Nature Reviews Drug Discovery | Published online 21 Sep 2018; doi:10.1038/nrd.2018.160

AGEING

Reversing muscle degeneration

> In mice, apelin supplementation reversed age-associated sarcopenia

Sarcopenia — the degenerative loss of skeletal muscle strength and mass with ageing — contributes to the progressive loss of autonomy in the elderly and is tightly correlated with the development of other age-associated pathologies. Several approaches aimed to counteract or delay sarcopenia have been investigated, but their effects are variable and are frequently associated with side-effects. Writing in *Nature Medicine*, Dray and colleagues now identify apelin as an exercise-induced myokine, the production of which is reduced during ageing and associated with decreased muscle mass and function. In mice, apelin supplementation reversed age-associated sarcopenia.

Apelin is an endogenous peptide, previously identified as an adipokine and shown to induce beneficial metabolic effects. Through analysis of the Multidomain Alzheimer Preventive Trial cohort of elderly people, Dray and colleagues first observed that age-related loss of muscle is associated with decreased plasma apelin immunoreactivity. The authors confirmed this finding in a mouse model of ageing, which was associated with loss of skeletal muscle apelin and apelin receptor gene expression.

Findlay/Alamy Stock Photo

Dray and colleagues next set out to investigate if muscle apelin production might be regulated by exercise. Stimulation of human muscle cells with forskolin or an electric stimulus (which mimic muscle contraction) increased apelin secretion in culture media. This upregulation was reduced in muscle cells from aged donors. Similarly, an age-dependent decrease in muscle apelin release into the bloodstream was observed in mice subjected to sciatic nerve electrical stimulation-induced muscle contraction or acute exercise.

Next, the authors assessed the effects of apelin loss on muscle. Compared with wild-type mice, systemic loss of apelin or its receptor in middle-aged 12-month-old mice resulted in accelerated muscle loss, reduced mitochondrial number and function and decreased muscle strength. Importantly, skeletal muscle-specific apelin knockdown in middle-aged mice similarly decreased muscle mass and function.

Conversely, intraperitoneal injection of middle-aged (12 months) and aged (24 months) mice with apelin daily for 28 days increased muscle weight and fibre hypertrophy, with a shift towards a greater proportion of larger fibres. Furthermore, daily apelin administration or muscle-specific apelin overexpression in aged mice increased muscle strength and function.

Mechanistically, apelin supplementation promoted mitochondriogenesis, protein synthesis, autophagy and anti-inflammatory pathways in sarcopenic myofibres of aged muscles and mice. Apelin also stimulated muscle regeneration in mice: in cardiotoxin-mediated regeneration experiments, expression of apelin and its receptor was upregulated in reconstructing muscle during regeneration, a response that was blunted in aged mice. However, daily treatment of cardiotoxin-injected aged mice with apelin increased the number of muscle stem cells and their proliferative capacity, thereby promoting muscle regeneration. Finally, analysis of plasma apelin levels in a group of elderly people during a 1-year exercise programme revealed that individuals who displayed increased plasma apelin levels 6 months after the beginning of the trial demonstrated the most improved Short Physical Performance Battery test score, highlighting the potential of measuring apelin levels as a diagnostic tool to predict the benefit of physical exercise.

In summary, these findings directly implicate apelin signalling as a positive factor relating to the benefit of exercise that deteriorates with ageing, and highlight its potential as a therapeutic target for age-associated sarcopenia.

Sarah Crunkhorn

ORIGINAL ARTICLE Vinel, C. et al. The exerkine apelin reverses age-associated sarcopenia. *Nat. Med.* **24**, 1360–1371 (2018)
FURTHER READING Whitham, M. & Febbraio, M. The ever-expanding myokinome: discovery challenges and therapeutic implications. *Nat. Rev. Drug Discov.* **15**, 719–729 (2016)