan and/or oxaliplatin. Robust and validated parameters widely employed for the description of rest-activity rhythms were computed (mean activity, r24, I<O, IS, IV and RA). Data were compared using parametric or non parametric analyses of variance (SPSSv.18).

Results. Every parameter significantly decreased during chemotherapy delivery (except for IV, which increased, indicating a higher fragmentation of the rhythm) as compared to baseline – i.e. from a mean of 0.36 to 0.26 for r24, p=0.002; and from 96.5 to 93.6 for I<O, p=0.036. The mean parameter values then gradually recovered to near baseline values. However, the dynamics of the rest-activity rhythm from "prechemo" to "latepostchemo" displayed inter-patient differences: 1) remained similar throughout the four timespans in 12 pts; 2) worsened during chemo but fully recovered afterwards for 16 pts; 3) never recovered after chemo for 12 pts, or 4) improved after baseline for 9 pts. These patterns were confirmed at individual patient level through daily cor-

relations of rest-activity data to the day-night alternation. The acute disruption was statistically validated for all parameters in females ($p<0.05$ for comparisons between 'baseline' and both 'duringchemo' and 'earlypostchemo'), but not for males ($p>0.05$ for any comparison between any pair of time spans).

Conclusion. These results show, for the first time, that chemo administration can acutely disrupt the circadian timing system of cancer pts. Moreover, female pts were more susceptible to this chemo-induced circadian disruption. Our results could account for the lesser benefit from a chronotherapy schedule with fixed doses and timing, in female as compared to male pts.

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Concomitant monitoring of skin surface temperature and rest-activity circadian rhythms as biomarkers for cancer chronotherapeutics.

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Body temperature is a robust biomarker of the circadian system that effectively coordinates peripheral molecular clocks (Burh et al., Science 2010). Furthermore, a negative correlation was found between temperature circadian amplitude and cancer progression, involving circadian reprogramming of tumor transcriptome (Li et al., Cancer Res 2010). Purpose: To evaluate the relevance of concomitantly monitored thermal skin and rest-activity as circadian biomarkers for guiding the personalization of cancer chronotherapeutics. Methods: 21 patients (pts) - 14 males, 7 females, aged 67.4 y (51 to 89), with colorectal (20 pts) or pancreatic cancer (1 pt) volunteered for this study. Skin temperature was measured every minute (min) for 4 days (d) using 4 thermal skin patches (VitalSense©) per pt. Patches were placed on 2 "warm" sites and 2 "cold" front chest sites according to infrared camera guiding. The number of wrist accelerations was measured every min using an actigraph (Minimotion Logger®). Missing data were interpolated (Matlab). Spectral analyses determined the dominant circadian period τ in each time series (MathematicaTM). Circadian mesors, amplitudes (AMP) and acrophases (φ) were computed with Cosinor for each time series and averaged for each pt temperature data (SPSSTM). Interpt variability was investigated. Results: Temperature data loss exceeded 20% for 17/84 patches (20.2%) without any influence of placement site. Spectral analysis of the 84 time series documented a mean circadian τ of 23.8 h (17.6 to 30.6), unaffected by placement site. "Cold" patches displayed lower mesors, higher AMP and earlier φ, compared to "warm" patches. Mean 24-h AMP and φ (± SEM) of the skin surface temperature were 0.65 ± 0.52°C and 4:10 am ± 19 min for the 21 pts. However, individual AMP varied up to 10-fold (0.01°C to 1.5°C), and φ's differed by up to 3 h (3:40 to 6:46 am) among pts. The mean dominant period of rest-activity was 23.9h [22.6-25.9], with large interpt variability regarding mesor (42 to 152 mvts/min), AMP (27 to 124 mvts/min) and φ at 14:22 (9:40 to 16:24). A weak correlation was found between the circadian amplitude of skin temperature and that of wrist activity. There was a trend toward higher temperature AMP and earlier φ of rest-activity and temperature in males as compared to females. Conclusions: The placement of skin thermal patches on chest sites critically affected circadian amplitude and acrophase. Statistically significant differences in 24-h amplitudes and acrophases of skin surface temperature and rest-activity were found among cancer patients. The findings support the concept of personalized cancer chronotherapeutics.

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Linking sleep timing and obesity

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Purpose. Sleep duration progressively shortens in industrialised societies over the past decades, and the resulting sleep debt is proposed to be a major factor in the aetiology of metabolic diseases. Individual sleep duration on work and free days depends on chronotype, with late types being sleep deprived on workdays and early types on weekends. The term social jetlag refers to the discrepancy between sleep timing on work and free days and can be used as a quantitative indicator of living against one's circadian clock. Here, we aimed at elucidating the role of social jetlag with regards to obesity.

Methods. We assessed sleep-wake behaviour on work and free days via an internet-based version of the Munich ChronoType Questionnaire (MCTQ). Social jetlag was quantified by subtracting mid-sleep on workdays (MSW) from mid-sleep on free days (MSF).

Demographic data were collected, *i.e.*, age, sex, weight and height, allowing the computation of Body Mass Index (BMI). We examined the relationship between chronotype, social jetlag and BMI by multiple regression within a sample of 64,110 respondents.

Results. Sleep duration is significantly shorter on work than on free days (rANOVA, p< .0001), and this discrepancy increases the later chronotype (significant covariate, p< .0001). BMI is modulated by age and sex (significant covariates, p< .0001), and independent of these demographic influences, the association between BMI and sleep duration is nearly two-fold for workdays as compared to free days (r = -.076 for workdays vs. r = -.049 on free days, p< .001) indicating a key role of social jetlag. A 4-step, linear multiple regression model, with BMI as a dependent variable, confirmed the importance of previously identified factors (age, sex and sleep duration). In addition, social jetlag and chronotype both were significantly associated to BMI scores (p< .001), with standardised ß coefficients indicating comparable effect sizes.

Conclusions. We suggest that circadian misalignment, as quantified by social jetlag, is a key factor to understand the increasing trend of excess weight. In addition, the significant relationship between chronotype and BMI indicates that future epidemiological research should consider internal time, in addition to age and sex in its analyses.

Human keratinocytes and melanocytes contain the molecular circadian clock machinery as seen in fibroblasts

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Physiology and behaviour of organisms are adapted to environmental changes by a molecular timing system, a multioscillatory network that generates circadian rhythms. A central clock is localized in the suprachiasmatic nuclei of the brain and is synchronized to the geophysical time to set the phase coherence between and within the oscillators localized in peripheral organs. At molecular level, circadian rhythms in central or peripheral oscillators are generated by similar transcriptional-translational feedback loops involving several clock genes. Clock gene oscillations were shown in human primary fibroblasts suggesting that fibroblasts might be involved together with other cell types (e.g. keratinocytes and melanocytes) in the timekeeping in skin, an organ that has several daily rhythmic functions (e.g. cell renewal). To investigate the presence of autonomous oscillators in human skin, primary keratinocyte and melanocyte cultures were established from abdominal skin biopsy of a healthy 36 year-old woman donor. Confluent P3 cultures were synchronized with dexamethasone and then harvested every four hours. Expression of the clock gene transcripts *Clock*, *Bmal1*, *Per1*, *Per2*, *Per3*, *Cry1*, *Cry2*, *RevErb alpha*, *Ror alpha* and *Ror beta* was assessed as well as their expression profiling over 52 hours by quantitative real-time PCR. Data for each gene were fitted to a cosinor-derived sinewave function. All sinewave functions were simultaneously fitted by a non linear least squares regression algorithm which imposed a common endogenous period. Our analysis shows that all clock genes are expressed in the human keratinocytes (except *Ror beta*) and melanocytes; the expression patterns of clock gene transcripts show circadian rhythmicity, *Bmal1* oscillations being in antiphase with those of *Per* transcripts, as it was described for most molecular clocks. This *in vitro* study shows that in human keratinocytes and melanocytes clock gene oscillations are robust, indicating the presence of a functional molecular machinery that is responsible for the generation of circadian rhythmic processes. These autonomous oscillators, together with the fibroblast oscillator, might act locally and/or interact with the central pacemaker. What could be the role of these clocks in skin physiology remains to be determined.

Role of histamine receptors in adult Drosophila circadian photoreception

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Light can synchronize the *Drosophila* circadian clock by two different ways: the visual system that includes the compound eye and the Hofbauer-Buchner eyelet and the Cryptochrome photoreceptor. The cellular and molecular pathway by which light information (rhodopsin reception) is transmitted to the brain clock is unknown. Histamine is the major neurotransmitter of arthropod photoreceptors and mutants devoided of histamine do not appear to synchronize to LD cycles. To understand how histaminergic photoreceptors talk to the clock neurons, we focused on the role of histamine receptors in circadian entrainment. Two Drosophila genes, *ort* and *hisCl1* encode histamine gated chloride channels and we show here that they both participate to circadian entrainment. When both genes are defective, flies do not synchronize to LD cycles, suggesting that no other pathway participates. A second set of experiments aimed at

defining where the histamine receptors are required for their circadian function, and glutamatergic neurons were found to participate to the pathway. Ongoing experiments aim at narrowing down the set of interneurons that required for circadian entrainment. Finally, specific connections were revealed between the two red light -sensitive rhodopsins RH1 and RH6, and the two different histamine receptors.

Nervous and endocrine clock outputs to control daily and seasonal reproduction

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In mammals, daily and seasonal time cues are generated by the biological clock of the suprachiasmatic nuclei (SCN). Downstream pathways involve VIP- and VP-ergic SCN projections as well as the autonomous nervous system which in turn controls the production of hormones, in particular the pineal hormone melatonin. Other secreted factors like prokineticin2 (PK2) have been implicated as clock output molecules. These nervous and endocrine clock outputs synchronise a number of biological functions, like sleep/wake cycle, metabolic activity, reproduction, with the daily and annual variations of the environment.

Successful reproduction requires precise timing, and it is now admitted that the hypothalamic clock is a key element in the synchronisation of reproduction both at daily and seasonal levels. In female rodents, SCN VP fibres contact and activate neurons of the anteroventral periventricular nuclei which synthesise kisspeptin, a potent stimulator of GnRH release, and SCN VIP fibres make direct contact onto GnRH neurones. This dual clock-driven peptidergic control appears critical to regulate the daily timing of the GnRH response to estrogens during proestrous. In addition, PK2- or PK2 receptor-deficient mice display altered oestrus cycles and reduced fertility. At a yearly scale, variation in nocturnal melatonin production is known to synchronise reproduction with the seasons. In recent years, melatonin was reported to regulate expression of genes critical for reproductive activity, in particular *TSH* and *TSH-regulated deiodinases* in the median eminence area, and *Kiss1* and *RF-amide related peptide* in the mediobasal hypothalamus of seasonal species.

Modelling the responses of a bistable melatonin pigment system

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Purpose: In bistable photopigment systems, light elicits photosensory responses and drives photoregeneration of the chromophore to restore photic responsiveness. Melanopsin in the human retina has been shown to express bistable properties both *in vitro* and *in vivo* (Melyan et al 2005; Mure et al, 2009). These studies have shown that prior light exposure can modulate the amplitude of subsequent photic responses of melanopsin. In the present study, we attempt to model the kinetics of the melanopsin photopigment system in response to modulations of light spectrum and intensity.

Methods: We modelled the responses of the melanopsin photopigment system based on data for the equilibrium and difference spectra of melanopsin obtained by Mure et al. 2009 in our laboratory applying the mathematical modeling of Stavenga and Hardie (2010). Light spectra of broadband natural and artificial light sources were used to generate prior light stimulations to drive the melanopsin system to a defined state of equilibrium. Theoretically, this corresponds to the proportions of melanopsin isoforms in the *11-cis* and *all-trans retinal* bound states. Mono- or polychromatic spectral templates were subsequently applied to examine the modulation of photic responsiveness.

Results: The results suggest that prior exposure to light sources dominated by long wavelength light increase the ability of the melanopsin system to respond to subsequent light exposures, while light sources dominated by shorter wavelength light decrease the response. Exploiting the bistable properties of melanopsin could allow for optimization of spectral light distribution in industrial, domestic and clinical phototherapy applications by appropriate use of the potentiating effects of long wavelength light.

Cumulative effects on sleep, mood and cognitive performances of combined dim light exposure and rotating shift-work in submariners

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INTRODUCTION: Working as a submariner is a tough job. A high psychological and cognitive functioning is necessary to achieve the effectiveness of the mission of a ballistic missile nuclear submarine. Deprivation of natural light may induce desynchronization of circadian rhythm and may therefore disturb individual and collective levels of alertness. Rotating shift-work applied during a 70-day patrol may also induce psychological and physiological disturbances. The aim of this study was to assess the effects

of natural light deprivation and of rotating shift-work on psychological and physiological parameters and on the cognitive performances.

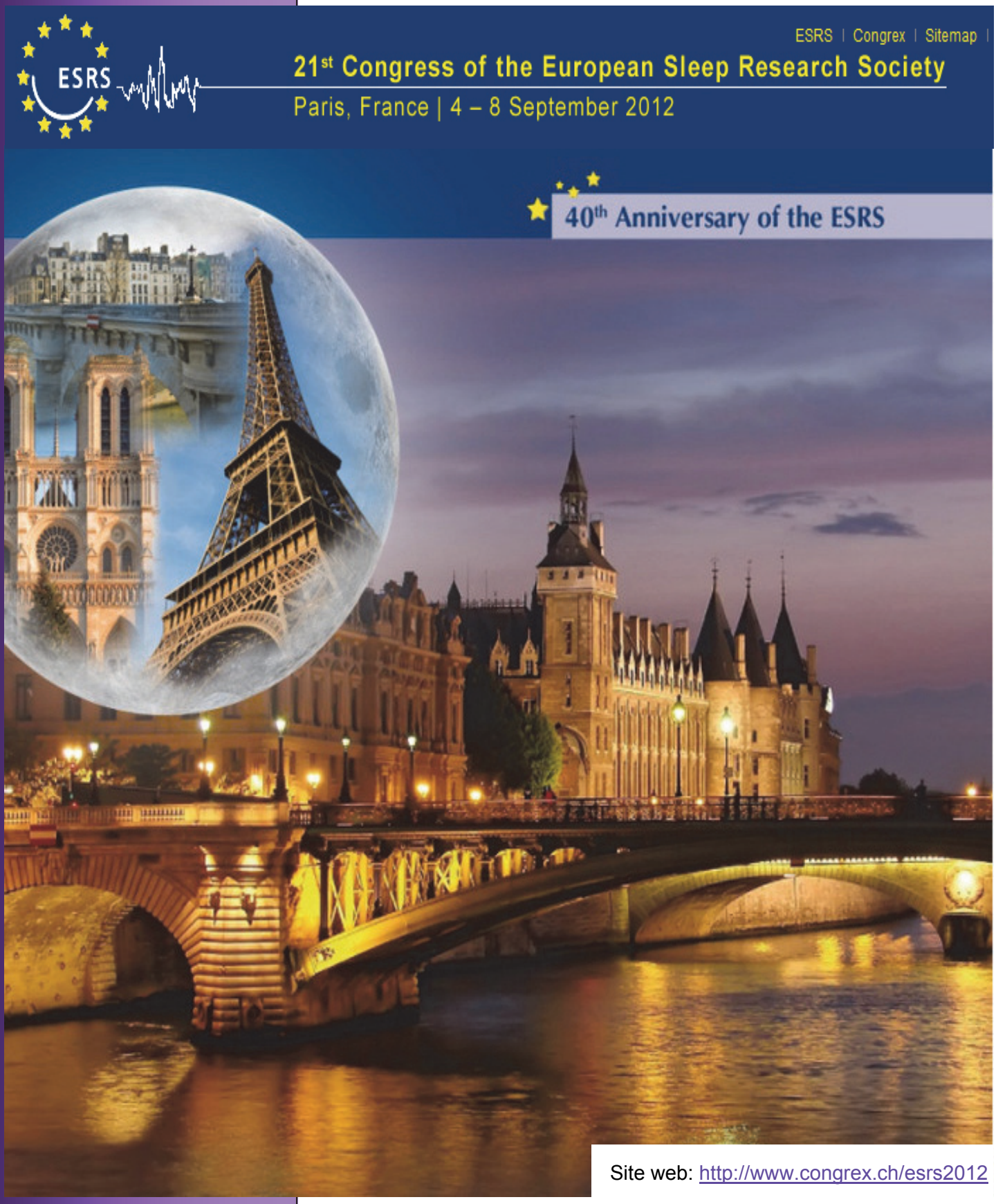
METHODS: Twenty-three submariners were involved in the study. The experimental procedure consisted in collecting (i) psychological state (typical and seasonal depression, perceived stress, well-being and anxiety level), (ii) night melatonin excretion (urine samples), (iii) variables of sleep efficiency (subjective scale of the sleep quality and actigraphy), and (iv) cognitive performances (Stroop test, declarative memory, and verbal fluency) of submariners. These data have been collected before the patrol (baseline), twice during the patrol, and twice after patrol (one week and two months after). Moreover, enlightenments were measured onboard.

RESULTS: Our first results showed that French submariners are exposed to low light levels. Concerning the psychological and cognitive assessments, we observed significant differences at baseline point between shift and non shift-workers: shift-workers were more psychologically disturbed and performed lower in cognitive tests than non shift-workers. Even if all submariners increased their depression score during the mission, the increase was greater for rotating shift-workers. They also exhibited higher cognitive degradations and more sleep disturbances than non shift-workers. Furthermore, the recovery, i.e. the return to baseline values, was longer in shift-workers (8 Wk) than in non shift-workers (1Wk).

DISCUSSION AND PERSPECTIVES: The natural light deprivation and rotating shift-work seem to have cumulative effects on psychological, physiological and cognitive functions in submariners. Improvements in artificial enlightenments and working conditions constitute a new challenge for applied biomedical research in order to reduce the environmental constraint on circadian clocks in submariners.

The 4th Conference of the Mediterranean Neuroscience Society *will be held* ***from September 30th to October 3rd 2012 in Istanbul, Turkey.***

Site web: http://www.mns2012.org/



Site web: http://www.congrex.ch/esrs2012

http://www.aging-sleep.com

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Description
Comités
Programme scientifique
Frais d'inscription
Dates importantes
Abstract
Symposium
Hébergement
Lieu - Accès
Contact

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Bienvenue

Selon les Nations Unies, le vieillissement de la population mondiale est sans précèdent et ce processus n'a pas son égal dans l'histoire de l'humanité. Naturellement, ce phénomène a des répercussions sur les pratiques médicales et les systèmes de santé à travers le monde.

Le sommeil est une fonction physiologique fondamentale nécessaire à un vieillissement réussi. L'accroissement du nombre des sujets âgés s'accompagne d'une augmentation des problèmes de sommeil.

La qualité du sommeil est étroitement liée à la qualité de vie et à la genèse de certaines maladies. Les troubles du sommeil contribuent à l'augmentation de la vulnérabilité face aux maladies et aux handicaps. L'évaluation et la prise en charge des troubles du sommeil chez le sujet âgé doivent être une priorité.

Aging and Sleep 2012 se fixe plusieurs objectifs :

• Analyser les travaux de recherche récents en médecine du sommeil gériatrique et comprendre leurs implications cliniques.

• Comprendre et synthétiser les informations sur la prévention, le diagnostic et le traitement des troubles du sommeil chez le sujet âgé.

• Décrire les liens entre les troubles du sommeil, le vieillissement normal, la fragilité, le handicap et les comorbidités.

• Enseigner la médecine du sommeil gériatrique aux professionnels de santé dans un contexte interdisciplinaire.

• Avoir les bases d'une approche éthique dans les choix thérapeutiques et la dispensation des soins en pratique gériatrique.

Je vous invite à joindre les gériatres, gérontologues, médecins du sommeil, pneumologues, chercheurs et autres professionnels de santé de nombreux pays qui se réuniront à l'Institut Pasteur de Paris les 28-29 juin 2011 pour la deuxième édition de Aging and Sleep.

Cordialement

Fannie Onen, M.D., Ph.D.
IASRG President (Paris, France)

Chronobiologistes...

encore un effort pour vos contributions à Rythmes.

Vous devez participer à la vie de la Société Francophone de Chronobiologie en envoyant vos contributions à Fabienne Aujard, rédactrice en chef de Rythmes

Seules sont acceptées les contributions sous forme informatique, textes et figures, noir et blanc et couleurs. Cela assure la qualité de ce qui est produit, d'autant plus appréciable si vous optez pour la lecture électronique, qui, elle, est en couleurs !

Vous devez envoyer vos contributions en document attaché. Les fichiers seront préférentiellement sauvegardés au format ∗.doc, ∗.rtf, ou ∗.txt après avoir été produits par un traitement de texte standard. Pour tout autre format que ces formats répandus, nous consulter.

Il est impératif de nous faire parvenir un fichier texte sans retours à la ligne multiples, tout en conservant l'accentuation. De même, ne mettez pas de lignes blanches pour marquer les paragraphes ni mises en page complexes, que nous devrons de toutes façons changer pour rester dans le style du journal.

Les images pourront être en tiff, bmp, gif, jpeg, jpg ou png. Rythmes est mis en page sur un PC, donc les formats PC sont préférés, car cela évite des manipulations.

Enfin, vous enverrez vos contributions par courrier électronique à bruno.claustrat@chu-lyon.fr

avec copie à pifferi@mnhn.fr.

Bruno Claustrat
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