DAY NIGHT RHYTHM DISORDERS, ETIOPATHOGENESIS, PHYSIOPATHOLOGY AND POSSIBLE REMEDIES

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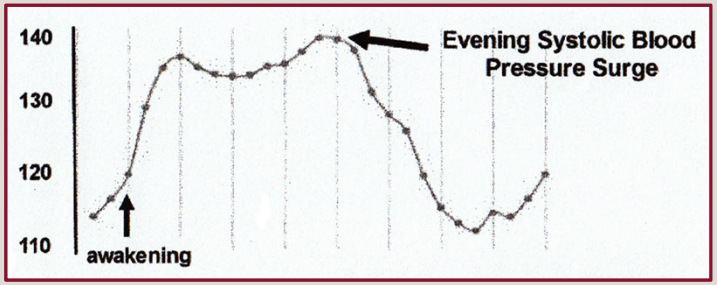
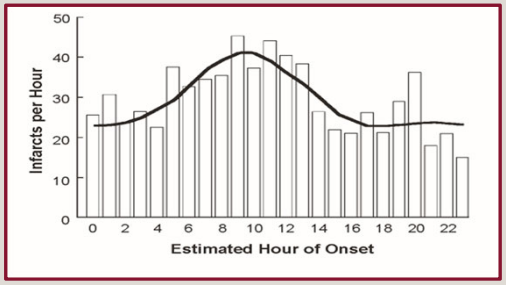
INTRODUCTORY SEMINARS TO SIM@B – Prato, Italy – 24 November 2023

CIRCADIAN RHYTHMS ARE UBIQUITOUS IN PHYSIOLOGY AND PATHOLOGY

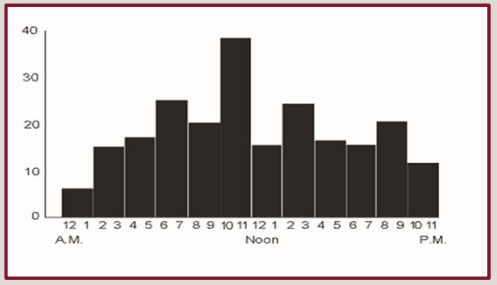
Systolic Blood Pressure (mmHg)



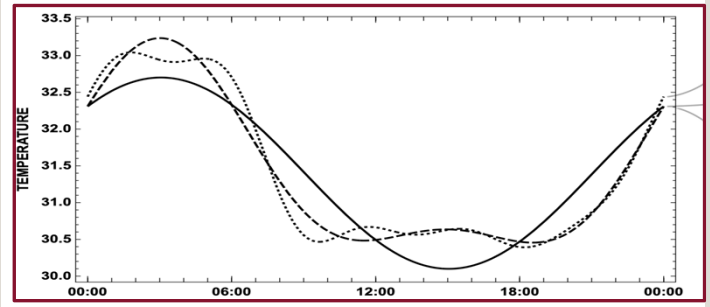
Myocardial Infarction (N/hour)



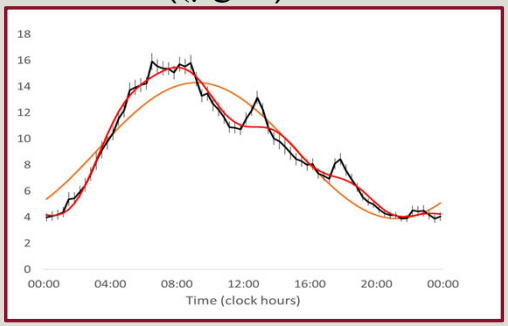
Thrombotic Stroke (N/hour)



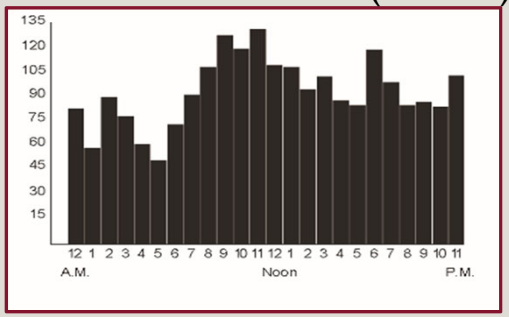
Skin Temperature (°C)



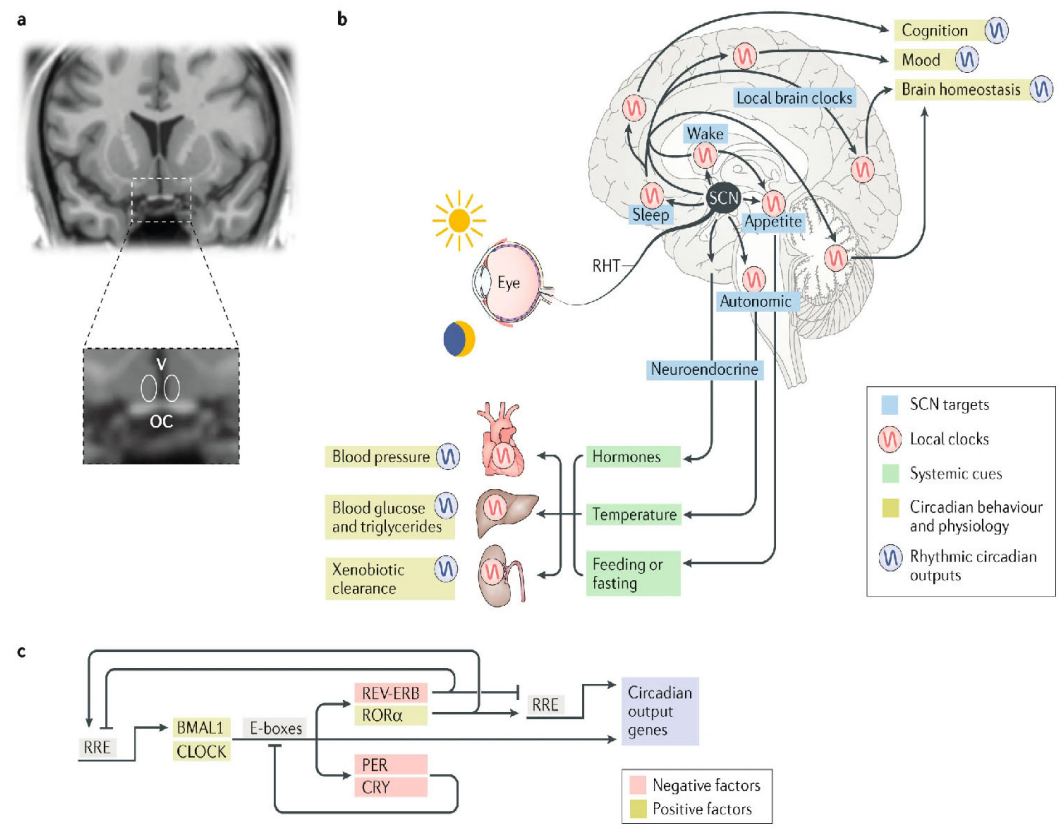
Cortisol ((µg/dl)



Sudden Cardiac Death (N/hour)



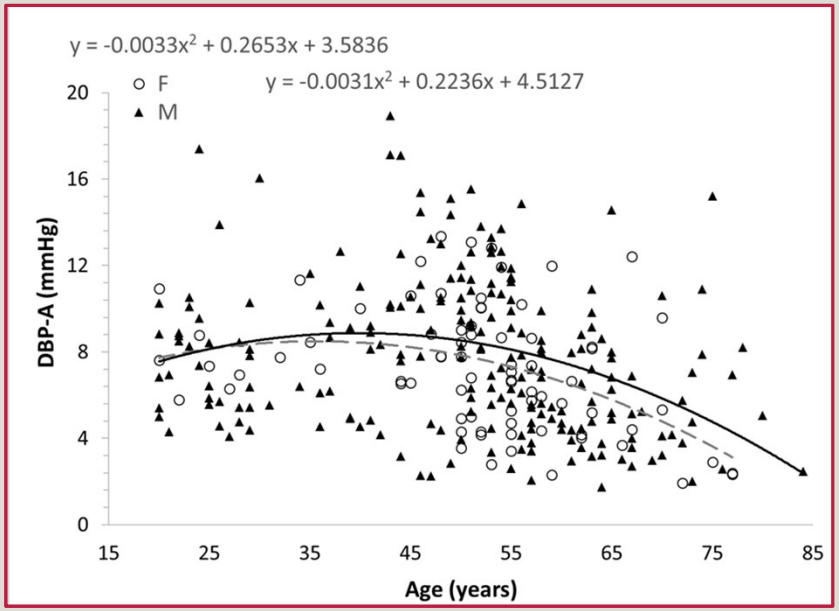
CIRCADIAN ORGANIZATION IN MAMMALS

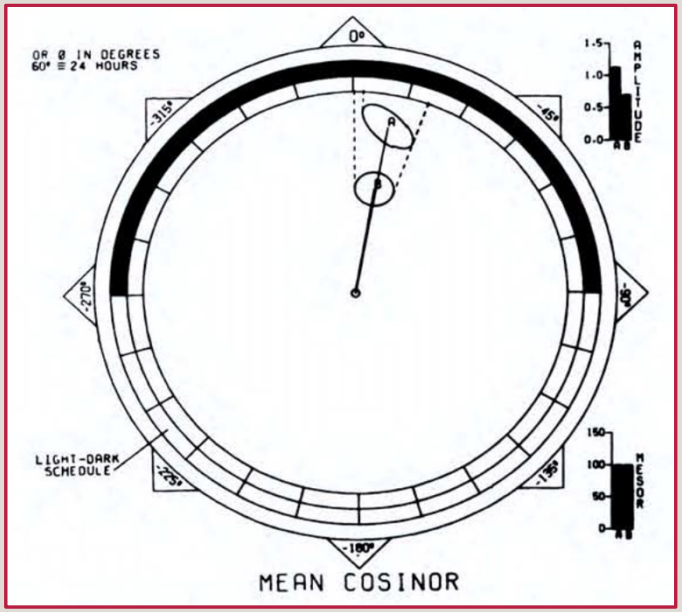


a The principal circadian clock, the suprachiasmatic nucleus (SCN), is located in the hypothalamus, which is highlighted by the box on the coronal MRI scan of a human brain. The inset shows an enlarged view, with the location of the SCN outlined. The optic chiasm (OC) lies across the base of the midline 3d ventricle (V). b The SCN receives direct retinal innervation via the retinohypothalamic tract (RHT) to ensure its synchronization to day–night cycles. The SCN clock projects to various brain centers, many of which contain local circadian clocks that direct behavioral (eg, feeding–fasting and sleep–wakefulness), autonomic and neuroendocrine circadian rhythms. These systemic cues synchronize the local molecular clocks of peripheral tissues, and these local clocks in turn direct local programs of circadian gene expression that regulate physiological rhythms critical to health (eg, rhythms relating to mental alertness, blood pressure, triglyceride metabolism and renal function). c Simplified schematic of the molecular transcriptional–translational feedback loops (TTFLs) of the mammalian circadian clock, in which heterodimeric complexes of CLOCK and BMAL1 proteins act via enhancer box (E-box) regulatory sequences to drive daytime expression of PER and CRY, which in turn combine to suppress CLOCK–BMAL1 activity at their own E-boxes. Subsequent degradation of PER and CRY in circadian night allows the cycle to start again. Additional feedback loops incorporating REV-ERB and RORα are also circadian regulated via E-boxes and control BMAL1 expression via REV response elements (RREs). This stabilizes and enhances the core TTFL. In turn, these core and ancillary loops drive local circadian programs of clock-controlled output genes, the first tiers of which are also regulated by CLOCK–BMAL1, PER–CRY and REV-ERB and RORα via E-boxes and RREs. More complex downstream cascades involving post-transcriptional, translational and post-translational mechanisms further sculpt the cellular circadian transcriptome and proteome.

From: Generation of circadian rhythms in the suprachiasmatic nucleus – Hastings et al. (2018) - https://doi.org/10.1038/s41583-018-0026-z

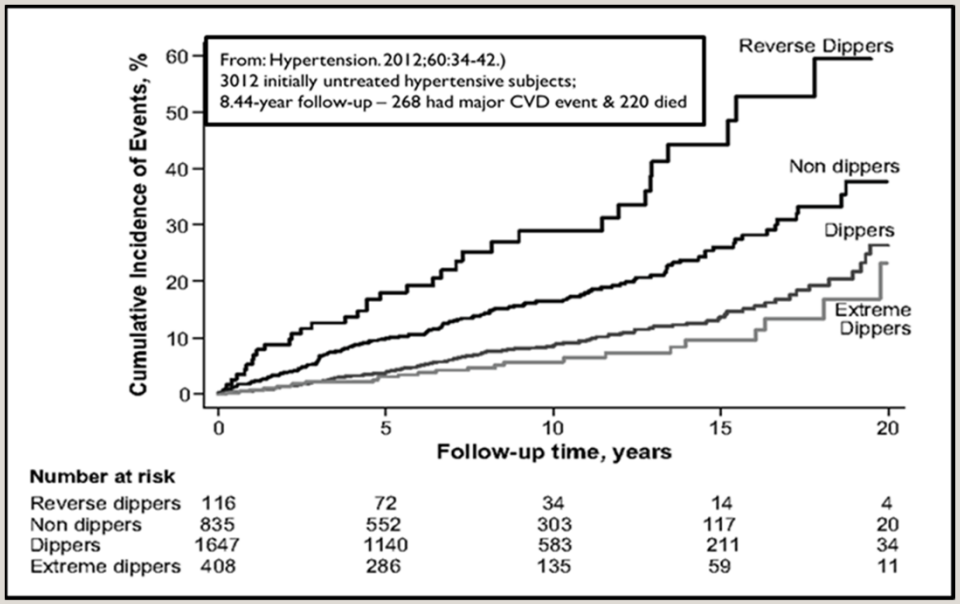
WEAKENING OF CIRCADIAN RHYTHMS WITH AGE



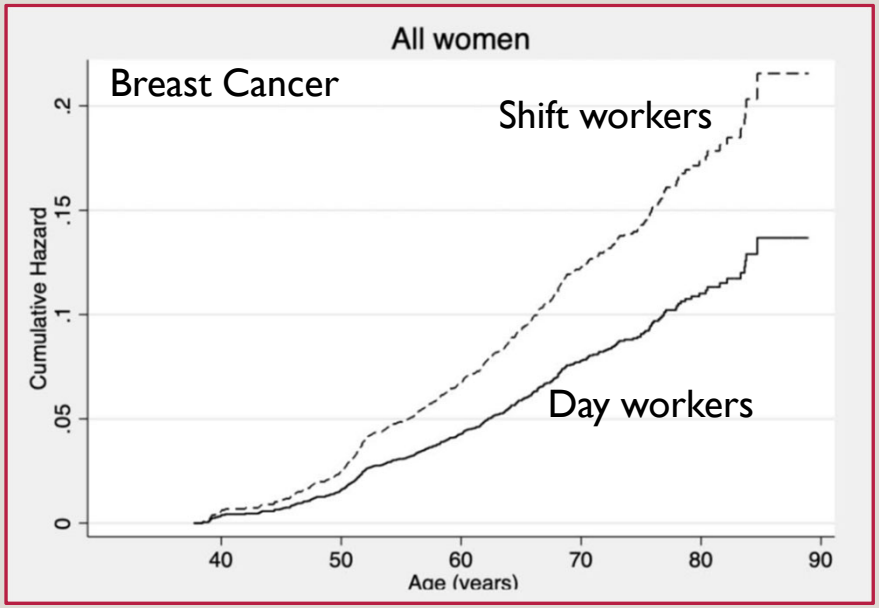


WEAKENED CIRCADIAN RHYTHM IS ASSOCIATED WITH INCREASED DISEASE RISK

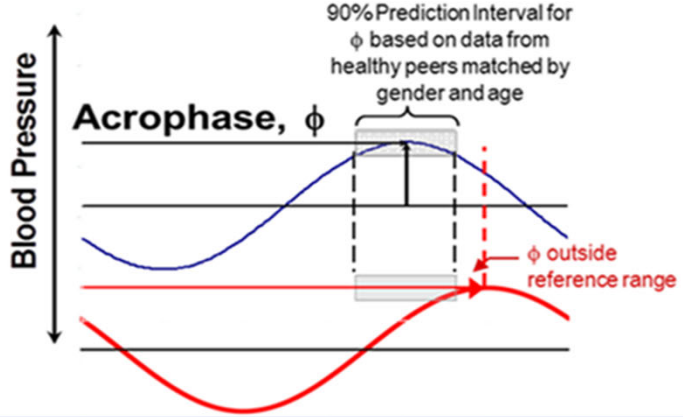
Hypertension. 2012;60:34-42

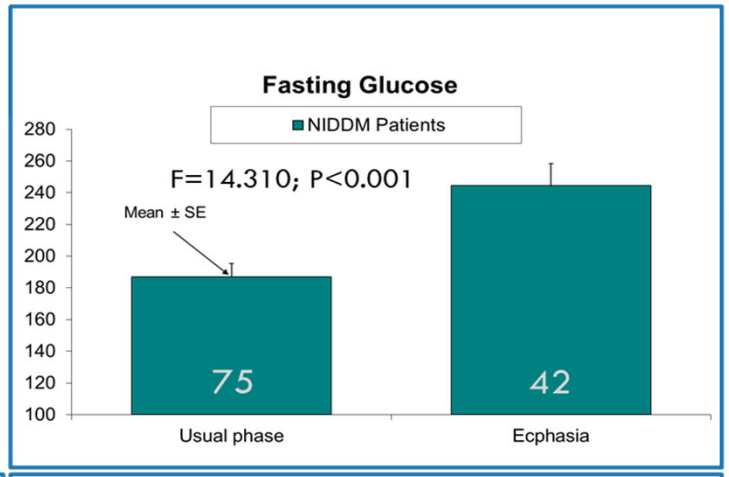


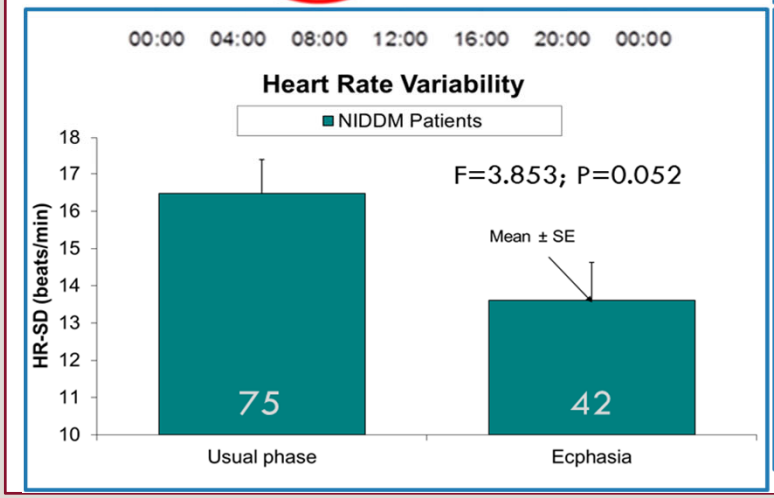
European Journal of Epidemiology (2023) 38:533–543

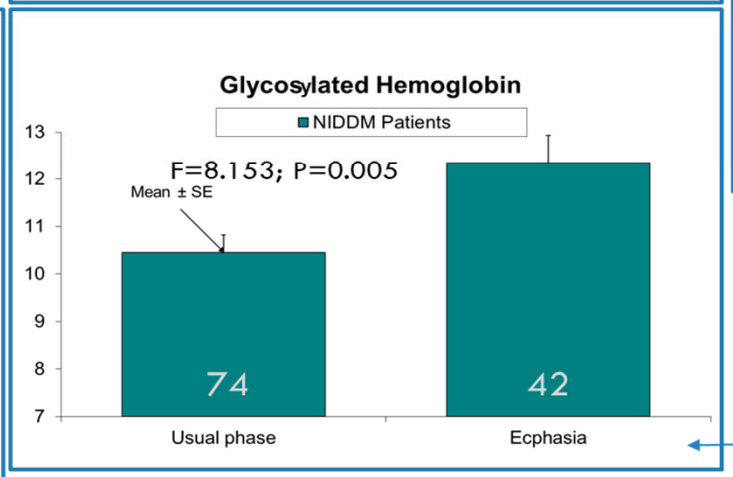


Ecphasia

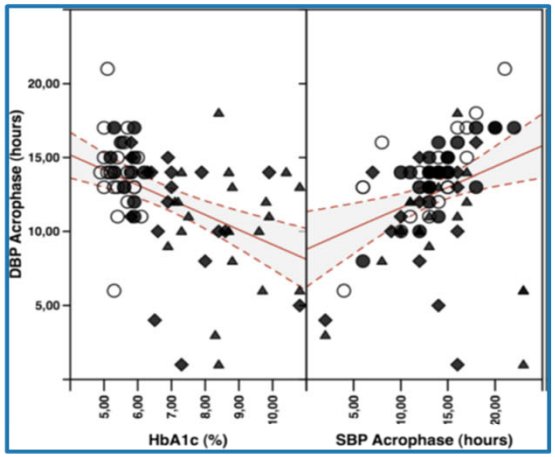








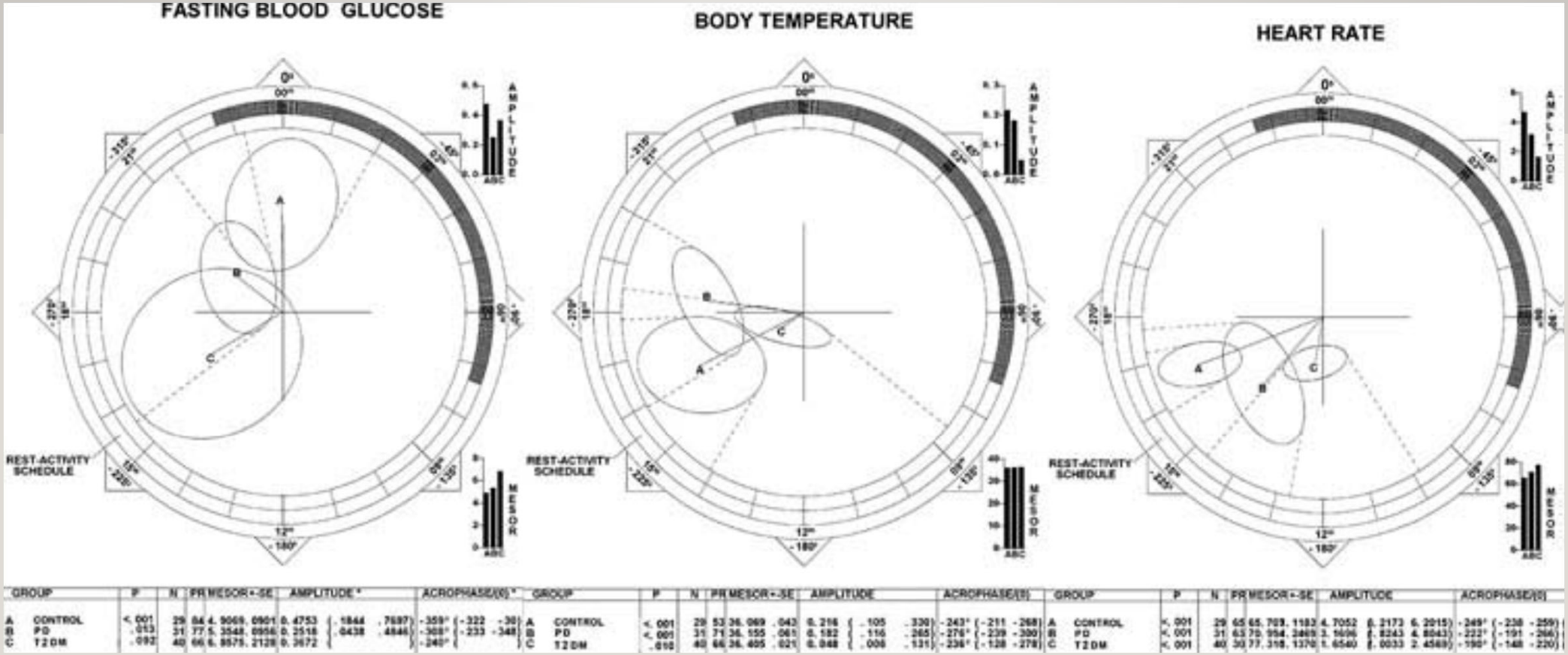
Results confirmed in independent study



Diabetology & Metabolic Syndrome 2012; 4(1): 51.

Int J Cardiol 2004; 97 (Suppl 2): S14.

Progressive disruption of 24-h rhythms in fasting blood glucose (FBG), body temperature (BT) and heart rate (HR) associated with metabolic dysfunction and the development of prediabetes (PD) and type 2 diabetes mellitus (T2DM) (40–69 years old)

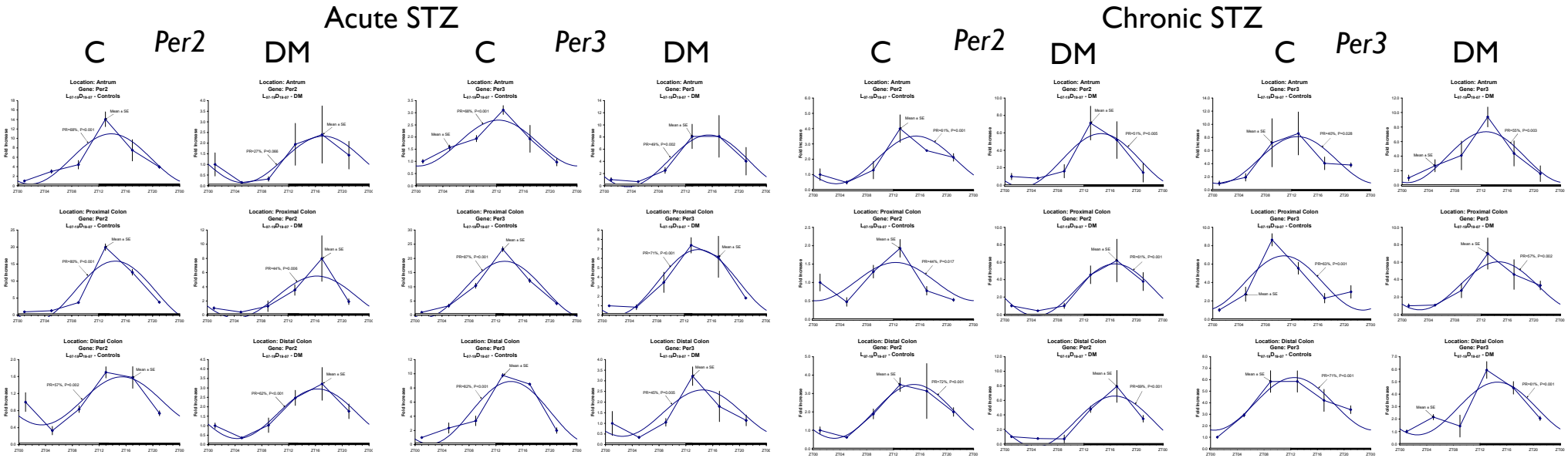


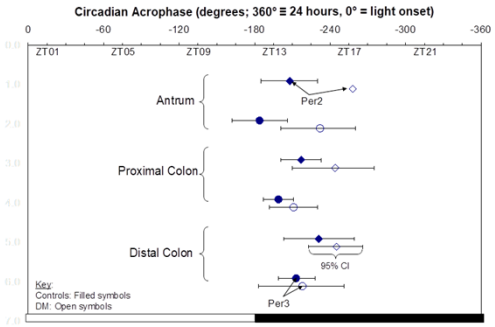
GROUP	P	N	PR	MESOR +-SE	AMPLITUDE *	ACROPHASE(θ) *
A CONTROL	<.001	29	84	4.9069, .0901	0.4753 (.1844 , .7687)	-359° (-322 , -30)
B PD	.013	31	77	5.3548, .0956	0.2518 (.0438 , .4846)	-308° (-233 , -348)
C T2DM	.092	40	66	5.8575, .2128	0.3672 ( )	-240° ( )

GROUP	P	N	PR	MESOR +-SE	AMPLITUDE	ACROPHASE(θ)
A CONTROL	<.001	29	53	36.089, .043	0.216 (.105 , .330)	-243° (-211 , -268)
B PD	<.001	31	71	36.155, .061	0.182 (.116 , .265)	-276° (-239 , -300)
C T2DM	.010	40	66	36.405, .021	0.048 (.006 , .131)	-236° (-128 , -278)

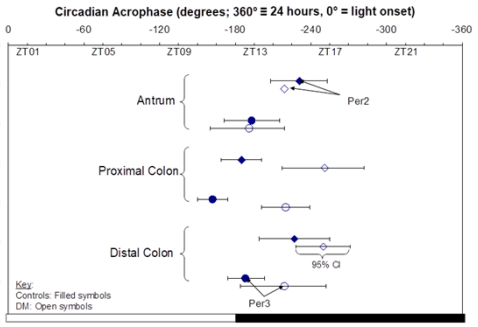
GROUP	P	N	PR	MESOR +-SE	AMPLITUDE	ACROPHASE(θ)
A CONTROL	K.001	29	65	65.703, .1183	4.7052 (3.2173 , 6.2015)	-249° (-238 , -259)
B PD	K.001	31	63	70.994, .2469	3.1696 (1.8243 , 4.5043)	-232° (-191 , -266)
C T2DM	K.001	40	30	77.318, .1370	1.6540 (.0033 , 3.4569)	-190° (-148 , -220)

https://doi.org/10.1080/07420528.2017.1347670

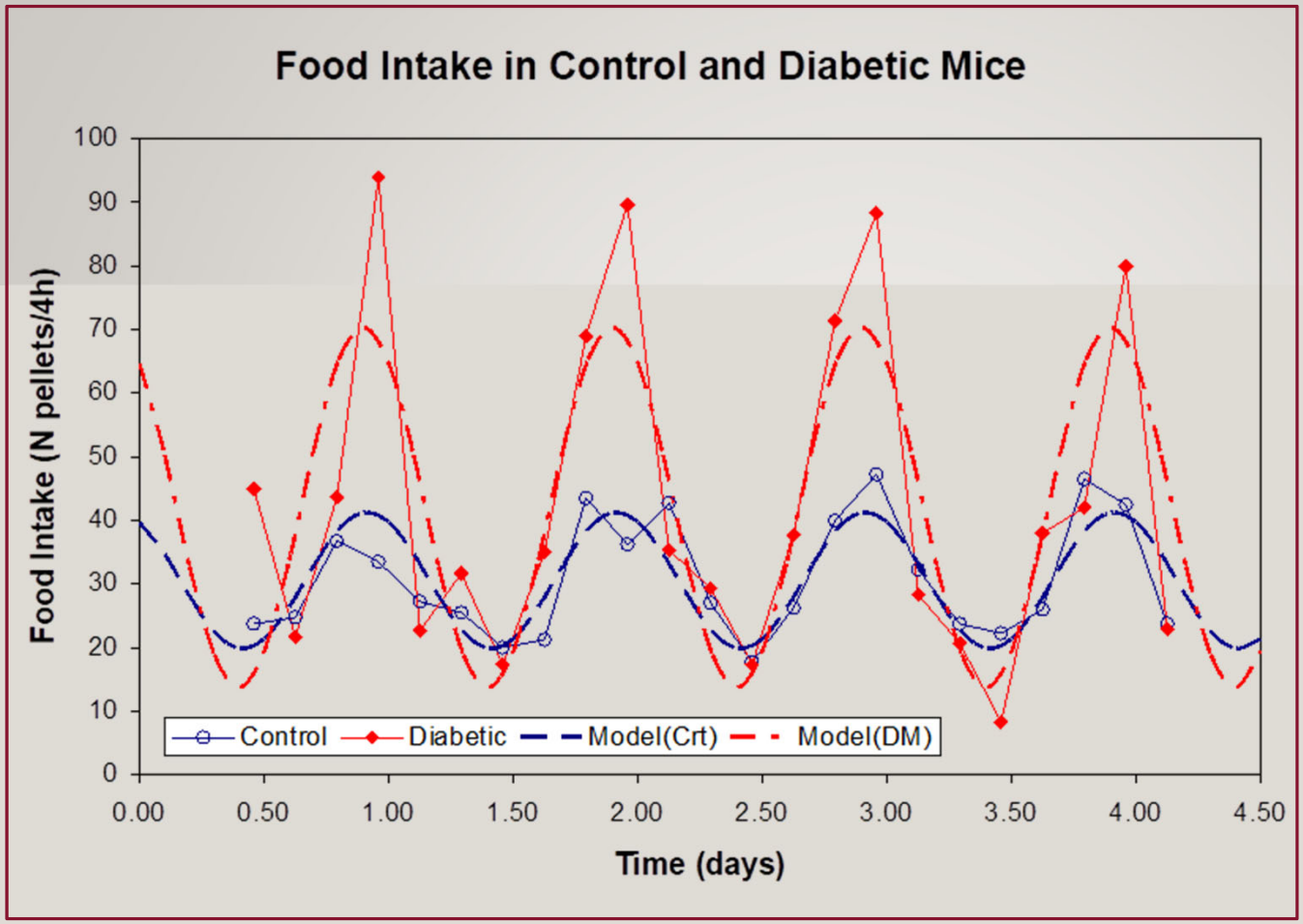




Diabetes shifts clock gene expression (*Per2* and *Per3*) within peripheral organs (GI tract) in C57BL/6J mice.
No effect on *Per* in liver, kidney and lung (not shown).



Mol Cell Biochem (2010) 338:203–213 -- DOI 10.1007/s11010-009-0354-4

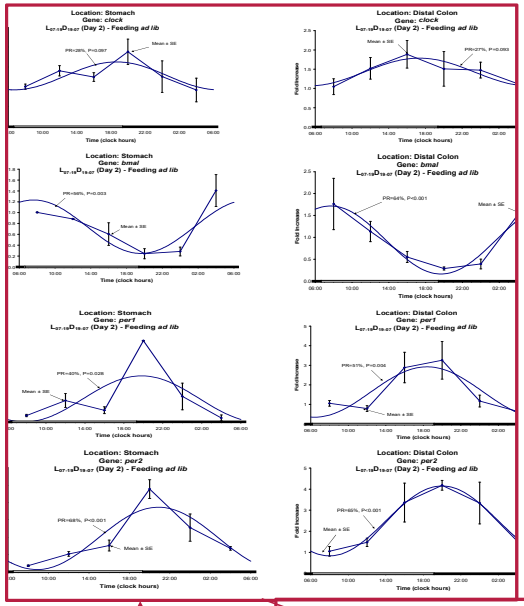


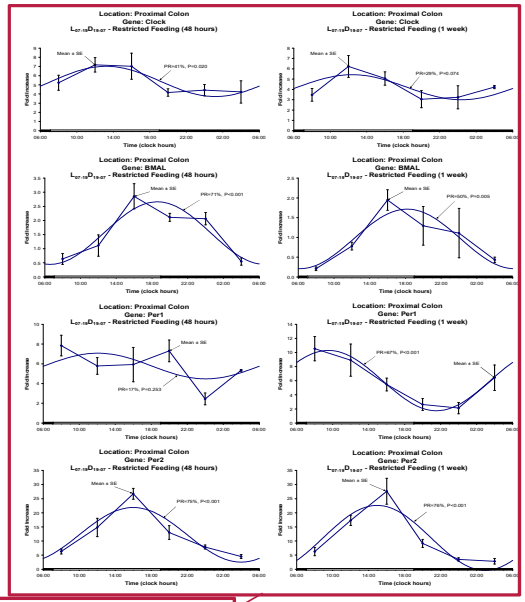
Comparison

MESOR: F=2.639, P=0.165
24h Amp: F=25.659, P=0.004
24h Phi: F=0.185, P=0.685

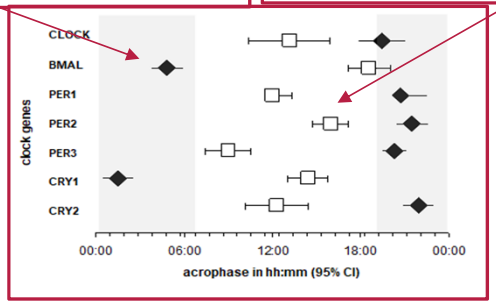
Mol Cell Biochem (2010) 338:203–213 -- DOI 10.1007/s11010-009-0354-4

MEAL TIMING AFFECTS CLOCK GENE EXPRESSION



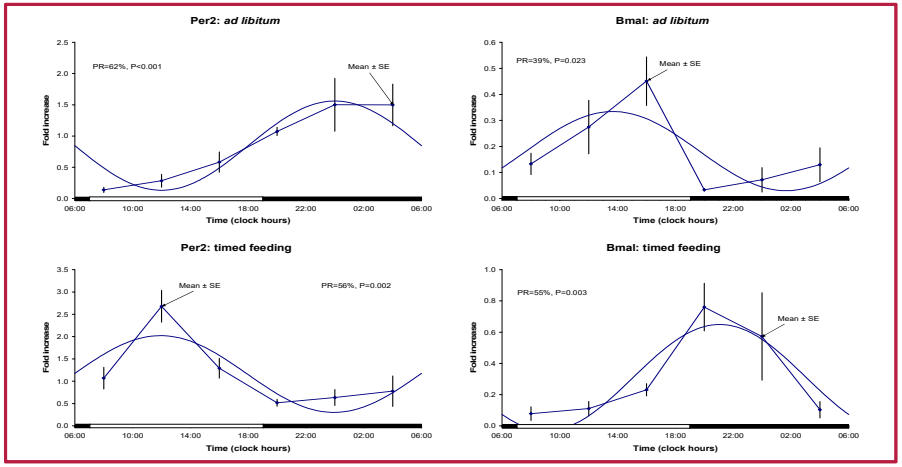


Colonic clock gene mRNA: feeding *ad lib*

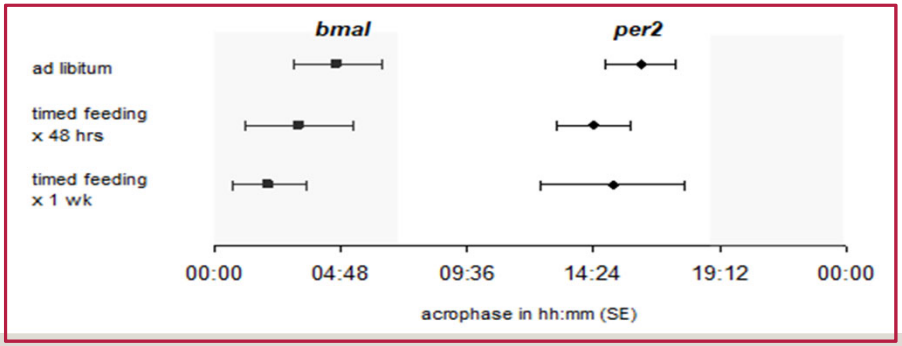


Colonic clock gene mRNA: timed feeding

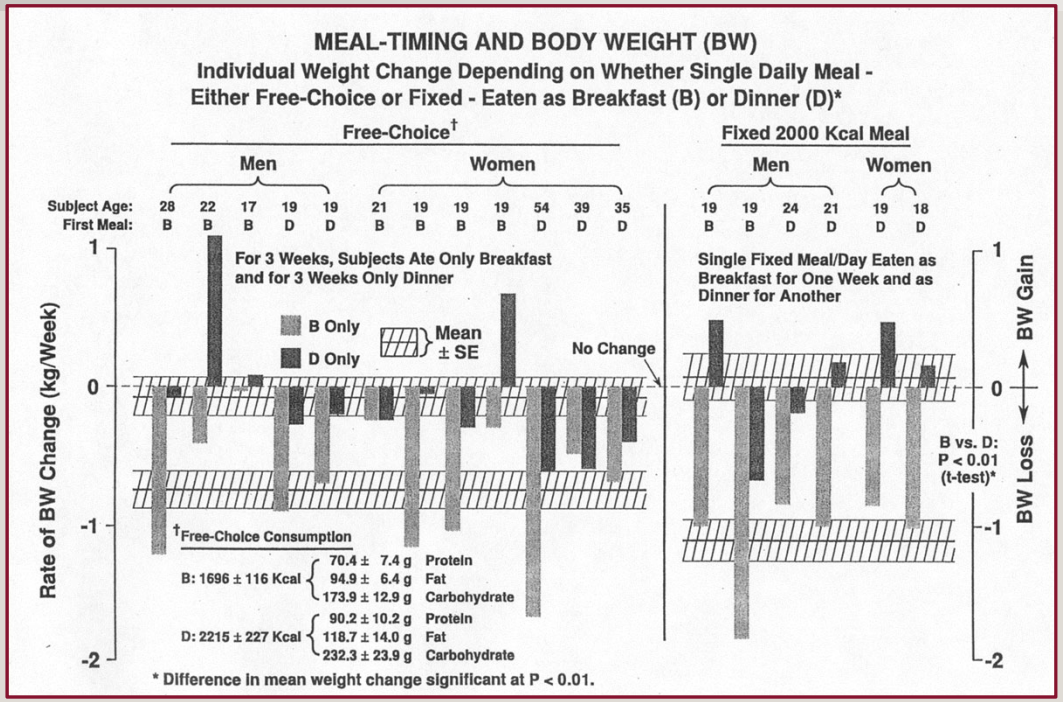
Clock gene expression at the protein level in intestinal tissues



Acrophase of clock gene expression in the SCN



IN HUMANS, BREAKFAST-ONLY BUT NOT DINNER-ONLY IS ASSOCIATED WITH WEIGHT LOSS



- Circadian rhythms persist during starvation
- Caloric restriction consistently prolongs life in several animal models
- Time-restricted feeding in singly-housed mice is harmful when food is available during rest span but not when offered during active span
- Time-restricted feeding is associated with larger circadian amplitude of circulating eosinophils, rectal temperature, corticosterone and liver glycogen
- TRF can prevent and reverse aspects of metabolic diseases
- In humans, time-restricted eating improved serum lipid and liver profiles and enhanced gut microbial richness

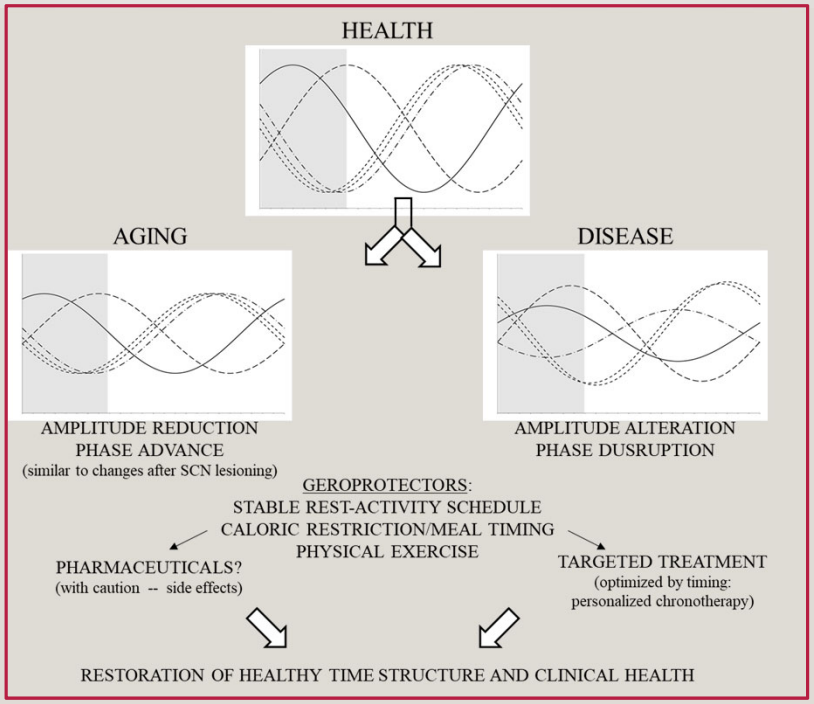
The Open Nutraceuticals Journal, 2012, 5, (Suppl 1-M2) 16-44
DOI: https://doi.org/10.1016/B978-0-12-819815-5.00004-5

CIRCADIAN RHYTHM OF DEFECATION AND CHRONORISK OF CONSTIPATION

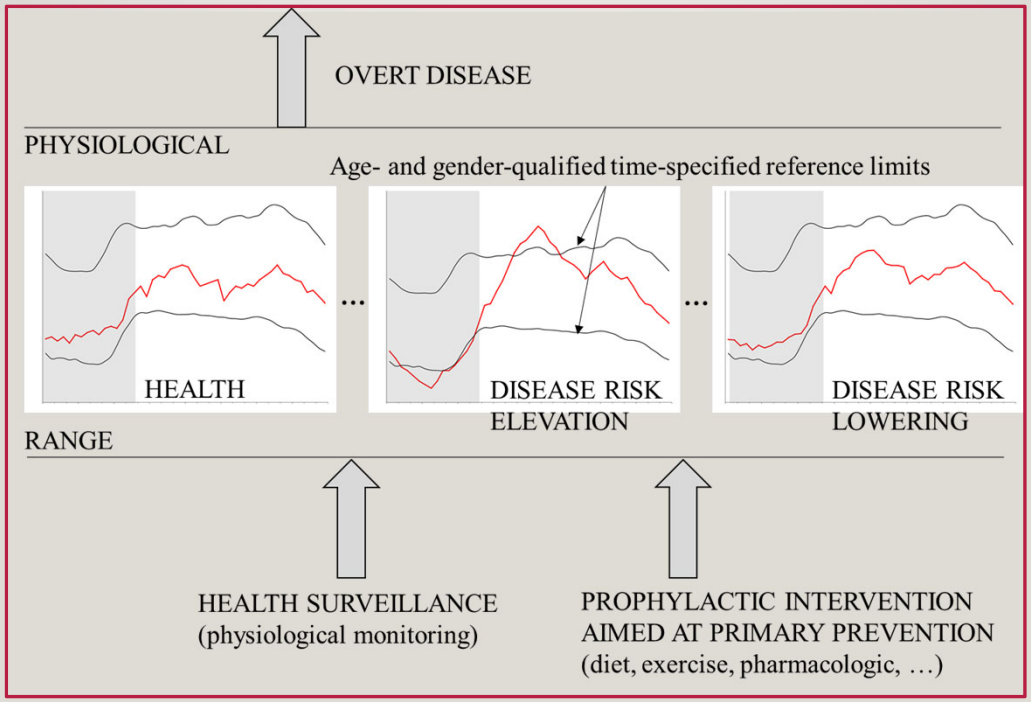
- The circadian rhythm of defecation is one of the major rhythms of health. About 30% of global population have a high risk for constipation, associated with cancer risk of colon, gall bladder and pancreas.
- Enterography was carried out on 294 healthy people (16-28y.), 44 constipated persons (30-60y) before and after treatment (forlax), and 65 retirees (60-77y).
- Constipation risk was less in 16-17y schoolchildren (7%) than in 18-28y students (21%). Constipation risk was less among those with morning (10%) than afternoon (41%) or evening (39%) elimination rhythm. QOL of patients with irregular defecation rhythm improved by 30% after restoration of rhythm regularity. Risk of constipation was higher in those older than 60y (73%) than in fertile women (40%).
- Timing of defecation rhythm may serve as biomarker of constipation (and cancer risk).

Shemerovsky CA et al. Circadian rhythm of defecation and chronorisk of constipation. In: Biomedical and Biosocial Problems of Integrative Anthropology, International Academy of Integrative Anthropology, St. Petersburg, 1998, pp. 251-253. [In Russian.]

DISTINGUISHING BETWEEN HEALTHY AGING AND INCREASED DISEASE RISK



PHYSIOLOGICAL MONITORING FOR HEALTH SURVEILLANCE

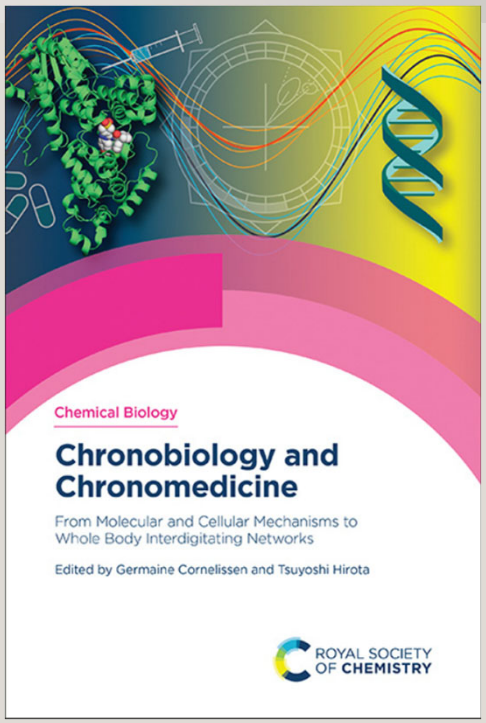


POSSIBLE REMEDIES: STRENGTHENING THE CIRCADIAN SYSTEM

- Lifestyle adjustments for health maintenance and optimization - Exposure to light and dark, a regular daily routine, exercise, and meal schedules are features amenable to manipulation to strengthen the circadian system. Exposure to bright light in the morning and melatonin administration in the evening have also long been known to be useful in the treatment of circadian rhythm sleep disorders.
- Clocking the drug - Chronotherapy and chronopharmacology aim at delivering a given treatment at the circadian stage of maximal efficacy while minimizing side effects.
- Drugging the clock - Conversely to altering the genome by means of gene editing, small-molecule modulators of the circadian clock are being developed that target the clock machinery at the molecular level. They target core or non-core clock proteins, modulating physiological effects as a consequence of agonist, inverse agonist, or antagonist interference. Among approved medications are lithium (bipolar disorder), metformin (T2DM), and rapamycin (cancer). New small-molecule compounds include longdaysin (inhibitor of casein kinase 1 lengthens the period, for cognitive deficits), and Nobiletin (activates ROR, protects against metabolic dysfunction by enhancing amplitude).

THANK YOU


UNIVERSITY OF MINNESOTA


Chemical Biology
Chronobiology and Chronomedicine
From Molecular and Cellular Mechanisms to Whole Body Interdigitating Networks
Edited by Germaine Cornelissen and Tsuyoshi Hirota
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