

## Modulating exercise-induced hormesis

### Does less equal more?

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**Modulating exercise-induced hormesis: does less equal more?**

Running title: Exercise-induced hormesis

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**ABSTRACT**

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

38 Key words: adaptation, stress, preconditioning.

39

## 40 INTRODUCTION

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

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

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

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

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

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

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

106

107 **INTERVENTIONS THAT ENHANCE EXERCISE-INDUCED HORMESIS**

## 108 *Restricting Dietary Carbohydrate Intake*

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

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



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

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

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

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

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

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

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

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

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

203

#### 204 *Blood Flow-Restricted Exercise*

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

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

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

255 Signs of damage, such as sarcolemmal disruption, high blood creatine kinase [CK]  
256 activity, and long-lasting fatigue, and rhabdomyolysis have been reported after the first  
257 session of low-load blood flow-restricted exercise (33, 82, 241), but rapid adaptation  
258 thereafter is likely. Performing a fixed number of repetitions per set (e.g., 15–15–15 or 30–  
259 15–15–15) causes little or no muscle damage (2, 111), but performing each set to failure  
260 causes more severe damage (33, 82, 241). The size of the cuff and the occlusion pressure  
261 can vary greatly. It can also be difficult to control arterial blood flow and venous return  
262 accurately (109). Collectively, these factors make it difficult to determine the optimal  
263 guidelines for blood flow restriction in combination with low-load resistance exercise.

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

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

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

289

290 *Application of Heat to Muscle*

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

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



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

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

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

333 macrophage infiltration (216); expression of IGF-1 (216), MyoD, and myogenin (68),  
334 calcineurin (154); and activity of Pax7<sup>+</sup>, MyoD<sup>+</sup>, and M-cadherin<sup>+</sup> satellite cells (96, 154, 216).  
335 Conversely, applying heat to muscle following injury reduces myeloperoxidase activity,  
336 production of RONS, lipid peroxidation, and fibrosis in rats (25, 71, 216).

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

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

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

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

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

371

### 372 *Mechanical Preloading*

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

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

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

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

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

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

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

435

## 436 **INTERVENTIONS THAT DAMPEN EXERCISE-INDUCED HORMESIS**

### 437 *Antioxidant Supplementation*

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

445 skeletal muscle. Other more recent studies have also shown that exhaustive endurance  
446 exercise increases oxidative stress in rat skeletal muscle (10, 91, 235). Although these  
447 studies provide vital proof of principle, understanding precisely how RONS regulate skeletal  
448 muscle adaptations to endurance training is difficult—mainly because few training programs  
449 regularly push individuals to exhaustion. Nevertheless, moderate- to high-intensity  
450 endurance exercise (70–85% of maximal oxygen uptake) is sufficient to increase oxidative  
451 stress in rat skeletal muscle, as measured by changes in GSSG levels (237, 238, 254).  
452 Moderate-intensity endurance cycling exercise is also sufficient to increase lipid  
453 peroxidation, as measured by F<sub>2</sub>-isoprostane content in skeletal muscle of humans (92).  
454 Bailey et al (7) provided the first direct evidence in humans that exercise in the form of  
455 maximal, single-leg knee extension increases intramuscular free radical accumulation.

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

468 muscle cells. Other proteins such as upstream stimulatory factor 1 also play an important  
469 role in regulating PGC-1 $\alpha$  activity in skeletal muscle (80).

470 *Antioxidants and mitochondrial biogenesis.* Research on the effects of antioxidants on  
471 mitochondrial biogenesis has used vitamins C and E (alone or in combination), coenzyme  
472 Q10, *N*-acetylcysteine,  $\beta$ -carotene and  $\alpha$ -lipoic acid in rats (54, 70, 208, 234) and humans  
473 (157, 163, 177, 251). Because of the large number of individual antioxidant supplements, a  
474 comprehensive examination of each antioxidant is beyond the scope of the current review  
475 (for review, see (120). This review is limited to evaluation of hormesis specifically in relation  
476 to vitamins C and E because they are two of the most common antioxidant supplements  
477 used alone or in combination by the general population (180) and in research (54, 70, 157,  
478 177, 208, 234, 251). Given the role of RONS in stimulating mitochondrial biogenesis in  
479 skeletal muscle (79, 201), many studies have investigated whether antioxidant supplements  
480 prevent adaptations to endurance training. Some training studies have found that vitamin C  
481 and/or vitamin E attenuates markers of mitochondrial biogenesis in muscle after training in  
482 rats (54, 234) and humans (157, 177). By contrast, other studies have found no significant  
483 effects of antioxidant supplements on markers of mitochondrial biogenesis (70, 208, 251,  
484 253).

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



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

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

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

513 always attenuate mitochondrial biogenesis probably because of redundancies within these  
514 pathways.

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

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

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

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

556

557 *NSAIDs*

558 Similar to antioxidants, NSAIDs represent another pharmacological intervention that  
559 may attenuate exercise-induced hormesis. NSAIDs are inhibitors of the cyclooxygenase  
560 (COX) pathway that converts free arachidonic acid to PGD<sub>2</sub>, PGE<sub>2</sub>, PGF<sub>2α</sub>, PGI<sub>2</sub>, and  
561 thromboxane A<sub>2</sub> (42, 232). PGs are autocrine/paracrine lipid mediators that propagate the  
562 inflammatory response to tissue injury by increasing blood flow, vascular permeability, and  
563 leukocyte chemotaxis (35). COX has two major isoforms. COX-1 is constitutively expressed,  
564 and COX-2 expression is generally low but is highly inducible in response to injurious stimuli  
565 (57, 139). Classical NSAIDs inhibit both COX-1 and COX-2 to varying degrees (36, 202).  
566 Undesirable side effects associated with disruption of homeostatic COX-1 activity have led  
567 to the development COX-2-specific inhibitors (coxibs) for treating pain and inflammation.  
568 During postexercise recovery, the activities of COX-1 and COX-2 (24) and concentrations of  
569 PGs (20, 93, 225, 227) increase transiently in skeletal muscle. Plasma PG concentrations also  
570 increase after exercise (39, 123, 218). These responses point to important roles for the  
571 COX/PG pathway in exercise adaptation. On the other hand, chronically elevated PG  
572 concentrations are associated with—and may contribute directly to—muscle wasting in  
573 states of chronic inflammation (97).

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

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

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

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

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

611 *Chronic effects of NSAIDs on muscle exercise adaptation.* Although nonselective NSAIDs may  
612 attenuate acute responses to exercise in humans (122, 123, 137, 138, 227, 229), it remains  
613 unclear whether these responses influence long-term adaptations to exercise. Oral  
614 ibuprofen treatment (400 mg/day) did not influence muscle hypertrophy or strength  
615 following 6 weeks of resistance training of the elbow flexors in young healthy men (99).  
616 However, this dose of ibuprofen was only one-third that used in acute exercise studies (122,  
617 123, 227, 229). By contrast, animal studies clearly show a deleterious effect of NSAID  
618 treatment on long-term muscle regeneration and hypertrophy, and specifically implicate the  
619 COX-2 isoform in this response (100, 124, 152, 198).

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

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

634 In summary, the COX/PG pathway appears to play an important role in acute exercise  
635 recovery, and NSAIDs inhibit the seemingly beneficial acute muscle adaptive responses to  
636 exercise (e.g., satellite cell proliferation and muscle protein synthesis). On the other hand,  
637 chronic activation of the COX/PG pathway may exert negative effects on muscle mass, and  
638 NSAID treatment may provide an effect countermeasure against such effects. In this review,  
639 we have highlighted an apparent discrepancy between the opposing effects of NSAIDs in  
640 different settings (e.g., acute versus chronic, young versus old subjects). The balance  
641 between PG species with differing bioactivity (e.g. PGF<sub>2α</sub> versus PGE<sub>2</sub>) (228) or differences in  
642 the underlying nature of the inflammatory response (acute self-resolving versus chronic  
643 nonresolving) (97, 122) may be important factors that influence the pharmacological actions  
644 of NSAIDs.

645

#### 646 *Cryotherapy*

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

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

660 *Effects of cryotherapy on inflammation and oxidative stress.* Studies have focused on how  
661 icing influences inflammation and oxidative stress in muscle following injury (Table 3).  
662 Superfusing rats with cold saline (3–8°C) for 10 min to 6 h after muscle contusion injury  
663 significantly reduced leukocyte rolling and adhesion to venules within damaged muscle for  
664 up to 1 day after injury (102, 188, 189). These effects may be mediated by downregulation  
665 of adhesion molecules on the surface of vessels and leukocytes in response to hypothermia  
666 (63, 78). Immunohistochemical analysis of muscle tissue revealed that this cryotherapy  
667 treatment decreased the number of neutrophils in muscle 1 day after injury (188, 189). In  
668 support of these findings, others have observed that icing after muscle strain injury in rats  
669 substantially reduced neutrophil activation in muscle, as indicated by lower  
670 myeloperoxidase activity 1 day after injury (25). Icing also restricted the production of RONS  
671 and lipid peroxidation at 1, 5, 10 and 15 days after injury in rats (25). Icing preserves the



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

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

694 *Effects of cryotherapy on training adaptations.* In addition to this research on acute muscle  
695 injury, a smaller body of research has investigated the effects of regular cryotherapy on  
696 muscle adaptations to exercise training. An early study demonstrated that, in rats regularly  
697 immersed in cold water (4°C) for 5 min after exercise bouts, greater ultrastructural damage  
698 to myofibrils was evident after 5 weeks of exhaustive running and 7 weeks of moderate  
699 running (46). Fu et al proposed that, by masking pain, cold water immersion allowed the  
700 rats to exercise at higher intensities the next day, which unexpectedly resulted in greater  
701 muscle damage (46). Subsequently, several human studies have also reported that regular  
702 cold water immersion after exercise attenuates muscle adaptations to training (44, 153,  
703 179, 246). The mechanisms by which regular cold water immersion dampened training  
704 adaptations in these studies are unknown. Hypothetically, a decrease in muscle blood flow  
705 in response to cold water immersion might reduce angiogenesis and protein synthesis in  
706 muscle during recovery from exercise. In turn, these responses may result in smaller gains in  
707 muscular endurance and strength.

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

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

718

## 719 **PERSPECTIVES AND FUTURE DIRECTIONS**

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

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

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

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

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

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

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

777

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1502 **Tables****Table 1.** Effects of glycogen concentration on physiological responses to exercise in human skeletal muscle.

Reference	Design	$\Delta\%$	Low glycogen	Findings
(242)	Acute	-82%	163 mmol·kg <sup>-1</sup> ·dw	↑AMPK activity
(9)	Acute	-75%	103 mmol·kg <sup>-1</sup> ·dw	↑p53 phosphorylation ↑Mitochondrial mRNA
(172)	Acute	-65%	166 mmol·kg <sup>-1</sup> ·dw	↑Mitochondrial mRNA
(13)	Acute	-47%	167 mmol·kg <sup>-1</sup> ·dw	↑Protein degradation
(72)	Acute	-30%	290 mmol·kg <sup>-1</sup> ·dw	↑Leucine oxidation ↓Net protein balance
(23)	Acute	-52%	180 mmol·kg <sup>-1</sup> ·dw	↔ Muscle protein synthesis
(255)	Acute	-69%	167 mmol·kg <sup>-1</sup> ·dw	↓SR Ca <sup>2+</sup> release rate
(50)	Acute	-68%	245 mmol·kg <sup>-1</sup> ·dw	↓ SR Ca <sup>2+</sup> release rate
(65)	Chronic	-68%	210 mmol·kg <sup>-1</sup>	↑Mitochondrial enzyme activity
(250)	Chronic	-50%	250 μmol·g <sup>-1</sup> ·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
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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 Timing: 5 min postinjury	6 and 12 h; 1–7, 14, and 28 d postinjury	Central nucleated fibers Fiber CSA, macrophage , TGF- $\beta$ 1, IGF-1, Pax7, collagen
(25)	Rat; acute crush injury	Topical icing Duration: 5 min Timing: 30 min and 2 $\times$ /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 <sup>+</sup> -K <sup>+</sup> ATPase, Ca <sup>2+</sup> 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 <sup>+</sup> 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 CS	Macrophages CS PGC-1α p38 MAPK p70S6K 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 <sup>2+</sup> 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

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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.