Role of nuclear receptors in exercise-induced muscle adaptations

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Role of nuclear receptors in exercise-induced muscle adaptations

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Abstract

Skeletal muscle is not only one of the largest, but also one of the most dynamic organs. For example, plasticity elicited by endurance or resistance exercise entail complex transcriptional programs that are still poorly understood. Various signaling pathways are engaged in the contracting muscle fiber and collectively culminate in the modulation of the activity of numerous transcription factors and coregulators. Since exercise confers many benefits for the prevention and treatment of a wide variety of pathologies, pharmacological activation of signaling pathways and transcription factors is an attractive avenue to elicit therapeutic effects. Members of the nuclear receptor superfamily are of particular interest due to the presence of well-defined DNA- and ligand-binding domains. In this review, we summarize the current understanding of the involvement of nuclear receptors in muscle biology and exercise adaptation.

1. Introduction

Skeletal muscle is the largest organ in our body, accounts for ~40% of body mass, contains approximately 50-75% of all body proteins, and takes up about 85% of glucose upon insulin stimulation (Frontera and Ochala 2015). Moreover, even though skeletal muscle only contributes ~30% to energy expenditure at rest, 90% of the 20 fold peak increase in energy expenditure during physical activity can be attributed to muscle. Accordingly, skeletal muscle is one of the main sites of metabolism of glucose, fatty acids, ketone bodies and lactate. The energy generated in this process is used for contraction and hence the generation of force, including that which is required to maintain posture and breathing. In addition, skeletal muscle function is instrumental to maintain body temperature, and is one of the main storage sites for glucose (in the form of glycogen), lipids (as neutral triglyceride lipid droplets) and amino acids. With the detection of myokines, muscle has also been defined as endocrine organ exerting auto-, para- and endocrine effects (Schnyder and Handschin 2015). Finally, skeletal muscle can contribute to the detoxification of predominantly endogenous metabolites, such as L-kynurenine or excessive ketone bodies (Svensson et al. 2016).

To be able to cope with these diverse functions, skeletal muscle is one of the most dynamic tissues. Upon different stimuli, massive adaptations are initiated and, if the respective stimuli persist, maintained chronically. Most strikingly, biochemical, metabolic and contractile properties are modulated by physical activity. Many different signaling pathways are activated during and after exercise bouts and collectively result in the regulation of a complex transcriptional program (Egan and Zierath 2013; Kupr and Handschin 2015; Hoppeler 2016) that varies between endurance and resistance exercise resulting in distinct and specific outcomes (Hawley et al. 2014; Camera et al. 2016; Qaisar et al. 2016). Importantly, these two types of exercise not only improve muscle endurance and strength, respectively, but also confer beneficial effects for the prevention and treatment of many different pathologies (Handschin and Spiegelman 2008; Booth et al. 2012; Pedersen and Saltin 2015).

Even though the epidemiological association of a sedentary life-style with the increased risk for many chronic diseases is clear, and inversely, the benefits of exercise have been demonstrated (Pedersen and Saltin 2015), the incidence of most of these pathologies is on the rise world-wide. Exercise interventions often fail due to lack of adherence and compliance. Moreover, subgroups of patients exist with exercise intolerance, defined either as the inability to train or as a detrimental outcome of physical activity. It is therefore intriguing to speculate that a better knowledge of the complex molecular mechanisms that underlie exercise adaptations in skeletal muscle could be leveraged to design so-called “exercise mimetics”, pharmacological interventions that elicit exercise-like effects (Handschin 2016). Of the transcription factors (TFs) that have been described in skeletal muscle plasticity, those belonging to the superfamily of nuclear hormone receptors (NRs) are of particular interest in this regard. NRs are the largest family of TFs in metazoans (Escriva et al. 2004; Bookout et al. 2006). With few exceptions, all of the NRs are characterized by a highly conserved domain structure (Fig. 1A) (Germain et al. 2006). An amino-terminal A/B domain, often with an intrinsic transcriptional activation function (AF-1), is followed by a DNA-binding domain C that entails a zinc finger-based DNA binding domain. A hinge region D then links to the ligand-binding and dimerization domain E/F, of which helix 12 includes the activation function 2 (AF-2). The NR superfamily includes the classic steroid hormone receptors, “orphan” receptors with no known endogenous ligand, and “adopted” NRs for which endogenous ligands have been identified. All of the NRs with functional DNA-binding domains are recruited to either individual or direct, inverted or everted repeats of canonical nucleotide hexamer half-sites with variable spacing (Fig. 1B). While most of the steroid hormone receptors bind as homodimers, other NRs can also be recruited to target sites as monomers or as heterodimers with

the common binding partners retinoid X receptors α, β or γ (RXRα/β/γ, official nomenclature NR2B1/2/3, see (Auwerx et al. 1999)). Type I NRs reside in the cytoplasm and translocate into the nucleus upon ligand binding and activation. Type II NRs are found in the nucleus, heterodimerize with RXRs, often sit on response elements and then exchange corepressors for coactivators when activated by ligands. Similarly, the Type III and Type IV NRs are retained in the nucleus and bind to DNA-response elements as homodimers to hexamer repeats (Type III) or as monomers or dimers, but only to a single hexamer half site (Type IV). NR ligands include hormones, lipids, steroids, retinoids, xenobiotics and synthetic compounds. Accordingly, many NRs sense the energy or the dietary status of a cell and regulate metabolism and energy expenditure (Pardee et al. 2011). Not surprisingly, various NRs have thus also been implicated in the regulation of myogenesis, skeletal muscle function and plasticity. In this review, these nuclear receptors and important cofactors are highlighted and their role in exercise-induced muscle adaptations as well as their potential as drug targets is discussed.

2. The NR superfamily and its role in exercise-induced skeletal muscle adaptation

A surprisingly high proportion of NRs in mice, 35 out of 49, demonstrates detectable gene expression in skeletal muscle (Table 1) (Bookout et al. 2006). However, a potential role in skeletal muscle function and exercise adaptation has been studied for only a subset of those (Fig. 2). Current knowledge and recent updates about these nuclear receptors is summarized in the following paragraphs (Table 2). Further information and primary literature can be found in additional excellent review articles on this topic, e.g. (Smith and Muscat 2005; Fan et al. 2011; Fan et al. 2013; Fan and Evans 2015; Mizunoya 2015).

2.1.1 Subfamily 1, Group A: Thyroid hormone receptors (TR) – Type II

Hypo- and hyperthyroidism have profound effects on whole body metabolism. The effect of thyroid hormone is mediated by two receptors, TRα (NR1A1) and TRβ (NR1A2). In skeletal muscle, hypothyroidism promotes a shift towards slow, oxidative and injection of thyroid hormone to fast, glycolytic muscle fibers, respectively (Smith and Muscat 2005; Mizunoya 2015). In loss-of-function studies, knockout of TRα, but not of TRβ, was likewise associated with an increase in oxidative muscle fibers (Yu et al. 2000). Interestingly however, concomitant ablation of both TRs exacerbated the switch from type II to type I fibers, indicating that TRβ might boost the action of TRα in skeletal muscle. TRα is furthermore induced by contraction in skeletal muscle leading to a modulation of carbohydrate and lipid metabolism (Lima et al. 2009). At least some of the effects of low levels of thyroid hormone on tricarboxylic acid (TCA) cycle activity and mitochondrial oxidative phosphorylation (OXPHOS) in skeletal muscle could be meditated by activation of the peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) (Irrcher et al. 2003), a master regulator of mitochondrial function and oxidative metabolism, potentially in a fiber type-specific manner (Bahi et al. 2005).

2.1.2. Subfamily 1, Group C: Peroxisome proliferator-activated receptors (PPAR) – Type II

In mammals, three PPARs, PPARα (NR1C1), PPARβ/δ (NR1C2) and PPARγ (NR1C3) have been identified, all of which are expressed in skeletal muscle and have been implicated in regulating lipid metabolism. The PPARs heterodimerize with RXRs and bind to PPAR-response elements consisting of a core of a direct repeat of two hexamer half sites with a spacing of 1 nucleotide (DR-1) in promoter and enhancer regions of their target genes.

PPARα, activated by free fatty acids and fibrate drugs, strongly controls fatty acid oxidation, TCA cycle activity and mitochondrial OXPHOS. Interestingly however, muscle lipid metabolism is only slightly altered in PPARα knockout animals, implying a functional compensation by PPARβ/δ, which shares many common target genes with PPARα (Muoio et al. 2002). Accordingly, muscle-specific overexpression of either of these PPARs results in elevated oxidative metabolism of fatty acids (Luquet et al. 2003; Finck et al. 2005). However, unexpectedly and diametrically opposite to PPARβ/δ, muscle-specific PPARα transgenic mice are susceptible to the development of insulin resistance, have a reduced endurance capacity and depict an oxidative to glycolytic fiber type switch (Gan et al. 2013). Inversely, more oxidative fibers are detected in muscle-specific PPARα knockout animals (Gan et al. 2013). This negative cross-talk between PPARα and PPARβ/δ is mediated by the miRNAs miR-208b and miR-499, which boost oxidative and repress glycolytic fiber determination (Gan et al. 2013).

The transcription of PPARβ/δ is induced by acute and chronic endurance exercise and subsequently promotes a glycolytic to oxidative fiber type switch linked to higher OXPHOS activity, reduced fat mass and improved glucose tolerance (Fan and Evans 2015). Muscle-specific overexpression of PPARβ/δ (Gan et al. 2011) or of PPARβ/δ fused to the strong VP16 transcriptional activation domain (Wang et

al. 2004) accordingly enhances endurance exercise performance. Similarly, administration of the synthetic PPARβ/δ ligand GW501516 improves oxidative metabolism and enhances the effect of endurance exercise training (Narkar et al. 2008). In contrast, skeletal muscle-specific ablation of the PPARβ/δ gene results in a shift towards glycolytic fibers, reduced fatty acid catabolism and OXPHOS activity, decreased exercise performance as well as exacerbated insulin resistance, glucose intolerance and obesity when fed a high fat diet (Schuler et al. 2006). Interestingly, PPARβ/δ controls the expression of PGC-1α and thereby enhances its own activity by boosting transcriptional coactivation (Schuler et al. 2006). Thus, as a downstream effector of PPARβ/δ, PGC-1α exerts potent effects on endurance exercise adaptations even in the absence of PPARβ/δ in skeletal muscle (Pérez-Schindler et al. 2014).

Of the three PPARs, PPARγ depicts the lowest expression in skeletal muscle. Nevertheless, a role in the control of muscle metabolism was implied by observations in muscle-specific PPARγ knockout mice that develop adiposity and at least a mild insulin resistance under high fat diet (Hevener et al. 2003; Norris et al. 2003). Animals with a muscle-specific transgenic overexpression of a modified PPARγ (harboring a mutation in the inhibitory phosphorylation site Ser86 and a C-terminal fusion to the CR1 region of the adenovirus E1a gene that strongly promotes transcriptional activity) are protected against diet-induced insulin resistance and glucose intolerance, secrete elevated levels of adiponectin from muscle and exhibit a switch towards more oxidative fibers, similar to PPARβ/δ (Amin et al. 2010).

2.1.3. Subfamily 1, Group D: Rev-Erb – Type IV

Rev-Erbα (NR1D1) and Rev-Erbβ (NR1D2) are nuclear receptors with a dual role regulating the circadian clock and cellular metabolism (Cho et al. 2012). Upon binding of heme, the endogenous ligand of these NRs (Yin et al. 2007), the Rev-Erbs recruit corepressors such as the nuclear receptor corepressor 1 (NCoR1) or the histone deacetylase 3 (HDAC3) and thus transcriptionally repress target genes. Gain- and loss-of-function studies of muscle Rev-Erbα revealed a prominent involvement in the regulation of mitochondrial biogenesis, mitophagy, promotion of a slow fiber type, and ultimately, higher endurance capacity (Woldt et al. 2013). Mechanistically, muscle-specific ablation of the Rev-Erbα gene was associated with reduced activity of the AMP-dependent protein kinase (AMPK)–Sirtuin 1 (SIRT1)–PGC-1α signaling axis (Woldt et al. 2013). Accordingly, mice treated with the Rev-Erbα agonist SR9009 exhibit increased activation of these factors (Woldt et al. 2013). A contribution of Rev-Erbβ to the control of lipid uptake has been postulated (Ramakrishnan et al. 2005). However, in contrast to the well-established role of Rev-Erbα in the control of oxidative muscle function, the function of Rev-Erbβ in skeletal muscle remains poorly understood.

2.1.4. Subfamily 1, Group F: Retinoid-related orphan receptors (ROR) – Type IV

The transcriptional activity of the RORs is negatively affected by the Rev-Erb receptors, at least in the control of the circadian clock. However, in regard to skeletal muscle function, RORα (NR1F1) elicits changes that are in part similar to those described for Rev-Erbα, in particular in the regulation of lipid metabolism (Fitzsimmons et al. 2012). In addition, RORα also affects muscle lipogenesis, cholesterol efflux, insulin sensitivity and glucose uptake. Mechanistically, these observations have been linked to a modulation of protein kinase B (PKB/Akt) and AMPK signaling coupled to a change in PGC-1α gene expression (Fitzsimmons et al. 2012). RORγ (NR1F3) is also highly expressed in skeletal muscle, but the function is less clear. Overexpression studies in muscle have linked RORγ to the regulation of genes involved in lipid and carbohydrate metabolism, and possibly muscle mass through the induction of the myostatin gene (Raichur et al. 2010). However, the physiological relevance of these observations is

unknown. Moreover, since RORγ induces RORα and Rev-Erbα, it is not clear whether these effects are direct or indirect (Raichur et al. 2010).

2.1.5. Subfamily 1, Group H: Liver X receptor (LXR) – Type II

LXRα (NR1H3) and LXRβ (NR1H2) have potent effects on cholesterol efflux in various tissues and cell types. Both receptors have been linked to anabolic pathways in skeletal muscle, including glycogen buildup and lipogenesis (Archer et al. 2014). Long-term treatment of mice with the synthetic LXR agonist T0901317 elevated lipogenesis and reverse cholesterol transport in wild-type and in LXRα, but to a lesser extent in LXRβ knockout animals, indicating that LXRβ might constitute the more relevant LXR variant in skeletal muscle (Hessvik et al. 2010). The anabolic function of the LXRs indicate that these receptors are involved in regeneration processes between exercise bouts to replenish intramuscular glycogen and lipid stores, e.g. when coactivated by PGC-1α (Summermatter et al. 2010).

2.1.6. Subfamily 1, Group I: Vitamin D receptor (VDR) – Type II

The VDR (NR1I1) is involved in regulating mineral metabolism. In humans, polymorphisms of the VDR gene are associated with aberrations in muscle strength (Pojednic and Ceglia 2014). In mice, VDR gene ablation results in muscle fiber atrophy, motor deficits, decreased locomotive activity after exercise and reduced neuromuscular maintenance (Girgis et al. 2014; Sakai et al. 2015). Endogenous VDR gene expression is induced after resistance training in rats (Makanae et al. 2015). Combined with studies using vitamin D administration in human patients, a positive role of the VDR in the control of muscle mass, fiber hypertrophy and anabolic capacity can be predicted (Pojednic and Ceglia 2014).

2.2.1. Subfamily 2, Group B: Retinoid X receptors (RXR) – Type III

In addition to their ability to homodimerize, the RXR family members RXRα (NR2B1), RXRβ (NR2B2) and RXRγ (NR2B3) are obligate heterodimerization partners for a number of NRs and thus play a unique role in modulating and integrating the function of these different receptors (Perez et al. 2012; Evans and Mangelsdorf 2014). While RXRβ is ubiquitously expressed, RXRα and RXRγ levels are enriched in some tissues, including skeletal muscle. Global RXRγ knockout animals have a leaner phenotype after a high fat diet feeding, which is most likely attributed to an upregulation of lipoprotein lipase in skeletal muscle (Haugen et al. 2004). However, little is known about the specific functions of all three RXRs in skeletal muscle. Intriguingly, NR/RXR heterodimers are classified as “permissive” and “non-permissive”. Permissive RXR heterodimers include the interactions with PPARs or LXRs and thus are activated by either RXR or PPAR/LXR ligands. In contrast, TR and VDR interact with RXR in a non-permissive manner and therefore are not activated by 9-cis retinoic acid or other RXR ligands (Perez et al. 2012). Activation of RXRs in skeletal muscle would thus be expected to be linked to increased action of permissive, but not of non-permissive NR heterodimerization partners.

2.3.1. Subfamily 3, Groups A and C: Estrogen receptor (ER), Androgen receptor (AR), Glucocorticoid receptor (GR) – Type I

Estrogens have primarily been linked to reduced inflammation and enhanced regeneration of skeletal muscle in ovariectomized rodents or postmenopausal women (Lowe et al. 2010; Diel 2014). In addition, it is now clear that estrogens also improve muscle mass and strength, even though it is disputed whether increased quantity or quality of muscle is the driver of these changes. Both ERs, ERα (NR3A1) and ERβ (NR3A2), are expressed in skeletal muscle, are induced by exercise (Wiik et al. 2005) and thought to contribute to the effects of estrogen in this tissue. Intriguingly, at least some of the effects of estrogen, e.g. activation of AMPK, might be mediated by non-genomic signaling pathways and thereby reinforce the receptor-dependent adaptations (Oosthuyse and Bosch 2012).

Male sex hormones elicit potent anabolic effects on skeletal muscle tissue, but also enhance muscle regeneration (O'Connell and Wu 2014). Most of these effects are mediated by activation of the AR (NR3C4), in particular the strong boost in muscle protein synthesis. Accordingly, muscle hypertrophy elicited by resistance training is attenuated by AR blockage (Inoue et al. 1994). Regulation of AR levels after resistance exercise seems to depend on a complex control of contractile and nutritional cues, and can vary between different fiber types (Gonzalez et al. 2016). Similarly, the contradicting results of physiological testosterone fluctuations and muscle hypertrophy in different human studies imply a more complex interaction between androgens, growth hormone and insulin-like growth factor 1 (IGF1) in this context (Gonzalez et al. 2016). However, the anabolic effect of superphysiological concentrations of testosterone consistently includes an improvement of muscle mass due to hypertrophy of type I and type II fibers as well as muscle strength and power while fatigability and muscle quality, defined as ratio between muscle strength to size, are less affected in humans (O'Connell and Wu 2014). The central role for the AR to regulate muscle development, mass, strength and fatigue-resistance was confirmed by experiments in male AR knockout mice (MacLean et al. 2008). Somewhat contradictory, a different AR knockout mouse model depicted a shift from oxidative towards glycolytic muscle fibers, thereby also linking the AR to the maintenance of slow-twitch, oxidative fibers (Altuwaijri et al. 2004).

In contrast to the positive effects of ERs and the AR on muscle mass and function, the GR (NR3C1) has been associated with atrophy of primarily type II muscle fibers (Kuo et al. 2013; Schakman et al. 2013). Cortisol, the ligand of the GR, is a stress hormone released during exercise, starvation or sepsis that contributes to the metabolic remodeling in various tissues (Kraemer and Ratamess 2005). In skeletal muscle, one effect of cortisol is the stimulation of protein breakdown and the inhibition of protein synthesis (Schakman et al. 2013). While short term elevation of cortisol is a normal response to acute exercise bouts, chronic elevation can be an indicator of overtraining or training-induced stress. The ratio between testosterone and cortisol has been proposed to correlate with the anabolic and catabolic state of skeletal muscle, respectively, even though this interpretation is debated (Kraemer and Ratamess 2005). The GR is upregulated by physical activity, most notably by eccentric resistance exercise bouts, but this induction is attenuated by chronic training, as is the rise in circulating cortisol. In line, a reduction in muscle mass is a common side effect in patients treated with corticosteroids. However, paradoxically, Duchenne muscular dystrophy patients profit from administration of glucocorticoids. Even though the mechanisms behind this therapeutic effect is unclear, anti-inflammatory properties, upregulation of utrophin, normalization of intramyocellular calcium homeostasis and stabilization of the muscle fiber membrane have been proposed to contribute to the positive outcome of glucocorticoid treatment in Duchenne patients (Matthews et al. 2016).

2.3.2. Subfamily 3, Group B: Estrogen-related receptors (ERR) – Type IV

ERRα (NR3B1), ERRβ (NR3B2) and ERRγ (NR3B3) are all substantially expressed in tissues with a high energetic demand, e.g. skeletal muscle (Fan and Evans 2015). Muscle-specific ERRα knockout animals exhibit an impaired muscle regeneration capacity, compromised antioxidant response, reduced oxidative capacity and angiogenesis (LaBarge et al. 2014). Moreover, these mice have a blunted response to high fat diet and exercise, including impaired exercise tolerance and muscle fitness (LaBarge et al. 2014; Perry et al. 2014; Huss et al. 2015). ERRα gene expression is induced by physical activity in animals and humans, and this receptor then coordinates the expression of genes involved in lipid uptake, metabolism and mitochondrial OXPHOS (Huss et al. 2015). Even though cholesterol has been recently postulated as endogenous ERRα ligand (Wei et al. 2016), the transcriptional activity of all three ERRs is thought to be mainly driven by coregulator binding. In the case of ERRα, the

coactivator PGC-1α seems of particular relevance for the regulation of target genes in skeletal muscle (Mootha et al. 2004). In fact, the genomic context of regulatory elements in target gene enhancers and promoters might dynamically determine the interaction and activity of these two proteins (Salatino et al. 2016).

ERRα and ERRγ have a considerable overlap in binding sites and accordingly regulate similar metabolic genes (Fan and Evans 2015). Nevertheless, differences in the regulation of the TCA cycle and the inability of ERRα to compensate for the loss of ERRγ in null mice highlight the specific roles for these two receptors (Eichner and Giguere 2011). Like ERRα, ERRγ is induced by exercise. Skeletal muscle-specific overexpression of ERRγ alone or when fused to VP16 leads to a switch to oxidative fiber types, induces mitochondrial biogenesis and angiogenesis, collectively resulting in an improved endurance capacity (Rangwala et al. 2010; Narkar et al. 2011). Many of these effects can also be elicited by treatment with the ERRγ-specific synthetic activator GSK4716 (Rangwala et al. 2010). Inversely, a reduced exercise capacity was observed in ERRγ muscle-specific knockouts (Gan et al. 2013).

ERRβ is the least characterized receptor of this group and despite high expression in skeletal muscle, regulation and function are largely unexplored. A partial redundancy between ERRβ and ERRγ in regard to the maintenance of type I fibers in mixed muscle beds has been proposed (Gan et al. 2013), but mechanistic aspects and a comprehensive analysis remain elusive.

2.4.1. Subfamily 4, Group A: Neuron-derived clone 77/Nerve growth factor IB (Nur77), neuron-derived orphan receptor 1 (Nor1) – Type IV

All three mammalian members of this group of NRs, Nur77 (NR4A1), nuclear receptor related 1 protein (Nurr1, NR4A2) and Nor1 (NR4A3) are induced by a single bout of exhaustive endurance exercise in human skeletal muscle (Mahoney et al. 2005), however little is known about the role of Nurr1 in this tissue. Nur77 is predominantly expressed in glycolytic muscle fibers and was first postulated to be involved in the control of glucose metabolism (Chao et al. 2007). Later findings surprisingly implied an involvement of Nur77 in the regulation of oxidative metabolism and accordingly, muscle specific overexpression of Nur77 results in an increase in the proportion of oxidative muscle fibers and mitochondrial DNA content with a concomitant shift from glucose utilization to fatty acid oxidation and improved fatigue resistance (Chao et al. 2012). Recently however, Nur77 activity was associated with muscle growth, most likely controlled by activation of the IGF1-Akt-mammalian target of rapamycin (mTOR) signaling axis leading to the upregulation of a hypertrophic gene program and a attenuation of the expression of the pro-atrophic myostatin as well as the E3 ubiquitin ligases MAFbx and MuRF1 (Tontonoz et al. 2015). However, while skeletal muscle-specific Nur77 mice do not depict increased muscle mass despite fiber hypertrophy, animals with a specific gene ablation of Nur77 in skeletal muscle exhibit reduced myofiber size and muscle mass (Tontonoz et al. 2015).

Like Nur77, Nor1 is also induced by acute exercise and β2-adrenergic signaling, however both in glycolytic and oxidative muscle fibers (Fan et al. 2013). Skeletal muscle-specific overexpression of Nor1 in mice results in an oxidative, high endurance phenotype with increased mitochondrial number and DNA, elevated myoglobin, enhanced ATP production and PGC-1α gene expression (Pearen et al. 2013). Intriguingly, a shift from type I and IIb towards type IIa and IIx muscle fibers is observed in these animals (Mizunoya 2015). These fatigue-resistant Nor1 transgenic animals also exhibit improved autophagy after endurance exercise, leading to better clearing of debris in the tissue (Goode et al. 2016). Unexpectedly, Nor1 overexpression was recently also linked to muscle hypertrophy and increased vascularization in skeletal muscle via activation of the mTOR signaling pathway (Goode et al. 2016).

2.5. NR coregulators

The transcriptional activity of NRs is affected by recruitment of coactivator and corepressor proteins, which can occur in a ligand-dependent and –independent manner. In skeletal muscle, several coregulators have been identified that modulate metabolic and contractile properties at least in part by binding to the NRs described in this review. Most prominently, muscle-specific overexpression of PGC-1α and the related PGC-1β are sufficient to promote a fiber type switch towards type I/IIa and IIx, respectively, even though it is not clear whether the latter occurs under physiological conditions (Eisele and Handschin 2014). Of these two coactivators, only PGC-1α levels and activity are clearly associated with physical activity (Lin et al. 2002; Kupr and Handschin 2015), and gain- and loss-of-function in skeletal muscle result in improved and impaired endurance capacity, respectively (Lin et al. 2002; Handschin et al. 2007). Recently, the PGC-1α4 isoform was identified to promote a hypertrophic response in skeletal muscle (Ruas et al. 2012) in contrast to the PGC-1α1, -1α2 and -1α3 isoforms that have been linked to an endurance program (Martinez-Redondo et al. 2015). The expression of the corepressor NCoR1 is higher in inactive skeletal muscle, and NCoR1 competes with PGC-1α for binding to ERRα (Pérez-Schindler et al. 2012). Accordingly, muscle-specific NCoR1 knockout mice recapitulate many of the metabolic adaptations that are also observed in PGC-1α transgenic animals (Pérez-Schindler et al. 2012). Similarly, overexpression and knockout of the corepressor receptor-interacting protein 140 (RIP140) results in decreased and elevated numbers of oxidative muscle fibers, respectively (Seth et al. 2007). This complex, still poorly understood regulatory network of coactivator and corepressor proteins is thus intricately linked to NR action in skeletal muscle plasticity (Schnyder et al. 2016).

2.6. "Exercise mimetics"

Several pharmacological agents have already been proposed to act as "exercise mimetics", including three that activate NRs: SR9009 (Rev-Erbα), GSK4716 (ERRγ) and GW501516 (PPARβ/δ) (Handschin 2016). With well-defined and conserved ligand-binding domains, it is conceivable that other NRs could also be targeted to take advantage of their function in skeletal muscle. Importantly however, for none of currently proposed "exercise mimetics", efficacy and safety has been tested in humans to date. The alarming use of some of these compounds as performance-enhancing drugs in athletes with a subsequent ban by the World Anti-Doping Agency underlines the need for a better understanding of the mechanisms, side effects, toxicity and dosage (Wall et al. 2016). The summary of NRs and coregulators in this review should further illustrate the regulatory complexity of skeletal muscle plasticity, which is vastly expanded by non-NR transcription factors and signaling pathways (Hoppeler 2016). Despite the results in animal models with a higher endurance capacity, the expected effects of pharmacological modulation of one NR in skeletal muscle are difficult to reconcile with the myriad of muscular and non-muscular adaptations elicited by *bona fide* physical activity (Booth and Laye 2009).

2.7. Open questions

Of the 35 NRs expressed in mouse skeletal muscle, we have discussed here 26 with a potential role in exercise adaptation and skeletal muscle plasticity. A majority of these promote an oxidative, high endurance phenotype (Fig. 2). The signaling networks and transcriptional hierarchies between these receptors are however not clear. Moreover, it is unknown whether the high number of NRs with seemingly overlapping function is a sign of transcriptional redundancy or represents specific regulation

of highly specialized adaptations. An oxidative phenotype can for example be achieved by a downregulation of type I and IIb fibers in the case of Nor1 or by the more classic shift from type IIb and IIx towards IIa and I as seen in overexpression studies with PPARβ/δ or ERRγ. Furthermore, the alternating classification of Nur77 and Nor1 as pro-oxidative and pro-glycolytic NRs highlight a potential discrepancy between the results obtained in different experimental contexts, e.g. cultured muscle cells compared to the constitutive transgenic elevation in skeletal muscle *in vivo*. These somewhat contradictory results in regard to the effects on glucose and lipid oxidation as well as glycolytic and oxidative fiber promotion, respectively, will therefore have to be clarified in future studies. Furthermore, whether the effects of Nur77 and Nor1 on muscle mass are primarily mediated by altered myogenesis or represent a *bona fide* modulation of atrophy and hypertrophy in regeneration and exercise in adult muscle remains to be shown. Similarly, the extensive study of anabolic steroids emerged with a consensus of increased muscle hypertrophy in humans. Nevertheless, results obtained in some, but not all AR knockout mouse models imply a role for the AR in promoting an oxidative, high endurance phenotype. Similarly, the effect of genetic ablation of the TRs on fiber type distribution might appear contradictory vis-à-vis the mitochondrial boost elicited by short term treatment with thyroid hormone. These and other examples demonstrate that the choice of model and the way of treatment might significantly alter the outcome. Therefore, caution should be used for the extrapolation of results from cell culture, non-conditional knockouts and transgenic animals to the physiological role of NRs in skeletal muscle in humans.

3. Concluding remarks

Endurance and resistance exercise confer many beneficial health effects, which substantially lower the risk for many chronic diseases and are a therapeutic pillar for a number of different pathologies. Even though the molecular mechanisms of muscle plasticity are still poorly understood, NRs are attractive drug targets to take advantage of some of the therapeutic effects of exercise. The ever increasing prevalence of chronic diseases, age-related afflictions and pathologies associated with exercise intolerance indicate that even partial “exercise mimetics” might confer a significant relieve for patients and overburdened health care systems. However, at the moment, it is not clear whether such drugs exist and if so, whether they can be effectively and safely used in patients. Therefore, physical activity and diet should stay at the forefront of disease prevention and treatment wherever possible (Booth et al. 2012; Pedersen and Saltin 2015) until better pharmacological interventions targeted at improving muscle function are available.

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Conflict of interest statement

The authors declare no conflict of interest.

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Figure Legends

Fig. 1. Structure and DNA-binding sites of NRs. A, Schematic representation of the different NR domains. B, Arrangements of DNA-binding sites of NRs. $(X)_n$ indicates a spacer of #n arbitrary nucleotides X between the hexamer half-sites. The repeats are accordingly designated as DR-n, IR-n or ER-n, e.g. DR-1 for a direct repeat with a spacer of one nucleotide.

Fig. 2. Regulation of endurance and resistance exercise adaptations in skeletal muscle by NRs and coregulators. For some NRs, including RORγ, Nur77, Nor1 or AR, a role in both the promotion of an oxidative and a glycolytic muscle phenotype has been proposed in different experimental models.

641 **Table 1. Human and mouse nuclear receptors.**

NR subfamily and group	NR nomenclature	Trivial name	Muscle expression (mus musculus)[%]
1A	NR1A1	TRα	H
	NR1A2	TRβ	L
1B	NR1B1	RARα	H
	NR1B2	RARβ	I
	NR1B3	RARγ	I
1C	NR1C1	PPARα	I
	NR1C2	PPARβ/δ	I
	NR1C3	PPARγ	I
1D	NR1D1	REVERBα	H
	NR1D2	REVERBβ	I
1F	NR1F1	RORα	H
	NR1F2	RORβ	L
	NR1F3	RORγ	H
1H	NR1H2	LXRβ	I
	NR1H3	LXRα	H
	NR1H4	FXRα	nd
	NR1H5*	FXRβ*	nd
1I	NR1I1	VDR	L
	NR1I2	PXR	nd
	NR1I3	CAR	nd
2A	NR2A1	HNF4α	nd
	NR2A2	HNF4γ	nd
2B	NR2B1	RXRα	H
	NR2B2	RXRβ	H
	NR2B3	RXRγ	H
2C	NR2C1	TR2	L
	NR2C2	TR4	I
2E	NR2E1	TLX	nd
	NR2E3	PNR	nd
2F	NR2F1	COUP-TFI	L

	NR2F2	COUP-TFII	I
	NR2F6	EAR2	I[#]
3A	NR3A1	ERα	I
	NR3A2	ERβ	nd
3B	NR3B1	ERRα	H
	NR3B2	ERRβ	I
	NR3B3	ERRγ	I
3C	NR3C1	GR	H
	NR3C2	MR	I
	NR3C3	PR	nd
	NR3C4	AR	H
4A	NR4A1	NUR77	H
	NR4A2	NURR1	I
	NR4A3	NOR1	H
5A	NR5A1	SF1	nd
	NR5A2	LRH1	nd
6A	NR6A1	GCNF1	L
0B	NR0B1	DAX1	nd
	NR0B2	SHP	nd

Footnotes: [%]NR gene expression in mouse muscle according to (Bookout et al. 2006). *FXRβ is a pseudogene in the human genome. [#]The expression of NR2F6/Ear2 was not reported in (Bookout et al. 2006) and muscle expression confirmed using BioGPS and GeneCards. Legend: H, high expression; I, intermediate expression; L, low expression; nd, not detected. NRs highlighted by grey shading were discussed in this review.

Table 2. Muscle phenotype of gain- and loss-of-function models for selected NRs.

NR nomenclature	Trivial name	Loss-of-function model	Muscle phenotype	Gain-of-function model	Muscle phenotype	Endogenous and pharmacological modulators (examples)
NR1A1	TRα	KO	oxidative fibers	pharmacol	mitochondrial biogenesis	thyroid hormone
NR1C1	PPARα	mKO	oxidative fibers	mTG	glycolytic fibers, reduced endurance	fibrate drugs, fatty acids
NR1C2	PPARβ/δ	mKO	glycolytic fibers	mTG	oxidative fibers, improved endurance	GW501516, fatty acids
NR1C3	PPARγ	mKO	glucose intolerance and insulin resistance	mTG	oxidative fibers	Thiazolidinediones, fatty acids
NR1D1	REVERBα	mKO	reduced endurance exercise performance	mTG	oxidative fibers, improved endurance	SR9009
NR1F1	RORα	KO	atrophy	mTG	oxidative fibers, lipid metabolism	
NR1F3	RORγ	KO	atrophy	mTG	lipid and carbohydrate metabolism	
NR1H2	LXRβ	KO	impaired glycogen buildup and lipogenesis			T0901317, oxysterols
NR1H3	LXRα	KO	impaired glycogen buildup and lipogenesis			T0901317, oxysterols
NR1I1	VDR	KO	atrophy, NMJ disruption			vitamin D_3
NR2B3	RXRγ	KO	lipolysis			9-cis retinoic acid
NR3A1	ERα	mKO	muscle weakness	pharmacol	hypertrophy	estradiol
NR3B1	ERRα	mKO	glycolytic, reduced			

			endurance exercise tolerance and regeneration			
NR3B3	ERRγ	mKO	reduced endurance exercise capacity	mTG	oxidative fibers, improved endurance	GSK4716
NR3C1	GR	mKO	regulation of protein metabolism and prevention of atrophy	pharmacol	atrophy	glucocorticoids
NR3C4	AR	mKO	shift from slow to fast fibers	pharmacol	hypertrophy	testosterone
NR4A1	NUR77	mKO	atrophy	mTG	hypertrophy, glucose utilization vs. oxidative metabolism *	
NR4A2	NURR1			mTG	oxidative phenotype vs. glycolytic fibers, high endurance, hypertrophy *	
NR4A3	NOR1			mTG	oxidative phenotype vs. glycolytic fibers, high endurance, hypertrophy *	

Footnotes: *conflicting data from different studies. Legend: KO, global knockout; mKO, muscle-specific knockout; mTG, muscle-specific transgenic; pharmacol, pharmacological modulation.

Fig. 1

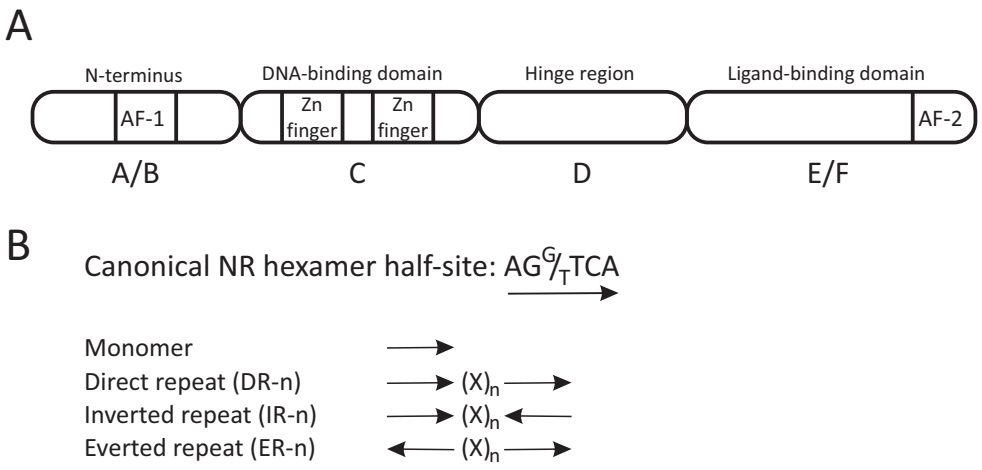
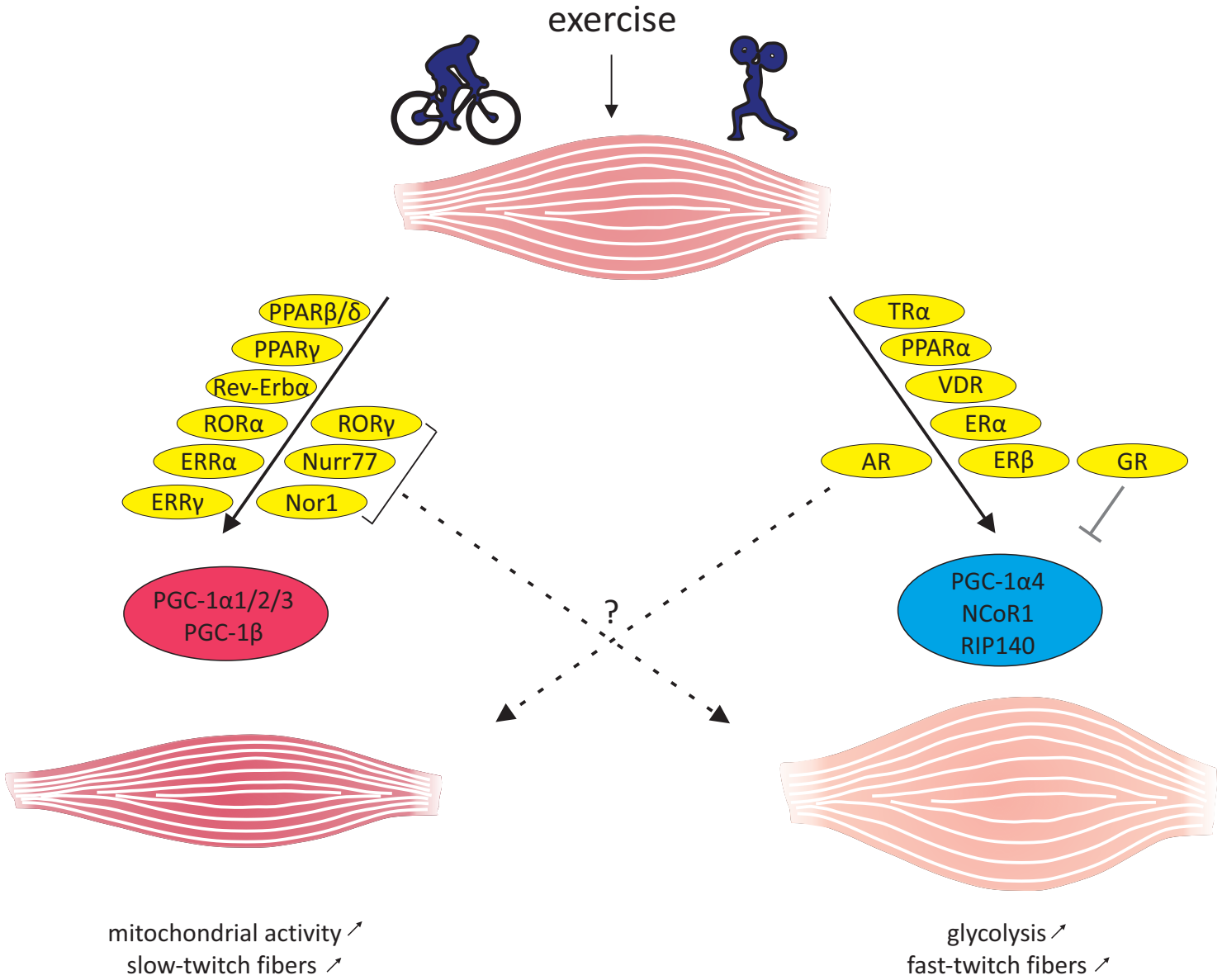

A
N-terminus
DNA-binding domain
Hinge region
Ligand-binding domain
AF-1
Zn finger
Zn finger
AF-2
A/B
C
D
E/F
B
Canonical NR hexamer half-site: AG G/T TCA
Monomer
Direct repeat (DR-n)
Inverted repeat (IR-n)
Everted repeat (ER-n)
(X)n

Fig. 2


exercise
PPARβ/δ
PPARγ
Rev-Erbα
RORα
RORγ
ERRα
Nurr77
ERRγ
Nor1
TRα
PPARα
VDR
ERα
AR
ERβ
GR
PGC-1α1/2/3
PGC-1β
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PGC-1α4
NCoR1
RIP140
mitochondrial activity ↗
slow-twitch fibers ↗
glycolysis ↗
fast-twitch fibers ↗