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Exercise Strengthens Circadian Clocks

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PERSPECTIVES

Exercise strengthens circadian clocks

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We all know that exercise can increase the strength of our muscles. In this issue of *The Journal of Physiology*, new research by Schroeder and colleagues (2012) demonstrates that exercise can also have a big impact on the circadian system, a network of structures that regulate daily rhythms in physiology. Circadian rhythms are maintained by precise cycles of molecular activity within cells. These cellular clocks are kept synchronized to the environment by a pacemaker structure deep in the brain, the suprachiasmatic nucleus. The suprachiasmatic nucleus normally keeps the body clock system in time by monitoring the external light–dark cycles and then imposing cycles of hormone release, body temperature, feeding, activity and many other functions. In some instances the signals from the suprachiasmatic nucleus are feeble, barely strong enough to keep the body clock system in order. This might occur when frequent jet lag or rotating shift work imposes light–dark signals that confuse the central pacemaker. Diminished pacemaker output signals are also observed in ageing and in some neurodegenerative disorders (Colwell, 2011). It is important to develop better treatments for these dampened pacemakers to allow strong daily modulation of physiology, especially in light of current research linking disrupted rhythms to diabetes, cancer progression, cardiovascular disease, mood disorders and a wide range of negative health consequences (Arendt, 2010).

Fortunately, progress can be made using laboratory mice, which do not need fancy equipment or personal trainers to increase their level of exercise. Simply making a running wheel available will do the trick, as well as allow researchers to schedule the timing of when the running wheel is unlocked and free for use. In the present study, the investigators first demonstrated that free access to a running wheel can improve the power of diurnal rhythms. Further experiments investigated setting the time the wheel was available, either early (in the first 6 h) or late (in the latter 6 h) of the active phase. Mice undertook equivalent amounts of daily voluntary exercise in these conditions, but the timing of the wheel access altered the normal diurnal rhythms in heart rate and body temperature. For example, exercise scheduled late in the active period shifted the time of peak heart rate and body temperature to a later time of day.

For a closer look at the cellular clocks within different tissues, the researchers measured circadian rhythms *in vitro* using a bioluminescent marker of a core clock protein, PER2. By observing the rhythms of PER2 expression the researchers could determine if exercise treatments altered key properties of the circadian system. They were surprised to find that exercise restricted to early in the active phase decreased the amplitude of the rhythm recorded from the circadian pacemaker, the suprachiasmatic nucleus. In contrast, at either time tested, scheduled exercise increased the amplitude of the rhythm recorded from another important clock in the network, the adrenal gland. Exercise also altered other key properties such as phase in adrenal and liver, and period in the suprachiasmatic nucleus, adrenal and heart. These studies suggested that exercise could be altering fundamental properties of circadian system components. Could scheduled exercise be used to fix a broken clock?

In prior research, mice deficient in the peptide vasoactive intestinal polypeptide (VIP) have been shown to have disruptions to their circadian system regulating physiology and behaviour. Thus, it was not surprising that these researchers found the VIP-deficient mice showed reduced power in circadian rhythms of physiology and reduced amplitude of rhythms recorded *in vitro*. Interestingly, exercise, particularly when scheduled in the second half of the active period, was able to reestablish key properties of the rhythms and dramatically increased the amplitude of circadian rhythms recorded from the suprachiasmatic nuclei of these mice.

Previous studies have also established that mice deficient in VIP show loss of synchrony among different cells in the suprachiasmatic nucleus (Aton *et al.* 2005). Mice lacking the receptor that VIP targets in the suprachiasmatic nucleus show reduced amplitude circadian rhythms measured from the suprachiasmatic tissue *in vitro* (Hughes *et al.* 2008). The current study supports those prior findings (as well as others that space limitations prevent citation here) and builds evidence for the VIP-deficient mouse as a promising model for the study of diminished circadian clock function. These studies in mice may help us to develop exercise-based treatments to strengthen the circadian system for populations such as ageing adults or rotating shift workers. Scheduled exercise has been shown to alter the timing of circadian rhythms in humans, even in older populations (Baehr *et al.* 2003). Future research will likely help us better understand the mechanism underlying these effects, and perhaps suggest a method of treatment for circadian disruption.

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