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Modulating exercise-induced hormesis: does less equal more?

Running title: Exercise-induced hormesis

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ABSTRACT

Hormesis encompasses the notion that low levels of stress stimulate or upregulate existing cellular and molecular pathways that improve the capacity of cells and organisms to withstand greater stress. This notion underlies much of what we know about how exercise conditions the body and induces long-term adaptations. During exercise, the body is exposed to various forms of stress, including thermal, metabolic, hypoxic, oxidative, and mechanical stress. These stressors activate biochemical messengers, which in turn activate various signaling pathways that regulate gene expression and adaptive responses. Historically, antioxidant supplements, nonsteroidal anti-inflammatory drugs, and cryotherapy have been favored to attenuate or counteract exercise-induced oxidative stress and inflammation. However, reactive oxygen species and inflammatory mediators are key signaling molecules in muscle, and such strategies may mitigate adaptations to exercise. Conversely, withholding dietary carbohydrate and restricting muscle blood flow during exercise may augment adaptations to exercise. In this review article, we combine, integrate, and apply knowledge about the fundamental mechanisms of exercise adaptation. We also critically evaluate the rationale for using interventions that target these mechanisms under the overarching concept of hormesis. There is currently insufficient evidence to establish whether these treatments exert dose-dependent effects on muscle adaptation. However, there appears to be some dissociation between the biochemical/molecular effects and functional/performance outcomes of some of these treatments. Although several of these treatments influence common kinases, transcription factors and proteins, it remains to be determined if these interventions complement or negate each other, and whether such effects are strong enough to influence adaptations to exercise.

23 Key words: adaptation, stress, preconditioning.

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INTRODUCTION

Hormesis refers to 'a process in which a low dose of a chemical agent or environmental factor that is damaging at high doses induces an adaptive beneficial effect on the cell or organism' (127). The concept of hormesis first originated in the 16th century from the musings of the Swiss physician and alchemist Paracelcus, who proposed that, "Solely the dose determines that a thing is not a poison" (15). The term 'hormesis' itself was first coined in 1943 by Southam and Ehrlich to explain their observation that a natural antibiotic in cedar wood inhibited the growth of wood-decaying fungi but had the opposite effect at low doses (204). Subsequently, the pioneering endocrinologist Hans Selye applied this notion to understanding how biological systems respond to and tolerate environmental stress (194).

Hormesis encompasses the fundamental concepts of 'conditioning' and 'adaptation'. The concept of conditioning was first recognized following observations that repeated, brief hypoxic exposure markedly reduced damage to the heart during subsequent myocardial infarction (141). We now accept that exposure to an agent conditions the system to respond in some manner (22). The concept of adaptation was originally recognized following experiments demonstrating that constant exposure of *Escherichia coli* to mutagens allowed each bacterium to handle mutagens more efficiently and to develop resistance to mutagenesis (184). Conditioning and adaptation are closely related, are considered to be synonymous, and are often used interchangeably. In essence, conditioning/adaptation captures the notion that low levels of stress stimulate or upregulate existing cellular and molecular pathways that improve the capacity of cells and organisms to withstand greater stress (22).

The notion of hormesis underlies much of what we know about how exercise conditions the body and induces long-term adaptation (32). However, hormesis was explicitly introduced into the lexicon of exercise physiology only relatively recently (175). On a gross population level, the dose–response nature of hormesis most likely explains why moderate levels of physical activity reduce the risk of illness and mortality, whereas excessive physical activity increases such risks (5, 103, 147).

During exercise, the body is exposed to various homeostatic perturbations, including thermal, metabolic, hypoxic, oxidative, and mechanical stress. These perturbations stimulate the release of biochemical messengers such as reactive oxygen and nitrogen species (RONS), Ca^{2+}, growth factors, cytokines, and eicosanoids. These messengers then activate signaling pathways including (but not limited to) various protein kinases, phosphatases, and deacetylases, which in turn regulate the molecular machinery controlling gene expression that elicits the appropriate adaptive responses (40). Through these signaling pathways, acute production of RONS and inflammatory mediators can ultimately promote adaptations in skeletal muscle such as mitochondrial biogenesis and remodeling/hypertrophy (53, 124, 125, 169, 197). Conversely, prolonged production of RONS and inflammatory mediators can activate proteolytic pathways, impede protein synthesis, and overwhelm endogenous defense mechanisms, which cause adverse effects such as muscle atrophy/weakness (37, 56, 62, 106, 203, 206). This dichotomy between the acute and chronic effects of certain physiological stimuli is important to consider within the context of hormesis in skeletal muscle.

Historically, the perception that exercise-induced oxidative stress and inflammation cause muscle fatigue and damage has provoked widespread interest in countermeasures

such as antioxidant supplements, NSAIDs, and cryotherapy (31, 236). However, advances in our understanding of the role of RONS and inflammatory mediators in muscle adaptations to exercise have generated debate about whether these strategies are actually beneficial—at least in young healthy people (74, 162, 190). Antioxidant supplements and NSAIDs may help to preserve or enhance muscle adaptations to exercise in older individuals with impaired antioxidant defense systems or chronic low-grade inflammation (120, 228). By contrast, in young people these interventions can attenuate exercise-induced increases in insulin sensitivity (177) and muscle protein synthesis (229). The advantages or disadvantages of these interventions may therefore vary between different exercising populations. At the other end of the hormesis continuum, interest has also emerged in the potential benefits of applying stress to skeletal muscle before, during, or after exercise to stimulate greater adaptation. This stress can be applied by restricting carbohydrate intake, occluding local blood supply using low-intensity isometric or eccentric contractions (mechanical 'preloading'), or passively heating muscle.

Considering the increasing attention on strategies to enhance exercise performance and assist recovery, it is timely to debate the scientific rationale for using interventions such as cryotherapy, antioxidant supplements, NSAIDs, mechanical preloading, dietary carbohydrate restriction, heat stress, and blood flow restriction to modulate adaptations to exercise. The purpose of this review is to combine, integrate, and apply knowledge about how these interventions influence skeletal muscle adaptations to exercise under the overarching concept of hormesis.

INTERVENTIONS THAT ENHANCE EXERCISE-INDUCED HORMESIS

Restricting Dietary Carbohydrate Intake

Modulating skeletal muscle glycogen content by restricting dietary carbohydrate intake between exercise sessions is a relatively recent strategy to enhance exercise-induced hormesis. Glycogen is an important substrate for oxidative phosphorylation in skeletal muscle, and low muscle glycogen content is a key determinant of muscle fatigue (11, 94, 205). Accordingly, maximizing muscle glycogen content by carbohydrate loading before exercise and delaying the rate at which glycogen content is depleted (by ingesting carbohydrate during exercise) are common practices for athletes (21). Recent studies have used various diet and/or exercise protocols to manipulate muscle glycogen content before exercise sessions to determine whether changes in glycogen availability influence adaptive responses [for review see (8, 69)]. There is growing evidence of beneficial effects on metabolic and mitochondrial adaptations when exercising with low compared with normal muscle glycogen content. This section briefly examines the putative mechanistic influence of low muscle glycogen content and any potential for biphasic responses that support the hormetic model of adaptation.

Training with low muscle glycogen content promotes metabolic adaptation. A primary concept within the paradigm of nutrient–training interactions in skeletal muscle is that substrate availability mediates the cellular response to contractile activity (32). However, such a paradigm oversimplifies the complexity of how substrate availability modulates adaptation. Hansen et al (65) first examined whether repeated bouts of exercise begun with low muscle glycogen content induces greater metabolic stress and disruption to homeostasis in skeletal muscle. They found that resting muscle glycogen content and citrate synthase activity were higher in subjects who started half of their training sessions with low

glycogen versus those who always started training with normal glycogen. They concluded that this was because glycogen depletion caused by the first session dictated that the second session began with reduced muscle glycogen content. Although differences in the distribution of the training stimulus may have influenced these findings, there seems little doubt that the key factor promoting the adaptive response was training 'low'.

The metabolic flexibility of healthy skeletal muscle permits shifts in substrate oxidation based on the availability of carbohydrates and fats [for review see (205)]. Consequently, imposing the need for greater use of fat as a fuel likely explains much of the augmented adaptation to exercise with low initial muscle glycogen content. The demand for ATP supply during prolonged moderate- to high-intensity exercise is likely to also increase the magnitude of the adaptive signal under low-glycogen conditions. In this regard, the adenosine monophosphate activated protein kinase (AMPK) may be a focal point for regulating the cellular response to exercise with low initial muscle glycogen content, given its role as an energy sensor (66, 67). AMPK contains a glycogen-binding domain on one of its three subunits that causes it to colocalize with glycogen (66, 67, 128). AMPK also regulates the activity of several signaling pathways including those that promote glucose transport, fatty acid uptake, and mitochondrial biogenesis (66). The few studies that have quantified AMPK phosphorylation or activity after exercise begun with low- compared with normal/high-glycogen content have shown that the greater AMPK response in skeletal muscle following exercise is associated with lower preexercise glycogen content (242, 249).

Several other putative mediators of skeletal muscle adaptations to endurance exercise are enhanced after exercise with low initial muscle glycogen content. The phosphorylation status and mRNA abundance of important regulators of mitochondrial biogenesis (e.g.,

tumor suppressor p53 and peroxisome proliferator-activated receptor coactivator [PGC-1α]) are more responsive to exercise with low compared with high initial muscle glycogen (9, 172). Similarly, mitochondrial enzyme activity increases after extended training periods during which exercise is repeatedly begun with low muscle glycogen content (65, 140, 250). Exercising with an initially low glycogen content also induces favorable metabolic responses, including greater oxidation of triacylglycerol and net uptake of glucose and fatty acids into skeletal muscle (75, 242, 250). Peroxisome proliferator-activated receptor δ expression increases in skeletal muscle after acute and chronic exercise (161), and likely plays an important function in alterations in muscle substrate metabolism following exercise training (17). Collectively, these findings suggest that manipulating carbohydrate availability before and/or during exercise stimulates several of the molecular and metabolic responses that promote adaptations to training.

Adverse responses to low glycogen content. Low glycogen availability limits its use for oxidative phosphorylation and may impair excitation–contraction coupling in muscle during exercise. Specifically, the reduction in Ca^{2+} release from the sarcoplasmic reticulum (SR) that accompanies muscle fatigue is associated with depletion of intramyofibrillar glycogen content (144, 256). In support of this *in situ* evidence, exercise studies have shown that depletion of muscle glycogen decreases Ca^{2+} release from the SR (50, 255). Importantly, SR Ca^{2+} release remains suppressed when carbohydrate intake is restricted in the early (4 h) postexercise recovery period. By contrast, resynthesis of muscle glycogen returns SR Ca^{2+} release rates to the preexercise levels (50). Together with the potential to promote shifts toward greater fat oxidation and inferior rates of carbohydrate oxidation, these responses could explain, at least in part, why acute exercise intensity is lower and endurance

performance following chronic training does not improve when using the 'train low' paradigm (75, 140, 250).

The increase in metabolic stress in skeletal muscle during exercise starting with low glycogen content may also modulate protein turnover. In principle, higher AMPK activity (resulting from low muscle glycogen content) could attenuate muscle protein synthesis by inhibiting translation/elongation. Increased metabolic stress associated with low muscle glycogen content may also exacerbate protein degradation (66, 72). Camera et al (23) demonstrated that starting a bout of resistance exercise with low muscle glycogen content neither promoted nor inhibited the myofibrillar protein synthesis. However, others have reported that starting exercise with low muscle glycogen content increases the rates of leucine oxidation and muscle protein degradation (13, 72). More research is needed to determine the effects of training with low muscle glycogen content on protein turnover—particularly during recovery between training sessions. Nevertheless, it is possible that exercise starting with low compared with high muscle glycogen content may increase muscle protein degradation.

Given the potential for conflicting beneficial and detrimental effects of training starting with suboptimal glycogen content on skeletal muscle adaptations, a key question is: how low should one go? If a biphasic response is dose dependent, one challenge is to titrate the threshold for muscle glycogen content that might enhance the metabolic adaptations without causing complications associated with fatigue or changes in the net protein balance (Table 1). Perhaps the more pertinent question is not 'how low', but for 'how long' or 'how often'. Although acute restriction of dietary carbohydrate provides a positive stimulus for metabolic adaptation, repeated depletion or long-term reduction in muscle glycogen

content may lead to overtraining (4). Therefore, the benefits of restricting carbohydrate during exercise or training with low initial muscle glycogen content must be balanced against the risk of fatigue.

Blood Flow-Restricted Exercise

In addition to nutritional interventions, it is also possible to enhance exercise-induced hormesis through physical interventions. One such example is applying a pressure cuff to the proximal regions of a limb during exercise. This practice first originated in Japan and was initially termed 'Kaatsu' training, which means 'adding pressure' (187). The first research published in English was a study by Shinohara et al (200), in which the combination of moderate resistance (40% of maximum voluntary contraction) and tourniquet ischemia resulted in a significant increase in strength (in contrast to no change in strength in the leg that exercised without ischemia). This training method is now more frequently referred to as 'blood flow-restricted exercise' (108). The basic physiological premise behind blood flow-restricted exercise is that it reduces blood flow and occludes the venous return from the limb (blood pooling). This combination of stimuli increases tissue hypoxia and the accumulation of metabolites, and thereby increases muscular stress during low-load resistance exercise (209-211). Blood flow-restricted exercise induces muscle hypertrophy and increases in muscle strength in the same range as traditional heavy-load strength training. Importantly, blood flow-restricted exercise induces effects that are absent (or minor) when low-load exercise is performed without blood flow restriction (108, 114).

206 Blood flow restriction results in several local and systemic responses that might
207 contribute to the enhanced hypertrophic stimulus when combined with low-load resistance
208 exercise [20–30% of 1 repetition maximum (RM)] (113, 240). In addition to metabolite
209 accumulation, the suggested mechanisms include increased recruitment of motor units
210 (rapid development of fatigue) (240), greater growth hormone secretion (215) and oxidative
211 stress (240), and muscle swelling (blood pooling) (110). Some of the mechanisms are
212 directly related, because metabolic accumulation causes rapid onset of fatigue (which
213 increases motor unit recruitment) and increases growth hormone secretion (215, 240).
214 Because it is difficult to separate these mechanisms, it remains unknown which of these
215 factors are most important. Nevertheless, combining blood flow restriction with low-load
216 resistance exercise increases the rate of muscle protein synthesis by activating similar
217 pathways to those activated after heavy-load strength training (e.g., mammalian target of
218 rapamycin [mTOR] signaling and MAPKs) (45, 47, 60, 239). Furthermore, low-load blood
219 flow-restricted exercise seems to induce a rapid and marked activation of satellite cells
220 (239). Interestingly, this satellite cell activation appears to exceed that which occurs after
221 traditional heavy-load strength training (145). Satellite cell activation induced by blood flow-
222 restricted exercise is accompanied by an increase in the number of myonuclei, which may
223 explain some of the muscle hypertrophy in response to blood flow-restricted exercise (18).
224 The 30–40% increase in cross-sectional area of both type I and II fibers after only seven
225 sessions of low-load, blood flow-restricted exercise supports the hypertrophic potential of
226 this method (145). Others have also reported rapid hypertrophy in response to high-
227 frequency (2×/day), low-load, blood flow-restricted exercise over 1–3 weeks (1, 3).

High-frequency, low-load blood flow-restricted exercise is generally a safe and effective training regimen because the low load induces less mechanical stress on muscle fibers than heavy-load strength training. In addition to the benefits described above, some studies also report no (or only minor) muscle damage and fast recovery after low-load, blood flow-restricted exercise (107, 112). However, the ischemia induced by blood flow restriction might cause some muscle damage and prolonged recovery if certain thresholds are passed. There are isolated reports of severe muscle damage resulting in rhabdomyolysis following blood flow-restricted exercise (82). Sarcolemmal and myofibrillar disruption and slow recovery of muscle function have also been reported after blood flow-restricted exercise in other studies (33, 241). These contrasting findings probably reflect differences in the training status of the study participants, degree of exhaustion, cuff pressure and size, and exercise intensity/volume.

Signs of damage, such as sarcolemmal disruption, high blood creatine kinase [CK] activity, and long-lasting fatigue, and rhabdomyolysis have been reported after the first session of low-load blood flow-restricted exercise (33, 82, 241), but rapid adaptation thereafter is likely. Performing a fixed number of repetitions per set (e.g., 15–15–15 or 30–15–15–15) causes little or no muscle damage (2, 111), but performing each set to failure causes more severe damage (33, 82, 241). The size of the cuff and the occlusion pressure can vary greatly. It can also be difficult to control arterial blood flow and venous return accurately (109). Collectively, these factors make it difficult to determine the optimal guidelines for blood flow restriction in combination with low-load resistance exercise.

Although the stress on the exercising muscle during low-load blood flow-restricted exercise is not well described, some interesting observations have been reported. In a

volume-matched protocol, blood flow-restricted exercise increased the acute expression of heat shock proteins (HSPs) in myofibrillar structures (33). Accumulation of small HSPs in myofibrillar structures was more abundant in type I fibers, indicating that low-load, blood flow-restricted exercise stresses type I fibers more than type II fibers, which contrasts with heavy-load strength training (43). This finding suggests that the combination of low-load resistance exercise and blood flow restriction preferentially stresses type I fibers. Provided that the stress remains within the optimal range, over the long term, such exercise also increases the hypertrophy of type I fibers. Importantly, in accordance with the hormesis theory, the dose is essential because excessive pressure and/or exercise volume/intensity may cause severe muscle damage, especially at the initiation of blood flow-restricted exercise.

In summary, applying a pressure cuff to restrict blood flow to an exercising limb—and thereby blocking venous return—increases the stress to the skeletal muscle during exercise. Blood flow restriction augments the effect of low-load resistance exercise on muscle hypertrophy. An important theme that arises from our evaluation is that blood flow restriction seems to shift muscular stress toward a more optimal range than that achieved with low-load exercise performed in isolation. However, the large variation in the application of blood flow restriction and exercise protocols makes it difficult to suggest an optimal protocol for low-load blood flow-restricted exercise at the present time. Acute blood flow restriction during exercise induces metabolic/hypoxic stress that ultimately leads to muscle hypertrophy. However, if used on a regular basis without sufficient recovery, blood flow-restricted exercise could induce a chronic cycle of muscle degradation and repair, which may impede rather than improve adaptations to training.

274

275 *Application of Heat to Muscle*

276 Applying heat to muscle is another physical intervention that may enhance exercise-
277 induced hormesis. Historically, heat has been used to treat severe muscle injuries (104),
278 although it may also improve recovery from less severe exercise-induced muscle damage.
279 The fundamental benefit of using heat in the management of muscle injuries involves an
280 increase in local blood flow (191, 245), which likely serves to improve the supply of oxygen
281 and nutrients to assist tissue repair (52). The alternative concept of using heat to
282 'precondition' cells and tissues against other forms of stress was recognized around 20 years
283 ago. It was termed 'cross-tolerance' (248), and is a classic example of hormesis. It has
284 stimulated interest in the potential for heat preconditioning to protect myocardial tissue
285 against infarction (121) and skeletal muscle against atrophy (142). An increasing number of
286 studies have investigated the effects of heat application before or after various forms of
287 muscle injury on muscle regeneration and the associated mechanisms (Table 2).

288 *Heat preconditioning.* There is convincing evidence that heat stress assists recovery from
289 muscle injury. Application of heat (41°C) before *in vitro* muscle contraction augments
290 protein synthesis and expression of HSP72 in muscle cells (55, 247). In rats, heat
291 preconditioning 12–48 h before muscle injury increases muscle fiber cross-sectional area
292 and number of centrally nucleated fibers (96). This form of treatment also minimizes fiber
293 degeneration (199) and mitochondrial damage (48) after injury, and assists in maintaining
294 muscle mass during reloading after immobilization in rats (199).

Various mechanisms have been identified to explain these effects including: (i) an increase in phosphocreatine content, which is associated with less necrosis (48, 181); (ii) maintenance of reactive oxygen species-scavenging activity (199); (iii) increased expression of myosin heavy chain protein and HSPs (193, 223); and (iv) more $Pax7^+$ satellite cells (96) in regenerating muscle. Heat preconditioning also reduces oxidative damage to muscle protein (193) and infiltration of mononuclear inflammatory cells (96, 199, 223) after muscle injury in rats. In addition to these studies on muscle injury, heat preconditioning increases the activity of PGC-1α and AMPK in C2C12 myotubes (84) and prevents muscle atrophy in response to immobilization (192) and hindlimb unloading in rats (142).

Research on the effects of heat preconditioning on recovery from exercise-induced muscle damage in humans has produced more variable findings. Some work indicates that heat stress before eccentric exercise can reduce muscle fatigue (77), promote faster recovery of strength and range of motion, and alleviate muscle soreness (149, 183). Heat preconditioning also increases the activation of Akt, mTOR, ribosomal protein S6, and eukaryotic translation initiation factor 4E-binding protein 1 (EIF4E-BP1) after resistance exercise (90). In contrast with these studies, others have reported no benefits of heat preconditioning on the recovery of strength, range of motion, edema, or soreness after eccentric exercise (86, 151).

Heat stress after muscle injury/exercise. Various animal studies have reported that applying heat after muscle injury increases muscle fiber cross-sectional area and number of centrally nucleated fibers (68, 71, 96, 154, 216). Consistent with the effects of heat preconditioning, these benefits of therapeutic heat treatment are conferred by upregulation of HSPs in muscle (71, 154). Heat application after muscle injury in rats also induces more rapid

318 macrophage infiltration (216); expression of IGF-1 (216), MyoD, and myogenin (68),
319 calcineurin (154); and activity of $Pax7^+$, $MyoD^+$, and M-$cadherin^+$ satellite cells (96, 154, 216).
320 Conversely, applying heat to muscle following injury reduces myeloperoxidase activity,
321 production of RONS, lipid peroxidation, and fibrosis in rats (25, 71, 216).

322 Relatively little is known about how applying heat to muscle after exercise influences
323 acute recovery of muscle function. One study reported that, compared with passive
324 recovery, hot water immersion (38°C for 14 min) after eccentric exercise improved the
325 recovery of strength, but not that of muscle power, swelling, or soreness (231). The same
326 group reported that hot water immersion did not help to maintain sprint or time trial
327 performance over 5 days of high-intensity cycling (230).

328 No studies have investigated the effects of regular heat application on chronic muscle
329 adaptations to training. However, evidence from a recent study on rats suggests some
330 potential benefits of heat to enhance training adaptations. In this study, rats that were
331 placed in a heat chamber at 41°C for 30 min immediately after treadmill running showed
332 greater chronic increases in the activity of citrate synthase and 3-hydroxyacyl CoA
333 dehydrogenase, and mitochondrial protein content in skeletal muscle after 3 weeks of
334 training (5 days/week) (217).

335 The transcription factor heat shock factor-1 (HSF-1) and it downstream effectors, HSPs,
336 are most likely central to the benefits of heat stress for healing of muscle injuries, as
337 demonstrated in animal studies outline below. HSF-1 and HSPs may assist muscle
338 regeneration by protecting muscle cells against oxidative damage, apoptosis, and ATP
339 depletion (16, 87-89, 118). HSPs may also promote repair of muscle tissue by activating the
340 signaling pathways involved in protein synthesis (e.g., Akt, p70S6 kinase, and ERK) (61) and

by regulating the activity of enzymes and transcription factors that can cause degeneration and/or atrophy of muscle fibers (38, 49, 105, 195). Importantly, without HSF-1 and HSP70, macrophage infiltration is delayed, and the expression of proinflammatory cytokines is dysregulated in regenerating muscle tissue (98, 148, 196). Heat stress may also increase muscle hypertrophy independently of HSPs by stimulating the expression of IGF-1, myogenin, and Pax7 (166). Increased expression of IGF-1 in response to heat stress likely complements the effects HSPs by orchestrating more efficient resolution of inflammation following muscle injury (160).

This review is the first summary and critical evaluation of the effects of applying heat to muscle with the goal of promoting repair and growth of muscle. Acute heat stress increases the activities of HSPs, satellite cells, PGC-1α, and AMPK, whereas it reduces oxidative damage in muscle after exercise/injury. Over the long term, these responses may augment training adaptations. Although the application of heat stress before or after muscle injury has shown promising results in muscle cell culture and animal studies, more work is required to establish whether these same benefits occur in humans.

Mechanical Preloading

A single bout of eccentric muscle contractions confers protection against subsequent bouts of muscle-damaging exercise. This response is referred to as the 'repeated-bout effect', and may last between 6 and 9 months (150). The repeated bout effect can also occur in the non-exercising contralateral limb, although the effect in the contralateral limb is smaller than that in the ipsilateral limb (73).

Recent interest has focused on trying to determine the minimum stimulus required to elicit protection against muscle damage, which is typically characterized by prolonged decreases (>1 d) in muscle function and delayed-onset muscle soreness (DOMS). Herein, we refer to this approach to strength training and conditioning as 'mechanical preloading'. Although this is a relatively new concept, it is a classic example of exercise-induced hormesis, whereby mild mechanical preloading of skeletal muscle induces positive adaptations. The first evidence for the benefits of mechanical preloading came from a study demonstrating that low-intensity isometric contractions (performed at 10% of maximal voluntary contraction strength) improved the recovery of strength by 50–60% and reduced peak muscle soreness by 30% after subsequent eccentric exercise performed 2 days later (101). These protective effects of mechanical pre-loading seem to last between 1 and 2 weeks (26).

Mode and intensity of contraction. The preloading effect does not appear to be specific to the type of muscle contraction. Preloading with as few as two maximum voluntary isometric contractions at a long muscle length (20° flexion) is sufficient to attenuate the loss of strength and range of motion, DOMS, and swelling after eccentric exercise performed 2 days later (27). As evidence of a dose response, 10 maximal voluntary isometric contractions at the same muscle length conferred even greater protective effects (27). The protective effect conferred by two maximal isometric contractions appears to last only a maximum of 1 week (28). Compared with low-intensity eccentric contractions (10% maximum strength), maximal isometric contractions performed at 20° flexion confer a greater degree of protection against subsequent muscle damage (30). However, the protective effect of maximal isometric contractions is less than that resulting from maximal eccentric

386 contractions (30). Four bouts of moderate-intensity eccentric exercise comprising eccentric
387 contractions at 40% of maximal voluntary isometric contraction, performed every 2 weeks,
388 confers a similar protective effect to one bout of maximal eccentric exercise (29). This
389 finding suggests that repeating submaximal eccentric exercise provides the same protection
390 as one bout of maximal eccentric exercise against the subsequent maximal eccentric
391 exercise. It remains to be determined whether regular lighter intensity eccentric
392 contractions (e.g., 10%) or maximal isometric contractions at a long muscle length increase
393 long-term muscle adaptations.

394 Integration of the findings of the small number of studies in this area shows that a few
395 eccentric contractions at low intensity or a few maximal isometric contractions at long
396 muscle length confer significant protection against subsequent muscle damage. In addition
397 to contracting muscles, this effect most likely also occurs in non-exercising muscles of the
398 contralateral limb. The mechanisms underpinning the effects of mechanical preloading on
399 muscle adaptation are currently unknown. Adaptation to maximal eccentric contractions
400 has been attributed to various factors, including neural changes (e.g., increased motor unit
401 recruitment/synchronization), remodeling of connective tissue, removal of weak fibers, and
402 longitudinal addition of sarcomeres (131). Light-intensity eccentric contractions and
403 isometric contractions do not cause any loss of strength or range of motion, muscle
404 swelling, or DOMS (27, 101). Without causing frank muscle damage, these types of
405 contractions may precondition skeletal muscle through other mechanisms. Such
406 mechanisms could include physical changes to the fascia and endomysium or metabolic
407 alterations in ATP availability, intracellular [Ca^{2+}], mitochondrial Ca^{2+} uptake, RONS signaling,

or proteolytic activity. Further research is warranted to examine these putative mechanisms in greater detail.

Because acute muscle damage resulting from mechanical preloading is minimal, it seems unlikely that long-term use of this form of preconditioning will increase the risk of maladaptation to training. However, the protective effect of mechanical preloading may diminish if it is used repeatedly because muscle probably adapts to such mechanical stimulation. Consistent with this premise, any benefits of mechanical preloading are probably relatively minor for resistance-trained individuals who regularly perform submaximal eccentric contractions and maximal isometric contractions in their training routines. Future studies in this area could investigate whether skeletal muscle remodeling/hypertrophy is still induced effectively if no muscle damage is induced throughout training.

INTERVENTIONS THAT DAMPEN EXERCISE-INDUCED HORMESIS

Antioxidant Supplementation

The notion of hormesis has been studied extensively in the context of oxidative stress and its opposing roles in skeletal muscle pathologies. It has also been examined as a potential stimulus for redox adaptations in skeletal muscle following endurance training. For the purposes of this review, the term ‘oxidative stress’ is defined as an imbalance between oxidants and antioxidants in favor of the oxidants, leading to a disruption of redox signaling and control and/or molecular damage (171). Davies et al (34) were the first to report that submaximal exercise to exhaustion increased the production of free radicals in rodent

skeletal muscle. Other more recent studies have also shown that exhaustive endurance exercise increases oxidative stress in rat skeletal muscle (10, 91, 235). Although these studies provide vital proof of principle, understanding precisely how RONS regulate skeletal muscle adaptations to endurance training is difficult—mainly because few training programs regularly push individuals to exhaustion. Nevertheless, moderate- to high-intensity endurance exercise (70–85% of maximal oxygen uptake) is sufficient to increase oxidative stress in rat skeletal muscle, as measured by changes in GSSG levels (237, 238, 254). Moderate-intensity endurance cycling exercise is also sufficient to increase lipid peroxidation, as measured by F_2-isoprostane content in skeletal muscle of humans (92). Bailey et al (7) provided the first direct evidence in humans that exercise in the form of maximal, single-leg knee extension increases intramuscular free radical accumulation.

Oxidative stress and mitochondrial biogenesis in skeletal muscle. Redox-sensitive kinases activated during muscle contraction include AMPK, activating transcription factor-2 (ATF-2), NFκB, and the MAP kinases p38 MAPK, JNK, and ERK (also called p44/42 MAPK) (53, 79, 185, 238). These kinases are all implicated in the regulation of mitochondrial biogenesis (83, 243)—at least partly through the transcriptional coactivator PGC-1α, which is a key regulator of mitochondrial biogenesis (173, 244). Although RONS were first proposed to regulate exercise-induced mitochondrial biogenesis over 30 years ago (34), it was Silveira et al who first published clear evidence linking RONS with the regulation of contraction-induced mitochondrial biogenesis in rat muscle cells (201). Importantly, this group demonstrated that antioxidants attenuated the increase in RONS production and PGC-1α mRNA expression (201). Hood et al (79) have since provided more direct evidence for the role of RONS (and antioxidants) in regulating the expression of AMPK and PGC-1α in skeletal

453 muscle cells. Other proteins such as upstream stimulatory factor 1 also play an important
454 role in regulating PGC-1α activity in skeletal muscle (80).

455 *Antioxidants and mitochondrial biogenesis.* Research on the effects of antioxidants on
456 mitochondrial biogenesis has used vitamins C and E (alone or in combination), coenzyme
457 Q10, *N*-acetylcysteine, β-carotene and α-lipoic acid in rats (54, 70, 208, 234) and humans
458 (157, 163, 177, 251). Because of the large number of individual antioxidant supplements, a
459 comprehensive examination of each antioxidant is beyond the scope of the current review
460 (for review, see (120). This review is limited to evaluation of hormesis specifically in relation
461 to vitamins C and E because they are two of the most common antioxidant supplements
462 used alone or in combination by the general population (180) and in research (54, 70, 157,
463 177, 208, 234, 251). Given the role of RONS in stimulating mitochondrial biogenesis in
464 skeletal muscle (79, 201), many studies have investigated whether antioxidant supplements
465 prevent adaptations to endurance training. Some training studies have found that vitamin C
466 and/or vitamin E attenuates markers of mitochondrial biogenesis in muscle after training in
467 rats (54, 234) and humans (157, 177). By contrast, other studies have found no significant
468 effects of antioxidant supplements on markers of mitochondrial biogenesis (70, 208, 251,
469 253).

470 Despite this evidence for a reduction in cellular adaptations to endurance training with
471 antioxidants (54, 157, 177, 234), no research has reported any change in maximum oxygen
472 uptake or exercise performance—at least in humans (157, 178, 251). Animal studies have
473 demonstrated that vitamin C supplementation reduces the improvements in exercise
474 performance after 6 weeks of exercise training (54, 126). Differences in the metabolism of

vitamin C in skeletal muscle between humans and rats may partially account for these differences.

Despite strong evidence that endurance exercise increases oxidative stress in human skeletal muscle (7, 92, 254), it remains uncertain whether vitamin C and/or E supplementation inhibits oxidative stress in human skeletal muscle during exercise. One reason for this uncertainty is the lack of suitable markers of RONS production and oxidative stress in skeletal muscle during exercise. Some studies have used plasma or blood to assess oxidative stress (70, 157). However, this is problematic because the degree of systemic oxidative stress in plasma/blood may not reflect the extent of local oxidative stress in skeletal muscle (235)**.** Furthermore, other markers of oxidative stress (e.g., thiobarbituric acid reactive substances (TBARS) or malondialdehyde) may not be specific or sensitive to antioxidant supplementation (182, 252).

In addition to discrepancies between the effects of antioxidants in animals compared with humans, there is also some disparity between the acute and chronic effects of antioxidants. For example, several acute exercise studies show that inhibiting RONS derived from xanthine oxidase with the xanthine oxidase inhibitor, allopurinol, inhibits the exercise-induced phosphorylation of redox-sensitive kinases such as p38 MAPK and ERK, which regulate mitochondrial biogenesis in rats (53, 91, 238). However, long-term treatment with allopurinol does not prevent the increases in skeletal muscle mitochondrial proteins or antioxidant enzymes following endurance training in rats (238). One possible reason for this disparity is that stimuli other than RONS, such as cytosolic Ca^{2+} (130, 155), AMP (130), and possibly NAD (51) also regulate mitochondrial biogenesis in skeletal muscle. Thus, although antioxidant supplements can inhibit RONS production in skeletal muscle, this may not

498 always attenuate mitochondrial biogenesis probably because of redundancies within these
499 pathways.

500 *Antioxidants and skeletal muscle hypertrophy.* There is substantial evidence linking oxidative
501 stress with muscle atrophy [for review see (170)]. Emerging evidence also implicates
502 oxidative stress in the regulation of skeletal muscle hypertrophy. A high daily oral dose of
503 vitamin C attenuates skeletal muscle hypertrophy and oxidative stress normally observed
504 following mechanical overload of the plantaris (119). Recent findings in rodents
505 demonstrate that the highly reactive oxidant, peroxynitrite regulates skeletal muscle
506 hypertrophy induced by overload (81). Peroxynitrite appears to operate by stimulating the
507 release of intracellular Ca^{2+}, which then activates mTOR to increase protein synthesis (119).

508 The few human studies to investigate the adaptations to resistance training combined
509 with antioxidant supplementation have reported variable findings. Two studies showed no
510 effect of vitamin C and E supplementation on improvements in skeletal muscle strength or
511 performance (14, 220). However, these studies used resistance training protocols that did
512 not induce skeletal muscle hypertrophy (14) or did not measure changes in lean muscle
513 mass (220). Paulsen et al (159) recently found that supplementation with vitamins C and E
514 attenuated the activities of several kinases involved in hypertrophy signaling, such as p70S6
515 kinase and the redox-sensitive kinases p38 MAPK and ERK 1/2 in skeletal muscle after 10
516 weeks of resistance training. In addition, supplementation attenuated bicep curl strength
517 following 10 weeks of training. By contrast, supplementation did not alter protein synthesis
518 or muscle hypertrophy following training (159). Thus, some evidence supports blunting of
519 the cell signaling pathways with antioxidant supplementation following resistance exercise,
520 although the effects on functional outcomes remain equivocal. More studies are required to

examine whether RONS regulate hypertrophy following resistance training in human skeletal muscle and whether antioxidant supplementation influences these adaptations to resistance exercise.

In summary, oxidative stress plays an important role in regulating the mitochondrial content and perhaps contractile protein content of skeletal muscle. Some evidence shows that supplementation with vitamins C and E can block acute increases in signaling pathways that control mitochondrial biogenesis and hypertrophy. However, these acute responses do not consistently translate to less mitochondrial biogenesis or muscle hypertrophy following chronic exercise training because of the apparent redundancy in skeletal muscle. That is, exercise training (either endurance or resistance) may induce mitochondrial biogenesis and hypertrophy despite elevated concentrations of RONS-scavenging antioxidants. The weight of current evidence suggests that vitamin C and E supplementation may dampen exercise-induced hormesis—at least at the cellular level. However, it remains uncertain whether these responses influence exercise performance in the long term. Importantly, antioxidant compounds have widely divergent properties, and this discussion of a specific class of agents does not rule out the effects of other components on RONS activity/regulation, nor a role for RONS in exercise-induced adaptation. The requirement for and efficacy of antioxidant supplements may vary with age and health status. There are conflicting and unresolved issues surrounding the influence of antioxidant supplementation on adaptations to training that require further investigation.

NSAIDs

Similar to antioxidants, NSAIDs represent another pharmacological intervention that may attenuate exercise-induced hormesis. NSAIDs are inhibitors of the cyclooxygenase (COX) pathway that converts free arachidonic acid to PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2, and thromboxane A_2 (42, 232). PGs are autocrine/paracrine lipid mediators that propagate the inflammatory response to tissue injury by increasing blood flow, vascular permeability, and leukocyte chemotaxis (35). COX has two major isoforms. COX-1 is constitutively expressed, and COX-2 expression is generally low but is highly inducible in response to injurious stimuli (57, 139). Classical NSAIDs inhibit both COX-1 and COX-2 to varying degrees (36, 202). Undesirable side effects associated with disruption of homeostatic COX-1 activity have led to the development COX-2-specific inhibitors (coxibs) for treating pain and inflammation. During postexercise recovery, the activities of COX-1 and COX-2 (24) and concentrations of PGs (20, 93, 225, 227) increase transiently in skeletal muscle. Plasma PG concentrations also increase after exercise (39, 123, 218). These responses point to important roles for the COX/PG pathway in exercise adaptation. On the other hand, chronically elevated PG concentrations are associated with—and may contribute directly to—muscle wasting in states of chronic inflammation (97).

Effect of NSAIDs on acute muscle responses to exercise. Classical NSAIDs (e.g., ibuprofen and indomethacin) administered at over-the-counter doses effectively block the acute exercise-induced increase in PG concentration in muscle (20, 135, 227) and plasma (123). Although not considered a classical NSAID, acetaminophen also appears to inhibit COX activity in muscle (227). Many studies have investigated the effect of NSAIDs on symptoms of exercise-induced muscle damage, although the literature on the efficacy of NSAIDs for reducing muscle soreness and/or improving exercise recovery is contradictory. Given that NSAIDs are

566 anti-inflammatory, it is surprising that studies to date have failed to observe any effect of
567 NSAIDs on systemic (95, 167, 222) or intramuscular (158) leukocyte responses to exercise
568 stress. Paradoxically, short-term NSAID treatment appears to increase plasma cytokine
569 concentrations (e.g., IL-6 and monocyte chemotactic protein-1) (41, 59, 138, 146) and
570 muscle COX-2 gene expression (19, 138) after exercise.

571 Together with a lack of a clear benefit of NSAIDs in reducing exercise-induced pain
572 and/or the acute inflammatory response in humans, various studies have shown potential
573 negative effects of NSAIDs in muscle after exercise. Oral ingestion of the nonselective
574 NSAIDs ibuprofen or acetaminophen blunts the increase in muscle protein synthesis during
575 postexercise recovery in young men (229). However, this effect was not replicated in a study
576 of patients with knee osteoarthritis who received ibuprofen (165). Another nonselective
577 NSAID (indomethacin) blocked the muscle satellite cell response to a 36 km run (117) and
578 maximal eccentric exercise (137) but did not alter muscle protein synthesis (138). Studies
579 have shown that COX-2-selective inhibitors do not influence muscle protein synthesis (19) or
580 satellite cell responses to exercise (158), suggesting that COX-1 rather than COX-2 may be
581 the primary isoform involved in human muscle responses to exercise.

582 The underlying mechanisms by which NSAIDs influence muscle adaptive responses to
583 exercise remain unclear, but several recent studies have provided useful insights. Impaired
584 satellite cell proliferation following maximal eccentric exercise with local indomethacin
585 infusion (135) did not alter the expression of growth factors and extracellular matrix-related
586 genes (138) or HSP (136) in muscle. Oral ibuprofen treatment blocked the normal increase
587 in serum PG concentration during early postexercise recovery (0–3 h) (123), and suppressed
588 phosphorylation of components of the ERK and mTOR signaling pathways in muscle (122).

589 These data provide the first evidence that PGs contribute to contraction-induced signaling in
590 human muscle and provide mechanistic support for a potentially detrimental effect of oral
591 nonselective NSAIDs (122, 125). Interestingly, mass spectrometry profiling of serum samples
592 collected throughout exercise recovery revealed suppression of both early proinflammatory
593 and later anti-inflammatory/proresolving lipid mediator circuits in subjects receiving
594 ibuprofen (123). Thus, NSAIDs may interfere with exercise recovery indirectly by delaying or
595 preventing timely resolution of the inflammatory response (123, 233).

596 *Chronic effects of NSAIDs on muscle exercise adaptation.* Although nonselective NSAIDs may
597 attenuate acute responses to exercise in humans (122, 123, 137, 138, 227, 229), it remains
598 unclear whether these responses influence long-term adaptations to exercise. Oral
599 ibuprofen treatment (400 mg/day) did not influence muscle hypertrophy or strength
600 following 6 weeks of resistance training of the elbow flexors in young healthy men (99).
601 However, this dose of ibuprofen was only one-third that used in acute exercise studies (122,
602 123, 227, 229). By contrast, animal studies clearly show a deleterious effect of NSAID
603 treatment on long-term muscle regeneration and hypertrophy, and specifically implicate the
604 COX-2 isoform in this response (100, 124, 152, 198).

605 In older adult subjects, gains in skeletal muscle size and strength following 12 weeks of
606 resistance training were greater in response to treatment with ibuprofen (1,200 mg/day) or
607 acetaminophen (4 g/day) compared with a placebo treatment (224). Another study also
608 revealed that ibuprofen augmented training-induced gains in muscle strength in elderly
609 subjects but did not influence muscle mass and tended to reduce satellite cell numbers in
610 muscle (164). By contrast, a lower dose of acetaminophen (1,000 mg/day) did not alter fat-
611 free-mass or muscle strength in older men after a period of resistance exercise training (85).

612 One mechanism through which NSAIDs may exert positive effects on muscle involves a
613 reduction in chronic low-grade inflammation that occurs with aging, thereby blocking the
614 pathway to muscle atrophy. NSAID treatment counteracts skeletal muscle wasting in animal
615 models of chronic inflammatory disease including cancer cachexia (129, 202, 207), arthritis
616 (56), and aging (176). Consistent with this hypothesis, older adults who received ibuprofen
617 throughout 12 weeks of resistance training showed a chronic reduction in the expression of
618 cytokine genes (e.g., IL-6, IL-10) and muscle ring finger 1 (MuRF-1) (226).

619 In summary, the COX/PG pathway appears to play an important role in acute exercise
620 recovery, and NSAIDs inhibit the seemingly beneficial acute muscle adaptive responses to
621 exercise (e.g., satellite cell proliferation and muscle protein synthesis). On the other hand,
622 chronic activation of the COX/PG pathway may exert negative effects on muscle mass, and
623 NSAID treatment may provide an effect countermeasure against such effects. In this review,
624 we have highlighted an apparent discrepancy between the opposing effects of NSAIDs in
625 different settings (e.g., acute versus chronic, young versus old subjects). The balance
626 between PG species with differing bioactivity (e.g. $PGF_{2\alpha}$ versus PGE_2) (228) or differences in
627 the underlying nature of the inflammatory response (acute self-resolving versus chronic
628 nonresolving) (97, 122) may be important factors that influence the pharmacological actions
629 of NSAIDs.

630

631 *Cryotherapy*

632 Cryotherapy in the form of ice massage and application of crushed ice has long been a
633 common treatment for soft tissue injuries (132). More recently, other forms of cryotherapy

634 such as cold water/ice baths and brief exposure to extreme cold air (−20 to −110°C) in
635 custom-made cryotherapy chambers have gained popularity as strategies to recover from
636 exercise. Traditionally, the physiological basis for using cryotherapy has been to relieve pain,
637 reduce tissue metabolism, and modify vascular responses to minimize edema (213). Acute
638 responses to primary muscle injury (e.g., necrosis and inflammation) can result in
639 'secondary injury' to healthy cells not damaged through the initial trauma (134). By reducing
640 the metabolic rate of tissues within and around the injury site, cryotherapy may protect the
641 healthy bystander cells from the ischemic environment in the immediate period after injury,
642 thereby reducing the risk of secondary cell injury or death (12). Some evidence from animal
643 studies support this notion (133, 134, 156, 186). However, the effects of cryotherapy on
644 muscle inflammation in humans are currently unknown.

645 *Effects of cryotherapy on inflammation and oxidative stress.* Studies have focused on how
646 icing influences inflammation and oxidative stress in muscle following injury (Table 3).
647 Superfusing rats with cold saline (3−8°C) for 10 min to 6 h after muscle contusion injury
648 significantly reduced leukocyte rolling and adhesion to venules within damaged muscle for
649 up to 1 day after injury (102, 188, 189). These effects may be mediated by downregulation
650 of adhesion molecules on the surface of vessels and leukocytes in response to hypothermia
651 (63, 78). Immunohistochemical analysis of muscle tissue revealed that this cryotherapy
652 treatment decreased the number of neutrophils in muscle 1 day after injury (188, 189). In
653 support of these findings, others have observed that icing after muscle strain injury in rats
654 substantially reduced neutrophil activation in muscle, as indicated by lower
655 myeloperoxidase activity 1 day after injury (25). Icing also restricted the production of RONS
656 and lipid peroxidation at 1, 5, 10 and 15 days after injury in rats (25). Icing preserves the

activity of Na^{+}-K^{+}-ATPase and Ca^{2+}-ATPase enzymes and mitochondrial membrane permeability, and it reduces mitochondrial swelling in muscle 1 day after contusion injury in rats (174). Because none of these studies assessed muscle regeneration in the weeks following injury, it is difficult to establish whether restricting neutrophil invasion and activation through cryotherapy results in better healing of muscle injuries. In principle, a decrease in neutrophil infiltration into muscle as a result of icing is potentially beneficial because activated neutrophils can damage skeletal muscle fibers (143, 168).

Effects of cryotherapy on muscle regeneration. Other studies in rats have shown that icing causes greater fibrosis and impairs muscle regeneration after muscle contusion and crush injuries. These effects are evident as early as 2 days after injury (76) and persist for up to 4 weeks (214). The potential mechanisms responsible for these effects include delayed macrophage infiltration and mRNA expression of transforming growth factor-β1 and IGF-1 in muscle, together with a delay in (or absence of) satellite cell activation (76, 214). Impaired muscle regeneration in response to icing may be attributed to the following sequence of events. By restricting neutrophil infiltration, icing may slow the rate of phagocytosis of necrotic muscle tissue in the first few hours after injury (219). Persistent necrosis may then delay the entry of macrophages into muscle tissue in the first few days after injury (58). Finally, by delaying macrophage infiltration, icing may reduce the capacity of these cells to (a) produce essential growth factors and chemotactic agents (64, 115, 116, 212), and (b) stimulate satellite cells to proliferate and differentiate (6, 221). The limited evidence that is currently available therefore suggests that cryotherapy is detrimental for muscle regeneration following injury.

679 *Effects of cryotherapy on training adaptations.* In addition to this research on acute muscle
680 injury, a smaller body of research has investigated the effects of regular cryotherapy on
681 muscle adaptations to exercise training. An early study demonstrated that, in rats regularly
682 immersed in cold water (4°C) for 5 min after exercise bouts, greater ultrastructural damage
683 to myofibrils was evident after 5 weeks of exhaustive running and 7 weeks of moderate
684 running (46). Fu et al proposed that, by masking pain, cold water immersion allowed the
685 rats to exercise at higher intensities the next day, which unexpectedly resulted in greater
686 muscle damage (46). Subsequently, several human studies have also reported that regular
687 cold water immersion after exercise attenuates muscle adaptations to training (44, 153,
688 179, 246). The mechanisms by which regular cold water immersion dampened training
689 adaptations in these studies are unknown. Hypothetically, a decrease in muscle blood flow
690 in response to cold water immersion might reduce angiogenesis and protein synthesis in
691 muscle during recovery from exercise. In turn, these responses may result in smaller gains in
692 muscular endurance and strength.

693 This review is the first critical evaluation of the short- and long-term effects of various
694 forms of cryotherapy on cellular responses in skeletal muscle. We have also outlined in
695 detail the putative mechanisms by which cryotherapy influences muscle repair and growth.
696 When applied acutely after exercise or muscle injury, cryotherapy may help to reduce
697 muscle soreness and minimize secondary tissue damage. However, by attenuating some key
698 inflammatory reactions (e.g., macrophage infiltration) in skeletal muscle, cryotherapy may
699 also block the production and release of important growth factors and the activity of
700 satellite cells, which are important mediators of muscle repair and adaptation. Therefore,

701 although cryotherapy offers some short-term benefits, these are possibly outweighed by
702 long-term detrimental effects.

703

704 **PERSPECTIVES AND FUTURE DIRECTIONS**

705 This is the first commentary to combine, summarize, and evaluate the efficacy of
706 various strategies to modulate exercise-induced hormesis. Some of these strategies (e.g.,
707 antioxidant supplementation, treatment with NSAIDs, restriction of dietary carbohydrate
708 intake) have been the subject of scientific scrutiny and debate. By contrast, other strategies
709 such as cryotherapy, blood flow restriction, heat stress, and mechanical preloading have
710 received less critical attention. In this review, we have detailed the conceptual frameworks
711 for the use of such strategies, have integrated these details with the current knowledge
712 about the basic biochemical and molecular machinery that regulate muscle adaptations to
713 exercise, and have applied this information to assess the advantages and disadvantages of
714 each strategy for modulating exercise-induced hormesis.

715 Table 4 summarizes the mechanisms of action of treatments that modulate exercise-
716 induced hormesis and describes some of the short- and long-term outcomes of these
717 treatments. A key finding from this review is that there appears to be some dissociation
718 between the biochemical/molecular effects and functional/performance outcomes of some
719 of these treatments (e.g., antioxidants, NSAIDs, restriction of dietary carbohydrate).
720 Conceivably, other signaling pathways that are less responsive to these treatments (or not
721 yet defined) may operate independently in the regulation of training adaptations. This
722 redundancy may promote fine-tuning of adaptive responses to exercise training (40). Few of

723 the interventions described in this review have been adequately tested to determine if or
724 how they exert dose-dependent effects on muscle adaptation. If such dose-dependent
725 effects do occur, they are likely to be subject to highly complex regulatory mechanisms.

726 A common feature of hormesis is that exposure to one type of hormetic agent can
727 protect cells/organisms against more types of stress (127). This concept of 'cross tolerance'
728 may be applied to some of the interventions that we have discussed. Several of the
729 interventions influence common kinases, transcription factors, and proteins (see Table 4).
730 For example, AMPK, p38 MAPK, PGC-1α, and HSP expression increases in response to heat
731 stress, carbohydrate restriction, and blood flow restriction, whereas the expression of most
732 of these factors decreases following antioxidant supplementation. Similarly, macrophage
733 infiltration, IGF-1, and Pax7 expression increases in response to heat stress, whereas these
734 factors are either blocked or activated more slowly after cryotherapy. It remains to be
735 determined whether these interventions complement or negate each other and whether
736 such effects are strong enough to alter terminal adaptive processes such as mitochondrial
737 biogenesis, substrate metabolism, or muscle repair/growth.

738 Several important questions have emerged from this review that warrant further
739 investigation. A primary issue relates to the threshold (i.e., dose, period of exposure) that
740 defines whether oxidative stress and inflammation are beneficial for or harmful to muscle
741 adaptations to exercise. This threshold would be difficult to titrate because it most likely
742 depends on the basal state of oxidative stress and inflammation at the start of exercise. In
743 turn, this basal state may depend on periodization of training and recovery, together with
744 age, health status, and diet. In addition, it is unclear whether undertaking different
745 strategies simultaneously enhances or attenuates exercise-induced hormesis and which

746 combination of strategies might offer complementary or additive benefits. As highlighted in
747 our review, some interventions such as NSAIDs and antioxidants exert different effects in
748 young compared with older individuals and in trained compared with untrained individuals.
749 Finally, the efficacy of a given intervention may depend on the capacity to 'periodize' such
750 interventions during different phases of a training program. For example, during training to
751 promote muscle hypertrophy and strength, interventions such as cryotherapy and the use
752 of NSAIDs may dampen rather than enhance adaptation. However, during periods of regular
753 competition when recovery is a priority, these strategies may be appropriate to alleviate
754 muscle soreness and restrict secondary tissue injury.

755 In conclusion, exercise-induced adaptations in skeletal muscle are regulated through
756 interactions between various mechanical, metabolic, and physiological stressors and
757 complex cellular machinery. Undoubtedly, a large body of work is still required to provide
758 greater clarity on the appropriate uses and applications of strategies to modify skeletal
759 muscle phenotypes. Exercise-induced hormesis is an intriguing notion that awaits further
760 exploration. To adapt a phrase from a well-known bard, to intervene or not intervene: that
761 remains the question.

762

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1487 **Tables**

Table 1. Effects of glycogen concentration on physiological responses to exercise in human skeletal muscle.

Reference	Design	Δ%	Low glycogen	Findings
(242)	Acute	−82%	163 mmol·kg^{-1}·dw	↑AMPK activity
(9)	Acute	−75%	103 mmol·kg^{-1}·dw	↑p53 phosphorylation ↑Mitochondrial mRNA
(172)	Acute	−65%	166 mmol·kg^{-1}·dw	↑Mitochondrial mRNA
(13)	Acute	−47%	167 mmol·kg^{-1}·dw	↑Protein degradation
(72)	Acute	−30%	290 mmol·kg^{-1}·dw	↑Leucine oxidation ↓Net protein balance
(23)	Acute	−52%	180 mmol·kg^{-1}·dw	↔ Muscle protein synthesis
(255)	Acute	−69%	167 mmol·kg^{-1}·dw	↓SR Ca^{2+} release rate
(50)	Acute	−68%	245 mmol·kg^{-1}·dw	↓ SR Ca^{2+} release rate
(65)	Chronic	−68%	210 mmol·kg^{-1}	↑Mitochondrial enzyme activity
(250)	Chronic	−50%	250 µmol·g^{-1}·dw	↑Mitochondrial enzymes ↑Fat oxidation

dw, dry weight; SR, sarcoplasmic reticulum.

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Table 2. Summary of studies investigating the effects of heat stress on muscle regeneration.

Reference	Study type	Treatment	Assessment period	Outcome variables
(48)	Rats; ischemia	Hot water @ 42.5°C Duration: 20 min Timing: 12 h preinjury	1.5 h postinjury	Electron microscopy, PCr, ATP, HSP72
(199)	Rats; downhill running	Heat chamber at 42°C Duration: 60 min Timing: 48 h preinjury	1, 2, 3, and 7 d postinjury	ROS production and scavenging, HSP72, histology
(223)	Rats; downhill running	Hot water @ 43°C; Duration: 20 min Timing: 48 h preinjury	2 h and 2 d postinjury	Histology, Akt, p70S6K, ERK1/2, JNK, HSP72, HSP25, MHC
(96)	Rats; cardiotoxin injury	Heat chamber at 41°C Duration: 60 min Timing: 24 h preinjury or 0 h postinjury	1, 3, 7, 14, and 28 d postinjury	Muscle mass, central nucleated fibers, fiber CSA, HSP72, Pax7
(25)	Rats; acute strain injury	Infrared lamp Duration: 5 min Timing: 30 min and 2×/day postinjury	1, 5, 10, and 15 d postinjury	Lipid peroxidation, antioxidant enzymes myeloperoxidase
(154)	Rats; cardiotoxin injury	Hot water @ 42°C Duration: 30 min Timing: 48 h postinjury and then every second day	7 and 15 d postinjury	Fiber CSA, myonuclei, Pax7, M-Cadherin, MyoD, HSP72, calcineurin
(71)	Rats; tenotomy	Heat chamber @ 40.5–41°C Duration: 30 min Timing: 24 h preinjury; 1–6 d postinjury	7 d postinjury	Muscle mass, histology, fiber CSA, HSP72, collagen, TGF-β1, MMP-2, MMP-9, TIMP
(216)	Rats; acute crush injury	Hot pack @ 42°C Duration: 20 min Timing: 5 min postinjury	6 and 12 h; 1–7, 14, and 28 d postinjury	Central nucleated fibers Fiber CSA, macrophages TGF-β1, IGF-1, Pax7, collagen
(68)	Rats; acute crush injury	Hot pack @ 42°C; Duration: 20 min Timing: 5 min postinjury	12 h; 1–5, 7, 14, and 28 d postinjury	MyoD, myogenin, PCNA Pax7

(217)	Mice; acute treadmill running	Heat chamber @ 41°C Duration: 30 min Timing: Immediately postexercise	30 min postexercise	AMPK, ACC, p38 MAPK, CaMKII, Akt, mTOR p70S6K

Abbreviations: PCr, phosphocreatine; MHC, myosin heavy chain; PCNA, proliferating cells nuclear antigen; ROS, reactive oxygen species; CaMK, calmodulin-dependent protein kinase; CSA, cross-sectional area; Akt, protein kinase B; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of matrix metalloproteinase. See Figure 1 for details of other abbreviations.

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Table 3. Studies investigating the effects of cryotherapy on muscle regeneration.

Reference	Study type	Treatment	Assessment period	Outcome variables
(214)	Rat; acute crush injury	Topical icing Duration: 20 min duration Timing: 5 min postinjury	6 and 12 h; 1–7, 14, and 28 d postinjury	Central nucleated fibers Fiber CSA, macrophage , TGF-β1, IGF-1, Pax7, collagen
(25)	Rat; acute crush injury	Topical icing Duration: 5 min Timing: 30 min and 2×/d postinjury	1, 5, 10, and 15 d postinjury	Lipid peroxidation Antioxidant enzymes Myeloperoxidase
(174)	Rat; acute contusion injury	Topical icing Duration: 5 min Timing: Immediately and 6 h postinjury	1 d postinjury	Lipid peroxidation Antioxidant enzymes Myeloperoxidase Na^+-K^+ ATPase, Ca^{2+} ATPase Lactate dehydrogenase
(76)	Rat; acute contusion injury	Topical icing Duration: 5 min; intermittently for 1 h Timing: Immediately postinjury or 24 h postinjury	1, 2, and 6 h; 1, 2, 5, and 7 d postinjury	Neutrophil infiltration Macrophage infiltration $Desmin^+$ myoblasts
(102)	Rat; acute contusion injury	Cold saline (3°C) infusion Duration: 10 min Timing: 5 min postinjury	15 min postinjury	Leukocyte rolling and adhesion
(189)	Rat; acute contusion injury	Cold saline (8°C) infusion Duration: 20 min Timing: ~20 min postinjury	1 h postinjury	Edema, microvascular perfusion, leukocyte rolling/adhesion Neutrophils and macrophages
(188)	Rat; acute contusion injury	Cold saline (8°C) infusion Duration: 6 h Timing: ~20 min postinjury	1 d postinjury	Edema, microvascular perfusion, leukocyte rolling/adhesion Neutrophils and macrophages Desmin expression

CSA, cross-sectional area; TGF, transforming growth factor

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Table 4. Summary of physiological and molecular responses, acute and chronic adaptations to treatments that enhance or dampen exercise-induced hormesis in skeletal muscle.

	Treatments that dampen hormesis				Treatments that enhance hormesis				
	Cryotherapy	NSAIDs	Antioxidant supplementation		Carbohydrate restriction		Heat stress		Blood flow restriction
Physiological rationale	Analgesia ↓ Muscle blood flow ↓ Inflammation ↑ Hydrostatic pressure	Analgesia ↓ Inflammation	↓ Oxidative stress		↑ Metabolic stress		↓ Muscle breakdown		↑ Metabolic stress ↑ Oxidative stress ↑ Blood pooling
Cells and signalling molecules upregulated	TGF-β	IL-6 MCP-1 Cyclooxygenase 2			AMPK ACC p53 PGC-1α CS	SDH HAD COXIV PDK4	Macrophages HSPs MyoD Myogenin mTOR	CS PGC-1α p38 MAPK p70S6K	Pax7 AMPK MAPK HSPs
Cells and signalling molecules downregulated	Neutrophils Macrophages IGF-1 Pax7	Prostaglandins ERK/RSK/MNK p70S6K/rpS6 Leukotrienes Resolving mediators	p38 MAPK ERK AMPK IL-6 NFκB	PGC-1α Tfam COX SOD			Macrophages NFκB AMPK ACC		
Acute effects	↓ Soreness	Soreness? ↔ Inflammation ↓ Protein synthesis ↓ Satellite cells			↓ SR Ca^{2+} release rate ↑ Protein breakdown		↓ Loss of strength* ↓ Soreness* ↓ Swelling ↑ Range of motion*		↑ Loss of strength ↑ Soreness ↑ Swelling
Chronic effects	↓ Fibre CSA ↑ Fibrosis ↓ Strength	Young healthy ↔ muscle mass?	↓ Antioxidant enzymes		↑ Mitochondrial enzymes ↑ Fat oxidation		↑ Mitochondrial enzymes ↑ Respiratory chain protein content		↑ Hypertrophy

	↔ strength?	↔ Performance
	Elderly	
	↑ muscle mass	
	↑ strength	

Abbreviations: TGF, transforming growth factor; MCP, monocyte chemotactic protein; AMPK, adenosine monophosphate activated protein kinase; ACC, acetyl-CoA-carboxylase; PGC, peroxisome proliferator-activated receptor coactivator; CS, citrate synthase; SDH, succinate dehydrogenase; HAD, hydroxyacyl-CoA-dehydrogenase; COX, cytochrome oxidase; PDK, pyruvate dehydrogenase kinase; HSP, heat shock protein; Pax, paired box protein; mTOR; mammalian target of rapamycin; Mnk, MAPK-interacting kinase; RSK, p90 ribosomal S6 kinase; rpS6, ribosomal S6 kinase; Tfam, mitochondrial transcription factor A; SOD, superoxide dismutase; CSA, cross-sectional area. ↔ no change. * conflicting evidence for an increase/decrease or no change.

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