Nature Reviews Endocrinology | Published online 24 Jun 2016; doi:10.1038/nrendo.2016.102

EXERCISE

Osteocalcin in the adaptation to exercise

H. Mark Weidman Photography / Alamy Stock Photo

> Osteocalcin also seems to be required for optimum exercise capacity

A bone hormone, osteocalcin, is required for adaptation to exercise and optimum exercise capacity, according to new research published in *Cell Metabolism*.

"Circulating osteocalcin levels increase markedly during endurance exercise in mice and humans," explains author Gerard Karsenty. This observation indicated that osteocalcin might be involved in the regulation of adaptation to exercise. In the current study, Karsenty and colleagues set out to investigate what role osteocalcin has in the response to exercise.

The researchers demonstrated that circulating levels of osteocalcin decrease in wild-type mice as they age, at the same time as their exercise capacity declines. Interestingly, one intraperitoneal injection of osteocalcin before exercise improved the exercise capacity of 3-month-old, 12-month-old and 15-month-old wild-type mice. These findings led Karsenty and co-workers to surmise that exogenous osteocalcin can reverse the age-associated decline in exercise capacity in mice.

Osteocalcin also seems to be required for optimum exercise capacity. In mice without osteocalcin signalling in myofibres ($Gprc6a_{Mck}^{-/-}$), the ability to perform exercise was reduced by up to 30%. To identify the mechanisms underlying this phenomenon, the investigators performed a transcriptomic analysis in muscle samples isolated from control and $Gprc6a_{Mck}^{-/-}$ mice after exercise. The greatest difference was found in the transcription levels of the gene that encodes Il-6, which was decreased by 80% in $Gprc6a_{Mck}^{-/-}$ mice. Levels of Il-6 are known to rise during exercise, initiating hepatic gluconeogenesis and the production of osteocalcin. "Hence, there is a feedforward regulatory loop initiated by bone (osteocalcin) acting on muscle (Il-6) that favours adaptation to exercise," explains Karsenty. The team were also able to identify osteocalcin's main mechanism of action, which is to mediate the uptake and catabolise nutrients in myofibres.

This work is moving forward in two directions. Firstly, Karsenty and co-workers are hoping to better understand the feedforward loop between osteocalcin and Il-6, including how it is implemented and operated. Secondly, the researchers would like to establish whether osteocalcin could be used to treat the age-related decline in exercise capacity in humans.

Claire Greenhill

ORIGINAL ARTICLE Mera, P. *et al.* Osteocalcin signaling in myofibers is necessary and sufficient for optimum adaptation to exercise. *Cell Metab.* http://dx.doi.org/10.1016/j.cmet.2016.05.004 (2016)