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Editorial

The lingering effects of testosterone abuse – it seems muscles have long memories

The World Anti-Doping Agency (WADA) has testosterone and its myriad of related derivatives in the form of anabolic steroids on its list of prohibited substances. The study by Shalender Bhasin published in the *New England Journal of Medicine* in 1996 (Bhasin et al., 1996) confirmed, in a randomized and controlled trial, numerous anecdotal reports that had long suggested that anabolic steroids promoted hypertrophy in human skeletal muscle and thus were performance enhancing. By acting on androgen receptors expressed by myonuclei and muscle stem (satellite) cells, or through a rapid intracellular androgen receptor-independent mode, testosterone stimulates muscle protein synthesis to increase muscle mass (Kadi, 2008). Subsequent work from the group of Bhasin showed that there was a dose–response effect of testosterone enanthate not only on human muscle fiber size also on the number of muscle satellite cells and myonuclei (Sinha-Hikim et al., 2003).

The positive relationship between muscle cell size and the number of myonuclei was clearly demonstrated by Kadi et al. (1999) who studied a wide range of muscle fiber sizes, including extremely large fibres obtained from self-reported anabolic steroid users. This and other work (e.g., Petrella et al., 2006) provided the basis for the myonuclear domain and ceiling effect hypotheses. Simply put, these suggest that each nucleus is responsible for managing a certain volume of cytoplasm and this has a maximum limit. If the myonuclear domain is below this "ceiling," then an increase in nuclear transcription and protein synthesis can drive hypertrophy in the muscle cell. However, once this ceiling is approached, additional nuclei are required to facilitate further growth, these nuclei being donated by the satellite cells.

The group of Kristian Gundersen in Oslo published a report from studies on mice which demonstrated an increase in myonuclear number in response to overload, which was shown to be maintained after overload. Interestingly, this was shown to be maintained after overload had ended and in the face of a declining muscle fiber cross-sectional area (Bruusgaard et al., 2010). This important observation prompted discussion about whether muscles might remain "primed" and more amenable to further hypertrophy at a later date. Given that anabolic steroids have also been shown to increase the myonuclear number in humans (Sinha-Hikim et al., 2003), would an athlete who had tested positive for anabolic steroid abuse and had served a 2-year competitive ban still be in position to reap the physiological benefits of the initial doping offence at a later date? In other words, having returned "clean" and no longer taking the prohibited substance, would athletes still have an unfair advantage? A second and more recently published study by Gundersen's group (Egner et al., 2013) shows that this is a real possibility. In this study when mice received testosterone propionate for 14 days myonuclear number was markedly increased. However, the unique part of the study was when the animals undertook a muscle loading regimen 3 weeks after drug treatment had been removed (i.e., when "clean"). The results showed that in the testosterone treated group mean muscle fibre area from the extensor digitorum longus increased by 31%, whilst there was no significant change in the sham treated animals. Indeed, this positive effect on adaptation was still shown to be present even when a delay of 3 months (equivalent to approximately 10 years in humans) was given between treatment withdrawal and the onset of the loading intervention. Thus, it seems that there is now convincing evidence to show that the administration of anabolic steroids can result in giving skeletal muscles "memory" in the form of more myonuclei, which results in a more adaptive response to training long after the initial effects of the drug have worn off.

These results provide a challenge to WADA in regard to the legitimacy of the length of competitive bans imposed on athletes, as it is now clear that there are serious concerns surrounding the reversibility, or permanence, of the drug-mediated performance-enhancing effects of anabolic steroids. However, given that muscle protein turnover rates are markedly higher in mice than in human beings, it is important that these data are confirmed in human studies.

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