Exercise-dependent IGF-I, IGFBPs, and type I collagen changes in human peritendinous connective tissue determined by microdialysis

Jens L. Olesen,1 Katja M. Heinemeier,1 Carsten Gemmer,1 Michael Kjær,1 Allan Flyvbjerg,2 and Henning Langberg1

1Institute of Sports Medicine, Bispebjerg Hospital, Copenhagen; and
2Medical Research Laboratories, Aarhus University Hospital, Aarhus, Denmark

Submitted 22 September 2005; accepted in final form 21 August 2006

Olesen JL, Heinemeier KM, Gemmer C, Kjaer M, Flyvbjerg A, Langberg H. Exercise-dependent IGF-I, IGFBPs, and type I collagen changes in human peritendinous connective tissue determined by microdialysis. J Appl Physiol 102: 214–220, 2007. First published September 14, 2006; doi:10.1152/japplphysiol.01205.2005.—Microdialysis studies indicate that mechanical loading of human tendon during exercise elevates type I collagen production in tendon. However, the possibility that the insertion of microdialysis fibers per se may increase the local collagen production due to trauma has not been explored. Insulin-like growth factor I (IGF-I) and its binding proteins (IGFBPs), which are known to stimulate collagen production in animal tendons, may regulate the translation of mechanical loading to collagen synthesis. Systemic and tissue levels of IGF-I, IGFBP, and type I collagen metabolism markers [procollagen I COOH-terminal propeptide (PICP) and COOH-terminal telopeptide of type I collagen] were measured by microdialysis in peritendinous tissue of the human Achilles tendon in an exercise group (performing a 36-km run, n = 6) and a control group (no intervention, n = 6). An increase in local PICP concentration was seen in both groups after 72 h and stayed elevated in the exercise group at 96 h (P < 0.05). IGFBP-1 in both serum and dialysate increased in the exercise group immediately after exercise (P < 0.05), whereas IGFBP-3 decreased systemically (P < 0.05). Elevation of local IGFBP-4 was observed in both the control and exercise groups after 48 h (P < 0.05). Total IGF-I did not change in locally or systemically in either group. Our results indicate an increased local production of PICP in human peritendinous tissue in response to prolonged mechanical loading with part of the increase due to trauma from the sampling technique. Care must therefore be emphasized to minimize the numbers of insertions with microdialysis. We demonstrated an elevation of IGFBP-1 both systemically and peritendinously in response to prolonged acute exercise. The local increased collagen synthesis was preceded by an elevation of local concentration of IGFBP-4, suggesting that IGFBP-4 may have a key role in the IGF-axis effect on the human collagen synthesis in vivo.

tendon; insulin-like growth factor I; insulin-like growth factor binding proteins; microdialysis; mechanical loading; human

HUMAN STUDIES INDICATE THAT tendon tissue is more dynamic in its response to mechanical loading than thought so far, with increased collagen type I synthesis observed after both acute exercise and prolonged training (23, 35, 37, 47).

Several cytokines and growth factors, such as insulin-like growth factor I (IGF-I), transforming growth factor-β, and interleukin-6, have been implicated in mediating the effect of increased loading of the fibroblasts in the tendon to produce collagen (5, 19, 23, 30, 50). Of these, IGF-I seems especially important given its activities in other tissues such as bone and skeletal muscle (3, 14, 41). The main IGF-I effect is mediated by circulating free IGF-I, which represents <1% of total IGF-I (53). To investigate the role of free IGF-I, it is therefore necessary to consider alterations of the specific IGF binding proteins (IGFBP-1 to -6).

The use of microdialysis in peritendinous tissue allows in vivo measurement of the type I collagen (23, 37) simultaneously with the substances believed to be involved in the collagen regulation. A recent study demonstrates that the technique can be used for IGF-I in skeletal muscle (11). However, the introduction of microdialysis fibers in tissue potentially can cause iatrogenic changes. Therefore, it is important to also consider unspecific changes in the tissue after probe insertion.

The aim of this study was to determine the exercise-induced changes in IGF-I and IGFBPs in tendon-related tissue and the extent to which this would be involved in the increase of collagen type I synthesis in relation to mechanical loading. We used the microdialysis technique in the peritendinous area of the human Achilles tendon before and the days following a 36-km run, an exercise bout that previously has been sufficient to induce increased collagen synthesis loading of the tendon (37). Because the microdialysis method has a risk of influencing the measured results due to its invasiveness, a control experiment was added, where any trauma to the tissue and thereby changes to IGF-axis or the collagen turnover would be examined.

We hypothesized that mechanical loading would induce a release of IGF-I in the peritendinous tissue from both sources stored in the matrix and from the plasma of the vasculature which would balance collagen expression with the accompanying collagen degradation that occurs during and after extreme activity.

METHODS

Exercise experiment. Six male volunteers were included in the study [mean age, 29 yr (range 25–45 yr); mean body mass index, 23 kg/m² (21–25 kg/m²)]. All subjects were experienced marathon runners and had been training for several years. None of the subjects had a previous history of Achilles tendon symptoms or injuries. Trained individuals were chosen to minimize the risk of the prolonged intervention being traumatic to the musculoskeletal system. None of the subjects was on any medication, and all were nonsmokers. All gave written informed consent, and the study was approved by the Ethical Committee of Copenhagen (KF 01-089/98).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
Experiments were started at 8 AM on all days. Subjects fasted from 12 PM on the days preceding experiment days and were told not to engage in any type of exercise or training for 48 h before the first day of the study and for the entire length of the experiment. To rule out any influence of dietary collagen on circulating and local levels of type I collagen metabolism markers, the participants were given a list of gelatin-rich foods and informed not to consume any of these for 48 h leading up to the experiment and during the experiment. The first day of the experiment consisted of a 3.5-h preexercise rest period, a 3-h exercise period, and a postexercise recovery period of 3.5 h. The microdialysis measurement was repeated each day until day 5 with each sampling period taking 3.5 h. The exercise intervention consisted of a 36-km run at a pace of 12 km/h. The running was performed on a flat route of 12 km, with several checkpoints along the route to ensure that a constant pace was kept for all runners. We did not measure oxygen uptake during the run, but considering that all individuals were young and trained and that they all were exhausted after 3 h indicates a relative work intensity of 70–80% of maximal oxygen uptake (1).

Microdialysis was performed throughout the rest periods, during which subjects lay in a supine position at room temperature. Microdialysis catheters were always removed before running, and afterward new catheters were inserted. During microdialysis, dialysate samples were collected at 30-min intervals for the first 90 min and at 60-min intervals for the remaining periods. Dialysis samples were weighed to eliminate the possibility of ultrafiltration, and afterward they were immediately frozen at −80°C until analysis. To minimize the influence of the insertions trauma on measured concentrations, only samples collected during the last 2 h of microdialysis were used for analysis.

**Control experiment.** To control for the effects of microdialysis probe insertion, a separate experiment was performed. Six healthy, trained male volunteers were examined (mean age: 25 yr, range 22–27 yr; mean body mass index: 23 kg/m², range 20–25 kg/m²). All participants gave informed consent, and approval was obtained from the Ethical Committee of Copenhagen (KF 01-089/98).

The volunteers fasted from 12 PM on the days preceding experiment days and were informed not to engage in any type of exercise or training for 48 h before the first day of the study and for the entire length of the experiment. Dietary intake of gelatin was restricted as in the exercise experiment. Experiments were started at 8 AM on all days. The protocol was similar to the exercise experiment; however, the 3-h exercise period on day 1 was replaced with a rest period.

**Microdialysis.** Microdialysis catheters were constructed of an 80-cm inlet of polyethylene tubing (inner diameter: 0.76 mm) connected to 30 mm of permeable membrane (hollow plasma separator tubes [Asahi, Tokyo, Japan]; diameter 4 mm; molecular mass cutoff 3,000 kDa) and an 8-cm outlet of polyethylene tubing (inner diameter 0.50 mm; outer diameter 0.63 mm). Before use, the catheters were sterilized, using ethylene oxide (ETO-sterilisation, Mærsk Medical, Lyngby, Denmark).

Microdialysis was performed in principle as described by Lönnroth et al. (39). Two microdialysis catheters were placed diagonally and ventrally to the Achilles tendon leaving the outlet of the catheter at the medial side of the tendon. The permeable portion of the membrane covered the area from 30 to 60 mm to the Achilles tendon. Pre- and postexercise catheters were placed around both the right and left Achilles tendons in each subject. Placement of the catheters was alternated between the two tendons the succeeding days following exercise/control day.

The microdialysis catheters were perfused via a high-precision syringe pump (CMA/100, Carnegie, Solna, Sweden) at a rate of 2 μl/min with a Ringer-acetate solution (Pharmacia and Upjohn). 3H-labeled human type IV collagen (130 kDa; specific activity 5.92 MBq/mg; NEN, Boston, MA) in an amount corresponding to an activity of 5.6 kBq/ml was used to estimate the in vivo relative recovery (RR) of procollagen I COOH-terminal propeptide (PICP) and COOH-terminal telopeptide of type I collagen (ICTP) as described by Langberg et al. (37). The level of PICP is correlated to type I collagen production, because one PICP is cleaved from every newly secreted type I collagen triple helix, whereas ICTP is a degradation product of type I collagen breakdown. The in vivo RR for IGF-I and IGFBPs was not estimated, because no radioactive markers for human use was commercially available. Therefore, microdialysis results concerning IGF-I and IGFBP are presented as dialysate concentrations.

**Blood sampling.** Blood samples were drawn from an antecubital vein, placed immediately on ice until centrifuged at 3,000 g for 15 min at 4°C. The serum was removed and stored at −80°C until analysis. Hematocrit was determined by the microhematocrit method at all times of blood sampling, and the measured blood concentrations for IGF-I, IGFBPs, PICP, and ICTP were corrected for changes in plasma volume (21).

IGF-I and IGFBP. Serum and dialysate total IGF-I were determined after acid-ethanol extraction by using noncompetitive time-resolved monoclonal immunofluorometric assays as previously described (18). The within-assay coefficient of variation for total IGF-I averaged <5%. The samples for each experiment were determined within the same assay.

Western ligand blotting (WLB) and SDS-PAGE were performed in serum and microdialysis according to the method of Hossenlopp et al. (25) as previously described (15–17, 34, 49) (Fig. 1). Two microliters of serum were subjected to SDS-PAGE (10% polyacrylamide) under nonreducing conditions. Specificity of the IGFBP-1, IGFBP-2, IGFBP-3, and IGFBP-4 bands on WLBs was supported by competitive coinubation with unlabeled recombinant human IGF-I purchased from Bachem (Budendorf, Switzerland). Autoradiograms of WLBs were quantified by densitometry with a Shimadzu CS-9001 PC dual-wavelength flying spot scanner (Shimadzu Europe, Duisburg, Germany). The relative density of the bands was measured as arbitrary absorbance units. Values are corrected in proportion to preexercise values, which are corrected to the value of 100 arbitrary units.

![Fig. 1. Autoradiograph of a representative Western ligand blot (WLB) displaying serum samples taken from a person in the control group.](image)
Collagen synthesis and degradation. Microdialysis and serum samples were analyzed for PICP and ICTP with a commercially available RIA kit (Orion Diagnostica, Espoo, Finland). Samples from each subject were analyzed in the same assay. The detection level of the kit is 1.2 μg/l for PICP and 0.5 μg/l for ICTP. Intra-assay precision is given as 3.1% for PICP at 54 μg/l and 6.2% for ICTP at 3.8 μg/l, while the interassay is given as 5.8% for PICP at 52 μg/l and 7.9% for ICTP at 3.3 μg/l.

Statistics. All values are reported as means ± SE. The data set was analyzed for deviations from Gaussian distribution using the Kolmogorov-Smirnov test. For each time point changes were determined by repeated-measures ANOVA with Newman-Keuls post hoc testing, using the Prism software package (Graphpad, San Diego, CA). For all statistical tests, the 0.05 level of confidence was accepted for significance. Microdialysis results for IGF-I, IGFBPs, PICP, and ICTP are given as the average of values observed in paired samples from the right and left leg of all subjects at pre- and postexercise time points. No systematic significant difference was seen between legs with regard to the obtained values of IGF-I, IGFBPs, PICP and ICTP.

One-way ANOVA with a Bonferroni multiple-comparison test was used to detect any differences between the exercise and control group at any given time point. Differences in mean values for PICP and ICTP between the two groups were checked using unpaired t-test.

RESULTS

Recovery of collagen. The relative recovery of type IV collagen determined by the internal reference calibration used for calculating PICP was found to be 58 ± 3% (control study) and 63 ± 2% (exercise study). For ICTP, the recovery was 43 ± 3% (control study) and 41 ± 3% (exercise study); there were no significant differences between the exercise and control group.

Type I collagen turnover. The calculated interstitial tissue concentration of PICP in dialysate for both the exercise and control group was significantly increased after 72 h compared with the preexercise levels (Fig. 2, A and B). The 96-h value was higher than 72 h in exercise group and still significantly elevated compared with basal level, whereas in the control group the value at 96 h was lower than 72 h and was no longer significantly elevated compared with basal level (Fig. 2, A and B). The interstitial level of PICP at 96 h in exercise group was significantly higher than the control group (Fig. 2, A and B). No changes were seen between the two groups at any other time points, although the values for the exercise group were numerically two- to threefold higher at all time points (Fig. 2, A and B).

Circulating levels of PICP and ICTP did not change during the time course either in exercise or control group, whereas a significant higher mean value for serum PICP was seen in the exercise study (Table 1).

For ICTP, no differences were seen over time or between groups in serum, and thus only mean data are shown. Concentration determined from tissue dialysate showed a significant higher mean value in the exercise group (Table 1).

IGF-I and IGFBP. For the exercise group, IGF-I was between 6.7 ± 1.0 μg/l (48 h) and 8.3 ± 1.0 μg/l (preexercise) with no significant changes over time but significantly higher compared with the control group at all time points (Table 2). Systemic IGF-I concentration for the exercise group ranged between 148.3 ± 9.8 μg/l (48 h) to 165.0 ± 11.3 μg/l (preexercise), and it was not significantly different over time. The systemic values of IGF-I for the control group were in the range of 223.1 ± 12.7 μg/l (48 h) to 242.5 ± 14.5 μg/l (postexercise), which were significantly higher than the exercise group at all time points but were not significantly different within the group during the experiment period (Table 2).

Immediately after exercise, both systemic and local IGFBP-1 was found to be significantly elevated compared with preexercise values in the exercise group. The concentrations of IGFBP-1 returned to basal levels from 24 h postrunning (Fig. 3, A and B). In the control group, no significant changes were measured for local or systemic IGFBP-1.

For circulating IGFBP-2, we observed a significant increase 48 h postexercise in the exercise group compared with preexercise values (Fig. 4). No significant changes were seen in the dialysate samples for the exercise group (Table 2). IGFBP-2 results for the control group did not display any significant changes in either systemic or local obtained samples.

Serum concentrations of IGFBP-3 obtained in the exercise group were significantly decreased immediately after exercise and returned to preexercise levels after 24 h (Fig. 5). The locally measured IGFBP-3 results in the exercise group did not change significantly over time, which is similar to what was seen in the control group for serum and dialysate IGFBP-3 (Table 2).
IGFs and Tendon Collagen Synthesis in Exercise

Table 1. Serum levels of markers for type I collagen metabolism markers and dialysate levels of ICTP

<table>
<thead>
<tr>
<th>Sample, μl/l</th>
<th>Exercise</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum, μl/l</td>
<td>PICP 203.0±5.0</td>
<td>153.0±5.0</td>
</tr>
<tr>
<td>ICP</td>
<td>3.9±0.1</td>
<td>4.1±0.1</td>
</tr>
<tr>
<td>Dialysate, μl/l</td>
<td>ICP 5.2±0.6</td>
<td>0.9±0.2*</td>
</tr>
</tbody>
</table>

Values are means ± SE. Data were pooled over all time points, because there were no significant changes between time points within groups (time = preexercise, postexercise, 24 h, 48 h, 72 h, and 96 h). PICP, procollagen I COOH-terminal propeptide; ICTP, COOH-terminal telopeptide of type I collagen. *Significantly different from exercise group, P < 0.05.

For IGFBP-4, a significant increase was observed peritendinously at 48 h for both exercise and control group (Fig. 6, A and B). In both groups, no changes were seen in circulating IGFBP-4 (Table 2).

DISCUSSION

In the present study, an elevated collagen synthesis around the human Achilles tendon was observed in response to prolonged mechanical loading. This is in agreement with earlier microdialysis studies (23, 37). However, the observed increase in the collagen synthesis marker PICP was partly due to insertion of microdialysis catheters per se. In addition, microdialysis was used for measuring interstitial concentration of IGF-I and IGFBPs in the proximity of human tendon tissue. The study indicated that IGFBP-4 could have an important role in the stimulation and regulation of the collagen synthesis in human tendon tissue.

Previous microdialysis studies in which tendon collagen were examined contained repeated insertions of microdialysis catheters (23, 37). Although robust changes were found, the studies did not elucidate the potential effect of the microdialysis catheters on collagen production per se. Knowledge of this possible iatrogenic factor is relevant because comparison of collagen data obtained by microdialysis in peritendinous tissue with results from a skin wound study demonstrates an identical time pattern in the increase of PICP (22, 37). Indeed, in the present study, a part of the initial increase in PICP was due to

Table 2. IGF-I and IGFBPs values obtained in serum and dialysate in control and exercise group before and after an intervention of 36-km run (exercise group) or 3-h rest (control group)

<table>
<thead>
<tr>
<th>Sample, μg/l</th>
<th>Preexercise</th>
<th>Postexercise</th>
<th>24 h</th>
<th>48 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-I, AU</td>
<td>240.3±12.2†</td>
<td>242.5±14.5†</td>
<td>234.8±14.3†</td>
<td>223.1±12.7†</td>
</tr>
<tr>
<td>IGFBI, AU</td>
<td>100±18.1</td>
<td>110±26.8</td>
<td>100±16.4</td>
<td>116±25.8</td>
</tr>
<tr>
<td>IGFBP2, AU</td>
<td>100±17.6</td>
<td>90±3.7</td>
<td>103±6.14</td>
<td>79±8.6</td>
</tr>
<tr>
<td>IGFBP3, AU</td>
<td>100±11.5</td>
<td>101.6±11.5</td>
<td>106.3±13.0</td>
<td>103.4±14.3</td>
</tr>
<tr>
<td>IGFBP4, AU</td>
<td>100±19.8</td>
<td>83.4±15.7</td>
<td>95.8±21.1</td>
<td>96.0±22.0</td>
</tr>
</tbody>
</table>

Values are means ± SE. IGF-I, insulin-like growth factor 1 (RIA and Western ligand blotting); IGF-II, insulin-like growth factor II (RIA and Western ligand blotting); IGFBP-1–4, insulin-like growth factor binding proteins 1–4 (Western ligand blotting); AU: arbitrary units. *Significantly different from preexercise values, P < 0.05. †Significantly different from exercise group, P < 0.05.

Fig. 3. Interstitial concentrations of IGFBP-1 (WLB) obtained in serum (A) or peritendinous microdialysate (B) before and after exercise in 6 healthy individuals. Values from the peritendinous tissue of the Achilles tendon were obtained minimum 90 min after insertion of microdialysis probes. AU, arbitrary units. Error bars represent SE. *Significantly different from preexercise value, P < 0.05.
the repeated insertions of microdialysis catheters. However, the trauma-induced PICP production peaked at 72 h, whereas an added mechanical stimulus had a prolonged effect beyond 72 h from the initial catheter insertion (Fig. 2, A and B). Thus exercise does result in a stimulation of collagen synthesis in tendon tissue. The levels of the degradation marker ICTP were constant throughout the measured period, indicating a net increase in local collagen type I production in response to mechanical loading (Table 1).

Overall, the exercise group had higher systemic PICP values compared with the control group (Table 1), which could be due to differences in the physical abilities of the participants, because the exercise group was composed of experienced marathon runners, whereas the control group contained competitive athletes not only from track and field but also from soccer and swimming. Systemic PICP is predominantly derived from bone, and a weight-bearing sport as long-distance running could provide greater stimulation of bone structures and hence result in a higher turnover of collagen synthesis than a less weight-bearing sport such as swimming (8, 28).

The linkage between mechanical loading or tissue trauma to an increase in collagen production could be through the IGF axis because IGF-I is produced by tendon fibroblasts and known to enhance tendon repair both in vivo and in vitro by increasing cell proliferation and collagen synthesis (2, 9, 10, 33, 52). With regard to systemic IGF-I concentration, an inconsistency exists in the literature concerning the reaction to strenuous acute exercise. Reports have shown both increases, no changes or a delayed decrease of IGF-I 24 h after exercise (26, 31, 32). In this study we did not observe any differences in peritendinous or systemic values of IGF-I within the two groups (Table 2).

Higher circulating level of IGF-I in the control group compared with the exercise group was found at all time points (Table 2). The reason for this constant higher concentration in controls is unknown. Systemic IGF-I levels are reported to be higher in fitter subjects and is correlated to lean body mass (13). In this study, both the exercise and control group were physically active with no differences in body mass index, but a precise measurement of lean body mass is lacking. In contrast to systemic values, peritendinous IGF-I values were consistently higher in the exercise group compared with control subjects (Table 2). It can be speculated that the higher level of IGF-I around the tendon in the exercise group was due to constant stimulation locally from preexperimental marathon training.

The higher circulating IGFBP-1 levels immediately after exercise (Fig. 3A) was expected (24, 31, 51), and it is in

---

Fig. 4. Serum IGFBP-2 WLB in response to a 36-km run for 6 individuals. Error bars represent SE. *Significantly different from preexercise value, $P < 0.05$.

Fig. 5. Serum IGFBP-3 WLB in response to a 36-km run for 6 individuals. Error bars represent SE. *Significantly different from preexercise value, $P < 0.05$.

Fig. 6. Dialysate concentrations of IGFBP-4 (WLB) obtained from the peritendinous tissue of the Achilles tendon after exercise (A) or rest (B) for 6 individuals. Values were obtained at a minimum of 90 min after insertion of microdialysis probes. Error bars represent SE. *Significantly different from preexercise value, $P < 0.05$. 

---

J Appl Physiol • VOL 102 • JANUARY 2007 • www.jap.org
accordance with the fact that IGFBP-1 is demonstrated to be elevated during a metabolically stressful situation (7, 38). The elevated IGFBP-1 concentration around the Achilles tendon (Fig. 3B) after exercise was probably due to a systemic elevation, because no IGFBP-1 production locally in tendon or connective tissue has been shown previously (6). Because of IGFBP-1’s capacity to cross the capillary barrier, an elevation in its concentration might release IGF-I for immediate use.

A known stimulator of IGFBP-2 is diminished nutritional intake (40), and it could be hypothesized that the late rise in systemic IGFBP-2 seen in the exercise group (Fig. 4) is due to a larger energy expenditure in the exercise group compared with the control group. However, a direct effect on collagen synthesis is not indicated by the data.

We found a systemic decrease in IGFBP-3 24 h after completion of the run, which reached basal levels the following day (Fig. 5). The decrease is in agreement with other studies that have demonstrated that IGFBP-3 is decreased following strenuous exercise, probably due to proteolysis, which enables IGF-I to reach the extravascular tissues (31, 48).

An important finding of the study was an elevation in local IGFBP-4 preceding the elevation of local PICP (Fig. 6, A and B). IGFBP-4 has been shown to be produced in fibroblasts and to have a localization predominantly to connective tissue (6, 20, 44, 45). Studies have demonstrated that IGFBP-4 inhibits IGF-I (29, 43); however, a large concentration of IGFBP-4 seems to have a reciprocal effect due to a protease-dependent mechanism and thus increases the bioavailability of IGF-I (42). Loading of skeletal muscle and tendon increase the IGFBP-4 mRNA expression (4, 46), and the inflammatory marker prostaglandin E2 can stimulate the secretion of IGFBP-4 (12). The elevation of IGFBP-4 observed both in the control and exercise group in the present study could therefore be due to an inflammatory response to the microdialysis insertion as well as a response to loading of the tendon for the exercise group. The precise role of IGFBP-4 in the tendon tissue was not elucidated in this experiment; however, two different hypotheses can be made. First, one can view the elevation as a local response to an increased stimulation of the connective tissue, which needs to be controlled, and IGFBP-4 would decrease the stimulation of IGF-I on the connective tissue (43). Second, a promoting effect on collagen synthesis could also be postulated, due to the fact that an increased synthesis of IGFBP-4 in the connective tissue could lead to a change in the binding of systemic IGF-I and thereby shut it from the vascular compartment to the target tissue to function as a “homing” molecule (27, 42).

We examined the IGF-axis profile for a time period less prolonged compared with the collagen type I profile. We based that on the literature, where any expected changes in IGF-I and IGFBPs would be displayed within the first 48 h after a stimulus (26, 31, 32). When it was observed that the IGFBP-4 elevation occurred 48 h after loading, the microdialysis material was too sparse to repeat the measurements. Data from our group, however, indicate that the elevation in IGFBP-4 is still present after 72 h around the human Achilles tendon measured after an 1 h up-hill run. (Olesen JL and Flyvberg A, unpublished.)

Because of a lack of a suitable tracer for estimation of the in vivo recovery of IGF-I and IGFBPs, only dialysate concentrations were determined. All microdialysis measurements were done on subjects in the resting state, and therefore it would be expected that the recoveries of IGF-I and IGFBPs were relatively constant. The relative recovery of several other substances (e.g., glucose and lactate), when determined in relation to exercise, has been found to remain constant during rest periods before and after exercise, whereas major changes in recovery are only seen when measurements were performed during exercise (36).

In conclusion, local type I collagen synthesis is increased perindently after prolonged mechanical loading, but part of the increase is due to trauma induced by the microdialysis technique, and therefore insertions should be minimized when measuring around the human tendon. After prolonged acute running, a rise is seen immediately in IGFBP-1 concentration both systemically and locally around the human tendon; furthermore, systemic IGFBP-3 is decreased after 24 h. Both changes enable an extravascular increase of IGF-I. A delayed local increase in IGFBP-4 is also observed preceding the increase in collagen type I synthesis. Thus IGFBP-4 could be a key factor in the IGF-axis when investigating the IGF-I effect on the human collagen synthesis in vivo (15–17, 34, 49).

ACKNOWLEDGMENTS

The authors address special thanks to Annie Høj, Birgitte Lilletorp, Ann-Marie Selestrøm, Karen Mathiassen, and Kirsten Nyborg for excellent technical assistance. Benjamin F. Miller is acknowledged for support during the study.

GRANTS

This study was supported by grants from the Danish Rheumatism Association, the Danish Medical Research Council, and the Clinical Institute, Aarhus University (22010154).

REFERENCES

IGFs and Tendon Collagen Synthesis in Exercise


