Group I Afferent Pathway Contributes to Functional Knee Stability

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1Trauma Research Group, German Armed Forces Hospital Ulm, Ulm; 2Institute of Sport and Sport Science, University of Freiburg, Freiburg; 3Institute of Orthopaedic Research and Biomechanics, University of Ulm, Ulm, Germany; and 4Department of Neurology, University Hospital Freiburg, Germany

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Friemert B, Franke S, Gollhofer A, Claes L, Faist M. Group I afferent pathway contributes to functional knee stability. J Neurophysiol 103: 616–622, 2010. First published December 2, 2009; doi:10.1152/jn.00172.2009. The hamstring reflex response has been suggested to play a substantial role in knee joint stabilization during anterior tibial translation. The present study was performed to determine which afferent pathways contribute to the hamstring reflex as well as the potential effects of specific afferent pathways on functional knee stability. Short- and medium-latency hamstring reflexes (SLR and MLR) were evoked by anterior tibial translation in 35 healthy subjects during standing with 30° knee flexion. Nerve cooling, tizanidine, and ischemia were employed to differentiate afferent pathways. Two hours of thigh cooling (n = 10) resulted in a significant increase in MLR latency and, to a lesser extent, SLR latency. No significant changes were recorded in reflex sizes or maximum tibial translation. The ingestion of tizanidine (n = 10), a suppressor of group II afferents, strongly reduced the MLR size while SLR size or latency of both reflex responses was not significantly affected. Maximum tibial translation was unchanged [5.3 ± 1.9 to 4.8 ± 2 (SD) mm; P = 0.410]. Ischemia in the thigh (n = 15) led to a highly significant depression in SLR size (89 ± 4%; P < 0.001) but only a slight and not significant decline of MLR size. In these subjects maximum tibial translation increased significantly (6.9 ± 1.6 to 9.4 ± 3.2 mm; P = 0.028). It is concluded that the hamstring SLR is mediated by Ia afferents, while group II afferents mainly contribute to the MLR. Suppression of SLR may increase maximum anterior tibial translation, thus indicating a possible functional role of Ia afferents in knee joint stabilization.

INTRODUCTION

Excessive anterior tibial translation is one of the main causes of anterior cruciate ligament (ACL) rupture (Woo et al. 1991). Although the underlying physiological mechanisms of knee joint stabilization are not well understood, it has been suggested that neuromuscular feedback mechanisms, in addition to the mechanical stability secured mainly by the ACL and other ligamental structures, may play a substantial role in the stabilization of the knee joint (Beard et al. 1993; Dhaher et al. 2003, 2005; Högervorst and Brand 1998; Johansson et al. 1991; More et al. 1993; Mrachacz-Kersting et al. 2003). A direct reflex arc between the ACL and the hamstrings was postulated as a candidate for this mechanism (Dyhr-Poulsen and Krosgaard 2000; Fujita et al. 2000; Gruber et al. 1986; Krosgaard and Solomonow 2002; Krosgaard et al. 2002; Miyatsu et al. 1993; Solomonow et al. 1987) This was recently confirmed by intraoperative mechanical stimulation of the ACL, but due to the small size of the hamstring reflex response, this particular reflex arc was not assumed to be protective (Friemert et al. 2005b). In human studies, latencies of the hamstring reflex activity in response to mechanically induced anterior tibial translation were published by several research groups (Beard et al. 1993; Bruhn 1999; Jennings and Seedhom 1994). In a previous study, we found in standing humans a multiphasic hamstring reflex activity with two distinct components: a short latency response (SLR) with a latency of ~20 ms and a medium latency response (MLR) with a latency of ~40 ms (Friemert et al. 2005a). In contrast to the aforementioned inconclusive intraoperative findings (Friemert et al. 2005b), it was suspected that this biphasic reflex response was mainly evoked by hamstring stretch reflexes (Friemert et al. 2005a). However, the afferent pathways of these different hamstring reflex components, and their potential for joint protection, have not yet been specified.

Therefore three different methods were employed to distinguish the afferent pathways mediating the hamstring reflex response after posterior-anterior tibial translation. Nerve cooling was used, as previously described (Grey et al. 2001; Schioppati and Nardone 1997), to identify the afferent fibers contributing to the SLR and MLR. Cooling evokes a decrease of conduction velocity depending on the fiber diameters (Franz and Iggo 1968; Paintal 1965) and likely results in delayed reflex latencies. Accordingly, the conduction velocity of small-diameter group II fibers is more affected than the conduction velocity of group Ia afferents that have a comparably larger diameter. Furthermore, tizanidine, an α2-adrenergic receptor agonist that distinctly reduces the transfer in the polysynaptic spinal pathway from group II afferents (Jankowska et al. 1998, 2002), was used to identify the reflex components transmitted by group II afferents (Corna et al. 1995; Skoog 1996). Ischemia, which mainly affects the larger-diameter group I fibers, was applied to assess the involvement of group I afferents within the different components of the hamstring reflex response (Priori et al. 1998). In a previous study, we were able to exclude a relevant contribution of cutaneous afferents to the MLR component after widespread local anesthesia of the calf (Friemert et al. 2005a).

To gain a better understanding of sensorimotor control of the knee joint, the present study aimed to determine which afferent pathways contribute to the different hamstring reflex components as well as their potential effects on functional knee stability.

METHODS

Subjects

The experiments were performed on a total of 35 subjects (26.5 ± 3.1 yr, 174 ± 3.5 cm, 74 ± 4.2 kg, 24 male, 11 female). None of the...
subjects had a history of neurological or orthopedic disorders. All participants gave written informed consent and the procedure was approved by the ethics committee of the University of Ulm in accordance with the Declaration of Helsinki.

After baseline measurements in all 35 subjects, the participants were divided into three different groups, and the procedure was repeated. The first group (n = 10) underwent cooling of the thigh to assess the effect on the latencies of the hamstring reflex. The second group (n = 10) received oral medication containing tizanidine to assess the contribution of group II afferents. In the third group (n = 15), ischemia was applied to determine the contribution of group I afferents.

General experimental procedure

To evoke ventral tibial translation, the subjects were asked to stand freely on both legs with a 30° flexion of the knee and slight outer rotation of the foot (<5°). A 0.6-kg piston with an impact of 300 N was driven into the proximal aspect of the calf. Tibial motion was monitored by a potentiometric position transducer (independent linearity: ±0.25 to ±0.0075%; repeatability: 0.002 mm; stroke length: 0–30 mm; Novotechnik, Ostfildern, Germany) attached to the tibias. Application of the transducer at the actual onset of tibial translation was assessed and then used as a trigger for the determination of latency responses. Maximum tibia translation was assessed by visual control as the maximum value on the plateau which was ~100–150 ms after the onset of tibia translation (Fig. 1). All subjects were tested in one series consisting of 15 ventral perturbations of the calf. Initial hamstring reflex activity was measured under baseline conditions in all subjects. The different procedures were then performed in groups consisting of 10 or 15 subjects, respectively.

Cooling procedure

A thin-walled plastic tube (size: 20 cm height * 60 cm length) was wrapped around the thigh, and it was ensured that concurrent cooling of ligamental structures of the knee did not occur. During the cooling procedure, the circulating water in the wrapped tube was automatically maintained at a temperature of 8°C by looping continuously through a basin containing a water cooler (Hilotherm, Pleidelsheim, Germany). Cooling was performed for 2–2.5 h. The flowing cool water generated a skin temperature of 10.9°C as measured at various locations of the thigh. During the measurements, the cooling tube was taken off to ensure accurate EMG signals. Detachment of the tube was performed when the subjects stood correct, i.e., equal to precoring condition in the testing device. Each measurement took 3 min.

Tizanidine treatment

Ten subjects were treated with fast-acting tizanidine (Sirdalud, Sanofi-Synthelabo, Berlin) at a dosage of 150 μg/kg body wt. Data were recorded before and 2 h after the treatment. At this time point the drug was fully active, resulting in considerable tiredness in each subject.

Ischemia

Ischemic block was induced in 15 subjects by attaching a pneumatic cuff (250 mmHg, Ulrich Medizintechnik, Ulm, Germany) around the proximal aspect of the thigh. In the first 15 min of ischemia, the subjects leaned back on a chair, bending the knees to 10°. For measurement of the reflex activity, subjects were then placed in the experimental apparatus. According to the findings of Grey et al. (2001), measurements were conducted within the initial 15 min period to test whether or not there was a significant decrease in SLR. This procedure was repeated at 90-s intervals until a distinct decline in the SLR component was observed in the EMG. Within these intervals, subjects were instructed to remain upright in a unilateral stance on their nonischemic leg.

EMG recording

Using bipolar surface electrodes, the electromyographic (EMG) activity of the hamstring muscles, namely the semitendinosus and biceps femoris, was recorded. Self-adhesive electrodes (Arbo Ag/AgCl-Sensor, Tyco Healthcare, Neustadt, Germany, interelectrode distance: 2 cm) were positioned over the muscle bellies of the hamstrings. The reference electrode was placed on the malleolus medialis. Prior to placement of the electrodes, the skin was shaved and residual grease was removed with alcohol. EMG signals were automatically amplified (×1,000), band-pass filtered (10–700 Hz), and taken without frequency filter and were analyzed by commercial evaluation software (Daisy Lab, Biovision, Weilheim, Germany). EMG signals were averaged and rectified.

EMG analysis

Latencies of the SLR and MLR EMG responses were calculated using the onset of tibial translation as the reference point (Fig. 1). In case of superimposed signal configuration, we used our evaluation algorithm to distinguish MLR from SLR (Friemert et al. 2005a). To predict the end of the SLR, i.e., to differentiate between SLR and MLR, the duration of the hamstring SLR was calculated by multiplying the time between the onset and the first peak of the SLR with the empirical factor of 3.28. This empirical factor was calculated from the ratio of the three parts of the hamstring tendon jerk reflex signal (for details, see Friemert et al. 2005a). A time window of 75 ms was sufficient to calculate both the latencies and the sizes of the SLR and the MLR. Whereas the SLR window (overall duration of baseline condition: 18.3 ± 2.9 ms) was analyzed by the evaluation algorithm developed by Friemert et al. (2005a), a time window of 30 ms was used for MLR analysis, which started at the calculating end of the SLR.

Statistical analysis

Results are expressed as mean values (±SD). During the cooling experiment, after tizanidine ingestion, and after ischemia treatment, paired Student’s t-test was used to determine the statistical significance of the differences between SLR and MLR latencies and size, both before and after intervention. To allow for interindividual com-
parison, the postintervention EMG activities of SLR and MLR were expressed as a percentage of the baseline values. Changes in tibial translation were also tested by the paired Student’s t-test. One-way ANOVA (post hoc test, Bonferroni) was used to test possible differences between the three groups for the preintervention values of tibial translation. For all testing procedures, a level of $P < 0.05$ was considered to be statistically significant.

RESULTS

The mean for the baseline condition in all 35 subjects showed after mechanically induced tibial translation a SLR after $20.6 \pm 1.2$ ms and a MLR after $37.8 \pm 1.6$ ms. A force transmission of 300 N resulted in a maximal tibial translation of $6.6 \pm 1.4$ mm. The interindividual differences between maximal tibial translation were not statistically significant among the three groups ($P = 0.173$). Regarding possible differences in SLR and MLR latency or reflex size between the lateral and medial hamstring, statistical testing revealed no significant difference for each testing condition. Therefore the following results represent the values of the medial hamstring.

Cooling

Figure 2A shows the effects of nerve cooling. Cooling led to a significant increase in the latency of the SLR from $21.4 \pm 1.3$ to $24.6 \pm 1.9$ ms ($P < 0.05$). MLR latency increased from $37.9 \pm 2.8$ to $42.8 \pm 3.3$ ms ($P < 0.05$), representing a stronger increase in latency ($3.2 \pm 1.4$ ms) when compared with the SLR value ($4.9 \pm 1.9$ ms; $P = 0.039$). The calculated difference between SLR and MLR increased significantly from $16.5 \pm 1.8$ to $18.3 \pm 2.3$ ms after nerve cooling ($P = 0.042$). Regarding EMG activity, nerve cooling had no statistically significant effect on either the size of SLR ($P = 0.125$) or MLR ($P = 0.120$), although both showed a tendency to increase. Also no significant influences of maximal tibial translation were found ($6.9 \pm 1.3$ to $7.4 \pm 1.3$ mm, $P = 0.101$). Typical traces of rectified hamstring EMG and tibia translation of a single subject before and after nerve cooling are superimposed in Fig. 2B.

Tizanidine

The ingestion of tizanidine did not significantly change the reflex latencies (SLR latency: $20.3 \pm 1.2$ vs. $20.4 \pm 1.3$ ms after ingestion; $P = 0.981$; MLR latency: $37.7 \pm 1.7$ vs. $37.2 \pm 2.1$ ms after ingestion; $P = 0.313$; Fig. 3A). After tizanidine ingestion, the MLR size was strongly reduced by $61 \pm 15\%$ of the EMG activity prior tizanidine ($P < 0.001$), whereas the decrease of SLR size showed no statistical significance ($25 \pm 17\%$; $P = 0.125$; Fig. 3B). No significant changes were seen in anterior tibial motion (maximum tibial translation: $5.3 \pm 1.9$ vs. $4.8 \pm 2$ mm after ingestion; $P = 0.410$). Typical traces of rectified hamstring EMG and tibia translation of a single subject before and after ingestion of tizanidine are superimposed in Fig. 3C.

Ischemia

Ischemia resulted in an almost complete suppression of the SLR in all subjects. The reduction in the size of SLR was $89 \pm 4\%$ of its previous value ($P < 0.001$; Fig. 4A). Therefore SLR latency could not be determined after ischemia (Fig. 4B). For MLR, a nonsignificant size reduction of $26 \pm 34\%$ was found ($P = 0.101$). There was no change in MLR latency ($37.8 \pm 0.9$ to $38.5 \pm 1.2$ ms; $P = 0.227$). During ischemia, maximum tibial translation demonstrated a statistically significant increase from $6.9 \pm 1.6$ to $9.4 \pm 3.2$ mm ($P = 0.028$; Fig. 4C). Typical traces of rectified hamstring EMG and tibia translation of a single subject before and after ischemia are superimposed in Fig. 4D. Note that the SLR is clearly depressed 15 min after ischemia. Immediately after ischemia, the maximum tibia translation is unchanged, but it is clearly increased 15 min after ischemia. Ten minutes after the end of ischemia, both SLR and tibia translation return to their values before ischemia.

The tibia translation typically shows a small bump after the SLR. In a subgroup of 20 subjects, the tibia motion traces were analyzed with respect to possible changes due to the latency of the SLR. The mean onset latency of the SLR in these 20 subjects was $21.2 \pm 3.0$ ms. In 17 of the 20 subjects, a small bump was seen that occurred with a mean latency of $23.2 \pm 6.1$ ms after the onset of the SLR. The mean duration of this bump was $31.0 \pm 11.6$ ms. This supports the view that the SLR may contribute to the restriction of anterior tibial displacement of the knee during the present experiments.

DISCUSSION

In standing subjects, a mechanically induced displacement of the anterior tibia produced a biphasic hamstring reflex

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**FIG. 2.** A: nerve cooling leads to a significant increase in latencies of the reflex components [SLR (filled triangles) $P < 0.001$; MLR (open squares) $P < 0.001$] shown as mean values $\pm$ SD of 10 subjects. B: typical data of rectified hamstring EMG and tibia translation before (gray traces) and after nerve cooling (black traces). The SLR and MLR latencies are prolonged after nerve cooling. Tibia translation is unchanged.
response labeled as SLR and MLR. Nerve cooling evoked a delay in latency for both reflex components, whereas the MLR was more affected than SLR. Ingestion of tizanidine produced a moderate decline in SLR activity and a strong reduction in MLR activity; however, the latency of these reflex responses was not adversely influenced. During ischemia, SLR was significantly reduced, whereas MLR size was decreased only to a minor extent. Anterior tibial translation was significantly increased exclusively during ischemia. We could demonstrate that this increase in tibia translation was not simply a direct effect of ischemia but was related to the time of the mechanical manifestation of the decrease of the hamstring SLR.

Previous studies have shown that Ia fibers typically contribute to the hamstring SLR (Faist et al. 1999; Friemert et al. 2005a), whereas group II afferents are primarily responsible for the incidence of the MLR (Grey et al. 2001; Schieppati and Nardone 1997). It has to be considered that due to their conduction velocity, group Ib afferents and cutaneous afferents might also be involved in these reflex responses (Brooke and McIlroy 1989; Dietz 1998). Following the administration of cooling, tizanidine, or ischemia, the present results indicate that the neural reflex mechanism of the hamstring responses consists of two parts: a SLR component mediated by group Ia afferents and a MLR component in which group II afferent fibers make a significant contribution.

After cooling, the relatively longer delay in the MLR compared with the SLR indicates that afferents involved in the MLR may be not the same as those in the SLR. The increased latency seen in the MLR, as well as the greater delay between the two reflex components, are likely to be related to an involvement of small-diameter group II afferents in which conduction velocity is decreased in association with nerve cooling (Paintal 1965; Schieppati and Nardone 1997).

Tizanidine is known to selectively suppress group II afferents (Corna et al. 1995; Jankowska et al. 1998, 2002; Skoog 1996) but does not impart a negative effect on the activity of Ia and Ia/Ib-inhibitory interneurons (Hammar and Jankowska 2003). Consistent with previous findings (Bras et al. 1989, 1990; Davies 1982; Davies et al. 1984; Jankowska et al. 1998), our results demonstrate that the second hamstring reflex component can mainly be attributed to group II, rather than group Ia, afferents. Additionally, the constant latency of MLR in the present study corresponds to the data of Corna et al. (Corna et al. 1995; Skoog 1996).

Ischemia was found to have a substantial effect on the hamstring reflex response. The significant reduction in the SLR reflex component suggests that most of the small-diameter afferents (e.g., Ia afferents) were blocked during ischemia. On the other hand, the MLR showed a tendency toward depression but did not reach significance. This supports the view that the afferent path-
ways involved in the MLR are different from those mediating the SLR. A potential explanation for this differential regulation was given by Grey et al. (2001). The origin of the soleus stretch reflex during gait was investigated following an episode of ischemia with the results suggesting a possible contribution to the MLR of small-diameter Ia afferents with slower conduction velocity and polysynaptic interneuronal connections.

Although we could show that the contribution of cutaneous afferents in the hamstring reflex response is unlikely (Friemert et al. 2005a), the role of the Ib afferent pathway in the hamstring reflex response remains unclear. Based on our testing protocol, the results do not support a potential contribution of Ib afferents to either the SLR or MLR. Locomotion studies have demonstrated that this specific afferent pathway acts on the interneuronal system, primarily activating the extensor muscles and reinforcing muscle activity in motor-related tasks (Duy sens et al. 2000; Faist et al. 2006; Pearson and Collins 1993). Dietz (1998) found in humans that Ib afferents may

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**FIG. 4.** A: 15 min of ischemia resulted in a significant reduction in SLR (black column, $P < 0.001$), while the reflex size of MLR only showed a trend (gray column, $P = 0.101$). Changes (means ± SD, $n = 15$) are expressed as percentage of the baseline. B: after disappearance of SLR reflex component, no SLR latency could be assessed from the signal configuration of the hamstring reflex response. MLR data (open squares) showed no significant differences before and during ischemia ($P = 0.227$). All data are expressed as means ± SD (n = 15). C: data (means ± SD) from 15 subjects show that, after disappearance of the SLR component, maximum tibial translation was significantly increased ($P = 0.028$). D: typical data of rectified hamstring EMG and tibia translation before (black trace) and after ischemia (gray traces) from top down, the bottom trace was 10 min after deflation of the cuff. The SLR is clearly depressed 15 min after ischemia, whereas it was only slightly depressed 10 min after inflation. The maximum tibia translation is clearly increased 15 min after ischemia while it showed no relevant changes for the remaining conditions. SLR and tibia translation returned to their initial values within 10 min after deflation of the cuff.
have a substantial conveying effect on the extensor muscles during the stance phase of gait. Grey et al. (2001) suggested that the latency of the reflex response mediated by group Ia afferents is slower than the Ia afferent pathway but faster than the group II afferent pathway. Histological studies have provided evidence that Golgi receptors, at least in the ACL, are connected with myelinated afferent fibers of 10–20 μm diam (Sjolander et al. 1989; Zimny and Wink 1991). As a result of the afferent diameter size, a conduction velocity of 75 m/s was assumed; this, in turn, allowed the assumption that Ib afferents contribute to the SLR. In a recent study by af Klint et al. (2009), it was shown that depending on the phase of the step cycle, force feedback contributes significantly to the soleus motor output with a latency within the MLR range. It was argued that this information may arise from the Golgi tendon organs in the Achilles tendon. In the present study, we cannot discern whether the afferent information is mediated from afferents of the muscle spindle or from Golgi tendon organs in the tendons of the hamstrings. It could also be mediated by afferents arising from ligamental structures such as the ACL.

Functional relevance

Regarding the potential contribution of the hamstring reflex components in restraining knee joint stability, the present findings led to the suggestion that the SLR component can stabilize the knee joint at least in the posterior-anterior plane. In contrast, the substantial decrease in the MLR following ingestion of tizanidine did not significantly change maximum anterior tibial translation. Previous studies have indicated that muscle stretch reflexes play a potential role in joint stiffness at the ankle and knee joints (Horita et al. 1996; Mrachacz-Kersting and Sinkjaer 2003; Sinkjaer 1997; Sinkjaer et al. 1988; Stein and Kearney 1995). In this manner, Toft et al. (1991) found that ankle extensor activity mediated up to two-thirds of the total ankle joint stiffness at low activity levels, whereas the reflex contribution at high torque level is of reduced functional relevance. Mrachacz-Kersting and Sinkjaer (2003) showed that the stretch reflex of the quadriceps muscle group strongly contributed to the total torque around the knee joint. Furthermore, Dhaher et al. (2003) found that reflexes of the thigh muscles after sudden valgus loading were probably elicited by receptors in the periarticular tissue, rather than by muscle spindle afferents, given the assessed latency of ~87 ms. Moreover using a similar study design, the same authors (Dhaher et al. 2005) reported a significant increase in stiffness of the knee joint during adduction-abduction of the knee; this was coupled with the observation of significant thigh muscle reflex excitation from periarticular tissue afferents of the knee joint. A strong correlation between knee laxity and reflex timing was shown by Shultz et al. (2004). They reported that an above-average anterior laxity of the knee corresponds to a 16-ms greater delay in biceps femoris reflex timing in contrast to subjects with a below-average knee laxity. This indicates a close relationship between muscle reflex activity and knee joint stability. Despite a potential coherence between thigh muscle activity and knee stability, none of these studies was able to demonstrate which afferent pathway actually stabilizes the knee joint under functional conditions.

With respect to tibial translation, the findings of Wojtys et al. (1996) indicated for the first time that reflexive activity of the thigh muscles may play a role in anterior knee stability. They found that, following excessive thigh muscle fatigue and the associated decline in muscle reflex activity, there is a decrease in knee stability in the posterior anterior direction. Recently, selective muscle-fatiguing exercise of the hamstring was shown to have deleterious effects on neuromuscular function of the hamstrings and anterior knee joint stability (Melnyk and Gollhofer 2007). Furthermore, Gruber et al. (2006) found an improvement in knee stability after balance training. This beneficial effect was attributed to a higher reflex activity of the thigh muscles in response to knee joint perturbation. However, an afferent pathway as a potential candidate for restraining anterior tibial translation has not been identified thus far. The present data indicate that the SLR component plays a major role in knee joint stability. This notion is in line with findings of Horita et al. (1996), who found after stretch shortening cycle fatigue a direct correlation between SLR and knee joint stiffness. More precisely, it was observed that a decline in the short-latency component of the vastus lateralis muscle corresponded with a decrease in knee joint stiffness during the early postlanding phase of a drop jump. Despite differences in the mechanical conditions of knee joint loading between the present study and that of Horita et al. (1996), a substantial contribution of the SLR to knee joint stability can be suggested in the case of a destabilising perturbation stimulus of the knee joint.

In conclusion, our findings demonstrate that anterior tibial translation evokes a hamstring SLR that is primarily mediated by Ia afferents, whereas group II afferents mainly contribute to the MLR. Furthermore, the results suggest that the SLR component may play a functional role in knee stabilization after anterior tibial translation during standing.

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