Block periodization training of endurance athletes: A theoretical approach based on molecular biology

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Abstract

Competitive endurance athletes are constantly looking for ways to maximize training adaptations and to push their performance to the limit. A fundamental feature of their training is the subdivision of the annual training plan into shorter periods (periodization of training). Block periodization has been proposed as an alternative training organization that could be incorporated into the annual training plan. Despite the plethora of studies investigating exercise induced adaptation in response to differing intensities of endurance exercise and following various feeding strategies, only a limited number of studies have examined the effect of different BP programs on adaption and performance in exercise endurance. Although these studies found increased adaptations in response to BP compared to traditional organisation models they do not currently provide an insight into the underpinning mechanisms. This review presents the current advances in the molecular biology underpinning adaptation to exercise and how this evidence may be used to understand BP training and therefore provides future recommendations into annual training organization. This approach involves discussion of several issues related to BP: A discussion on whether monotonous training blunts molecular responses to exercise, if periodization of training alters myocellular responses to endurance training and finally the addition of strength training to BP. The author also discusses new research findings supporting the existence of skeletal muscle ‘memory’ and compares this evidence to findings that highlight the importance of maintenance sessions and/or manipulation strategies of muscle glycogen concentration during BP training. Finally, based on the current evidence, the author recommends strategies to maximize adaptation to training in response to BP in competitive endurance athletes.

Introduction

Coaching scientists have evolved a number of training theories based predominantly on years of experience of working with various levels of athletes and perhaps to a lesser degree on empirical research literature. A key component of training theory is periodization. The term periodization of training is used to denote the subdivision of the annual training period into shorter periods/training cycles (Issurin, 2010). The block periodization (BP) model was conceptualized in order to overcome limitations of traditional training models (Issurin, 2010). In contrast to, “the simultaneous development of many targeted abilities” of traditional models (Issurin, 2010), the block periodization approach proposed cycles of highly concentrated specialized workloads targeting specific abilities (Issurin, 2010). In that way, block periodization was designed to overcome possible incompatibilities between divergent exercise training programs. Recently, several studies examined the efficacy of BP versus traditional organized training in endurance athletes and reported enhanced training adaptations with BP (i.e. higher improvement in maximal oxygen uptake, VO2 max). Although, periodization constitutes the cornerstone of the planning and training process, a molecular justification is lacking. Thus, the purpose of the present review is to critically discuss block periodization training organization for endurance athletes (including strength training) in the context of the emerging molecular literature underpinning adaptation to exercise, and not to compare BP with traditional models. However, as molecular data is not always available with respect to block periodization, some issues are approached theoretically and molecular findings are used to formulate hypotheses and to provide practical recommendations that could be used within BP programs. Furthermore, several studies have examined issues related to block periodization training (i.e. molecular responses to concurrent strength and endurance training) and their findings are critically discussed and used to formulate an integrative approach to block periodization training for endurance sports. If there is limited information at the molecular level in athletes, data from animal and alternative human models (untrained participants) are used only when this may provide a reflection of the potential impact this may have on athletes. As the present review attempts to unite applied sport performance with molecular exercise physiology, this could therefore be of interest to both molecular exercise physiologists and coaching scientists. Table 1 includes the basic coaching science terminology to facilitate readers who are unfamiliar with this type of specific terminology.

Block periodization of endurance training

The last few years a number of studies have segregated high and low intensity training (HIT and LIT respectively) by using training blocks that included mainly HIT or LIT and compared...
Molecular aspects of block periodization training

The block periodization studies of Rønnestad et al. (2012a, 2012b, 2015b) used polarized training, which has been shown to be superior compared to threshold training (Neal et al., 2012; Stöggl and Sperlrich, 2014) and intensified training comprising of high intensity interval training (Stöggl and Sperlrich, 2014). It is noteworthy, that the well-trained endurance athletes in the study of Stöggl and Sperlrich (2014) experienced a ~3.7% reduction in body mass after 2 (sixteen days) blocks of HIT. Unfortunately, the source (fat/lean mass) of the reduction in total mass was not specified. However, even if the body mass loss was due to fat reduction, improvements in VO2 max were lower compared to polarized training. Stöggl and Sperlrich (2014) hypothesized that the smaller improvements to VO2 peak after HIT compared to polarized training may have been due to a plateau after the first 16 days block of HIT. The findings of Rønnestad et al. (2012a, 2012b, 2015b) are extremely important considering that the participants were well-trained and elite endurance athletes; in particular the latter study (Rønnestad et al., 2015b) was conducted on elite skiers, where, at the end of the preparatory phase those elite athletes had already performed a substantial volume of traditional training. In this context, an emerging question is whether the observed favorable adaptations in the BP studies of Rønnestad et al. (2012a, 2012b, 2015b) are due purely to the change of training stimulus or to the block periodization model (i.e., focused HIT and LIT training versus concurrent HIT and LIT training in traditional models).

Does monotony of training blunt molecular responses to exercise?

In practice, endurance coaches and athletes manipulate training intensity and volume during their annual training plan in order to avoid stagnation in adaptation (caused mainly by training monotony) and to potentially augment training adaptations. This strategy is supported, at least partially, by molecular findings. In a study by Perry et al. (2010) 9 males with low endurance training background performed a 2 week HIT block (7 HIT cycling sessions, interspersed with 1 or 2 rest days, each HIT session included: 10 × 4 min at ~90% of VO2 peak with 2 min rest). Peroxisome proliferator activated receptor γ co-activator-1α (PGC1α), citrate synthase (CS) and β-Hydroxyacyl CoA Dehydrogenase (β-HAD) mRNA responses were gradually diminished compared to the first HIT session. This occurred in

Table 1. Basic coaching terminology used in the present review

| Periodization | Subdivision of the annual plan into shorter periods/cycles (Issurin, 2010). |
| Block periodization (BP) | The subdivision of the annual plan involves short periods (blocks) of highly concentrated workloads (Issurin, 2010). A block could be dedicated to development of a specific target and not to simultaneous training development of many abilities (i.e., technical skills, motor skills, maximal strength, muscle power, aerobic and anaerobic capacity). In the present review the focus is restricted mainly to the organization of low and high intensity training of endurance athletes in concentrated blocks (HIT and LIT blocks respectively). Addition of strength training to BP training is also discussed. |
| Traditional organization model | This terminology refers to simultaneous high and low intensity training. A typical week (microcycle) in this model may include 2 HIT sessions plus 4-5 low intensity training sessions. |
| Concurrent strength and endurance training | Combined training/development of strength and endurance. |
| Polarized training | The majority of training time consists of low intensity training (~75-80% time spent training). Time devoted to high intensity training is ~15-20%, while only limited training time is devoted to moderate intensities (Neal et al., 2012). |
| Threshold training | Approximately half of training time is performed at a speed, power or heart rate corresponding to the lactate threshold, while the other half includes low intensity training (Neal et al., 2012). |
| High intensity training (HIT) | Refers to intense exercise (heart rate > 88% of maximal heart rate (i.e. 6 x 5 min at 88-100% of maximal heart rate separated by 2.5 recovery). In the present review the HIT includes interval training (i.e. continuous method can also be performed at intensities corresponding to ~ 88% of maximal heart rate). |
| Low intensity training (LIT) | Is referred to high volume, long duration and low intensity training (i.e. duration of minimum 1 h for each session at 60-82% of maximal heart rate, continuous method). |
| Tapering | Reduction of training volume prior to the competition. |

this approach with traditional models that typically use concurrent HIT and LIT. Breil et al. (2010) and García-Pallarés et al. (2010) reported that BP is superior to traditional periodization but a limitation of their studies was a higher volume of HIT during BP training. To overcome the limitation of different volumes of HIT between the different training periodization models, a series of studies performed by Rønnestad et al. (2012a, 2012b, 2015b) matched HIT (6 x 5 min or 5 x 6 min at 88-100% of maximal heart rate separated by 2.5 or 3 min recovery respectively) and LIT volumes (duration of minimum 1 h for each session at 60-82% of maximal heart rate) so that any differences between groups could be attributed to the organization model. These studies included only limited moderate intensity training. Initially, Rønnestad et al. (2012a, 2012b) compared BP training with traditional organized training in competitive well-trained male cyclists who performed the training intervention at the preparatory phase (in the beginning of the season). During a 4 or 12 week intervention period cyclists performed the same volume of HIT and LIT. Cyclists of the BP organization group performed five HIT sessions in 1 intensified week block and in the next 3 weeks they performed only 1 HIT session, while the majority of their training constituted of LIT (Rønnestad et al., 2012a, 2012b) and they repeated this 4 week cycle 3 times (Rønnestad et al., 2012a). On the other hand, the traditional organization of training included 2 HIT sessions per week and high volume LIT. A relative change in VO2 max was larger in the BP group compared to the traditional group after 4 (Rønnestad et al., 2012b) and 12 weeks (Rønnestad et al., 2012a). In the 4 week study (Rønnestad et al., 2012b) power output corresponded to a lactate concentration of 2 mmol/L that increased only after BP training yet was not significant compared to traditional training. However, after 12 weeks (Rønnestad et al., 2012a) there was a trend towards larger relative increases in power output corresponding to a lactate concentration of 2 mmol/L in the BP group compared to the traditional group (p = 0.054). A similar study design was also used in elite cross country skiers (Rønnestad et al., 2015b). Skiers in the BP group performed 1 “hard” week including 5 HIT sessions, a moderate week with 3 HIT sessions (week 3), while the remaining 3 weeks of the 5 week intervention period included 1 HIT session and high volume LIT training (weeks 2,4,5). As in the cycling studies the traditional group performed 2 HIT sessions per week plus LIT training, while in the middle of the intervention (week 3) they performed 3 HIT sessions. VO2 max and power output corresponding to a lactate concentration of 4 mmol/L increased only in the BP group. Peak aerobic power output (Wmax) increased in BP group only across several studies (Rønnestad et al., 2012a, 2012b, 2015b), and effect size (ES) of relative changes in Wmax indicated a moderate effect (BP group versus traditional group). Collectively, the studies of Rønnestad et al. (2012a, 2012b, 2015b) support that BP training of HIT and LIT enhances endurance exercise adaptations compared to traditional training organization.

the 3rd HIT session for PGC1α and in the 5th HIT session for CS and β-HAD (muscle biopsies were performed pre and post the 1st, 3rd, 5th and 7th sessions). The higher mRNA levels for CS and β-HAD were achieved after the third HIT session (5 days after commencement of the experiment). Interestingly, PGC1α mRNA levels were elevated initially and gradually decreased over the 2 week period, while PGC1α protein content gradually increased (Kim et al., 2006). The above findings are in line with the findings of Nielsen et al. (2002) who reported attenuated AMPK activation in response to 20 min cycling at 80% of VO₂ peak in endurance trained subjects (VO₂ peak > 59 ml/kg/min) compared to sedentary. It is important to note that exercise causes the movement of PGC1α from the cytosol into the nucleus (Wright et al., 2006) and translocation of PGC1α to the mitochondria (Drake et al., 2008; Wright et al., 2009). The findings of Perry et al. (2010) support the notion that cumulative endurance training bouts on PGC1α translocation. The data presented in this section supports the notion that cumulative endurance training bouts blunt expression of key molecules involved in endurance training adaptations and this may be linked to stagnation in protein content changes (i.e. a gradual decrease in PGC1α mRNA levels may be responsible for the plateau in PGC1α protein content observed only 10 days after commencement of exercise in Perry et al., 2010). Attenuated molecular responses in the above studies i.e. PGC1α mRNA (which may be responsible for plateau in PGC1α protein content) and activity of AMPK are likely to be due to a similar stimulus being prescribed. This highlights the importance of manipulating training parameters (i.e. intensity, volume) during the training process. The issue of whether manipulation of training variables affects transcriptional responses is discussed in the next section (entitled: Does block periodization training alter myocellular responses?).

The studies of Rønnestad et al. (2012a, 2012b, 2015b) used 1 week intensified blocks followed by 3 weeks low intensity endurance training. In the context of the above findings (Benzniane et al., 2008; Perry et al., 2010; Stepto et al., 2012) it is tempting to speculate that a longer block of intensified training would be optimal as key acute molecular responses are blunted after cumulative endurance training bouts. PGC1α mRNA expression and phosphorylation of AMPK that were attenuated in the trained state seem to be depended of exercise intensity (Wadley et al., 2005; Egan et al., 2010). The notion that sensitivity of these exercise-intensity-dependent genes, involved in mitochondrial biogenesis, are gradually blunted and, HIT blocks of longer duration may have negative consequences (i.e. loss of body weight, Støggl and Sperlrich, 2014) underline the need for precise determination of an ideal HIT block duration. The 1 week HIT block duration in the Rønnestad studies seems to be efficient, however, the optimal duration of high intensity blocks in BP training organization remains to be established, and requires future examination. Moreover, it will be important for future research to examine if the mediation of a LIT block could potentially salvage or even potentiate activation of molecular pathways associated with endurance training adaptations within skeletal muscle (i.e. PGC1α, AMPK) in a subsequent HIT block.

**Does block periodization training alter myocellular responses?**

**Changes in training stimulus after molecular responses**

Two papers from the same lab (Ludén et al., 2010; Murach et al., 2014) investigated molecular aspects of tapering and reported some very interesting findings which can be considered relevant to BP training. Their study included competitive runners who performed a 3 week taper program after 8 weeks heavy midseason training. They found that the 50% reduction of training volume (reduction in moderate running and maintenance of intense training) during the tapering period exclusively increased size, force and power of myosin heavy chain II isoforms (MHCIId) in single muscle fibers (Ludén et al., 2010) in response to a fixed intensity 8 km run at ~ 90% of maximal heart rate, compared to those in response to an identical run performed after the heavy training period. More specifically, myogenic regulatory 4 (MRF4, a protein involved in myogenesis) and heat shock protein 72 (HSP72, a stress-inducible chaperone which has protective functions in stressed cells e.g. Madden et al., 2007) gene expression increased after tapering in response to the 8 km run, while Muscle RING-finger protein-1 (MuRF1) mRNA content increase was lower after tapering compared to heavy training in skeletal muscle tissue (Ludén et al., 2010). When the analysis was performed in single muscle fibers they found (Murach et al., 2014) significant higher mRNA increases in fibroblast growth factor –inducible 14 (FGF14) in MHCIId fibers (compared with FGF14 mRNA changes in MHCIId fibers 4h post an identical run performed after heavy midseason training) and this was specifically related to hypertrophy of fast fibers (Raue et al., 2012). HSP72 gene expression was slightly higher in the tapered state in MHCIId fibers. Furthermore, addition of HIT and speed endurance training to aerobic moderate intensity training (Bängsbo et al., 2009) or substitution of regular training with HIT and speed endurance training (Gunnarsson et al., 2013) have shown to improve endurance performance. These performance improvements in moderately-trained (Bängsbo et al., 2009) and well-trained endurance athletes (Gunnarsson et al., 2013) occurred despite a substantial reduction in training volume. Some molecular aspects in the study of Gunnarsson et al. (2013) were published recently and revealed that a change in training variables (i.e. intensity, duration and training volume) alters molecular responses in response to an exhaustive exercise protocol performed pre and post a 7 week intervention program (Thomassen et al., 2016). Notable changes included increased phosphorylation of Phospholemman, Ser68 (FXYD1, a protein that regulates ion transport), CaMKII γ/δ Thr-287, and mTOR Ser-2448 (mammalian target of rapamycin, a protein involved in muscle protein synthesis/hyper trophy) and a decrease of AMPKa Thr-172 phosphorylation. These findings highlight that manipulation of training, the cornerstone of training periodization, affects muscle plasticity by altering expression of selective genes. An emerging question is to what extent periodization of training enables skeletal muscle to regain its sensitivity to a training stimulus. Furthermore, additional research is required to clarify which signaling cascades are affected after alternating HIT and LI T blocks.
Enhanced training adaptations in response to BP training: A result of simply changing the stimulus or a genuine effect?

In the case of BP of endurance training HIT and LIT are performed in specific blocks (HIT and LIT blocks, respectively) which succeed each other during the training season. Whether this manipulation of training alters adaptation to skeletal muscle at the cellular and molecular level as demonstrated in tapering studies is currently unknown. It is possible that the favorable training adaptation outcomes in the BP studies of Rønnestad et al. (2012a, 2012b, 2015b) discussed above, were the result of changing the stimulus that participants were already typically accustomed. The studies by Rønnestad et al. (2012a, 2015b) were characterized by training monotony (lack of variation) in the control group, while more recently (Rønnestad et al., 2015b) the group included a small variation of HIT sessions in the traditional periodization group (these studies are discussed in detail in the section entitled: Block periodization of endurance training). However, a plausible suggestion is that BP training provides a much more severe change (i.e., 5 HIT sessions during a week) compared to no or slight variation in the weekly number of HIT sessions experienced during traditional training. An alternative and intriguing hypothesis, that requires future examination, could be that the separation of HIT and LIT in focused training blocks may promote beneficial training adaptations. Interestingly, it seems that HIT and LIT promote similar muscle adaptations yet through different signaling pathways as Gibala et al. (2008) found that HIT acutely increases PGC1α mRNA levels without changes in the activity of calcium-calmodulin kinases (CaMKKs), Laursen (2010), based on the findings of Gibala et al. (2008) and Rose et al. (2007), reported increases in CaMKII activity and expression after low intensity continuous exercise, suggesting that it was the mixing of the different signals that converge to promote PGC1α transcription and subsequently help to maximize endurance training adaptation. This suggestion is in line with the polarized training theory. Furthermore, since p-AMPK but not p-CaMKII is blunted in response to a block of intensified training (Benziane et al., 2008), it is tempting to speculate that in BP training organization p-CaMKII remains high during the HIT block, but this requires future examination.

Increases in myonuclei content in response to a block of intensified training

Novel research findings suggest satellite cells have the ability to be incorporated as myonuclei without hypertrophy of the fiber following endurance exercise in trained individuals. In a study by McKenzie (2015) ten trained cyclists performed a block of 10 days intensified training with carbohydrate (45 g pre and 1.2 g/kg bw post each session) or carbohydrate (45 g pre and 1.2 g/kg bw post each session) + protein (15g × 0.4 g protein/kg bw) supplementation (supplementation administered during and immediately after each training session of intensified and reduced training blocks). During the intensified training block they doubled their training volume compared to normal training and subsequently had a 10 day block of highly reduced training volume (training volume was 60% of normal training volume). In the case of carbohydrate supplementation myonuclei content increased in both MHCI and MHCII fibers from pre to post intensified training and 10 days after intensified training in MHCII fibers only. Although those trained subjects had high SC content prior to commencement of the intensified block, compared to previous literature of untrained groups, SC content increased during the recovery period in MHCI fibers, while there were no changes in MHCII fibers. Despite increased myonuclei content there was no associated fiber hypertrophy (as was the case with protein supplementation). The doubling of training volume included an increase in various intensities of training and not HIT exclusively, however they condensed an intense training stimulus in a short period of time. These data are in line with recent findings in untrained humans (Joannise et al., 2013, 2015). Joannise et al. (2013), in untrained women, used 10 × 1 minutes of cycling at 90% of maximal heart rate (3 sessions per week for 6 weeks) and in the absence of increased hypertrophy, or myonuclear accretion, they found increased SC content in type I/III hybrid fibers suggesting that SCs may play a role in muscle fiber type transformation. On the contrary, Fry et al. (2014) used HIT (45 min of cycling at 70% of the heart rate reserve, 3 sessions per week for 12 weeks) in sedentary old subjects and found increased SC, myonuclear content and increased hypertrophy in type I muscle fibers, but no fiber type transitions. Since, mitochondrial biogenesis requires transcription of both the nuclear and mitochondrial genomes (Drake et al., 2015), it could be speculated that the increase in myonuclei is required for mitochondrial biogenesis, however the precise role of increased myonuclear content in response to intensified endurance training and more specifically to mitochondrial biogenesis remains to be fully elucidated. A role in mitochondrial biogenesis can be inferred by an elegantly designed study by Lee et al. (2015) in rats which is discussed later in this review under the section: Cellular mechanisms of muscle memory. Thus, the limited available data suggest that a block of intensified endurance training increases myonuclear content in the absence of fiber hypertrophy.

Carbohydrate periodization to maximize block periodization training adaptations

In the last decade several studies support a role for training under low glycogen to augment endurance training adaptation (Hansen et al., 2004; Yeo et al., 2008; Morton et al., 2009; Philip et al., 2012; Bartlett et al., 2013b, 2014; Hammond et al., 2016; Impye et al., 2016). Manipulation of glycogen content involves training and nutritional periodization schemes. Since BP training is an alternative to traditional training organization the concept of “train low (glycogen) – compete high” probably needs to be adjusted to BP training in order to maximize training adaptations. Initially, in a study by Hansen et al. (2004) seven untrained men followed a 10 week training program where one leg was trained daily, while the other leg was trained twice every second day by performing matched-work knee extension exercise. Condensing the training into one day resulted in significant lower muscle glycogen levels and thus the second training of the day commenced with reduced muscle glycogen context. Time to exhaustion, resting muscle glycogen content and activity of CS were increased in the leg trained twice every second day compared to every day training. A similar experimental design was also used in well-trained (Yeo et al., 2008) cyclists or triathletes. Cycle training twice a day: HIT in the morning (100 min at 70% of VO2peak) followed 1–2 hours later by HIT (8 × 5 min maximal effort bouts, 1 min active recovery between bouts) for 3 weeks, resulted in higher activity of CS and β-HAD compared to the training every day group, while resting muscle glycogen increased only in the training twice a day group. Training intensity of the HIT protocol was lower during the first 2 weeks and this was perhaps related to lower muscle glycogen levels or to other factors such as fatigue. A different “train low” strategy (sleep low-train low) was introduced by Bartlett et al. (2013b) where an evening training session of cycling bouts at 60–90% of peak power output (PPO) with 2 min active recovery at 50% of PPO until the subjects were unable to perform 30 s of cycling at 60% of PPO was used to deplete muscle glycogen levels in active men and was followed by overnight fast. In that way, the next morning endurance training (HIT, 6 × 3 min at 90% of VO2max with 3 min active recovery at 50% of VO2max) was performed under extremely low levels of muscle glycogen (mean value–103 mmol/krig dry wt) which increased tumor protein p53 (tumour suppressor) signaling and expression of several genes associated with mitochondrial biogenesis and
substrate utilization in skeletal muscle (pyruvate dehydrogenase kinase 4, mitochondrial transcription factor A, cytochrome-c oxidase IV and PGC1α). Evidence is growing that the tumor suppressor protein p53 is an important factor for mitochondrial biogenesis (Bartlett et al., 2013a) and further work is needed to examine whether very low muscle glycogen levels could enhance p53 signaling in well-trained and elite endurance athletes as demonstrated in active men (Bartlett et al., 2013b).

To overcome reduced ability for high intensity exercise with low muscle glycogen content, Lane et al. (2015) adopted an experimental design (train high-sleep low) in which competitive cyclists (VO2 peak ~ 67 ml/kg/min) performed HIT in the afternoon and long duration aerobic exercise the following morning. Therefore, HIT was performed with normal glycogen content, while the 120 min steady-state aerobic cycling exercise was performed with either normal (fed, half of their prescribed energy intake was consumed prior to the evening HIT session and the other half immediately post) or reduced glycogen content (overnight fast). Although, overnight fast resulted in increased phosphorylation of AMPK Thr172, P38MAPK Thr180/Tyr182 and acetyl-CoA carboxylase (ACCSer79) there were no further changes after the 120 min trial with the exception of p-ACC Ser79. Surprisingly, PGC1α mRNA content after the 120 min cycling trial increased only in the fed state which is in contrast to the train low theory. However, the “train-high-sleep low” strategy used by Lane et al. (2015) only partially depleted glycogen stores as participants started the aerobic cycling trial with ~ 350 mg mmol/kg dry wt glycogen concentration. The same strategy (train high-sleep low) was applied to a cohort of endurance trained triathletes (VO2 max ~60 ml/kg/min) for 3 weeks and improved 10 km running performance and submaximal efficiency (Marquet et al., 2016). Commencing exercise with significantly low glycogen content (a glycogen threshold) may therefore be the key to evoke a series of molecular events associated with mitochondrial biogenesis (Philp et al., 2012). This was demonstrated in an acute study by Psilander et al. (2012). They also used well trained cyclists (VO2 max ~65 ml/kg/min) and incorporated a combination of exercise (45 min cycling at 75% of VO2 max followed by 8 × 4 min at 88% of VO2 max with 4 min active recovery plus 45 min at 70% of VO2 max) and carbohydrate restriction to achieve extremely low muscle glycogen levels 14 h later and prior to 6 × 10 min cycling exercise at 60-82.5% of VO2 max. Commencing exercise with highly reduced glycogen content resulted in an 8-fold increase of PGC1α mRNA content which was significantly higher compared to the normal glycogen group. In a study by Jensen et al. (2015) highly trained triathletes performed a 4h ride at ~ 56% of VO2 max where they consumed only water and during the first 4h recovery period consumed water or carbohydrate supplement (1.07 g/kg bw during the first 2 h and 1.05 g/kg bw during the subsequent 2 h). Although muscle glycogen content was significantly lower 4 h post-exercise in the water group (~264 mmol/kg dry wt), compared to pre and carbohydrate supplementation groups, no differences were observed between groups for gene expression of PGC1α.

Collectively, current data suggests that in well-trained endurance athlete’s exercise with severely low muscle glycogen is a promising tool to enhance endurance training adaptations; however has a negative impact on the capacity to perform high intensity exercise. Based on the above findings a modified concept of “train low– compete high” could be proposed for BP. This adjusted approach could involve training with high-normal glycogen levels during HIT blocks and training with low glycogen levels during LIT blocks. However, the latter should be applied with caution (i.e. in selective blocks) in order to avoid fatigue (also see practical recommendations and Fig. 1).

![Figure 1. The organization of high and low intensity endurance training in specific training cycles/blocks (block periodization training, BP) has been recently proposed as an alternative training organization model. High intensity training (HIT) blocks include high intensity sessions, while low intensity training (LIT) blocks include mainly low intensity training sessions. The present figure summarizes practical recommendations regarding: Duration of blocks, use of HIT and strength maintenance sessions, addition of strength during block periodization training (BP) and carbohydrate periodization during BP training to maximize training adaptations in response to BP training. AMPK: AMP-activated protein kinase.](image-url)
Addition of strength training to block periodization for endurance athletes

Cumulative evidence support that addition of strength to endurance training improves performance in endurance events (Yamamoto et al., 2008, 2010; Rønnessad et al., 2010; Aagaard et al., 2011; Rønnessad et al., 2011b; Beattie et al., 2014; Vikmoen et al., 2015). Mechanistically, improved endurance performance after strength training maybe due to improvements in exercise economy (Sunde et al., 2010; Balsalobre-Fernández et al., 2016) and muscle power (Paavolainen et al., 2000). For that reason, strength training should be included in the annual training plan. Therefore, in the subsequent sections of this review the author discusses the current state of evidence addressing the combination of strength and endurance training within a BP training program for endurance athletes.

Effect of concurrent strength and endurance training on strength and muscle hypertrophy

In a study by Rønnessad et al. (2011a) 12 well trained cyclists performed heavy resistance exercise (initially 10 repetition maximum (RM) sets were used and gradually reduced to 4-6 RM sets during the last 6 weeks, 3 sets throughout the intervention period, 5 leg exercises) twice a week for 12 weeks. Concurrently, they performed high volume (~ 10 h of endurance training per week) endurance training which was performed 4-6 hours after strength training in the 2 days per week devoted to strength development. They found deteriorated 1 RM strength, thigh muscle cross sectional area and muscle power compared to strength training only which is in line with previous studies reporting no hypertrophic gains after strength training undertaken in addition to endurance training in athletes (Aagaard et al., 2011; Beattie et al., 2016). The study of Rønnessad et al. (2011a) was extremely important as it used well trained endurance athletes and incorporated an experimental protocol that highly mimicked real training scenarios in endurance sports (high volume endurance training + heavy resistance training).

The consequences of blunted hypertrophic gains after concurrent strength and endurance training (interference phenomenon) can be both negative and beneficial for the endurance athlete. For instance, Vikmoen et al. (2015) found that addition of strength training to endurance training improved 40 min time trial performance and reported a significant correlation between changes in mean power output during the 40 min time trial test and changes in CSA of the quadriceps muscles. On the other hand, an increase in muscle mass may deteriorate performance as endurance athletes have to support and propel the extra muscle mass (Baar, 2014). Furthermore, in a recent review Mujika et al. (2016) supported that negligible losses of lower-body lean mass which improve overall power to weight ratio may be beneficial for some endurance athletes (i.e. hill climbers). Therefore, achievement of an ideal strength-to-weight ratio should be the primary goal of a concurrent training program for endurance athletes.

Several mechanisms have been proposed to explain the interference between endurance and strength/resistance training at the molecular level. The prevailing concept is that AMPK increases in the context of energetic stress denoted by AMP/ATP or glycogen changes and interferes with the mammalian target of rapamycin complex 1 (mTORC1) signaling cascade considered as the predominant pathway for muscle protein synthesis and subsequent hypertrophy. AMPK inhibits mTORC1 signaling pathway through phosphorylation of Tuberous sclerosis (TSC 2) (Inoki et al., 2003; Cheng et al., 2007) and/or raptor (Gwinn et al., 2008). Other less popular and less studied negative regulators of mTORC1 include: development and DNA damage response 1 (REDD1) (Hayasaka et al., 2014) and siruin 1 (SIRT1) (Baar, 2014). Contrary to the early molecular mechanisms, others have suggested a "delayed" mechanism of interference (Hamilton and Philip, 2013) as Burd et al. (2012) found impaired satellite cell responses (which seem to be involved in long term hypertrophic adaptations, Fry et al., 2013) after concurrent resistance (3 x 10 of unilateral leg extensions and presses, 75% of 1 RM) and endurance (90 min of cycling at 60% $W_{max}$) training compared to resistance training alone in recreationally active males. Ribosome biogenesis may also be responsible for the interference between endurance and strength training (Wen et al., 2016).

Strategies to combine strength and endurance training

A rest interval > 3h has been recommended to allow AMPK and SIRT1 activity to reach resting values prior commencement of resistance exercise (RE) as a strategy to overcome the interference phenomenon (Baar, 2014). This strategy could be applied by endurance athletes and coaches who target to concurrently increased muscle mass (in order to achieve an optimal strength-to-weight ratio) and improve endurance capacity. An opposite strategy has recently been proposed by Mujika et al. (2016) for endurance athletes (cyclists) who aim to avoid additional muscle hypertrophy and its negative effects. Mujika et al. (2016) suggested that those athletes should perform the strength training under elevated AMPK levels. In other words performing endurance and strength training in close proximity may allow those athletes to improve their strength (i.e. through neural mechanisms) without concomitant increases in muscle mass. Furthermore, endurance plus RE performed in close proximity did not enhance endurance training adaptations (i.e. CS activity) after 8 weeks in trained cyclists (Psilander et al., 2015). Although further research is needed, current data do not support an additive or negative effect of resistance training on endurance training adaptations in well trained endurance athletes. Collectively, endurance coaches should design their training plans on a personalized basis in order to meet the individual needs of each athlete.

Endurance athletes willing to use BP model have several options to optimally combine endurance and strength training. However, it is possible that the incorporation of strength training in the HIT block may negatively affect the quality of HIT and it is therefore probably not recommended. Thus, it seems it would be better for endurance athletes to perform the strength training during LIIT blocks. Furthermore, as reported earlier, they can use short or prolonged (> 3 hours) rest intervals between endurance and strength training in order to perform the strength training with high or resting AMPK levels, respectively. Parameters related to achievement of an optimum strength-to-weight ratio and the unique demands of each sport should be taken into consideration before selection of the appropriate strategy. For instance, highly ectomorphic endurance athletes may need some hypertrophy in order to achieve an ideal strength-to-weight ratio or to reduce the risk of injury, while this is probably not the case for a mesomorph individual. Furthermore, some endurance sports (i.e. kayaking) demand both high aerobic capacity as well as muscle strength and thus relatively large rest intervals are probably required to avoid the interference between concurrent strength and endurance training.
Molecular aspects of block periodization training

Maintenance session versus muscle 'memory' mechanisms in BP training

Maintenance session

In BP training theory each block includes highly concentrated specialized workloads to improve few abilities, while other abilities need to be maintained (Issurin, 2010). In other words the major principle of BP training denotes that the "mixed" training of many athletic abilities (i.e. maximal strength, aerobic capacity, anaerobic capacity, muscle power) are not as effective as the training of limited abilities (i.e. only aerobic capacity). However, the training of limited abilities increases the risk of detraining (losses of adaptations when a specific type of training is not performed during a training block) which creates the need for the use of a maintenance session (a training session that aims to provide a sufficient stimulus to prevent previous adaptations from being lost). In line with this principle of BP training Rønnestad et al. (2012a, 2012b, 2015b) used a HIT maintenance session (6 × 5 min or 5 × 6 min at 88-100% of maximal heart rate separated by 2.5 or 3 min recovery, respectively) per week during the LIT block. Furthermore, Rønnestad et al. (2015) reported that cessation of strength training in elite cyclists contributes to the loss or reduction of adaptations achieved by concurrent endurance and strength training. Contrary, a weekly strength session was sufficient to preserve previously achieved increases of strength and muscle cross-sectional area (Rønnestad et al., 2010). Consequently, a maintenance session appears to be essential to prevent loss or exacerbation of already acquired adaptations. However, the minimal maintenance dose required to prevent losses in both endurance and strength adaptations is currently unknown and should be determined by future research.

Cell memory mechanisms

On the other hand, the existence of potential cell memory mechanism has been proposed, and it has been suggested that these mechanisms support fast and efficient regain of adaptations that have been achieved in the past. Currently, our deeper understanding of cell memory mechanisms is poor and thus it should be noted that it is premature to draw definitive conclusions and much more evidence is required to provide practical recommendations for training based on preliminary research findings (mainly in rodents/cellular models). However, theoretically muscle memory mechanisms could play a key role in designing periodized training programs. For instance, the absence of maintenance sessions or an inadequate maintenance dose could lead to minor losses of adaptations which should be regained rapidly in the next training blocks. Thus, in this section muscle memory mechanisms are discussed, but were not considered in formulating training recommendations.

It is suggested that involvement of myonuclei are crucial for regaining of previously acquired adaptations (Gundersen, 2016) with muscle memory recently defined as: "The capacity of skeletal muscle to respond differently to environmental stimuli in an adaptive or maladaptive manner if the stimuli have been previously encountered" (Sharples et al., 2016). Gundersen et al. (2016) suggested that since the myonuclei gained following hypertrophy are not subsequently lost during atrophy, recruitment of new myonuclei is not always prerequisite for skeletal muscle hypertrophy in response to re-training. These speculations are largely based on the findings of Egner et al. (2013). Egner et al. (2013) provided a mechanistic explanation for past observations (Taaffe and Marcus, 1997) that after a period of inactivity previous training contributes to improved reacquisition of muscle mass. Specifically, they found in mice that a 2 week pharmacological (testosterone) treatment and muscle overload (synergist muscle ablation) increased myonuclei content (66% and 51% in the soleus after testosterone treatment and synergist muscle ablation, respectively). Testosterone was administered to mice by implantation of pellets containing testosterone propionate evoking hypertrophy. Three weeks after pellet withdrawal they observed only a minor and non-significant reduction of myonuclei number (Egner et al., 2013) which was still 42% higher in soleus compared to the control group. Interestingly, despite the retention of myonuclei during testosterone withdrawal muscle hypertrophy gains from the preceding testosterone treatment were completely lost, while a subsequent 2 week overload period resulted in higher hypertrophy in soleus (44% increase) and EDL (42% increase) compared to the sham control group (17% and 21% increases for soleus and EDL, respectively). This demonstrates that the retention of myonuclei during testosterone withdrawal contributes to a more efficient restoration of muscle mass to a later hypertrophic stimulus. The pharmacological data of Egner et al. (2013) were confirmed and extended by a recent training study in rats (Lee et al., 2015). Lee et al. (2015) reported that previous resistance trained rats had higher CSA compared to rats that followed an identical resistance training regimen, but without previous training. In addition to myonuclei the role of epigenetic modifications (i.e. DNA methylation, histone modification) in muscle memory has also been recently examined as discussed in Sharples et al., 2016. There is evidence (by Sharples et al., 2015) that muscle cells in-vitro retain elevated DNA methylation into late proliferative life (over 30 divisions), in genes associated with muscle regeneration, following an early proliferative life inflammatory encounter with Tumor necrosis factor-a (TNF-alpha) for 24 h, where TNF-alpha has also been shown to be elevated acutely post resistance exercise to enable satellite cell activation (Mackey et al., 2007; Mikkelsen et al., 2009; van de Vyver and Myburgh, 2012) and to be important for satellite cell division in-vitro (Foulstone et al., 2004; Stewart et al., 2003; Al-Shanti et al., 2008; Sharples et al., 2010). Although, this study focused on muscle mass, as the muscle cells were subsequently dosed at late proliferative life with a more chronic TNF exposure evoking catabolism/protein degradation in muscle cells/fibres. It is this first study suggesting that epigenetics may play a role in the muscle remembering earlier life encounters from inflammation/catabolism. This therefore could suggest that a similar mechanism, yet perhaps on other muscle growth genes, maybe be involved in 'remembering' earlier anabolic occurrences such as resistance exercise, that may affect adaptation of muscle when similar anabolic events are experienced in the future.

In addition to fast reacquisition of muscle mass, cellular mechanisms may also promote quick regain of previously achieved endurance training adaptations. Retraining (specifically in resistance training) after a prolonged period of inactivity resulted in higher activity of some enzymes that participate in the Krebs cycle/electron transport chain, PGC1α protein expression, mRNA levels of proteins associated with mitochondrial fusion/fission (i.e. mitofusin-2, mitochondrial fission 1 protein and dynamin-1-like protein) in re-trained rats compared to rats trained for first time (Lee et al., 2015). The findings of Lee et al. (2015) raise several intriguing possibilities. For example, could these findings be extrapolated to humans? How they applicable for training design? As mitochondrial biogenesis requires transcription of both the nuclear and mitochondrial genomes (Drake et al., 2015) myonuclei retention may provide a stimulus for a quicker response of the muscle following endurance training. This hypothesis is in line with observations from applied practitioners that have described an increased ability of a muscle to respond faster to exercise stimulus that have been experienced previously (Sharples et al., 2016). Based on the muscle memory theory and findings of Lee
et al. (2015) it is tempting to speculate that increased myonuclei content after strength or intensified endurance training blocks (McKenzie, 2015) may support quick and efficient restoration of a) skeletal muscle hypertrophy (if it is needed to achieve an optimal strength-to-weight ratio) and, b) mitochondrial adaptations in response to subsequent training blocks. The rapid restoration of training adaptations (achieved in previous blocks) overcomes the problem of possible detraining effects when a certain type of training is not performed in a particular training block or the maintenance sessions are inadequate to prevent minor adaptation losses. For instance, during a HIT block, rapid achievement of previous training status means that fewer HIT sessions will be devoted to regain previously acquired adaptations, while more HIT sessions will be devoted to maximally improve oxidative capacity and anaerobic metabolism. Thus, although the combination of strength and endurance training does not seem to augment “typical” endurance adaptations in well-trained endurance athletes (Psilander et al., 2015) a new role of strength/resistance training may be to support fast restoration of endurance adaptations (by increasing myonuclei content) after a detraining period or perhaps following integration in to a BP training program. A similar assumption can be made about blocks of intensified endurance training as it has also been shown to increase myonuclei content (in combination with carbohydrate supplementation, McKenzie, 2015; Luden et al., 2016).

Although such scientific findings look very promising we are far away from a complete understanding of mechanisms of cell memory for both strength/hypertrophic and endurance/metabolic adaptations. Furthermore, the use of maintenance training sessions seems to be essential and in contrast to muscle memory science which is still in its infancy. Thus, regarding muscle memory mechanisms, a much stronger rational needs to be justified from studies in athletic populations to allow the development of practical recommendations. Fig. 2 Depicts the common training practice which supports the use of a maintenance training session in order to prevent losses to adaptation during BP training and a hypothetical scenario based on new research findings which support the existence of muscle memory mechanisms that could promote fast regain of adaptations achieved in previous training blocks.

**Maintenance training session versus cell memory mechanisms**

**A. Muscle memory scenario**

- Strength training Block
- Intensified training Block

- Increased myonuclei content
- Epigenetic modifications

**B. Use of a maintenance session**

- Low-intensity training Block
- High-intensity maintenance session

- Endurance training blocks late in the season
- Strength maintenance session

**Figure 2.** It is suggested that myonuclei gained following exercise are not lost during detraining and are crucial for the regaining of previously acquired adaptations. In addition to myonuclei the role of epigenetic modifications in muscle memory has also been recently suggested. The rapid restoration of training adaptations (due to the existence of muscle memory mechanisms) overcomes the problem of possible detraining effects when a certain type of training is not performed in a particular training block or the maintenance sessions are inadequate to prevent minor adaptations losses. This scenario is hypothetical and much stronger rational needs to be developed in studies in athletic populations. On the other hand the use of maintenance sessions (sessions that aim to provide a sufficient stimulus to prevent adaptations losses) is common practice in the training process.

**Practical recommendations**

Research in BP training is still in its infancy and mechanistic studies are required before definitive conclusions can be drawn. As mentioned previously it is currently unknown whether favorable training adaptation outcomes in the studies of Rønnestad et al. (2012a, 2012b, 2015b) are purely a result of changing the stimulus to what those participants were typically used to or simply to the nature of BP training per se (separate HIT and LIT training in focused training blocks). Thus, at this
stage, BP provides an alternative strategy to train (and not a superior alternative) that can be used to complement traditional models. In this section practical recommendations for BP training are proposed (Fig. 1).

1. Rønnestad et al. (2012a, 2012b, 2015b) used 1 week HIT blocks. This duration seems to be efficient; however, HIT blocks of longer duration could also be tolerable. For instance, Thomassen et al. (2016) used 3 speed endurance exercise sessions (10-12 × 30s maximal uphill sprints, followed by 4.5 min low-intensity cycling) + 1-2 HIT (4-5 × 4 min of cycling at 90-95% of maximal heart rate, followed by 2 min rest) sessions (total of 4-5 sessions) per week for 7 weeks in well-trained cyclists. Notably, in the study of Thomassen et al. (2016) the 7 week intensified training program caused beneficial responses such as a higher FXYD1 Ser-68 phosphorylation after exhaustive exercise compared to phosphorylation levels achieved after an identical exhaustive exercise protocol performed pre-training. From a practical perspective, several parameters should be taken into consideration when designing BP blocks duration. For example, a prolonged block of intensified training (as that used by Thomassen et al., 2016) is, probably more suitable for middle distance runners compared to long distance runners. In contrast, high volume HIT is more important for long distance runners (i.e. marathon runners) and prolonged absence from HIT training because of long duration HIT blocks could not be recommended. Additionally, duration of HIT and LIT blocks should be adjusted according to the training goals of each training cycle of the annual plan. Prolonged intensified blocks could take place close to the competition (i.e. pre-competitive season), while at the begging of the season the duration of LIT blocks should be longer.

2. Addition of strength to the HIT blocks may have a negative impact on the quality of HIT and is not recommended. For that reason, strength training could be performed during HIT blocks. The rest interval could be > 3 hours when some small hypertrophic gains are required to achieve an ideal strength-to-weight ratio or extremely short (i.e. 5-15 min in order to coincide with high AMPK levels) when the training goal is muscle maintenance. A weekly strength training session could be used during the HIT blocks to prevent losses of adaptation.

3. As reported earlier it seems that pre-exercise reductions of muscle glycogen concentrations must be high enough to augment endurance training adaptations. On the other hand, such extreme reductions limit the quality of HIT. In this context, a plausible recommendation is to train with normal glycogen levels during HIT blocks and apply the train low approach during LIT blocks or at least during selective LIT blocks in order to avoid overtraining. Although current data does not support an exacerbated signaling role for reduced muscle glycogen levels in pathways associated with muscle hypertrophy (studies reviewed by Kruiman et al., 2015), refueling prior to resistance training is recommended to avoid negative energy status (Perez-Schindler et al., 2014).

Conclusions and perspectives

Although a plethora of studies examined physiological, biochemical and molecular aspects of acute and chronic endurance exercise/training and sports nutrition, very little is known about the contribution of different training organization models on endurance adaptations. This is somewhat surprising considering that all athletes use annual periodized training models. In the present review the limited block periodization of endurance training studies were discussed, as BP training provides an alternative strategy to organize training.

Molecular aspects of block periodization training

Considering the lack of mechanistic data, the difficulty in recruiting competitive endurance athletes to research studies and their reluctance to undergo repetitive invasive muscle biopsies, in this review an attempt was made to gather and critically discuss relevant recent research findings, combining molecular with applied BP training studies. This included molecular responses following blocks of intensified endurance training, molecular responses to concurrent strength and endurance training, a discussion about cell memory mechanisms in parallel with a basic principle of BP training which propose the use of a maintenance session to prevent adaptations losses. This review (although in an indirect manner) may therefore provide a preliminary molecular basis for BP training of endurance athletes. The author also suggests that the molecular mechanisms underpinning optimal adaptation to training periodization constitute a neglected research area and an excellent potential theme for future research. Research in this area could therefore, produce new knowledge for optimal training organization that will maximize training adaptations.

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Conflicts of interest

The author declares no conflicts of interests.

References


Molecular aspects of block periodization training


