Circadian rhythms

The vast majority of plants and animals undergo a series of physiological changes in a 24 hour period. These changes were initially directly connecting to environmental stimulants based on the fluctuations of light and darkness throughout the day. However, organisms have developed mechanisms to retain these cycles even in the absence of environmental cues. These are known as circadian rhythms (from the Latin "circa" for around and "dies" for day).

Jet Lag and Glucocorticoids

"Jet Lag"is characterized by a lack of synchronization between circadian rhythms and external time patterns. This phenomenon is accompanied by a series of physiological and psychological disturbances that result in mild to moderate amounts of discomfort in humans the severity of which are dependent upon speed, direction, and distance traveled (all qualifiers that increase the discrepancy between external time pattern and internal rhythms. Short term symptoms include changes in mood, decreased alertness, and nighttime insomnia. Chronic exposure to jet lag may result in accelerated malignant growth, mood disorders, and the atrophying of the temporal lobe (leading to spatial cognitive defects). In rats, repeatedly inducing jet lag results in cardiomyopathies and shorter lifespans. (5)

Luckily, the ability of adrenal glucocorticoids to control circadian rhythms has led scientists to an exciting discovery: a virtual cure for jet lag! Recent studies have demonstrated a direct link between the adrenal clock, regulated by glucocorticoids, and endocrine and behavioral reentrainment after jet lag has occured. Experiments involving the manipulation of the adrenal clock by selectively inhibiting glucocorticoid synthesis through timed administration of metyrapone prior to inducing jet lag in rats have resulted in shifts in glucocortocoid rhythm. This, in turn, leads a faster rates of behavioral reentrainment which, when applied to humans, will lead to a more immediate alleviation of symptoms. (5)

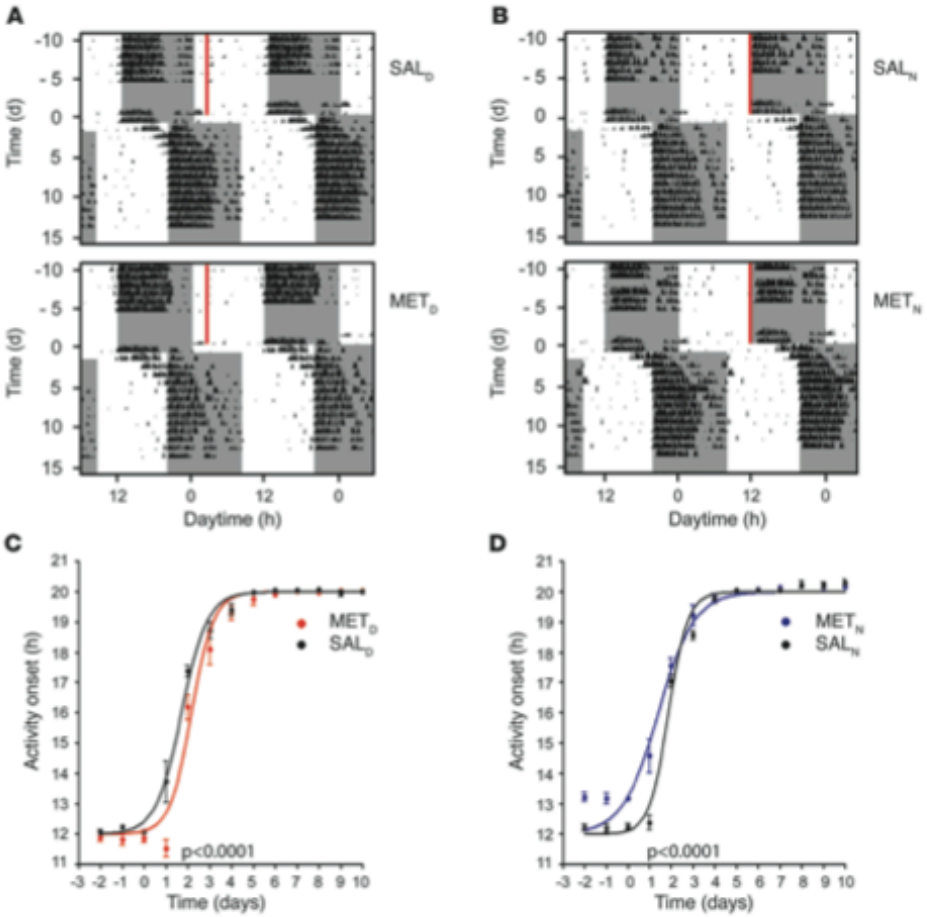

Figure 6
MET injection prior to jet lag affects behavioral resetting kinetics in a phase-delay paradigm. After injection of MET or saline for 16 days, animals were released into an 8-hour phase delay paradigm. (**A** and **B**) Representative double-plotted actograms of SAL_D and MET_D mice (**A**) and SAL_N and MET_N mice (**B**) 2 weeks before and 2 weeks after 8-hour phase delay of the LD cycle. Time and duration of MET treatment is shown by red bars. Dark phases are denoted by gray shading. (**C** and **D**) Resetting kinetics of activity onsets of MET_D and SAL_D mice (**C**) and MET_N and SAL_N mice (**D**). The curves of injected animals differed significantly from that of saline-treated control animals ($P < 0.0001$, MET_D vs. SAL_D and MET_N vs. SAL_N; $n = 6$ per group). Differences between MET- and saline-injected animals were still significant ($P = 0.0105$) when the shift was shortened to 7 hours, caused by delayed onset after MET injection at ZT12. All values are average ± SEM.

Cell Proliferation

Recent studies have revealed a connection between the circadian rhythms of cell proliferation (the growth and production of cells) and glucocorticoids, identifying the hormones as being able to act as both stimulators and inhibitors of cell proliferation. This is specifically demonstrated through experiments in which varying levels of dexamethasone are administered to subjects. While the regulation of the cell cycle is partially cell-autonomous, since only certain cell types are effected by hormone regulation, scientists have observed severely compromised cell cycle rhythms in zebrafish mutants lacking a pituitary gland due to the fact that several pituitary cell type subsets required signaling

from corticotrope lineage.

These findings have been exploited for theraputic use. Coriticoid mediated therapy is already employed to treat rheumatoid arthritis and asthma. However, the mediation of apoptosis and the cell cycle by glucocorticoids has incredible implications for the treatment of cancer. Glucocorticoid induced apoptosis in blood cell lineage has been shown to aid in the treatment of leukemia. Conversely, in order to avoid negative influences of radio and chemotherapies as a result of the anti-proliferative effect, chronotherapeutic approaches can be attempted in order to maximize the benifits while allowing traditional therapies their full efficacies. In addition to these findings, the deregulated glucocorticoid rhythms found in many cancer patients have been linked to higher survival rate. As such it is vitally important that more research be done on the mechanisms underlying glucocorticoid control over the cell cycle in order to increase cancer treatment efficacy.

Glucocorticoid Regulation of Circadian Rhythms

Glucocorticoids are a class of steriodal hormones that function to maintain homeostasis in the vast majority of vertebrate cells. These hormones are released by the adrenal gland on a circadian rhythm in mammals. In humans, these rhythms occur on a diurnal cycle, with the highest levels of glucocorticoids released in the morning the reason for which has been proposed to be maintenance of energy balance (2)

Conversely, glucocorticoids themselves have been demonstrated to control the cycling of circadian rhythms due the manner in which central rhythms are regulated. Central circadian rhythms are generated by a small hypothalamic nucleus known as the superchiasmatic nucleus. This clock is regulated by as many as 17 genes. Recent studies have identified that several of these genes are glucocorticoid receptor target genes. In other words, the genes that regulate circadian rhythms are in turn regulated by glucocorticoids themselves. (3)