Staying Off The Dance Floor:
When No Rhythm is Better Than Bad Rhythm

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Editorial Focus

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Editorial Focus on: “Circadian Rhythm Disorganization Produces Profound Cardiovascular and Renal Disease in Hamsters”
By Martino, _et al._
The title of this Editorial Focus summarizes just one of the intriguing findings presented in this issue of the American Journal of Physiology: Regulatory Integrative and Comparative Physiology by Martino, et al. (8). They report profound cardiorenal pathology in hamsters carrying a mutation in an important circadian clock gene, casein kinase-1 epsilon, that in heterozygous animals (tau/+) results in a decrease in the free running circadian period from about 24 to 22 hours. This pathology is observed when the tau/+ animals are entrained to a 24-hour day which results in an abnormal phase relationship between the locomotor activity rhythm and the LD cycle, as well as a fragmented pattern of locomotor behavior, compared to wild-type hamsters. Cardiorenal pathology is not observed in tau/+ hamsters rendered rhythmless by prior ablation of the master circadian clock located in the hypothalamic suprachiasmatic nucleus (SCN). Of equal importance is the finding that the cardiorenal pathology is not observed in tau/+ hamsters when the heterozygous mutant animals are entrained to a LD cycle similar in period to their genotype (22 hours). The finding that the cardiovascular and renal pathologies are only observed in mutant animals after a prolonged entrainment to a LD cycle not closely in synchrony with their endogenous circadian period indicates that the adverse effects of the tau mutation are due to the circadian desynchrony itself, and not to direct effects of the mutated casein kinase gene on cardiorenal function. In contrast to the heterozygous animals, homozygous tau mutant hamsters do not show the cardiorenal pathology during exposure to a 24 hr day, and because of their extremely short circadian period (about 20 hrs) do not readily synchronize to a 24 hr LD cycle. This also supports the hypothesis that the cardiorenal pathology observed in the tau/+ hamster is due to circadian misalignment rather than a direct gene effect.

What makes the finding of such profound cardiovascular and renal disease in tau/+ hamsters entrained to a 24 hr, but not 22 hr, LD cycle particularly noteworthy is that, “circadian disorganization has never been shown as a casual risk factor in organ disease” (8), despite the fact that one of the guiding principles of the entire field of circadian biology has been the concept that overall circadian temporal organization is critical for the health and well being of the organism. In their now classic papers presented at the 1960 Cold Spring Harbor Symposium, Colin Pittendrigh and Jürgen
Aschoff, two of the founding fathers of the field of circadian biology, emphasized the importance of the internal circadian clock and temporal organization for the survival of the organism (1, 14). The importance of “external synchronization,” whereby the internal circadian clock synchronizes the behavior of the organism to the 24-hr changes in the physical environment is intuitively obvious. Less intuitive, but considered of equal biological significance, has been the importance of the circadian clock for “internal synchronization”. Such internal synchrony coordinates the timing and phase relationship of hundreds, if not thousands of internal rhythms with one another for maximal performance/survival. Many of us have pushed for the importance of internal synchrony for years recognizing, however, that we had a “skeleton in our circadian closet.” If you remove the heart – you die, the lungs – you die, the liver – you die, the master circadian clock in the SCN – nothing! In fact, in the case of the heterozygous tau mutant hamster, removing the SCN even protects you from cardiorenal disease when otherwise your internal master central clock would not be in proper synchrony with the entraining LD cycle. (I am actually uncertain as to whether or not no rhythm is better than a bad rhythm as my title implies, however, I will come back to this issue at the end of this editorial.)

It is important to stress and make the distinction that it is “circadian rhythm dysregulation” that is producing cardiovascular and renal disease in the tau+/ hamsters as opposed to a direct gene effect, because recent studies have found that 1) the molecular transcriptional-translational feedback loop that represents the core molecular clock is found in most cells and tissues of the body (12), 2) the genetic disruption of this molecular machinery via mutations or gene deletion in mice has been associated with a variety of peripheral and CNS disorders (3, 7, 9, 15), and 3) many of the components of the core molecular circadian clock appear to be components of other networks and pathways that are fundamental to normal cell function (6). For example, a mutation in the circadian clock gene, Clock, that results in lengthening of the circadian period and in the alteration in the expression of other circadian clock genes in mice (4), also leads to enhanced obesity and signs of the metabolic syndrome in mice on a high fat diet (16). However, because circadian clock genes have been implicated in the regulation of various metabolic pathways (6, 7), the metabolic effects could be due to either a global or tissue circadian disruption, or to a pleiotropic effect of the mutant Clock gene on cellular
metabolism at central or peripheral levels. The lack of any abnormal cardiovascular pathologies in four month old tau+/+ hamsters in the Martino, et al. study also suggests that the cardiovascular disease that is observed in older animals occurs only after an extended period of circadian desynchronization. As noted by Martino, et al., when all the data are taken together, that is when defining under what experimental conditions the tau+/+ hamsters do or do not develop cardiovascular and renal diseases, the results indicate that the mutation is not disrupting the tissue molecular clock per se, but instead it is the overall “global disturbances or desynchrony” of normal circadian rhythmicity that is leading to the cardiorenal pathology. In particular, Martino, et al. hypothesize that rhythms in peripheral tissues are being produced or influenced by their own intrinsic 22 hr clock, as well as by 24 hr signals that are coming from the master circadian clock in the SCN that has a similar 22 hr intrinsic period, but is sending out 24 hr signals due to its entrainment to the 24 hr LD cycle.

Over the years, many circadian biologists realized we actually had two skeletons in the circadian closet surrounding the concept of the importance of internal synchronization. Not only did ablation of the master circadian clock, and the seemingly loss of all coherent 24 hour rhythmicity, have little if any negative health consequences for the organism, neither did we have clear evidence linking circadian disruption to diseased organ or tissue function or to the overall health of the organism. Despite a few sporadic reports of decreased longevity in rodents exposed to repeated phase shifts in the LD cycle, including in cardiomyopathic hamsters (2, 11, 13), there is actually little evidence that circadian disorganization is “bad for an animal.” There has always been a certain irony to this conundrum since for many years the adverse mental and physical effects associated with shift work (and jet lag) have been assumed to be mainly caused by a disruption of normal circadian timing in humans (5, 10), while constantly phase shifting the circadian clock in animals seemed to have little negative health consequences on any organ systems. However, the finding that the genetic disruption of the circadian period of the clock in tau+/+ hamsters has an impact on cardiovascular and renal disease under one entraining LD cycle, and not another, and our recent finding that reversing the LD cycle of mice every 5 days has no effect on body weight unless the animals are “challenged” with a stressor that induces an inflammatory bowel response (unpublished results),
indicates that the effects of circadian desynchronization may be profound once experimental or genetic manipulations are used that allow one to uncover the effects of circadian disruption.

It should be noted that it is only in the last 5-10 years that it has been established that the same molecular machinery that underlies the generation of circadian rhythms in the SCN cells is actually present in most of the cells and tissues of the body, and that this daily clock is regulating the diurnal expression of 100’s of clock-controlled genes. Discovering the biological mechanisms that not only link the multitude of circadian clocks throughout the body, but also how these clocks are linked to many different processes at the cellular and molecular levels, represents a truly exciting area of biology. In addition, it represents a new frontier for medicine – one I like to call the da Vinci era. da Vinci drew a helicopter in the 15th century; he had the blueprint even though it took almost 500 years to actually build the helicopter. Circadian biologists have a pretty good blueprint of the molecular circadian clock, and are putting together the blueprint for how these clocks are linked to each other and to a multitude of cellular processes that underlie health and disease. Hopefully, it will not take 500 years to figure out how disrupting this circadian organization, either globally or locally, underlies a range of central and peripheral pathological conditions. As the paper by Martino, et al. makes clear, the effects of such disruption can be profound for cardiovascular and renal disease. We will need to exploit many different genetic and non-genetic animal models under a range of environmental conditions in order to elucidate the extent to which full circadian disruption may lead to tissue specific as well as global disease states, particularly age-related mental and physical diseases, before we understand how disrupted rhythms, as well as perhaps no rhythms at all (Fig. 1), impact the health and well being of the organism.
References:

Figure 1:

A cartoon of two happy clocks (ends) and one sad clock in middle to represent a major conclusion from the accompanying paper by Martino, *et al.* (Ref #9): disorganization of circadian timing can lead to cardiorenal disease (middle clock), while normal temporal organization (left clock), or the lack of any temporal organization (right clock) is not associated with this disease state in older *tau* mutant hamsters. However, it is probably premature to conclude that the lack of circadian rhythmicity is without adverse health consequences. We will need to exploit many different genetic and non-genetic animal models under a range of environmental conditions in order to elucidate the full extent to which circadian disruption may lead to tissue specific, as well as global disease states, particularly age-related mental and physical diseases, before we understand how disrupted rhythms, as well as perhaps no rhythms at all, impact the health and well being of the organism. (Drawing by Deanna Arble and Fred W. Turek.)
215x73mm (150 x 150 DPI)