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Review

Skeletal muscle RAS and exercise performance

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Abstract

A local renin–angiotensin system (RAS) may be suggested by evidence of gene expression of RAS components within the tissue as well as physiological responsiveness of this gene expression. This review will focus on the evidence supporting the existence of the constituent elements of a physiologically functional paracrine muscle RAS. The effect of local skeletal muscle RAS on human exercise performance will be explored via its relation with pharmacological intervention and genetic studies.

The most likely configuration of the muscle RAS is a combination of in situ synthesis and uptake from the circulation of RAS components. A reduction in angiotensin-converting enzyme (ACE) activity reverses the decline in physical performance due to peripheral muscle factors in those with congestive heart failure and may halt or slow decline in muscle strength in elderly women. Genetic studies suggest that increased ACE and angiotensin II (Ang II) mediate greater strength gains perhaps via muscle hypertrophy whereas lower ACE levels and reduced bradykinin (BK) degradation mediate enhanced endurance performance perhaps via changes in substrate availability, muscle fibre type and efficiency.

Keywords: Renin–angiotensin system; Muscle; Exercise; Performance; ACE

Contents

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1. Introduction

Renin cleaves angiotensinogen to generate the non-pressor decapeptide angiotensin I (Ang I). The octapeptide angiotensin II (Ang II) is then derived primarily by the action of angiotensin-converting enzyme (ACE) which may either be circulating (after release by a carboxypeptidase) or an integral membrane protein (Beldent, Michaud, Wei, Chauvet, & Corvol, 1993; Zisman, 1998). ACE also catalyses inactivation of bradykinin (BK) and in this context is known as kininase II. Thus, ACE simultaneously generates a potent vasoconstrictor (Ang II) and inactivates a potent vasodilator (BK).

Our original concept of a circulating renin–angiotensin system (RAS) producing Ang II has altered as our knowledge about the function, receptors and existence of other effector peptides (Ang-(1–7), Ang III and Ang IV) generated by the RAS has developed. In addition, the existence of a local RAS has been established in several tissues and our understanding as to their role continues. Recent data implicate a skeletal muscle RAS with local de novo angiotensin II production and intrinsic ACE activity that is physiologically responsive. Moreover, pharmacological manipulation of specific aspects of the RAS in addition to genetic studies suggest that a muscle RAS may have significant functional implications in regard to human performance.

2. Local renin–angiotensin systems

A local RAS may be suggested by evidence of gene expression of RAS components within the tissue as well as physiological responsiveness of this gene expression. In addition, local generation of Ang II and the presence of Ang II receptors that are physiologically active (i.e. demonstration of the effects of both Ang II and Ang II receptor antagonists on the tissue) are important. These criteria have been variously met and local RAS have been described in adipose tissue (Jonsson, Game, Head, & Frewin, 1994), heart (Danser, Saris, Schuijt, & van Kats, 1999; De Mello & Danser, 2000; Neri Serneri et al., 1996), lung (Pieruzzi, Abassi, & Keiser, 1995) brain (Allen, MacGregor, McKinley, & Mendelsohn, 1999) and pancreas (Leung & Carlsson, 2001; Sernia, 2001).

As has been suggested (Danser et al., 1999) local Ang II production may depend either on in situ synthesis of all RAS components (renin, angiotensinogen and ACE), uptake of these constituents from the circulation, or a combination of in situ synthesis and uptake. The skeletal muscle RAS reflects the latter.

2.1. Skeletal muscle ACE

Evidence for a relatively independent human skeletal muscle ACE first came from the study of biopsy specimens that demonstrated muscle ACE activity did not correlate with serum ACE (Reneland & Lithell, 1994). Skeletal muscle membrane fractions from rats and dogs confirm not only the presence of ACE but intact paracrine kininase-II activity accounting for 50% of BK hydrolysis (Dragovic, Minhall, Jackman, Wang, & Erdos, 1996). Cultured skeletal muscle myoblasts also exhibited ACE activity (Dragovic et al., 1996) and rabbit skeletal muscle membranes demonstrate an ACE effect on BK degradation in addition to Ang II production (Ward, Russell, & Vaghy, 1995).

Local ACE is an important determinate of muscle function since isolated rat muscle perfused with a solution excluding ACE, renin, and angiotensinogen, still demonstrate marked vasoconstriction to topical Ang I that is prevented by ACE inhibition (Vicaut, 1993). Any variation in ACE expression may therefore be expected to influence Ang II production and BK degradation. More recently, immunohistochemistry of human muscle biopsies has localised ACE to the endothelial cells of capillaries in skeletal muscle (Schaufelberger, Drexler, Schieffer, & Swedberg, 1998). ACE gene expression is variable and, quantified by the number of ACE-mRNA transcripts, is related to muscle fibre area with an inverse relationship to capillary density (Schaufelberger et al. 1998). This would suggest physiological responsiveness of ACE gene expression.

2.2. Skeletal muscle Angiotenisin II receptors

There are two Ang II receptors: type 1 (AT_1) and type 2 (AT_2). Most of the known effects of Ang II, including vasoconstriction, hypertrophy, cellular growth, catecholamine release, and aldosterone secretion, are mediated by AT_1 (Matsubara, 1998; Timmermans et al., 1993; Munzenmaier & Greene,

1996) while AT_2 appears to attenuate these effects (Nouet, 2000). AT_1 mediates myocyte hypertrophy whereas AT_2 inhibits proliferative processes (Matsubara, 1998; Yang et al., 2002). The AT_2 receptor also mediates vasodilation (Munzenmaier & Greene, 1996) via activation of the endothelial BK type 2 (B2BK) receptor-mediated nitric oxide system (Tsutsumi et al., 1999).

Since Ang II binds to AT_1 and AT_2 with a similar affinity the cellular response may depend on the relative expression, or responsiveness, of these receptors within individual tissues. Recent evidence confirmed the presence of both receptors throughout the rat skeletal muscle microcirculation (Nora, Mnzenmaier, & Hansen-Smith, 1998) and in skeletal muscle fibres (Linderman & Greene, 2001). In human skeletal muscle published evidence only confirms the presence of the AT_1 receptor although both receptors may exist in foetal skeletal muscle (Malendowicz et al., 2000). The apparent absence of AT_2 receptors in human skeletal muscle is compatible with clinical evidence that AT_1 receptor antagonism in addition to ACE inhibition does not confer added benefit in congestive heart failure (CHF) (Pitt et al., 2000).

2.3. Skeletal muscle Ang II production

The peripheral vasculature has long been known to be an important site of Ang I conversion in humans (Admiraal et al., 1993; Gasic, Heinz, & Kleinbloesm, 1990). Due to difficulties in the tissue extraction and assessment of Ang II activity it is currently conceptually more correct to consider skeletal muscle Ang II a product of the skeletal muscle vascular bed. It is uncertain whether Ang II is secreted by skeletal muscle cells themselves or if the vascular endothelium accounts for much of the Ang II production (Ohishi et al., 1997; Phillips, Rook, Siddle, Bruce, & Woledge, 1993). Sequestration of Ang II from the circulation with intracellular accumulation following endocytosis of AT_1 receptors with Ang II (Thomas, 1999) may allow a cellular mechanism whereby stored Ang II is later used locally.

Whatever the mechanism, over half the Ang II in the venous drainage of skeletal muscle is thought to be secondary to local de novo Ang II synthesis from the conversion of locally produced and circulating Ang I (Danser et al., 1992). Ang I and Ang II measured in arterial and venous plasma across the skeletal muscle vascular bed during constant infusion of 125I-Ang I into the left ventricle of pigs reveals 67% of venous Ang I and 59% of venous Ang II to be derived from de novo production. This would suggest Ang I production in skeletal muscle contributes to the circulating pool and that some circulating Ang II is derived from local production (Danser et al., 1992). In healthy humans incremental doses of infused Ang I and Ang II exert the same maximal effect in decreasing forearm blood flow (FBF), with similar potencies (Saris, van Dijk, Kroon, Schalekamp, & Danser, 2000). Forearm fractional Ang I-to-Ang II conversion is only 36%, ACE inhibition reduces this to 1% and abolishes the effects of Ang I, suggesting that locally generated Ang II is functionally important (Saris et al., 2000). Since the extraction rates for Ang I across vascular beds are high, it is likely that local vascular ACE, rather than pulmonary ACE, is the main source of Ang II generation (Admiraal, Derkx, Danser, Pieterman, & Schalekamp, 1990; Admiraal et al., 1993; Campbell, 1985; Hilgers et al., 1989; Schalekamp, 1991).

There is evidence that muscle ACE gene expression can be functionally upregulated in the rat following two-kidney, one clip (2K1C) hypertension for 4 weeks (Muller et al., 1997). Incremental doses of infused Ang I in isolated rat hindlimbs leads to a dose-dependent increase in venous Ang II that is greater in 2K1C rats than controls. Induction of local Ang I formation by renin infusion also increases Ang II in 2K1C rats compared to control. The skeletal muscle vascular bed can therefore upregulate ACE with a functional increase in the conversion of exogenous and locally generated Ang I to Ang II.

There is no published evidence regarding specific muscle renin and it may currently be most appropriate to consider the configuration of the muscle RAS as a combination of in situ synthesis and uptake from the circulation (Table 1).

3. Human performance and the muscle RAS

Information regarding the effect of skeletal muscle RAS on human exercise performance is currently derived from two main sources: the effects of drugs specifically inhibiting aspects of the RAS, and genetic studies of the RAS.

Table 1
Summary of skeletal muscle RAS constituents

RAS component	Presence	Location	Reference
Angiotensinogen	Inferred	Induction of local Ang I following renin infusion Local Ang I production in pigs	Muller et al. (1997) Danser et al. (1992)
ACE	Yes	Endothelial cells of capillaries Skeletal muscle membrane Human muscle biopsies	Schaufelberger et al. (1998) Dragovic et al. (1996) Reneland & Lithell (1994)
Ang I–Ang II conversion	Yes	Human skeletal muscle de novo synthesis Peripheral muscle vascular bed Skeletal muscle membrane	Danser et al. (1992) Saris et al. (2000); van Dijk et al. (2000) Ward et al. (1995)
AT_1 receptor	Yes	Rat skeletal muscle fibre and microvessels Human skeletal muscle	Linderman & Greene (2001) Malendowicz et al. (2000)
AT_2 receptor	Yes	Rat skeletal muscle fibre and microvessels	Linderman & Greene (2001)

3.1. *Pharmacological insights*

Increased RAS activity with elevated plasma and tissue Ang II is an important contributor to cardiac and vascular remodelling in patients with CHF (Unger, 2002). This has a detrimental effect on skeletal muscle perfusion and fibre type ratio with a subsequent reduction in peak aerobic capacity (Coats, 1996; Harridge, Magnusson, & Gordon, 1996; LeJemtel, Maskin, & Lucido, 1986; Minotti et al., 1991). Exercise capacity does not correlate with the degree of LV dysfunction (Sullivan & Hawthorne, 1995) but peak oxygen consumption does correlate closely with ultrastructural changes in skeletal muscle (Munzel, Kurz, & Drexler, 1993). A reduction in ACE may mediate peripheral muscle effects that contribute to the efficacy of ACE inhibition. Indeed, ACE inhibition enhances peak aerobic capacity and induces improvement in skeletal muscle perfusion in patients with CHF (Drexler, Banhardt, & Meinertz, 1989; Mancini, Davis, & Wexler, 1987) though not necessarily in healthy subjects over 2 weeks (Predel, Rohden, Heine, Prinz, & Rost, 1994). Chronic therapy with ACE inhibitors in CHF improves endothelial function, peripheral oxygen extraction and exercise performance greater than acute improvements in cardiac output (Drexler, Munzel, Riede, & Just, 1991).

Maximum oxidative capacity and effective muscle mass measured by 31P magnetic resonance spectroscopy during aerobic exercise decrease by 30 and 65%, respectively in CHF (Kemp et al., 1996). This is corroborated by muscle biopsies demonstrating reduced muscle oxidative capacity (Drexler et al., 1992; Mettauer et al., 2001) and a reduction in mitochondrial density that correlates with peak VO_2 (Drexler et al., 1992). In addition, rat models of CHF demonstrate alterations in skeletal muscle fibre ratio with an increased proportion of fatigue-sensitive fast type II fibres and a decreased proportion of slow-twitch, fatigue-resistant type 1 fibres (De Sousa, Veksler, Bigard, Mateo, & Ventura-Clapier, 2000). The proportion of slow-twitch type 1 fibres also falls in humans with CHF (Drexler et al., 1992; Sullivan, Green, & Cobb, 1990), perhaps contributing to the reduced metabolic efficiency seen (Kemp et al., 1996), but is preserved by ACE inhibition (Sabbah et al., 1996).

These changes in fibre type ratio are probably crucial to the effect seen on muscle performance: in competitive cyclists with a similar $\dot{V}O_{2\,max}$ those with a higher lactate threshold and greater endurance have a greater percentage of type 1 fibres (Coyle, Sidossis, Horowitz, & Beltz, 1992). Slow-twitch fibres have a high oxidative capacity but the muscle of CHF patients reveal a decrease in citrate synthase activity and a concomitant reduction in oxidative capacity (De Sousa et al., 2000). ACE inhibitors improve peak $\dot{V}O_2$ in CHF specifically by reducing the limitation due to peripheral muscle factors (Jondeau, Dubourg, & Bourdarias, 1997). Moreover, these effects are partly mediated via antagonism of Ang II since AT_1 receptor blockade activates the perfusion of exercising muscle (raised delta $\dot{V}O_2$/delta work rate, a measure of aerobic work efficiency) (Guazzi, Palermo, Pontone, Susini, & Agostoni, 1999).

A decreased capillary-to-fibre ratio also occurs in CHF (Drexler et al., 1992; De Sousa et al., 2000) which may negatively impact on substrate delivery and hence muscle efficiency and therefore performance. ACE, upregulated in CHF, may be key to this effect since ACE expression has an inverse relationship to capillary density (Schaufelberger et al., 1998). Conversely, a reduction in ACE enhances muscle perfusion and insulin-mediated glucose disposal (Donnely, 1992; Kudoh & Matsuki, 2000).

A reduction in ACE activity has also been found to prevent reduction in physical performance and in muscle strength in those without CHF (Onder et al., 2002). The rate of decline in leg muscle strength in hypertensive women who have taken ACE inhibitors continuously is significantly lower over 3 years than those on other drugs. Interestingly, the I allele of the human ACE gene, which is associated with lower serum and tissue ACE activity, confers an improved response in muscle strength gain in postmenopausal women treated with HRT (Woods, Onambele, et al., 2001). The HOPE trial has also suggested that a reduction in ACE may have beneficial peripheral effects since it reduced mortality in patients at high risk of ischaemic heart disease as well as reducing the incidence of diabetes despite the absence of LV dysfunction (Yusuf et al., 2000).

3.2. The ACE I/D polymorphism and human performance

The human ACE gene contains a polymorphism consisting of the presence (insertion, I) or absence (deletion, D) of a 287 base pair sequence in intron 16 (Rigat et al., 1990). Hence, three genotypes exist: II, ID and DD, the distributions of which within a Caucasian population are roughly 25, 50 and 25%, respectively. Although this polymorphism occurs in an intron it is an exceptionally strong and consistent marker for ACE activity in many different Caucasian populations (Agerholm-Larsen, Tybjserg-Hansen, Schnohn, & Nordestgaard, 1999; Busjahn et al., 1997; Cambien et al., 1994; Danser et al., 1998; Kohno et al., 1999; Martinez et al., 2000; Rossi et al., 1999) and accounts for up to 47% of the variance in plasma ACE (Rigat et al., 1990). ACE is consistently highest in the DD subjects, intermediate in the ID and lowest in the II subjects. The ACE polymorphism also appears to be a determinant of ACE at a cellular level (Costerousse, Allegrini, Lopez, & Alhenc-Gelas, 1993; Danser et al., 1995; Davis, Millner, & Roberts, 2000; Mizuiri, Hemmi, & Kumanomidou, 1997) and thus may influence Ang II production.

The contractile responses of internal mammary arteries to Ang I and Ang II and the maximal Ang II-induced response indicate that Ang I conversion is greatest in the presence of the D allele (Buikema et al., 1996). This may be secondary to increased tissue conversion of Ang I since DD subjects have a significantly enhanced forearm vasoconstrictor response to Ang I infusion that is not accompanied by differences in serum Ang II levels (van Dijk et al., 2000). An influence on local Ang II production may occur within the peripheral muscular bed and not readily equilibrate with plasma although other workers have found greater plasma Ang II concentrations following Ang I infusion in DD subjects (Brown, Blais, Gandhi, & Adam, 1998; Ueda, Elliott, Morton, & Connell, 1995).The ACE polymorphism also affects BK degradation, this being least in II subjects (Brown et al., 1998). Reduced BK degradation may favourably alter substrate metabolism in II subjects with improvements in the efficiency and contractile function of skeletal muscle, beneficial effects in endurance exercise. This indeed would appear to be the case with an excess of II subjects in elite runners with a significant linear trend of increasing I allele frequency with distance run (Myerson et al., 1999). Similarly, elite Australian rowers exhibit an excess of the I allele and the II genotype (Gayagay et al., 1998). Interestingly rowers exhibit a preponderance of type 1 muscle fibres similar to endurance runners. As discussed previously, it is a reduction in type 1 fibres that is blamed for some of the reduction in muscle efficiency in CHF that is reversed by reducing ACE activity (akin to the effect of the I allele). Conversely, the D allele has been associated with power-oriented performance, being found in excess in short-distance swimmers (Woods, Hickmann, et al., 2001) and other power-oriented athletes (Nazarov et al., 2001). Although not all reports support these findings the common denominator among negative studies has been the selection of athletes from mixed sporting disciplines, cohorts that are unlikely to yield reliable information in a population association study (Karjalainen et al., 1999; Rankinen et al., 2000; Taylor, Mamotte, Fallon, & Bockxmeer,

1999). In prospective training studies the I allele has also been associated with greater improvement in endurance performance (Montgomery et al., 1998) and the D allele with greater strength gains in the quadriceps muscle (Folland et al., 2000).

In the search for a physiological link between the ACE genotype and elite human performance the study of central cardio-respiratory factors such as $\dot{V}O_{2\,max}$ has revealed no consistent effect (Hagberg, Ferrell, McCole, Wilund, & Moore, 1998; Rankinen et al., 2000; Sonna et al., 2001; Woods et al., 2002;). This is corroborated by a genome-wide scan for markers linked with $\dot{V}O_{2\,max}$ that found none on chromosome 17, the location of the ACE gene (Bouchard et al., 2000). Greater endurance of a fairly small muscle group, the upper arm, for II subjects after training (Montgomery et al., 1998), and an increased arterio-venous oxygen difference during maximal exercise in II postmenopausal women (Hagberg et al., 1998) suggests that the influence of ACE may instead be due to local muscle effects. Further, examination of delta efficiency (DE) (the ratio of the change in work performed per minute to the change in energy expended per minute), the most valid measure of the efficiency of muscular contraction (Gaesser & Brooks, 1975) reveals that DE rises significantly with training only in those of II genotype (Williams et al., 2000). This is supported by the greater peripheral tissue oxygenation and lesser rise in lactate, reflecting greater muscle efficiency, that occurs in II compared to DD subjects during exercise in patients with chronic airways disease (Kanazawa, Otsuka, Hirata, & Yoshikawa, 2002).

Taken together the data would suggest that the D allele is associated with power-oriented athletic performance, perhaps secondary to the effect of a greater ACE level on Ang II production and its subsequent hypertrophic effect on muscle growth and subsequently strength. Conversely, an increase in muscle efficiency contributes to the enhanced endurance associated with the I allele.

4. Potential mechanisms by which skeletal muscle RAS may affect performance

AT_1-mediated Ang II is crucial for optimal overload-induced skeletal muscle hypertrophy (Gordon, Davis, Carlson, & Booth, 2001). In surgically-induced plantaris and/or soleus muscle overload inhibiting endogenous Ang II production by ACE inhibition markedly attenuates muscle hypertrophy which is restored by local Ang II perfusion. AT_1 receptor antagonism also attenuates hypertrophy but is not rescued by Ang II perfusion. It is locally elevated Ang II that is vital since the contralateral soleus does not recover the hypertrophic response despite Ang II entering the systemic circulation, inducing cardiac hypertrophy similar to the perfused soleus. (Gordon et al., 2001).

Ang II may also be important in the redirection of blood flow from type I muscle fibres to the type II fibres (Rattigan, Dora, Tong, & Clark, 1996) that are favoured in power performance (a sprinter may have 80% fast-twitch fibres, an endurance athlete 20%). Ang II infused into rat hindlimbs increases the contraction-induced oxygen uptake and the tension during tetanic stimulation (Rattigan et al., 1996). Greater local Ang II production would therefore facilitate muscle contraction for maximal power while having potentially deleterious effects on efficiency and endurance (Fig. 1). This is again consistent with the genetic data. It is also supported by the reduced metabolic efficiency following Ang II administration in rats (Brink, Wellen, & Delafontaine, 1996) with skeletal muscle wasting secondary to enhanced protein degradation (Brink et al., 2001). This muscle wasting seems inconsistent with the otherwise hypertrophic effects of Ang II in humans but was predominantly due to an anorexigenic response (Rattigan et al., 1996). In addition the co-stimulation of AT_2 receptors in rat skeletal muscle antagonizes the hypertrophic effect of the sole AT_1 receptor stimulation that occurs in human skeletal muscle (where AT_2 receptors have not been documented).

Other actions of Ang II that might influence performance include the facilitation of sympathetic transmission by enhancing noradrenaline release from peripheral sympathetic nerve terminals and the CNS (Saxena, 1992; Story & Ziogas, 1987). Other effects concern Ang II as a direct stimulator of cellular growth (hypertrophic and hyperplastic) in human VSMCs (Campbell-Boswell & Robertson, 1989; Daemen, Lombardi, Bosman, & Schwartz, 1991), and the induction of various endogenous growth factors; fibroblast growth factor, transforming growth

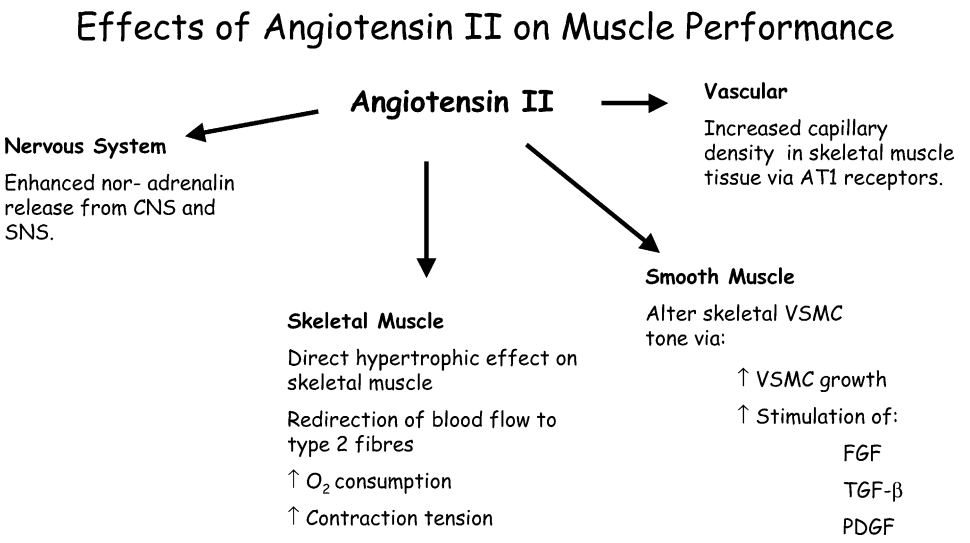

Fig. 1. Illustration of the mechanisms of angiotensin II on muscle performance.

factor-β_1, platelet derived growth factor (Dzau, 1994; Huckle & Earp, 1994; Rosendorff, 1996).

Of the other RAS peptides Ang-(1–7) is of particular interest since it can be generated by several enzymes including neutral endopeptidase 24.11 (NEP), from Ang I, bypassing the prerequisite formation of Ang II. NEP is expressed in rabbit skeletal muscle membranes (14) and cultured human skeletal muscle adult myoblasts and myotubes (Vaghy, Russell, Lantry, Stephens, & Ward, 1995). The actions of Ang-(1–7) are most often opposite those of Ang II and include an anti-proliferative effect on VSMC (Stroth & Unger, 1999). It also displays an anti-hypertensive effect not mediated by AT_1 or AT_2 but involving the synthesis and release of vasodilator prostaglandins and nitric oxide Stroth & Unger, 1999. Ang-(1–7) is also a substrate for ACE being converted to an inactive metabolite Ang-(1–5) (Ferrario & Iyer, 1998).

Thus, a reduction in ACE activity leads not only to an attenuation of Ang II production and a decrease in BK degradation but also to an increase in Ang-(1–7) (as it is not converted to Ang-(1–5) by ACE), further favouring vasodilation and potential substrate delivery. Conversely, genetically determined high ACE expression in rats is associated with low circulating and tissue NEP activity (Oliveri, Ocaranza, Campos, Lavandero, & Jalil, 2001) suggesting the existence of a modulating effect of ACE expression on NEP activity. This could determine lower Ang-(1–7) tissue levels in addition to higher Ang II.

The role of muscle RAS in the regulation of both regional substrate metabolism and vascular tone may affect performance. Selective skeletal muscle ACE inhibition in humans by local retrodialysis increases interstitial glucose and decreases the serum interstitial gradient for glucose by facilitating transcapillary glucose transport (Frossard et al., 2000; Muller et al., 1997). Similarly, acute ACE inhibition, but not AT_1 receptor antagonism, enhances insulin-stimulated glucose transport activity in rat skeletal muscle. BK administration produces a very similar effect which can be completely abolished by pre-treatment with either a B2BK receptor antagonist or a nitric oxide synthase inhibitor (Henriksen et al., 1999), suggesting that a B2BK receptor-mediated increase in nitric oxide production in skeletal muscle facilitates glucose uptake (Henriksen et al., 1999; Shiuchi et al., 2001). This may at least in part be due to a BK-NO-mediated increase in GLUT4 translocation (Shiuchi et al., 2002). BK also acts as a potent vasodilator via the release of nitric oxide (Rett, Wicklmayr, & Dietze, 1990). Muscle work increases muscle blood flow and glucose uptake in humans, an effect reproduced by BK infusion in the human forearm (Dietze, Wicklmayr, Rett, Jacob, & Henriksen, 1996). Indeed, a concomitant increase in BK in the venous effluent from working muscle

occurs. However, if the BK-generating protease in muscle tissue (kallikrein) is inhibited with aprotinin these responses are significantly diminished (Dietze et al., 1996).

Acute exercise stimulates NO release and may have a synergistic role with prostaglandin in mediating vasodilatation and hyperaemia during muscular contraction since their inhibition during acute exercise reduces microvascular flow in human quadriceps (Boushel et al., 2002). Recently, microdialysis in human calf muscle has confirmed an elevation of tissue BK with exercise (Langberg, Bjorn, Boushel, Hellsten, & Kjaer, 2002) perhaps supporting a role for BK-NO-induced hyperaemia. Interestingly, the oxidative capacity of muscle (greatest in the type 1 fibres that correlate with efficiency in cyclists) (Coyle et al., 1992) is in direct correlation and may be interdependent with muscle kallikrein (Shimojo, Chao, Chao, Margolius, & Mayfield, 1987). Conversely, it is known that NO opposes ANG II-induced increases in arterial pressure and in skeletal muscle resistance during dynamic exercise (Symons, Stebbins, & Musch, 1999). Genetic studies support these findings as the DD genotype of the ACE gene, associated with increased bradykinin degradation, has also been associated with significant blunting of NO vasodilatory responses in forearm vessels (Butler, Morris, Burchell, & Struthers, 1999).

5. Conclusion

A physiologically functional skeletal muscle RAS exists. It is capable of de novo angiotensin II production and interaction with the kallikrein–kinin system. As such there is significant potential for an influence on human performance. Pharmacological and genetic studies support an active role for paracrine RAS in determining our final performance. This has implications not just for elite athletes but for further pharmacological manipulation of any disease state where muscle function is suboptimal, including aging.

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