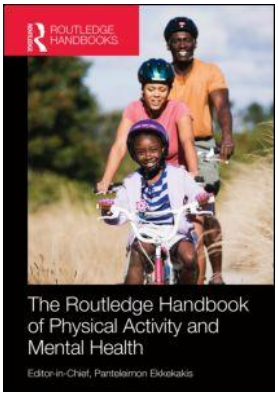

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IMPACT OF PHYSICAL ACTIVITY ON DIURNAL RHYTHMS

A potential mechanism for exercise-induced stress resistance and stress resilience

Monika Fleshner, Robert S. Thompson, and Benjamin N. Greenwood

Individuals vary in their susceptibility to the negative consequences of stressor exposure. The mechanisms for these differences include many factors that are beyond our control including genetic differences, age, or gender. Results from our work and others', however, suggest that maintaining a physically active lifestyle, a behavioral choice that is within our control, can reduce stress vulnerability and increase stress resistance and stress resilience.

There is clear evidence in the human literature that people who regularly exercise have a reduction in their risk for developing stress-exacerbated disorders (see Gerber & Puhse, 2009 for review) including cardiovascular disease (Lavie, Milani, O'Keefe, & Lavie, 2011; Mosca et al., 2011; Soderman, Lisspers, & Sundin, 2007), obesity (Brumby et al., 2011), mood disorders (e.g., anxiety and depression; Dinas, Koutedakis, & Flouris, 2011; Lincoln, Shepherd, Johnson, & Castaneda-Sceppa, 2011; Mata et al., 2011; Mehnert et al., 2011), attention deficit disorder (Archer & Kostrzewa, 2011), inflammatory bowel disease (Packer, Hoffman-Goetz, & Ward, 2010), communicable illness (Brown & Siegel, 1988), and sleep disorders (Elder et al., 2011). Most of these studies not only report improvements in these disease states, but also either directly assess or strongly suggest that reductions in the negative impact of stressor exposure may be an important mediator for the positive effects of exercise. We propose, therefore, that regular, moderate physical activity reduces the negative effects of stress on mental and physical health by increasing both stress resistance and stress resilience.

What are stress resistance and stress resilience?

The acute stress response is a highly adaptive cascade of physiological reactions that work in concert to facilitate successful fight/flight responses and increase an organism's chances of survival. Why then would stress resistance be a good thing? It is important to recognize that stress resistance does not imply the absence of the stress response. Rather it has been suggested that increased stress resistance allows an organism to experience greater stressor intensities and/or longer stressor duration before stress consequences cross over from adaptive to maladaptive (Fleshner, Maier, Lyons, & Raskind, 2011). In contrast, stress resilience is directed at recovery. Resilience, by definition, is having or showing power of recovery (Williams, 1979). Thus, changes in stress

resilience are only realized after an organism has suffered negative consequences of stress. Stress resilient organisms, therefore, require less time and/or treatment to recover after crossing the tipping point from adaptive to maladaptive effects (Fleshner et al., 2011).

Using a well-established animal model of stress (learned helplessness), we have evidence that 6 weeks of wheel running, but not treadmill training (Moraska, Deak, Spencer, Roth, & Fleshner, 2000), improves both stress resistance and stress resilience in rats. Specifically, physically active, compared to sedentary, rats are protected against stress-induced immunosuppression (Moraska & Fleshner, 2001), mood disruptions (i.e., learned helplessness behavior, depression and anxiety (Greenwood & Fleshner, 2011; Greenwood, Foley, et al., 2003; Moraska & Fleshner, 2001), and improve their recovery after suffering negative stress effects (Greenwood, Strong, Dorey, & Fleshner, 2007; Moraska & Fleshner, 2001).

Mechanisms for stress-buffering effects of exercise

Six weeks of wheel running constrains activation of stress-responsive neurocircuitry

There are several ways that the central neurocircuitry of the stress response is changed in physically active rats, and such adaptations can be mechanistically linked to stress resistance effects. For example, 6 weeks, but not 3 weeks, of wheel running constrains activation of the serotonin (5-HT) neurons in the dorsal raphe nucleus (DRN) during exposure to uncontrollable stress (Greenwood, Foley, Burhans, Maier, & Fleshner, 2005). This constraint is evidenced by a reduction in c-Fos expression in 5-HT neurons and upregulation of $5HT_{1A}$ inhibitory autoreceptors (Greenwood, Foley, Burhans, et al., 2005; Greenwood, Foley, Day, et al., 2005). Given that the exaggerated DRN 5-HT neuronal response produced by uncontrollable stress is both necessary and sufficient to produce learned helplessness behaviors (Maier & Watkins, 2005), constraint in this response is likely a critical mechanism responsible for exercise-evoked protection against uncontrollable stress effects on mood and anxiety (see Greenwood & Fleshner, 2011 for a recent review). In addition, we have equally compelling evidence that 6 weeks of wheel running constrains central autonomic neurocircuitry responsible for activating the peripheral sympathetic nervous system (SNS) response to stress (M. Fleshner, 2000). Rats that ran for 6 weeks on running wheels have reduced c-Fos expression in primary central autonomic regulatory centers (Greenwood, Kennedy, et al., 2003), including a rostral ventral lateral medulla, A5 noradrenergic neurons, and locus coeruleus (LC). The beneficial consequences of constraint over stress-evoked autonomic responses include protection against immunosuppression and inflammatory protein increases (i.e., interleukin-1beta), both of which are mediated by excessive SNS responses (Fleshner, 2006; Johnson et al., 2005; Kennedy et al., 2005).

It is important to note that exercise does not eliminate the stress response; rather it constrains it, thus preventing an excessive response. Uncontrollable tail shock is a potent stressor, designed to reveal maladaptive consequences of the stress response. It drives the stress response to exhaustion, as evidenced by desensitization of DRN inhibitory $5HT_{1A}$ autoreceptors (Rozeske et al., 2011) and LC and splenic catecholamine depletion (Greenwood, Kennedy, et al., 2003). In animals that are allowed to habitually voluntarily run in wheels for 6 weeks, this extreme response is prevented. Interestingly, the changes produced by 6 weeks of wheel running, which help buffer against the maladaptive effects of stress, persist after wheel running has ceased. Greenwood, Loughridge, Sadaoui, Christianson, and Fleshner (2012) reported that exercise-evoked protection against stress-induced deficits in shuttle box escape learning persists for 15 days, but was lost 25 days, after forced exercise cessation. The results to date are therefore

consistent with the idea that persistent adaptations in specific neurotransmitters, neuropeptides, and/or growth factors in physically active organisms likely contribute to reductions in stress vulnerability.

Voluntary wheel running is rewarding

The mesolimbic reward pathway includes a major dopaminergic projection from the ventral tegmental area (VTA) to the nucleus accumbens (Acb). Activation of this pathway has been implicated in the treatment of depression (Nestler & Carlezon, 2006; Yadid & Friedman, 2008) and anxiety (Pezze & Feldon, 2004; Talalaenko et al., 1994), and may play an etiological role in stress resistance produced by exercise. Physical activity is a powerful natural reward as evidenced by spontaneous wheel running behavior in many animal species. In addition, rats will work (learn to press a lever) to gain access to a running wheel (Belke, 2000a, 2000b; Iversen, 1993). We have recently reported that rats display (1) a conditioned place preference for wheel running, (2) an increase in the reward-related plasticity marker FosB/ΔFosB and Δ-opioid receptor mRNA in Acb, and (3) increased levels of tyrosine hydroxylase (TH) mRNA in the VTA (Greenwood et al., 2011). These observations support the idea that wheel running elicits plasticity in the mesolimbic reward pathway. Future work is required to determine whether such changes contribute to exercise-evoked increases in stress resistance and resilience.

Controllability of wheel running is not necessary for stress resistance

Research in humans and animals indicates that the experience of choice can itself improve mental health and produce stress resistance. A series of recently completed studies in our laboratory began to explore if controllability of wheel running behavior is critical for stress-buffering effects. Rats were housed for 6 weeks with either (1) a locked wheel, (2) a voluntary running wheel, (3) a yoked motorized wheel, or (4) were trained daily on a treadmill. The motorized wheel was programmed to rotate at a speed, pattern, and duration that mimicked voluntary wheel running. Rats in the motorized wheel thus ran a similar distance, pattern, and duration as the voluntary running animals; however, they had no control over their running behavior. In other words, the physical activity patterns between the groups were equal, and only the choice to run was different. After 6 weeks, rats were exposed to uncontrollable tail shock and tested for negative behavioral consequences (shuttle box escape learning, social exploration, and exaggerated fear conditioning). Results indicated that choosing to run is not critical to reveal stress-buffering effects. Rats that were forced to run in wheels and rats that voluntarily ran in wheels were equally protected against the behavioral consequences of uncontrollable stress. This result was surprising to us given the fact that forced treadmill training, despite producing significant fitness benefits, failed to produce any stress-buffering effects. The critical difference between treadmill training and forced wheel running could lie in the pattern of the behavior or the ability of the behavior to influence diurnal/circadian rhythms. Rats forced to run in treadmills are typically made to run continuously for a brief period. In contrast, rats that run voluntarily in wheels (and the rats forced to run in motorized wheels in the study described above) run in a markedly different pattern. These rats run in brief, repeated bursts throughout the active cycle. It is possible that this pattern of exercise is particularly able to influence diurnal/circadian physiology. Wheel running may therefore be producing stress resistance and resilience by influencing diurnal/circadian rhythms.

New ideas: diurnal/circadian effects of exercise contribute to exercise-induced stress resistance and resilience

Diurnal rhythms of physiology and behavior are driven by both circadian and non-circadian mechanism. Those effects that are circadian occur in the absence of photic or non-photic diurnal cues and are generated by a core set of clock genes that regulate their own expression in an approximately 24-hour transcriptional-translational feedback loop. It is clear from the stress literature that disruptions in diurnal/circadian rhythms are ubiquitous in people suffering from negative mental and physical consequences of stress, including metabolic disease (Arble, Ramsey, Bass, & Turek, 2010; Cagampang, Poore, & Hanson, 2011), cardiovascular disease (Portaluppi et al., 2012; Takeda & Maemura, 2011), and depression/anxiety (Bunney & Potkin, 2008; McClung, 2007). Interestingly, many of the biological rhythm changes are normalized in patients who are successfully treated with antidepressants, including SSRIs (Bunney & Potkin, 2008) and desipramine (Jiang et al., 2011). It remains unclear if changes found in diurnal/circadian rhythms are symptomatic of the disease state or etiologically linked to these negative outcomes. With recent advances in animal models that allow direct genetic manipulations, however, evidence is accumulating that disrupting rhythms by genetically knocking out components of the clock genes may indeed directly contribute to disease development. Circadian locomotor output kaput (CLOCK) and Brain and Muscle ARNT-Like protein (BMAL) gene knockout mice, for example, develop hyperinsulinemia and diabetes (Marcheva et al., 2010), Cryptochorme (Cry1/Cry2)-deleted mice develop hypertension (Okamura, Doi, Yamaguchi, & Fustin, 2011), and CLOCKΔ19 mice express anxiety behavior (Coque et al., 2011).

The impact of stress on biological rhythms has been reported many times, but the precise nature of the disruption remains an active area of research. The most consistent observation reported in the literature is that exposure to intense, repeated, or chronic stressors dampens rhythms and flattens amplitudes such that the peak-to-trough, but not the period or frequency, of the physiological or behavioral rhythm is impacted. The types of diurnal rhythms dampened by exposure to a variety of stressors include rhythms of mean arterial pressure (Thompson, Strong, & Fleshner, 2012), heart rate (Meerlo, Sgoifo, & Turek, 2002; Thompson, Strong, & Fleshner, 2012), core body temperature (Kant et al., 1991; Meerlo et al., 2002; Sgoifo et al., 2002; Thompson et al., 2012), glucocorticoids (Fleshner, Deak, et al., 1995; Ushijima, Morikawa, To, Higuchi, & Ohdo, 2006), and wheel running or spontaneous activity behavior (Meerlo et al., 2002; Moraska & Fleshner, 2001; Sgoifo et al., 2002; Solberg, Horton, & Turek, 1999).

Figure 21.1 is an example our recent data revealing the impact of exposure to acute uncontrollable tail shock stress (100, 1.5mA, 5-s tail shocks) on diurnal rhythms. Adult male F344 rats were instrumented with biotelemetric devices that allow automated moment-to-moment recording of spontaneous activity, core body temperature, heart rate, and EEG. After 2 weeks of recovery, rats (8/group) were exposed to tail shock stress or remained in their home cages. Figure 21.1 reveals that stress produced an expected stress-induced hyperthermic (SIH) response. SIH is a well-characterized phenomenon in humans (Oka, Oka, & Hori, 2001) and animals (Lkhagvasuren, Nakamura, Oka, Sudo, & Nakamura, 2011). Telemetry data were collected after all rats were returned to their home cages and remained undisturbed for 6 days. Figure 21.1 reveals that rats not exposed to stress have clear diurnal rhythms in core body temperature. In stark contrast, rats exposed to stress have a dampened diurnal rhythm due to an elevation in the trough body temperature during light. Using a diurnal rhythm, non-linear, least squares, dual harmonic analysis (Gronfier, Wright, Kronauer, Jewett, & Czeisler, 2004), we concluded that the amplitude was reliably flattened for 72 hours. We did not find a reliable change in the phase of the rhythm.

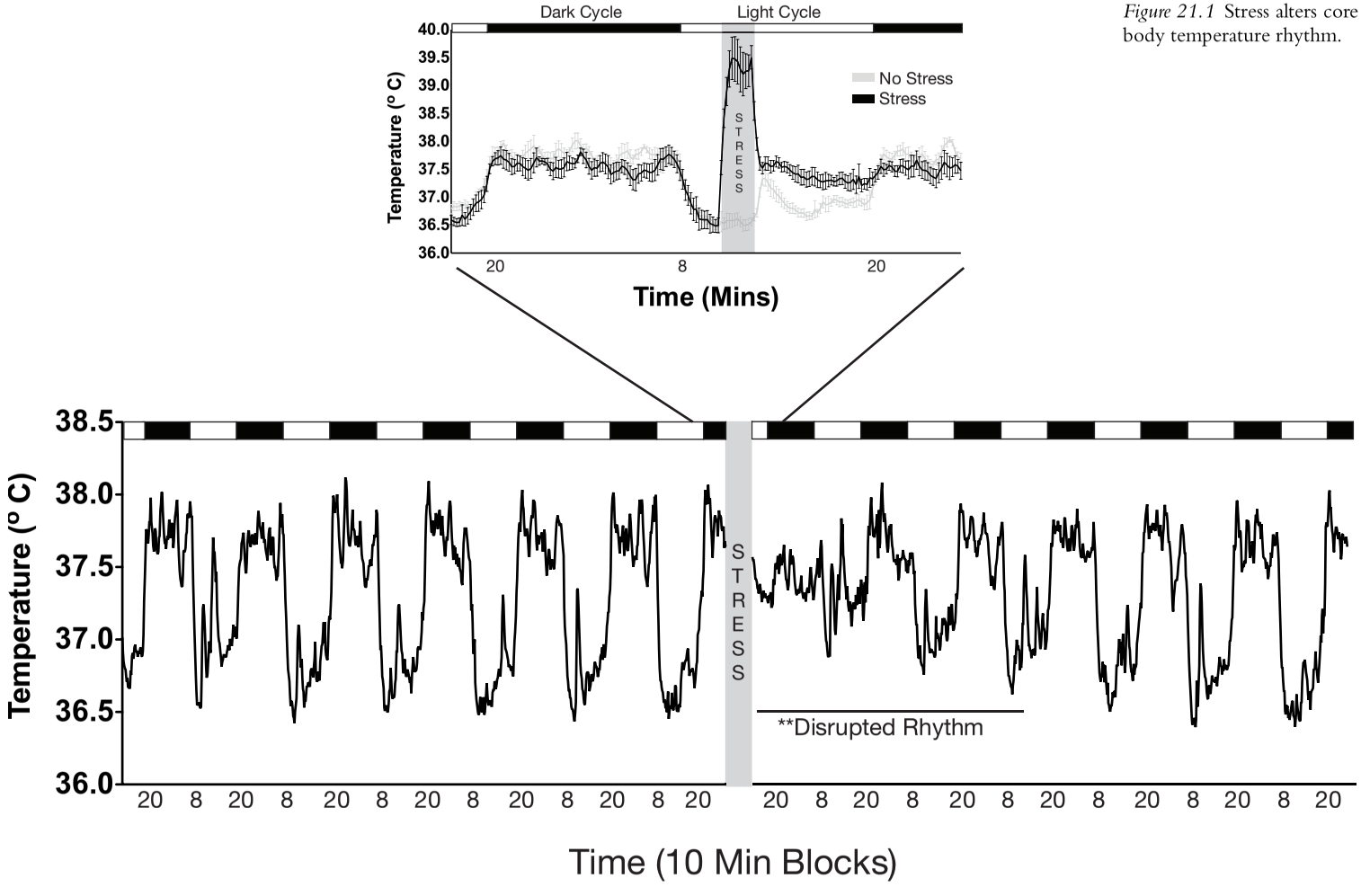

Figure 21.1 Stress alters core body temperature rhythm.

The mechanisms for stress-induced amplitude flattening of diurnal behavioral and biological rhythms are unknown. Amplitude flattening could be produced by dyssynchrony in circadian clocks. It has been reported, for example, that exposure to chronic unpredictable stress reduces the amplitude of rhythmic expression of period 2 (Per2) protein in the brain's "master clock," the suprachiasmatic nucleus. Diurnal/circadian rhythms and clock gene expression are synchronized to the environment. The most important synchronizing (entraining) environmental stimulus is light (Morin & Allen, 2006; Pickard, 1985). In addition, there are several other very powerful non-photic entrainment cues as well, including feeding schedules (Girotti et al., 2006; Mendoza, 2007), behavioral patterns (Edgar & Dement, 1991), temperature (Buhr, Yoo, & Takahashi, 2010), and adrenal hormones (Amir & Stewart, 2009; Segall, Perrin, Walker, Stewart, & Amir, 2006).

Treatment of stress-related mood disorders often includes clock "resetting"

Restoring circadian rhythms may be a new way to successfully manage depression (Gorwood, 2010). In fact, many therapeutic strategies currently in use target the circadian system. These include both pharmaceutical strategies such as agomelatine (melatonin receptor agonist and a $5HT_{2c}$ antagonist, (Gorwood, 2010) and adenosine A_{2a} receptor antagonists (Batalha et al., 2012), and non-pharmacological entrainment strategies such as bright light (Ashkenazy, Einat, & Kronfeld-Schor, 2009; McClung, 2007), sleep deprivation (Bunney & Potkin, 2008), temperature (Lowry, Lightman, & Nutt, 2009), and scheduled activity/exercise (Barr-Anderson, AuYoung, Whitt-Glover, Glenn, & Yancey, 2011). Thus there is interest in exploiting the restoration of circadian/diurnal rhythms for effective therapeutic strategies to treat stress-related mood disorders.

We hypothesize that just as regular exercise can be used therapeutically to perhaps restore circadian disruptions, it may also function to increase central and peripheral clock synchrony, thus resulting in greater rhythm amplitudes and hence increased resistance to stress-induced amplitude flattening. In fact, there is recent evidence that through a daily rhythm of endogenous dopamine release in multiple brain regions, exercise can directly modulate clock gene expression in the brain (Hood et al., 2010). In addition, exercise has been reported to coordinate clock gene regulation in muscle of humans (Zambon et al., 2003). Thus it is feasible to propose that habitual exercise synchronizes clock genes across specific brain neurocircuitry and peripheral tissues, and that this robust synchronization would increase the amplitude of physiological and behavioral rhythms, making it more difficult to disrupt them with stress. This new hypothesis and our evidence to support it is preliminary but promising.

Figure 21.2 shows core body temperature diurnal rhythms in sedentary and wheel running rats measured with biotelemetry (4/group). Rats that run in a wheel for 6 weeks, but not 1 or 3 weeks, have higher peak levels of core body temperature, leading to a greater amplitude of the rhythm of core body temperature compared to rats that remain sedentary for 6 weeks. This is intriguing because this time course is mirrored for the impact of wheel running on stress resistance as well. Rats are protected against stress-evoked increases in anxiety/depression if they run for 6 weeks, but not 3 weeks (Greenwood, Foley, Burhans, et al., 2005).

Exposure to uncontrollable tail shock additionally produces flattened diurnal rhythms of corticosterone (Fleshner, Deak, et al., 1995). This is due primarily to an elevation in trough corticosterone concentrations. As depicted in Figure 21.3, sedentary male F344 rats (8/group) exposed to uncontrollable tail shock have elevated trough levels of corticosterone measured 24 hours after stress, at 0900, when low trough levels of corticosterone should be found. In contrast, this effect of stress on elevating trough levels of corticosterone is reduced in rats that ran for 6 weeks prior to stress.

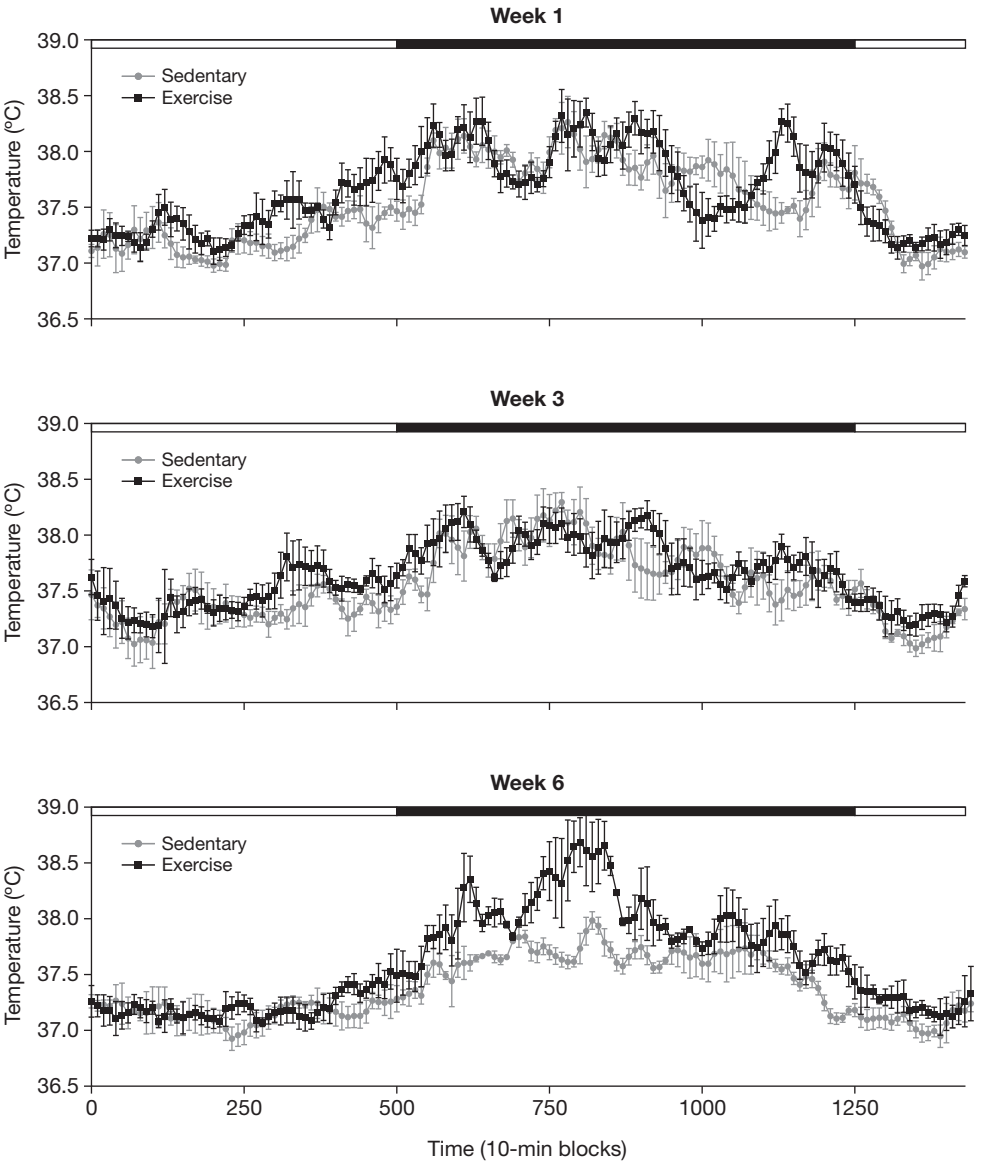

Figure 21.2 Core body temperature has greater peak amplitude after 6 weeks of wheel running.

Finally, Figure 21.4 shows that exposure to uncontrollable tail shock stress can disrupt the normal expression of clock genes, and exercise may prevent this effect. Male F344 rats (7–16/group) were allowed to run on wheels for 6 weeks (exercise) or remained sedentary. Rats were then exposed to either uncontrollable tail shock stress or no stress and were sacrificed immediately after stressor termination between Zeitgeber Time (ZT) 5–7. Using *in situ* hybridization, we measured the expression of period 1 (Per1) clock gene mRNA in the dentate gyrus (DG) of the hippocampus. DG was assessed because it is known to be activated by wheel running (Clark, Bhattacharya, Miller, & Rhodes, 2011) and is linked to stress-related mood

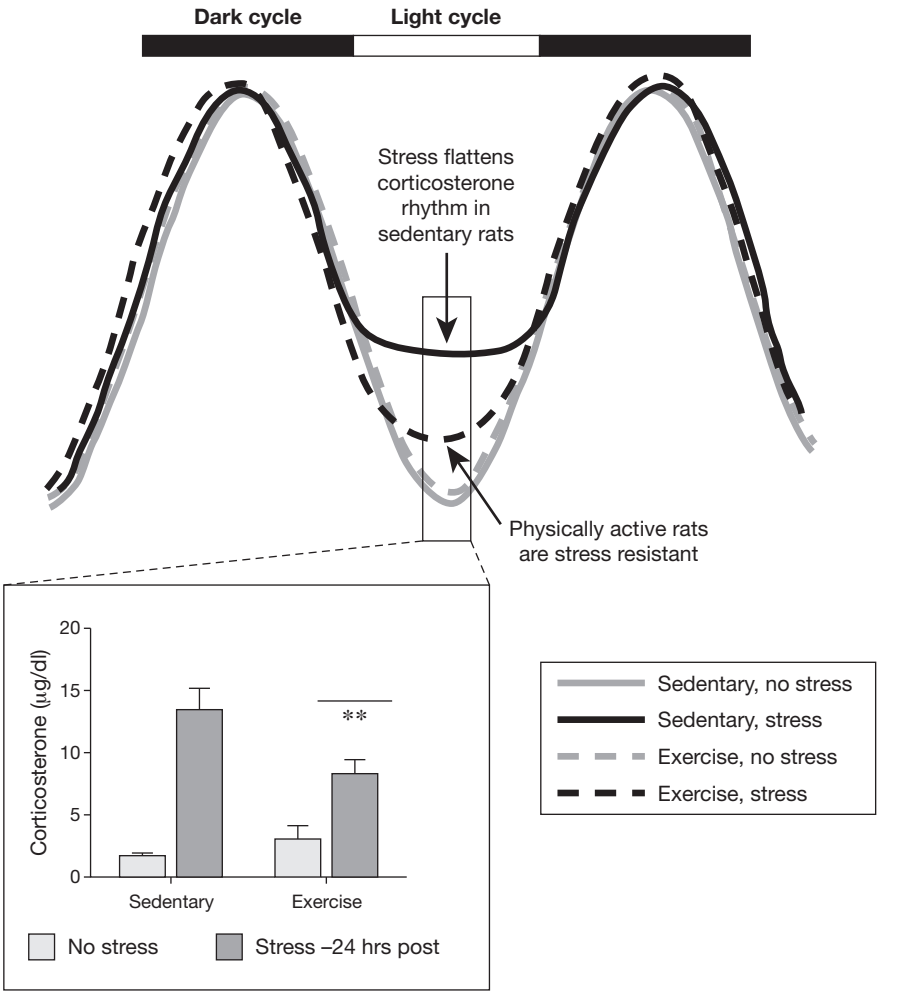

Figure 21.3 Flattened corticosterone rhythm after stress is prevented by wheel running.

disorders and corticosterone regulation (de Kloet, Karst, & Joels, 2008; Joels, 2007). Exposure to stress reduced levels of Per1 mRNA in the DG of sedentary rats. Exercise not only altered basal expression of Per1 mRNA in the DG at this clock time, it prevented the ability of stress to suppress Per1 mRNA in the DG. These data provide intriguing preliminary evidence that exercise can affect expression of clock genes in specific brain regions and can prevent shifts in clock gene expression produced by stress; thus providing a potential mechanism for how exercise might impact diurnal/circadian rhythms of behavior and physiology.

Conclusions and future directions

Individuals vary in their vulnerability to experience the negative consequences of stressor exposure. Maintaining a physically active lifestyle, a behavioral choice that is within our control, can reduce stress vulnerability and increase stress resistance and resilience. The fact that regular

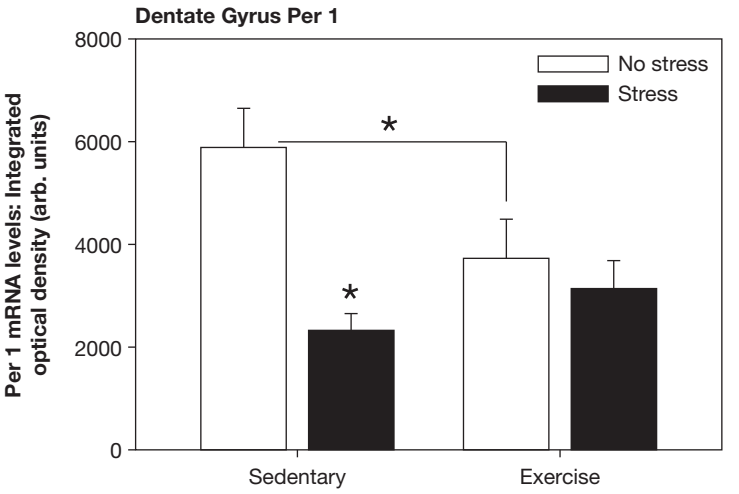

Figure 21.4 Hippocampal clock genes are disrupted by stress and protected by wheel running.

habitual exercise produces global protections against the negative consequences of stress that range from immunosuppression and learning deficits, to depression and anxiety, suggests that the mechanisms could be many and/or biologically fundamental. We have identified a variety of specific neurobiological changes in the brain that function to confer protection, and may be important as future pharmaceutical targets for treatment. In addition, our recent work suggests that there is something special about the habitual pattern of exercise that promotes broad stress resistance and stress resilience. In this chapter we propose the novel hypothesis that regular, habitual exercise in the active part of the diurnal cycle is a powerful non-photic entrainment cue that may function to synchronize both central and peripheral tissue clocks such that the synchronized output results in greater amplitude rhythms that are resistant to stress-evoked flattening. Future work should explore the mechanisms for this effect, and whether synchrony of diurnal/circadian rhythms is mechanistically linked to the increase in stress resistance and resilience produced by exercise.

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