Analgesic and anti-inflammatory drugs in sports: implications for exercise performance and training adaptations

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Abstract

Over-the-counter analgesics, such as anti-inflammatory drugs (NSAIDs) and paracetamol, are widely consumed by athletes worldwide to increase pain tolerance, or dampen pain and reduce inflammation from injuries. Given that these drugs also can modulate tissue protein turnover, it is important to scrutinize the implications of acute and chronic use of these drugs in relation to exercise performance and the development of long-term training adaptations. In this review we aim to provide an overview of the studies investigating the effects of analgesic drugs on exercise performance and training adaptations relevant for athletic development. There is emerging evidence that paracetamol might acutely improve important endurance parameters as well as aspects of neuromuscular performance, possibly through increased pain tolerance. Both NSAIDs and paracetamol have been demonstrated to inhibit cyclooxygenase (COX) activity, which might explain the reduced anabolic response to acute exercise bouts. Consistent with this, NSAIDs have been reported to interfere with muscle hypertrophy and strength gains in response to chronic resistance training in young individuals. Although it remains to be established whether any of these observations also translate into detriments in sport-specific performance or reduced training adaptations in elite athletes, the extensive use of these drugs certainly raises practical, ethical and important safety concerns that need to be adressed. Overall, we encourage greater awareness among athletes, coaches and support staff on the potential adverse effects of these drugs. A risk-benefit analysis and professional guidance is strongly advised before the athlete considers analgesic medicine for training or competition.

Keywords: acetaminophen, endurance, ibuprofen, NSAID, muscle adaptations, paracetamol, recovery, strength

Summary Box

What is already known?

- Over-the-counter analgesics, such as anti-inflammatory drugs (NSAIDs) and paracetamol, are widely consumed by athletes worldwide.
- Although these drugs are used to reduce short-term pain and inflammation, they have also been shown to modulate muscle protein turnover through the effects on the cycloocygenase (COX) enzyme pathways.

What is new?

- There is emerging evidence that ingestion of paracetamol might enhance important endurance parameters as well as aspects of neuromuscular performance, possibly through increased pain tolerance.
- Analgesic drugs have been shown to reduce the anabolic response to acute exercise bouts, and attenuate long-term gains in muscle mass and strength in young healthy individuals.
- While further studies are required to better unravel the consequences of using analgesic drugs in elite athletes, the current data call for greater awareness among coaches, medicine and science support staff with regards to potential adverse effects and the associated ethical issues surrounding the frequent use of these drugs.

Introduction

Analgesic drugs are medicines that are used to relieve pain (i.e. "painkillers") without loss of consciousness or sensory perception (as opposed to anasthetics). A large number of medicines have these properties, including opioids (narcotics), non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol. While opioids require prescription and are banned within sports, NSAIDs (such as ibuprofen, indometacin, ketoprofen, naproxen, acetylsalicylic acid and diclofenac) and paracetamol are sold over-the-counter and are currently not classified as doping agents. The use of over-the-counter analgesic drugs is commonplace in elite sports as well as in recreational and student athletes [1,2]. It has been reported that the use of NSAIDs is much higher in Olympic athletes compared with age-matched controls [1,3]. In addition, both male and female football players participating in the FIFA World Cup, over 50% of the players used a NSAID at least once during the tournament, and about 7 players per national team were using NSAIDs prior to every match [4]. These authors highlighted that the reported frequency of NSAID use is probably underestimated, since self-medication or treatment already prescribed by club physicians is typically not included in published reports. The use of other analgesics such as paracetamol was far less common. This could be due to the fact that paracetamol, typically, has weaker anti-inflammatory effects than NSAIDs [5]. High use of NSAID medication has also been reported in collegiate athletes [2,6], athletes at the Sydney Olympics in 2000 [7], in high-caliber track and field athletes [8], triathletes [9], and marathon runners [10].

Athletes reported that they used NSAIDs to reduce pain and inflammation associated with training, competition or soft tissue injuries, or to gain a competitive advantage [1,2]. The high use of analgesic drugs takes place despite the fact that most sports organizations declare that unnecessary medication should be minimized due to potential short- and long-term adverse effects. For example, the FIFA Medical Assessment and Research Centre (F-MARC)

campaigned to reduce the use of NSAIDs prior to the 2010 FIFA World Cup. Despite this initiative, the reported intake of NSAIDs remained unchanged from the 2010 to the 2014 tournament [4].

One of the primary ways that over-the-counter analgesic drugs exert their pain-reducing effect is by inhibiting the activity of cyclooxygenase (COX), a family of enzymes that facilitate the production of prostaglandins (Fig. 1). The COX enzymes exist in three isoforms (COX-1, COX-2 and a splice variant termed COX-3), and NSAIDs are often classified based on their specificity towards the two main isoforms. Non-selective COX-inhibitors are generally considered to block both main isoforms whereas specific inhibitors are more prone to block either COX-1 or COX-2 [11]. Although paracetamol is not classified as an NSAID, it is now generally accepted that this drug has a spectrum of actions similar to NSAIDs and inhibits COX activity through the peroxidase function of these enzymes [5]. However, paracetamol also has antipyretic effects and central sites of actions (e.g. in the central nervous system) that might differ from NSAIDs [5].

Given the widespread use of analgesic drugs in the athletic population, a number of questions have been raised regarding the effects of these drugs on acute exercise performance and the influence on chronic training adaptations that are critical for long term athleteic development. It is particularly pertinent to study such effects given that the formation of prostaglandins may not only regulate pain and inflammation, but also modualte the protein turnover machinery controlling tissue remodelling for the adaptive responses to exercise. Thus, it makes the expectation tenable that if an athlete regularly uses analgesic drugs, to reduce pain associated with training or competition, there could be unwanted negative consequences for the long-term adaptive training response.

Accordingly, the purpose of this article is to give an overview of the studies investigating the effects of analgesic drugs on exercise performance and training adaptations in contexts relevant for athletes. While NSAIDs are widely used by athletes to alleviate symptoms of muscle damage and delayed onset muscle soreness (DOMS), or to speed up recovery of muscle function after such events, it is beyond the scope of this work and the reader is directed to previous reviews [12,13]. In additon, the influence of analgesic drugs for repair from a muscle injury will not be covered in detail in this article and the reader is referred to other work [14,15].

Exercise performance

Given that the ability of an athlete to tolerate pain could be an important factor in high-intensity exercise performance, it is understandable that analgesic drugs have been investigated in the context of endurance- and neuromuscular performance. There is indeed both anecdotal and research evidence of the use of narcotic analgesics in athletes long before the modern era of doping [16]. The nostalgic reader might recall the fate of one of Britain's most successful cyclists, Tom Simpson, who died on the slopes of Mont Ventoux during the 1967 Tour de France after he had taken amphetamine and alcohol, which contributed to a failure to effectively regulate exercise tolerance that led to a fatal case of heat exhaustion.

With regards to non-banned substances, the first two studies conducted in the 1990s examined the effects of acetylsalicylic acid (aspirin). Lisse et al. gave 17 healthy male volunteers a single dose of 650 mg of aspirin or a placebo in a double-blind, cross-over manner 30 min before running a 2 mile (3.2 km) time trial and reported no difference between the groups [17]. A few years later, Roi et al. carried out a single-blind, cross-over study to assess the effect of aspirin on maximal exercise capacity [18]. In this work, 18 young men were given 1000 mg of aspirin, chewable buffered aspirin (1000 mg), or a placebo prior to completing a maximal incremental

cycle ergometer test. The results showed no significant effect of the drug on ventilation, maximal oxygen uptake, heart rate or blood lactate, supporting the earlier observation that a single dose of aspirin did not affect endurance performance.

More recently, Mauger et al. had 13 male trained cyclists to perform a self-paced 10-mile (16.1 km) cycle time-trial, following either paracetamol (3 x 500 mg) or a placebo [19]. In the paracetamol trial, completion time was faster and the participants cycled at a 4% higher mean power output with higher heart rate and blood lactate levels, but without changes in perceived pain or exertion. These findings suggested that exercise performance was, at least in part, regulated by pain perception, and hence paracetamol could improve exercise performance through increased pain tolerance and lower perceived exertion. This is also supported by animal data showing that ibuprofen improved swimming performance (time to exhaustion) in rats, plausibly through the prevention of exercise-induced fatigue [20].

In a follow-up study to the cycle time-trial, the same group sought to determine whether paracetamol could also improve exercise capacity in the heat [21]. The background to this hypothesis comes from the fact that paracetamol has antipyretic effects for fever management, and perhaps also in afebrile patients [22]. The results of the study showed that an acute dose of paracetamol (20 mg/kg lean body mass) allowed participants (11 recreationally active men) to cycle longer in hot conditions (30°C), on average by a staggering 4 min (+17%). This was accompanied by significantly lower core, skin and body temperature, and lower perceived thermal strain [21]. The authors concluded that paracetamol may reduce the thermal challenge of exercise, and therefore improve performance in hot conditions.

While the two aforementioned studies indicated improved endurance performance capacity with acute paracetamol consumption, Foster et al. explored the effect of paracetamol on repeated sprint-cycling performance [23]. Nine recreationally active men completed 8 x 30 s sprints with 2 min active rest intervals in a randomized, cross-over design after consuming either 1500 mg (3 x 500 mg) of paracetamol or a placebo. Following the ingestion of paracetamol, participants cycled at a greater mean power output during sprint 6, 7 and 8, and the relative decrement in mean power output was also reduced. The authors suggested that paracetamol improved performance through the reduction of self-perceived pain for a given work rate, thus enabling them to complete the exercise closer to their true performance limit. These results gave further credibility to the thesis that increased pain tolerance can improve exercise performance.

It has also been proposed that nociceptive afferent feedback and the associated sensation of pain might modulate both central and peripheral fatigue, hence playing a role in neuromuscular fatigue development [24,25]. To examine this idea, Morgan et al. had 13 active men to conduct 60 x 3 s maximum voluntary contractions separated by a 2 s passive recovery [26]. The protocol was executed in a randomized cross-over order after subjects ingesting either 1000 mg of paracetamol or a placebo. Mean torque was greater in the paracetamol trial compared with placebo, and this was associated with an attenuated decline in the EMG amplitude in the latter stages of the trial. Collectively, these findings suggested that paracetamol ingestion might improve repeated maximal voluntary contractions by enabling a better preservation of muscle activation during exercise. As the attenuation of neuromuscular fatigue following paracetamol ingestion was not associated with altered maximal voluntary activation (central fatigue) or peripheral neuromuscular excitability, the authors speculated that the ergogenic effect of

paracetamol was due to a reduction in the magnitude of muscle afferent feedback and consequently an attenuation of neuromuscular fatigue development.

Overall, the human studies on acute exercise performance to date are certainly intriguing, suggesting that analgesic drugs, in this case paracetamol, can improve both short- and long-term performance parameters through various physiological mechanisms related to the analgesic or antipyretic effect of these drugs. Although the conflicting findings between the early aspirin studies and the later paracetamol studies warrant further research, they indicate potential differences in the biological impact of the drugs on processes related to exercice capacity. Alternatively, differences might simply be due to the disparity in drug dosages or specific protocols of the performance tests used. More importantly, however, these studies have generally been conducted with recreationally trained individuals, and therefore it remains to be seen whether highly trained elite athletes, already accustomed to training at the highest level (volume and intensity), also experience augmented performance when taking these drugs for competitive advantage. Moreover, because all of these studies are cross-sectional in nature, it is unknown how these interventions might work if used in a chronic training paradigm. Specifically, one might pose the interesting, yet ethically dubious question, whether regular use of analgesics could promote greater tolerance to training stress and hence promote augmented adaptations. Although this sounds like an attractive hypothesis, it will be evident in the next sections that chronically blocking prostaglandin formation might come with negative consequences for the adaptive response.

Exercise-induced protein synthesis

The first human studies exploring the effects of analgesic drugs on acute muscle adaptive responses came from Todd Trappe's laboratory at Ball State University [27]. Twenty-four young

men were assigned to one of three groups that received either ibuprofen (1200 mg/day), paracetamol (4000 mg/day), or a placebo after high intensity resistance exercise consisting of 10–14 sets of 10 eccentric repetitions with the knee extensors (120% of concentric 1 RM) [27]. Post-exercise (24 h) skeletal muscle protein synthesis rates increased 76% in placebo, yet were unchanged in the ibuprofen and the paracetamol group. This increase in protein synthesis was accompanied by increased levels of prostaglandin F2alpha ($PGF_{2\alpha}$) in the placebo group, but not in the two intervention groups [28]. These results suggested that over-the-counter doses of both ibuprofen and paracetamol suppress the protein synthesis response in skeletal muscle after high intensity muscle damaging eccentric exercise, and this response was mediated through a common mechanism; i.e. reduced $PGF_{2\alpha}$ formation. This is in line with animal data that convincingly showed that NSAIDs attenuate protein synthesis through prostaglandin inhibition [29,30]. In a follow-up study from the Trappe laboratory, the hypothesis was tested that the prostaglandin-mediated increase in protein synthesis was regulated specifically by the COX-2 enzyme [31]. Thus, 16 young men were randomly assigned to either 600 mg of a selective COX-2 inhibitor (celecoxib) or a placebo. Interestingly, post-exercise (10 sets of 10 eccentric repetitions) muscle protein synthesis was not suppressed by the COX-2 inhibitor, suggesting that the COX-1 enzyme could be responsible for the COX-mediated increase in muscle protein synthesis following resistance exercise.

Although these findings suggested that non-selective COX-inhibiting drugs could attenuate muscle protein synthesis, the body of evidence is equivocal. Mikkelsen et al. had 8 healthy men complete 200 maximal eccentric contractions with each leg [32]. To block prostaglandin synthesis locally in the skeletal muscle, indomethacin was infused via microdialysis catheters in to *m. vastus lateralis* of one leg. The results showed that myofibrillar and collagen protein synthesis were unaffected by the local NSAID infusion. In addition, in older osteoarthritic patients,

ibuprofen did not influence skeletal muscle protein synthesis 24 h after aerobic exercise [33]. Similar results were noted in elderly men with elevated systemic inflammation, where no effect of a high dose of ibuprofen on the post-exercise (3 h) muscle protein synthetic response following acute resistance exercise was evident [34]. The reason for the discepancies between studies examining NSAIDs and protein synthesis may be due to the different protocols and measurement techniques. It is possible that the duration of the NSAID infusion (7.5 h) in the Mikkelsen et al. study [32] was not comparable to the orally consumed doses in Trappe's original study [27]. Moreover, changes seen in mixed-muscle protein synthesis [27] could possibly be masked when measuring specific protein fractions, i.e. myofibrillar, sarcoplasmic and collagen protein synthesis [32 33].

Molecular responses regulating protein turnover

Satellite cell activity

A few studies have assessed the impact of NSAIDs on the myogenic stem cell response to acute exercise bouts. The myogenic stem cell niche, called satellite cells, are activated in response to exercise and are thought to be important contributors to the repair and remodelling of existing muscle fibres through the formation of new myonuclei [35,36]. Mackey et al. explored satellite cell counts in male endurance athletes after a 36-km run [37]. Compared with pre-exercise levels, a 27% increase in the number of satellite cells was observed on day 8 after exercise in the placebo group, while satellite cell levels remained similar in the NSAID group that received 100 mg of indomethacin per day. These results were the first to suggest that ingestion of anti-inflammatory drugs could attenuate the exercise-induced increase in satellite cell number in trained athletes. In a subsequent study [38], 8 men performed 200 maximal eccentric contractions with each leg and a NSAID was infused via a microdialysis catheter into the vastus lateralis muscle of one leg (same study as mentioned earlier investigating the protein synthetic response

[32]). The main finding was that the NSAID infusion suppressed the exercise-induced increase in the number of satellite cells 8 days after exercise. These results gave further support to the role of COX-activity in regulating satellite cell activity after exercise. Interestingly, however, when a COX-2-specific inhibitor (celecoxib) was used in 33 young men and women, neither intramuscular prostaglandin E2 (PGE_2) levels nor satellite cell activity after resistance exercise was altered [39], indicating that the satellite cell response, just like the protein synthetic response, is regulated by COX-1 rather than COX-2. Contrary to the idea that NSAIDs might dampen the regenerative process, Mackey et al. recently reported that satellite cell activation was expedited by 1200 mg of ibuprofen taken 2 weeks before and 4 weeks after an electrical stimulation-induced injury to the leg extensor muscles [40]. Thus, it appears that the nature of the specific exercise and/or damaging challange probably detemines how, and to what extent, satellite cell processes are affected by NSAID administration. Collectively, however, it appears NSAIDs have the capacity to interfere with the normal myogenic stem cell response to acute exercise bouts.

Translational signalling

The acute exercise-induced increase in muscle protein synthesis is generally thought to be driven by augmented protein translation, regulated by the mechanistic Target of Rapamycin (mTOR) complex [41]. Two recent studies have explored the acute muscle translational signalling response with or without an analgesic drug in young individuals. In a study performed by Markworth et al., 16 healthy male volunteers ingested 1200 mg of ibuprofen (or placebo) in three doses administered both before and following a bout of unaccustomed resistance exercise (3 sets of 8-10 reps at 80% of 1 RM in three different leg exercises) [42]. The ibuprofen treatment prevented the sustained elevation of MEK-ERK signaling at 3 h and 24 h post-exercise, and this was associated with suppressed

phosphorylation of ribosomal protein S6. These data suggested that the early translational signalling response could be attenuated with NSAIDs, perhaps explaining the previous reports of an attenuated protein synthetic response after acute resistance exercise.

Recently, similar findings were observed for paracetamol in a double-blind, randomized, crossover study. Eight young men performed two trials of unilateral knee extension resistance exercise (8 sets, 10 reps, 65% of 1 RM) with consumption of either paracetamol (1000 mg/6 h) or placebo prior to and immediately after the bout [43]. Muscle biopsies were collected at rest and 1 h and 3 h post-exercise. At 1 h post-exercise, phosphorylation of ribosomal protein S6 was increased in both groups, but was greater extent in the placebo group. At 3 h, the phosphorylation of p70S6 kinase was elevated only in placebo. Localization of mTOR to the lysosome (LAMP2) in myosin heavy chain-II fibers increased 3 h post-exercise only in the placebo. Furthermore, myostatin mRNA expression was reduced 1 h post-exercise only in the placebo condition, and myogenic factor 6 (MYF6) mRNA was increased 1 h and 3 h post-exercise only with paracetamol. Collectively, these studies suggest that both ibuprofen and paracetamol have the potential to modulate early signalling responses that regulate muscle protein turnover.

Lipid mediator response

Recent research has highlighted that tissue inflammation and regeneration do not solely work through the COX enzymes [44]. In fact, there are many other lipid mediators with autocrine/ paracrine signalling functions that can affect the skeletal muscle in response to exercise challanges. These bioactive lipid mediators, synthesized endogenously from polyunsaturated fatty acids, are mostly known for their key role in the inflammatory response through the classical eicosanoids such as the prostaglandins and leukotrienes. However, classes of lipid

mediators with anti-inflammatory and resolving bioactivity, such as lipoxins, resolvins and protectins, have also been implicated [44]. These mediators act to antagonize the pro-inflammatory response while at the same time actively promoting tissue healing and regeneration [44]. Recent research suggest that these lipid metabolites can have direct regulatory effects on the skeletal muscle. For example, 12/15-hydroxyeicosatetraenoic acids (HETEs) have been found to increase rates of protein breakdown in C2C12 myoblasts and myotubes [45,46], and several pro-resolving lipid mediators play important roles in satellite cell differentiation and myogenesis [44,47]. Interestingly, a recent study using LC-MS-based lipidomics revealed suppression of both early pro-inflammatory and later anti-inflammatory circulating lipid mediator responses in subjects orally receiving 400 mg ibuprofen [48]. Although this response has not yet been explored in skeletal muscle, this research opens up the possibility that NSAIDs might indirectly interfere with exercise-induced adaptations by delaying or preventing timely resolution of the inflammatory response. This is in line with the notion of a "recovery dichotomy" where accelerated recovery with the use of interventions might assist in the resolution of function, but could be at the detriment to longer term adaptation and athletic development. Practitioners should therefore identify the primary goal of the training or competition stimulus and decide if shorter-term recovery is a priority (such as in a congested competiton period) over the potential adaptive response. The idea of exercise-induced hormesis is something one should be mindful of to facilitate the optimal outcome that must be based on the individual needs and situation, to balance sufficient stimulus with adequate recovery to optimise performance [49].

In summary, it seems clear that analgesic drugs have the potential to modulate adaptive cellular responses to acute exercise bouts as reflected in the findings on muscle protein synthesis, satellite cell activity, translational signalling and lipid mediator responses. However the

findings are equivocal, most likely due to the different exercise protocols, subject cohorts (age and training status), and drug types, doses and frequency used. It is important to highlight that much of the experimental work on acute adaptive responses have been done using a very high number of eccentric muscle contractions, which is a powerful muscle damaging insult that provokes greater muscle stress than most athletes typically would encounter during training sessions. Thus, an important mission for future research is to better characterize the effect of different training variables (e.g. exercise mode, muscle contraction type, intensity, volume), as well as different drug treatment (e.g. drug type, dose, frequency and length of treatment) on the acute signalling and subsequent adaptative responses that translate to changes in behaviour/performance.

Training adaptations

Although analgesic drugs clearly have the capacity to affect acute cellular responses to exercise, this has little relevance for the athlete unless the effects are also translated into altered long-term training adaptations. While animal studies have reported reduced muscle hypertrophy in response to overload with NSAID administration [50,51], relatively few studies have assessed whether chronic consumption of analgesic drugs affects training adaptations in humans. Three studies [52-54] explored the effect in older individuals (60 to 80 years old) and one study examined 50-70 year old knee osteoarthritis patients [55]. Although it is questionable whether any inferences to training adaptations in athletes can be made from these studies, it is worth noting that Trappe et al. reported that daily doses of 1200 mg ibuprofen or 4000 mg paracetamol during 12 weeks of resistance training resulted in enhanced muscle mass and strength gains of 25–50% above the placebo-consuming group [52]. These data when coupled with subsequent mechanistic work from the same group [56], and the cross-sectional data on lean muscle mass and self-reported NSAID use [57], and the treatment of ibuprofen to limit sarcopenia in older rats [58], all lend support

to the idea that NSAIDs might positively influence training adaptations in older individuals, perhaps related to their higher basal inflammatory state [59].

Only two studies have assessed the influence of analgesic drugs on specific training adaptations in young individuals. The first study showed that 400 mg of ibuprofen taken immediately after each training session did not influence muscle hypertrophy, strength improvements or perceived muscle soreness in young (n=18) resistance-trained subjects [60]. The training protocol consisted of 6 sets of biceps curls 2-3 days/wk for 6 wk. The drugs were consumed on training days only, resulting in a total intake of 800-1200 mg/wk. Although one could argue that the single-dose administration in close proximity to the training sessions might actually reflect what many athletes would do in real-life, the lack of an effect on training adaptations in this study is likely due to the lower total dose taken when compared with previous acute studies where the standard dose has been the maximal-over-the counter dose of 1200 mg ibuprofen (3 x 400 mg over a day).

The second study was a single-blind, randomized controlled training study in young moderately active men and women [61]. The subjects were randomized to either an experimental group receiving 1200 mg ibuprofen (n=15) or to a control group receiving a very low dose of 75 mg acetylsalicylic acid (n=16) per day during 8 weeks of resistance exercise of the knee extensor muscles. The results showed that quadriceps muscle volume was significantly attenuated in the ibuprofen group (3.7%) compared with the control group that received low dose aspirin (7.5%). The negative effects of a higher-doses of ibuprofen were also evident on some, but not all strength measurements. Collectively, these results showed that higher doses of NSAIDs have the capacity to attenuate adaptations induced by resistance training in younger individuals.

The effects of NSAIDs on mitochondrial biogenisis indices have also been examined [62]. Unexpectedly, we noted decreased mitochondrial phosphorylation in response to the resistance training intervention, with no effect of the high- or lower NSAID intake. This decreased mitochondrial function occurred despite increased citrate synthase activity, that was independent of the drug intake. These findings are in contrast to previous work in the elderly where 12 weeks of resistance training led to greater increases in muscle size and CS activity with ibuprofen [63]. This further highlights differences between young and elderly in the biological response of NSAIDs taken concurrently with exercsie training.

In summary, because only two studies have examined the impact of analgesic drugs on training adaptations in healthy young participants, there are little data to base firm conclusions. Notwithstanding, it appears that higher- but not lower doses of NSAIDs have the capacity to diminish some important training adaptations to resistance training. No study has explored the effects of paracetamol on training adaptions in young individuals, but based on the observed similar effects of NSAIDs on translational processes, a negative response would not be surprising. Hitherto, studies in elite athletes or on adaptations related to endurance-type training are completely absent. Given the very strong interest in the potential blunting of the training-induced adaptive responses with recovery interventions, there is a pressing need to understand the implications of analgesic use in well-trained cohorts engaging in strength, endurance and concurrent exercise training paradigms.

Safety and ethical considerations

The use of pharmacological methods, in this case using analgesic drugs to modulate exercise performance or adaptations, is an extremely emotive topic and raises ethical concerns and questions about safety, potential side-effects, and issues around drug use for competitive

advantage which are tantamonunt to doping. It also raises questions from a practical point of view. It is easy to realize a moral conflict between using the drugs to be able to compete and train, as opposed to not being able to train or compete at all. Anecdotally, many marathon runners will consume analgesics before and during the race in the belief that there will be some benefit in easing the consequences of the race. However, a relevantly recent study reported the use of analgesics prior to the race did not offer protection from pain during or after the marathon compared with controls [10]. Similarly, the pain sensation associated with muscle damage from eccentric contractions is typically not modulated by these drugs [12]. From an applied perspective, the practitioner and athlete must consider the cost-benefit. On balance, the benefits of taking analgesics to reduce exercise-induced pain look to be very limited indeed, and the risk of potential unwanted side-effects appear to be high, particualary when the doses are higher and prolonged. Even though present data indicate an attenuated training response, support exists at least for paracetamol to potentially enhance performance capacity. Consequently, there are reports strongly advocating that paracetamol should be added to the WADA doping list [64]. This is, however, a complicated matter since there are a plethora of other drugs and substances that might have analgesic effects and to draw a line that defines what substances should be banned and what should be allowed is complex in the extreme, especially since there could be a genuine medical reason for taking them.

Regardless of the doping issue, it seems reasonable to propose that athletes using medicines to reduce pain sensations are likely to be at greater risk of injury and tissue damage. Although the influential of the temporal pattern of NSAIDs use on muscle repair is not known in detail [15], there are some data suggesting that any potential benefit of NSAIDs in the early phases (first weeks) after extensive fibre damage [40] might not be maintained in the longer term or after more normal physiological loading is possible [14]. Furthermore, chronically dampening the pain

response might also lead to athletes returning to play/competition prematurely, thereby increasing the propensity for injury or re-occurance of previous injuries.

It is also clear that all analgesic drugs come with potential adverse effects. Paracetamol has been associated with liver toxicity, and indeed paracetamol overdosing is the most common cause of liver failure in the UK [65]. The use of NSAIDs can cause gastrointestinal complications and bleeding [66]. As NSAIDs also affect thrombocyte function and aggregation, there is a risk of more severe bleeding following trauma. This is of genuine concern for athletes in collision sports or where the likelyhood of contact is high and hence an increased risk of acute trauma or soft tissue injury. It is important to highlight that athletes taking NSAIDs during activities such as the marathon, are reported to have a five times greater incidence of adverse serious events such as gastrointestinal cramps and bleeding, haematuria, cardiovascular events or temporary kidney failure, which tend to increase with larger analgesic doses [10]. Furthermore, in a large cohort of Finnish Olympic athletes, every fifth individual reported some NSAID-related adverse effect [67]. Moreover, NSAIDs can increase the overall risk of myocardial infarctions, sudden cardiac arrests and overall mortality rates [66,68,69]. The risks also vary across different analgesics; for example, the increased mortality risk appears to be much higher with diclofenac compared with aspirin or paracetamol [66]. Even though the absolute risk is still very low in healthy individuals, these risks are greater with larger doses and/or with chronic use of these pharmalogical interventions [70].

Limitations and directions for future research

It is somewhat frustrating that despite the number of studies conducted to date, there are conflicting results and several unresolved questions that are pertinent to the understanding of how analgesic and anti-inflammatory drugs can affect exercise performance and training

adaptations. Thus, to date, there is no clear message to the athletes on how they can use these drugs while at the same time minimising unwanted effects. Although there are some emerging data suggesting that ingestion of paracetamol in association with isolated exercise performance-events might improve performance, it is unknown if this is the case for the highly trained athlete. Thus, there is a need for studies examining the impact of analgesics on applied sport-performance outcomes in high caliber athletes to determine the application to athletic populations. It is also important to acknowledge that we have relatively little information on the precise mechanisms of how analgesics or anti-inflammatories modulate the adaptive training response. As research has clearly shown, the cellular response to acute exercise does not always reflect the end-point adaptations to training and there is an urgent need for studies examining the relationship between the acute adaptive signal and its relationship to the long-term training effect. As evident in this review, the dose and length of drug treatment matters, and to date we have very little information on any potential dose-response relationships between drug intake and performance and/or adaptations.

Perspectives

Given the alarmingly high intake of analgesic and anti-inflammatory drugs in elite sports, we encourage greater awareness among athletes, coaches, support staff and sports organizations about the possible adverse health effects of these drugs. It is also important to highlight that frequent use of NSAIDs, and plausibly also paracetamol, could hamper chronic training adaptations, and consequently reduce long-term athletic development. This issue is particularly important to raise, since there is now some preliminary evidence suggesting that these drugs might acutally enhance exercise performance in some situations. Thus, it is imperative that we continue to investigate the effects of analgesic drugs on elite athletic performance and training adaptations, and that the ethical issues associated with such practices within sports are openly

and transparently discussed. Given that over-the-counter painkillers are effective when used as medicinally intended (i.e. for alleviating short-term pain symptoms) there is still probably a time and a place for these interventions to be used by elite athletes. Collectively, however, all athletes should, together with coaches, medicine and science support staff, do a careful risk-benefit analysis before using analgesic and anti-inflammatory drugs regularly in association with training or competition.

References

1. Alaranta A, Alaranta H, Helenius I. Use of prescription drugs in athletes. *Sports Med.* 2008;38(6):449-463.
2. Warner DC, Schnepf G, Barrett MS, Dian D, Swigonski NL. Prevalence, attitudes, and behaviors related to the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in student athletes. *J Adolesc Health.* 2002;30(3):150-153.
3. Berglund B. Sports medicine update. *Scand J Med Sci Sports.* 2001;11(6):369-371.
4. Tscholl PM, Vaso M, Weber A, Dvorak J. High prevalence of medication use in professional football tournaments including the World Cups between 2002 and 2014: a narrative review with a focus on NSAIDs. *Br J Sports Med.* 2015;49(9):580-582.
5. Graham GG, Davies MJ, Day RO, Mohamudally A, Scott KF. The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. *Inflammopharmacology.* 2013;21(3):201-232.
6. Holmes N, Cronholm PF, Duffy AJ, 3rd, Webner D. Nonsteroidal anti-inflammatory drug use in collegiate football players. *Clin J Sport Med.* 2013;23(4):283-286.
7. Corrigan B, Kazlauskas R. Medication use in athletes selected for doping control at the Sydney Olympics (2000). *Clin J Sport Med.* 2003;13(1):33-40.
8. Tscholl P, Alonso JM, Dolle G, Junge A, Dvorak J. The use of drugs and nutritional supplements in top-level track and field athletes. *Am J Sports Med.* 2010;38(1):133-140.
9. Wharam PC, Speedy DB, Noakes TD, Thompson JM, Reid SA, Holtzhausen LM. NSAID use increases the risk of developing hyponatremia during an Ironman triathlon. *Med Sci Sports Exerc.* 2006;38(4):618-622.
10. Kuster M, Renner B, Oppel P, Niederweis U, Brune K. Consumption of analgesics before a marathon and the incidence of cardiovascular, gastrointestinal and renal problems: a cohort study. *BMJ Open.* 2013;3(4).
11. Vane JR, Botting RM. Anti-inflammatory drugs and their mechanism of action. *Inflamm Res.* 1998;47 Suppl 2:S78-87.
12. Howatson G, van Someren KA. The prevention and treatment of exercise-induced muscle damage. *Sports Med.* 2008;38(6):483-503.
13. Baldwin Lanier A. Use of nonsteroidal anti-inflammatory drugs following exercise-induced muscle injury. *Sports Med.* 2003;33(3):177-185.
14. Mackey AL, Mikkelsen UR, Magnusson SP, Kjaer M. Rehabilitation of muscle after injury - the role of anti-inflammatory drugs. *Scand J Med Sci Sports.* 2012;22(4):e8-14.
15. Urso ML. Anti-inflammatory interventions and skeletal muscle injury: benefit or detriment? *J Appl Physiol (1985).* 2013;115(6):920-928.
16. Reardon CL, Creado S. Drug abuse in athletes. *Subst Abuse Rehabil.* 2014;5:95-105.
17. Lisse JR, MacDonald K, Thurmond-Anderle ME, Fuchs JE, Jr. A double-blind, placebo-controlled study of acetylsalicylic acid (ASA) in trained runners. *J Sports Med Phys Fitness.* 1991;31(4):561-564.
18. Roi GS, Garagiola U, Verza P, et al. Aspirin does not affect exercise performance. *Int J Sports Med.* 1994;15(5):224-227.
19. Mauger AR, Jones AM, Williams CA. Influence of acetaminophen on performance during time trial cycling. *J Appl Physiol (1985).* 2010;108(1):98-104.
20. Lima FD, Stamm DN, Della Pace ID, et al. Ibuprofen intake increases exercise time to exhaustion: A possible role for preventing exercise-induced fatigue. *Scand J Med Sci Sports.* 2016;26(10):1160-1170.

21. Mauger AR, Taylor L, Harding C, Wright B, Foster J, Castle PC. Acute acetaminophen (paracetamol) ingestion improves time to exhaustion during exercise in the heat. *Exp Physiol.* 2014;99(1):164-171.
22. Kasner SE, Wein T, Piriyawat P, et al. Acetaminophen for altering body temperature in acute stroke: a randomized clinical trial. *Stroke.* 2002;33(1):130-134.
23. Foster J, Taylor L, Chrismas BC, Watkins SL, Mauger AR. The influence of acetaminophen on repeated sprint cycling performance. *Eur J Appl Physiol.* 2014;114(1):41-48.
24. Blain GM, Mangum TS, Sidhu SK, et al. Group III/IV muscle afferents limit the intramuscular metabolic perturbation during whole body exercise in humans. *J Physiol.* 2016;594(18):5303-5315.
25. Hureau TJ, Romer LM, Amann M. The 'sensory tolerance limit': A hypothetical construct determining exercise performance? *Eur J Sport Sci.* 2018;18(1):13-24.
26. Morgan PT, Bowtell JL, Vanhatalo A, Jones AM, Bailey SJ. Acute acetaminophen ingestion improves performance and muscle activation during maximal intermittent knee extensor exercise. *Eur J Appl Physiol.* 2018;118(3):595-605.
27. Trappe TA, White F, Lambert CP, Cesar D, Hellerstein M, Evans WJ. Effect of ibuprofen and acetaminophen on postexercise muscle protein synthesis. *Am J Physiol Endocrinol Metab.* 2002;282(3):E551-556.
28. Trappe TA, Fluckey JD, White F, Lambert CP, Evans WJ. Skeletal muscle PGF(2)(alpha) and PGE(2) in response to eccentric resistance exercise: influence of ibuprofen acetaminophen. *J Clin Endocrinol Metab.* 2001;86(10):5067-5070.
29. Palmer RM, Reeds PJ, Atkinson T, Smith RH. The influence of changes in tension on protein synthesis and prostaglandin release in isolated rabbit muscles. *Biochem J.* 1983;214(3):1011-1014.
30. Rodemann HP, Goldberg AL. Arachidonic acid, prostaglandin E2 and F2 alpha influence rates of protein turnover in skeletal and cardiac muscle. *J Biol Chem.* 1982;257(4):1632-1638.
31. Burd NA, Dickinson JM, Lemoine JK, et al. Effect of a cyclooxygenase-2 inhibitor on postexercise muscle protein synthesis in humans. *Am J Physiol Endocrinol Metab.* 2010;298(2):E354-361.
32. Mikkelsen UR, Schjerling P, Helmark IC, et al. Local NSAID infusion does not affect protein synthesis and gene expression in human muscle after eccentric exercise. *Scand J Med Sci Sports.* 2011;21(5):630-644.
33. Petersen SG, Miller BF, Hansen M, Kjaer M, Holm L. Exercise and NSAIDs: effect on muscle protein synthesis in patients with knee osteoarthritis. *Med Sci Sports Exerc.* 2011;43(3):425-431.
34. Dideriksen K, Reitelseder S, Malmgaard-Clausen NM, et al. No effect of anti-inflammatory medication on postprandial and postexercise muscle protein synthesis in elderly men with slightly elevated systemic inflammation. *Exp Gerontol.* 2016;83:120-129.
35. White TP, Esser KA. Satellite cell and growth factor involvement in skeletal muscle growth. *Med Sci Sports Exerc.* 1989;21(5 Suppl):S158-163.
36. Allen DL, Roy RR, Edgerton VR. Myonuclear domains in muscle adaptation and disease. *Muscle Nerve.* 1999;22(10):1350-1360.
37. Mackey AL, Kjaer M, Dandanell S, et al. The influence of anti-inflammatory medication on exercise-induced myogenic precursor cell responses in humans. *J Appl Physiol (1985).* 2007;103(2):425-431.

38. Mikkelsen UR, Langberg H, Helmark IC, et al. Local NSAID infusion inhibits satellite cell proliferation in human skeletal muscle after eccentric exercise. *J Appl Physiol (1985).* 2009;107(5):1600-1611.
39. Paulsen G, Egner IM, Drange M, et al. A COX-2 inhibitor reduces muscle soreness, but does not influence recovery and adaptation after eccentric exercise. *Scand J Med Sci Sports.* 2010;20(1):e195-207.
40. Mackey AL, Rasmussen LK, Kadi F, et al. Activation of satellite cells and the regeneration of human skeletal muscle are expedited by ingestion of nonsteroidal anti-inflammatory medication. *FASEB J.* 2016;30(6):2266-2281.
41. Hornberger TA, Sukhija KB, Chien S. Regulation of mTOR by mechanically induced signaling events in skeletal muscle. *Cell Cycle.* 2006;5(13):1391-1396.
42. Markworth JF, Vella LD, Figueiredo VC, Cameron-Smith D. Ibuprofen treatment blunts early translational signaling responses in human skeletal muscle following resistance exercise. *J Appl Physiol (1985).* 2014;117(1):20-28.
43. D'Lugos AC, Patel SH, Ormsby JC, et al. Prior acetaminophen consumption impacts the early adaptive cellular response of human skeletal muscle to resistance exercise. *J Appl Physiol (1985).* 2018.
44. Markworth JF, Maddipati KR, Cameron-Smith D. Emerging roles of pro-resolving lipid mediators in immunological and adaptive responses to exercise-induced muscle injury. *Exerc Immunol Rev.* 2016;22:110-134.
45. Whitehouse AS, Khal J, Tisdale MJ. Induction of protein catabolism in myotubes by 15(S)-hydroxyeicosatetraenoic acid through increased expression of the ubiquitin-proteasome pathway. *Br J Cancer.* 2003;89(4):737-745.
46. Bhattacharya A, Hamilton R, Jernigan A, et al. Genetic ablation of 12/15-lipoxygenase but not 5-lipoxygenase protects against denervation-induced muscle atrophy. *Free Radic Biol Med.* 2014;67:30-40.
47. Ho ATV, Palla AR, Blake MR, et al. Prostaglandin E2 is essential for efficacious skeletal muscle stem-cell function, augmenting regeneration and strength. *Proc Natl Acad Sci U S A.* 2017;114(26):6675-6684.
48. Markworth JF, Vella L, Lingard BS, et al. Human inflammatory and resolving lipid mediator responses to resistance exercise and ibuprofen treatment. *Am J Physiol Regul Integr Comp Physiol.* 2013;305(11):R1281-1296.
49. Peake JM, Markworth JF, Nosaka K, Raastad T, Wadley GD, Coffey VG. Modulating exercise-induced hormesis: Does less equal more? *J Appl Physiol (1985).* 2015;119(3):172-189.
50. Soltow QA, Betters JL, Sellman JE, Lira VA, Long JH, Criswell DS. Ibuprofen inhibits skeletal muscle hypertrophy in rats. *Med Sci Sports Exerc.* 2006;38(5):840-846.
51. Bondesen BA, Mills ST, Pavlath GK. The COX-2 pathway regulates growth of atrophied muscle via multiple mechanisms. *Am J Physiol Cell Physiol.* 2006;290(6):C1651-1659.
52. Trappe TA, Carroll CC, Dickinson JM, et al. Influence of acetaminophen and ibuprofen on skeletal muscle adaptations to resistance exercise in older adults. *Am J Physiol Regul Integr Comp Physiol.* 2011;300(3):R655-662.
53. Jankowski CM, Gozansky WS, MacLean PS, et al. N-acetyl-4-aminophenol and musculoskeletal adaptations to resistance exercise training. *Eur J Appl Physiol.* 2013;113(5):1127-1136.
54. Jankowski CM, Shea K, Barry DW, et al. Timing of Ibuprofen Use and Musculoskeletal Adaptations to Exercise Training in Older Adults. *Bone Rep.* 2015;1:1-8.
55. Petersen SG, Beyer N, Hansen M, et al. Nonsteroidal anti-inflammatory drug or glucosamine reduced pain and improved muscle strength with resistance training in a

randomized controlled trial of knee osteoarthritis patients. *Arch Phys Med Rehabil.* 2011;92(8):1185-1193.
56. Standley RA, Liu SZ, Jemiolo B, Trappe SW, Trappe TA. Prostaglandin E2 induces transcription of skeletal muscle mass regulators interleukin-6 and muscle RING finger-1 in humans. *Prostaglandins Leukot Essent Fatty Acids.* 2013;88(5):361-364.
57. Landi F, Marzetti E, Liperoti R, et al. Nonsteroidal anti-inflammatory drug (NSAID) use and sarcopenia in older people: results from the ilSIRENTE study. *J Am Med Dir Assoc.* 2013;14(8):626 e629-613.
58. Rieu I, Magne H, Savary-Auzeloux I, et al. Reduction of low grade inflammation restores blunting of postprandial muscle anabolism and limits sarcopenia in old rats. *J Physiol.* 2009;587(Pt 22):5483-5492.
59. Trappe TA, Liu SZ. Effects of prostaglandins and COX-inhibiting drugs on skeletal muscle adaptations to exercise. *J Appl Physiol (1985).* 2013;115(6):909-919.
60. Krentz JR, Quest B, Farthing JP, Quest DW, Chilibeck PD. The effects of ibuprofen on muscle hypertrophy, strength, and soreness during resistance training. *Appl Physiol Nutr Metab.* 2008;33(3):470-475.
61. Lilja M, Mandic M, Apro W, et al. High doses of anti-inflammatory drugs compromise muscle strength and hypertrophic adaptations to resistance training in young adults. *Acta Physiol (Oxf).* 2018;222(2).
62. Cardinale DA, Lilja M, Mandic M, Gustafsson T, Larsen FJ, Lundberg TR. Resistance Training with Co-ingestion of Anti-inflammatory Drugs Attenuates Mitochondrial Function. *Front Physiol.* 2017;8:1074.
63. Trappe TA, Ratchford SM, Brower BE, et al. COX Inhibitor Influence on Skeletal Muscle Fiber Size and Metabolic Adaptations to Resistance Exercise in Older Adults. *J Gerontol A Biol Sci Med Sci.* 2016;71(10):1289-1294.
64. Lippi G, Sanchis-Gomar F. Acetaminophen and sport performance: doping or what? *Eur J Appl Physiol.* 2014;114(4):881-882.
65. Ryder SD, Beckingham IJ. ABC of diseases of liver, pancreas, and biliary system. Other causes of parenchymal liver disease. *BMJ.* 2001;322(7281):290-292.
66. Andrade SE, Martinez C, Walker AM. Comparative safety evaluation of non-narcotic analgesics. *J Clin Epidemiol.* 1998;51(12):1357-1365.
67. Alaranta A, Alaranta H, Heliovaara M, Airaksinen M, Helenius I. Ample use of physician-prescribed medications in Finnish elite athletes. *Int J Sports Med.* 2006;27(11):919-925.
68. Sondergaard KB, Weeke P, Wissenberg M, et al. Non-steroidal anti-inflammatory drug use is associated with increased risk of out-of-hospital cardiac arrest: a nationwide case-time-control study. *Eur Heart J Cardiovasc Pharmacother.* 2017;3(2):100-107.
69. Bally M, Dendukuri N, Rich B, et al. Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data. *BMJ.* 2017;357:j1909.
70. Bally M, Beauchamp ME, Abrahamowicz M, Nadeau L, Brophy JM. Risk of acute myocardial infarction with real-world NSAIDs depends on dose and timing of exposure. *Pharmacoepidemiol Drug Saf.* 2018;27(1):69-77.

Figures

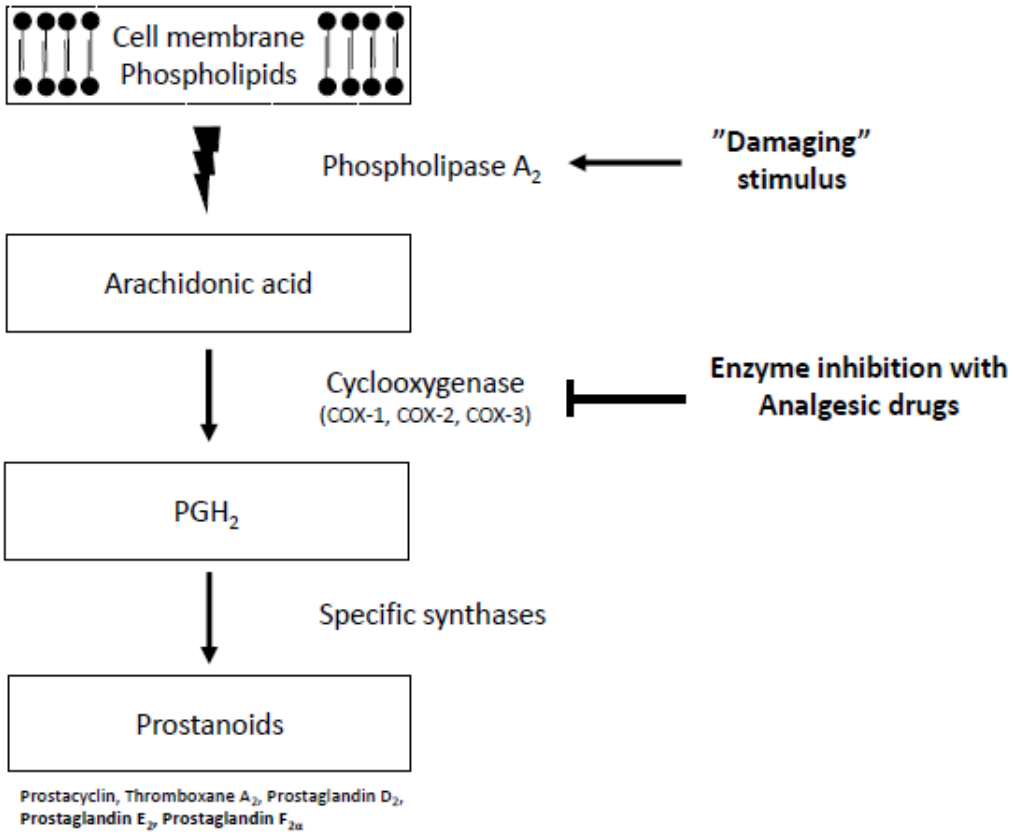

Figure 1. Schematic overview of prostaglandin biosynthesis in response to a damaging stimulus such as an intense exercise challenge or tissue injury. Prostaglandins are synthesized from arachidonic acid, which is liberated from the cell membrane. Analgesic drugs work in part by inhibiting cyclooxygenase (COX) activity, thereby reducing the production of several prostaglandins that have been implicated in skeletal muscle remodelling, particularly the ones highlighted in bold.

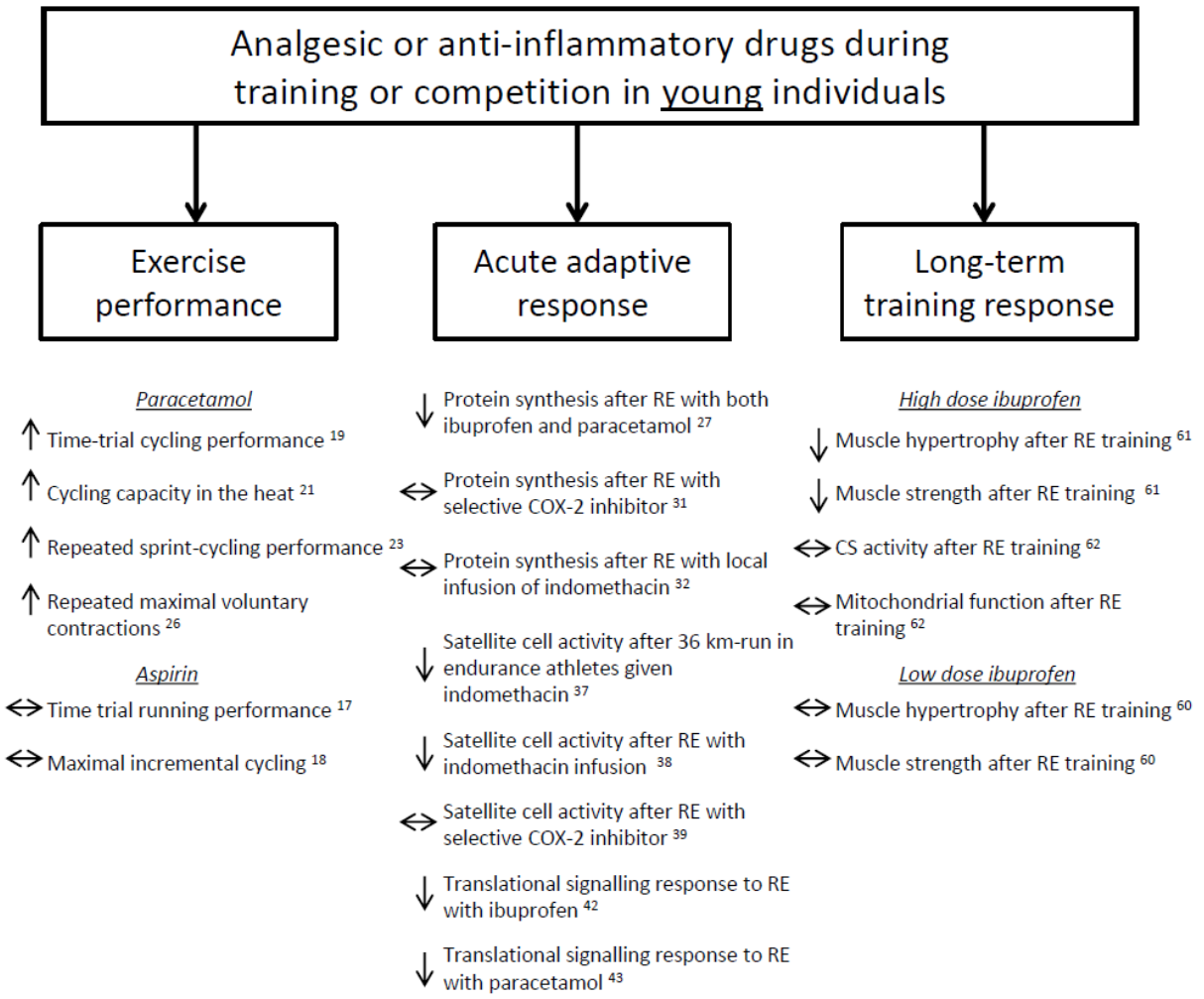

Figure 2. Summary of key studies reporting on the effects of analgesic or anti-inflammatory drugs on exercise performance or training adaptations in young individuals. RE = Resistance exercise. Arrows pointing up indicate positive effect of the medical treatment, arrows pointing down indicate negative effect, and horizontal arrows indicate no effect.