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Exercise Sets the Muscle Clock with a Calcium Assist

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Circadian clocks exist in virtually every cell of the body, including skeletal muscle. The clocks function to temporally align the transcription of cellular processes with the active and rest phases of the day. While behavioral outcomes such as physical activity have historically been used to as an output measure to test for changes in circadian rhythms, emerging research has determined that physical activity/exercise alone can directly alter the muscle clock to manage the timing or phase of muscle circadian rhythms (Kemler *et al.*, 2020). Broadly, the skeletal muscle circadian clock contributes to the observed daily oscillations of metabolism, structure, and function (Schroder *et al.*, 2015; Dyar *et al.*, 2018). Therefore, exercise induced shifts in the muscle clock can have downstream effects on the daily timing of a myriad of cellular processes to impact muscle health and function.

In this issue of *The Journal of Physiology*, Small and colleagues (Small *et al.*, 2020) expand our understanding of the direct effect of exercise and muscle contractions on expression of the core circadian clock genes in both human and mouse skeletal muscle. The authors report that 15 minutes of intense (80% VO_2max) cycling exercise in humans, 18 minutes of ex vivo contractions with mouse muscle and 30 minutes of electrical pulse stimulation-induced contractions in C2C12 myotubes all increase the expression of the circadian gene, *PER2*/*Per2*, at 60 minutes following exercise. This finding is supported from data mining of the MetaMex online exercise transcriptome tool, showing that both aerobic and resistance exercise paradigms increase *PER2* expression between 0h-3h post-exercise in a variety of published human experiments. The findings that exercise and/or contractions selectively target the core clock gene, *PER2/Per2*, highlight there is a direct effect of exercise on the muscle clock that is conserved across mammalian models of exercise/muscle contractions.

To reveal the mechanistic link between exercise and circadian clock function, the authors examined the transcriptional regulation of *Per2* expression in their stimulated C2C12 myotube model. Previous work in the circadian field identified that the *Per* genes contain cAMP-response elements (CRE) in their promoter regions, implicating the CRE binding protein (CREB) as a potential mediator of contraction-induced *Per2* upregulation (Tischkau *et al.*, 2003). Small and colleagues show that contractions induce CREB phosphorylation at Ser133 in skeletal muscle. Moreover, the authors identify that contraction induced CREB phosphorylation is calcium dependent, as addition of the calcium channel blocker nifedipine

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abolished the increase in CREB phosphorylation. The authors then demonstrate contractions increased pCREB binding at the *Per2* promoter, delineating the direct interaction between contractions, phosphorylation of CREB and its role transcriptionally regulating Per2 expression. Similar to the contraction-induced changes in phosphorylation, CREB genomic binding was also abolished when contractions were induced in the presence of nifedipine. Importantly, the addition of ionomycin, a calcium ionophore, mimicked the effects of contractions alone on CREB phosphorylation and *Per2* promoter binding, highlighting the importance of calcium as a second messenger with the interaction between exercise and the muscle circadian clock.

One last note about the investigation by Small and colleagues is the conserved nature of the exercise- and/or contraction-induced changes in core circadian clock gene expression. Too often, temporal considerations (i.e., time of day) have been overlooked in previous rodent exercise interventions, especially when attempting to draw parallel conclusions between human and rodent experimental outcomes. For instance, subjecting rodents to treadmill exercise during the light phase is equivalent to having humans exercise in the middle of their rest phase. Not only do these oddly timed exercise bouts increase stress for the rodent, but they also may introduce confounding systemic circadian effects. The data from Small and colleagues highlight the translational potential of exercise interventions across species.

Exploring the mechanistic interplay between exercise and core circadian clock gene expression is an essential first step for understanding how circadian rhythms can mediate exercise responses and adaptation. Further, once the connection between exercise and the muscle clock have been identified and characterized in a healthy system, implementing/integration of this new knowledge into models of circadian disruption (e.g., shift-work and various age-related diseases) will be improved. This work by Small and colleagues represents an exciting launchpad for the continued integration of circadian concepts into exercise physiology, highlighting a key role of calcium in the core clock gene transcriptional response to a single bout of muscle contractions.

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