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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 16th 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), 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 α])
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 δ 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 Ca²⁺ 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 Ca²⁺ release from the SR (50, 255). Importantly, SR
172 Ca²⁺ 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 Ca²⁺
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⁺ 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 α 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⁺, MyoD⁺, and M-cadherin⁺ 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 α , 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 F₂-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 α 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, β -carotene and α -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 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 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 PGD₂, PGE₂, PGF_{2α}, PGI₂, and
561 thromboxane A₂ (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. $\text{PGF}_{2\alpha}$ versus PGE_2) (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 Na^+ - K^+ -ATPase and 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- β 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 α , 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 ⁻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
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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- β 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 ⁺ -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 CS HSPs MyoD Myogenin mTOR	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.