Reflex Inhibition of Normal Cramp Following Electrical Stimulation of the Muscle Tendon

Serajul I. Khan and John A. Burne
School of Medical Sciences, University of Sydney, Lidcombe, New South Wales, Australia

Submitted 1 April 2007; accepted in final form 10 July 2007

Khan SI, Burne JA. Reflex inhibition of normal cramp following electrical stimulation of the muscle tendon. J Neurophysiol 98: 1102–1107, 2007. First published July 18, 2007; doi:10.1152/jn.00371.2007. Muscle cramp was induced in one head of the gastrocnemius muscle (GA) in eight of thirteen subjects using maximum voluntary contraction when the muscle was in the shortened position. Cramp in GA was painful, involuntary, and localized. Induction of cramp was indicated by the presence of electromyographic (EMG) activity in one head of GA while the other head remained silent. In all cramping subjects, reflex inhibition of cramp electrical activity was observed following Achilles tendon electrical stimulation and they all reported subjective relief of cramp. Thus muscle cramp can be inhibited by stimulation of tendon afferents in the cramped muscle. When the inhibition of cramp-generated EMG and voluntary EMG was compared at similar tendon afferents in the cramped muscle. When the inhibition of cramp was induced in one head of the gastrocnemius muscle (GA) in 2007. First published July 18, 2007; doi:10.1152/jn.00371.2007. EMG was compared at similar tendon afferents in the cramped muscle. When the inhibition of cramp was induced in one head of the gastrocnemius muscle (GA) in eight of thirteen subjects using maximum voluntary contraction when the muscle was in the shortened position. Cramp in GA was painful, involuntary, and localized. Induction of cramp was indicated by the presence of electromyographic (EMG) activity in one head of GA while the other head remained silent. In all cramping subjects, reflex inhibition of cramp electrical activity was observed following Achilles tendon electrical stimulation and they all reported subjective relief of cramp. Thus muscle cramp can be inhibited by stimulation of tendon afferents in the cramped muscle. When the inhibition of cramp-generated EMG and voluntary EMG was compared at similar mean EMG levels, the area and timing of the two phases of inhibition (I₁, I₂) did not differ significantly. This strongly suggests that the same reflex pathway was the source of the inhibition in both cases. Thus the cramp-generated EMG is also likely to be driven by spinal synaptic input to the motorneurons. We have found that the muscle conditions that appear necessary to facilitate cramp, a near to maximal contraction of the shortened muscle, are also the conditions that render the inhibition generated by tendon afferents ineffective. When the strength of tendon inhibition in cramping subjects was compared with that in subjects that failed to cramp, it was found to be significantly weaker under the same experimental conditions. It is likely that reduced inhibitory feedback from tendon afferents has an important role in generating cramp.

INTRODUCTION

Common muscle cramp is characterized by sudden, localized, involuntary, sustained, and painful contraction attended by visible and palpable knotting of part or all of the affected muscle (Baldissera et al. 1991; Denny-Brown et al. 1948; Ross et al. 1995). Cramp is typically of short duration but may warrant medical intervention if associated with long-lasting pain (Mills et al. 1982). Its physiology is poorly understood, largely due to its inaccessibility to experimental investigation. It is difficult to induce in many normal subjects, it is typically of short duration, and there is no animal model.

Cramp is accompanied by active muscle contraction, as evidenced by high levels of muscle electrical activity. The origin of the electrical activity remains unclear. The generator may lie within the CNS or in peripheral neuromuscular membranes. Whatever the location of the generator, it appears to be facilitated by a variety of factors that include strong voluntary contraction, exercise (Layzer et al. 1986; Miles et al. 1994; Schwellnus et al. 1997), sleep (Gootnick 1943; Nicholson et al. 1945), pregnancy (Oba 1967; Page et al. 1953), and several pathologies such as myopathy, neuropathy, motoneuron disease (Brown 1951; McGee 1990), metabolic disorders (Layzer et al. 1967; McArdele 1951; Tarui et al. 1965), electrolyte imbalance (Edsall 1908; Oswald 1925; Talbott 1935), and endocrine pathology (Satoh et al. 1983). However, the link between these factors and the involuntary muscle electrical activity that accompanies cramp remains unclear. In summary, both intramuscular and neural mechanisms appear to contribute to cramp but no integrating theory has been proposed.

Earlier studies suggested a cramp generator within peripheral nerve segments. It was reported that cramp could be induced by electrical stimulation of motor fibers distal to an anesthetic block (Lambert 1969). Fasciculations, which are thought to be related to cramp (Denny-Brown 1953; Layzer 1971; Roth 1984), may also persist after peripheral nerve block (Conradi 1982; Layzer et al. 1971; Tahlmoush et al. 1991) or complete section of the nerve (Forster et al. 1946). A generator within the motorneuron is also suggested by theories of motorneuron hyperexcitability or bistability (Baldissera et al. 1991). Bistability indicates an anomalous state in which a self-sustained depolarization and repetitive firing of alpha motor neurons is triggered by a depolarizing pulse or intracellularly injected current (or possibly a short synaptic excitation) and terminated by a hyperpolarizing current pulse (or synaptic inhibition) (Hagbarth et al. 1966). Originally bistability was described as a reflex phenomenon consisting of a long-latency prolonged contraction of the soleus muscle that was evoked by a burst of Ia afferent volleys and terminated by a brief synaptic inhibition (Hultborn et al. 1975).

A limitation of the peripheral generator model is the difficulty of incorporating the known systemic and metabolic effects that can be more easily integrated into a reflex model by muscle afferents. A few observations suggest that central or reflex factors are able to modulate cramp-related electrical activity. Voluntary contraction of the antagonist muscle, without stretching the cramped muscle, causes an inconsistent reduction of cramp discharge, suggesting spinal reflex inhibition (Norris et al. 1957). The Hoffmann (H) reflex is enhanced after cramp (Ross et al. 1976) and transcutaneous nerve stimulation at sites remote from the cramped muscle are reported to relieve severe, long-lasting, and widespread muscle cramp (Mills et al. 1982).

Muscle stretching is reported to abruptly interrupt cramp induced by voluntary contraction or high-frequency stimulation of peripheral nerve (Baldissera et al. 1991; Denny-Brown 1945). Common muscle cramp is characterized by sudden, localized, involuntary, sustained, and painful contraction attended by visible and palpable knotting of part or all of the affected muscle (Baldissera et al. 1991; Denny-Brown et al. 1948; Ross et al. 1995). Cramp is typically of short duration but may warrant medical intervention if associated with long-lasting pain (Mills et al. 1982). Its physiology is poorly understood, largely due to its inaccessibility to experimental investigation. It is difficult to induce in many normal subjects, it is typically of short duration, and there is no animal model.

Common muscle cramp is characterized by sudden, localized, involuntary, sustained, and painful contraction attended by visible and palpable knotting of part or all of the affected muscle (Baldissera et al. 1991; Denny-Brown et al. 1948; Ross et al. 1995). Cramp is typically of short duration but may warrant medical intervention if associated with long-lasting pain (Mills et al. 1982). Its physiology is poorly understood, largely due to its inaccessibility to experimental investigation. It is difficult to induce in many normal subjects, it is typically of short duration, and there is no animal model.

Cramp is accompanied by active muscle contraction, as evidenced by high levels of muscle electrical activity. The origin of the electrical activity remains unclear. The generator may lie within the CNS or in peripheral neuromuscular membranes. Whatever the location of the generator, it appears to be facilitated by a variety of factors that include strong voluntary contraction, exercise (Layzer et al. 1986; Miles et al. 1994; Schwellnus et al. 1997), sleep (Gootnick 1943; Nicholson et al. 1945), pregnancy (Oba 1967; Page et al. 1953), and several pathologies such as myopathy, neuropathy, motoneuron disease (Brown 1951; McGee 1990), metabolic disorders (Layzer et al. 1967; McArdele 1951; Tarui et al. 1965), electrolyte imbalance (Edsall 1908; Oswald 1925; Talbott 1935), and endocrine pathology (Satoh et al. 1983). However, the link between these factors and the involuntary muscle electrical activity that accompanies cramp remains unclear. In summary, both intramuscular and neural mechanisms appear to contribute to cramp but no integrating theory has been proposed.

Earlier studies suggested a cramp generator within peripheral nerve segments. It was reported that cramp could be induced by electrical stimulation of motor fibers distal to an anesthetic block (Lambert 1969). Fasciculations, which are thought to be related to cramp (Denny-Brown 1953; Layzer 1971; Roth 1984), may also persist after peripheral nerve block (Conradi 1982; Layzer et al. 1971; Tahlmoush et al. 1991) or complete section of the nerve (Forster et al. 1946). A generator within the motorneuron is also suggested by theories of motorneuron hyperexcitability or bistability (Baldissera et al. 1991). Bistability indicates an anomalous state in which a self-sustained depolarization and repetitive firing of alpha motor neurons is triggered by a depolarizing pulse or intracellularly injected current (or possibly a short synaptic excitation) and terminated by a hyperpolarizing current pulse (or synaptic inhibition) (Hagbarth et al. 1966). Originally bistability was described as a reflex phenomenon consisting of a long-latency prolonged contraction of the soleus muscle that was evoked by a burst of Ia afferent volleys and terminated by a brief synaptic inhibition (Hultborn et al. 1975). A limitation of the peripheral generator model is the difficulty of incorporating the known systemic and metabolic effects that can be more easily integrated into a reflex model by muscle afferents. A few observations suggest that central or reflex factors are able to modulate cramp-related electrical activity. Voluntary contraction of the antagonist muscle, without stretching the cramped muscle, causes an inconsistent reduction of cramp discharge, suggesting spinal reflex inhibition (Norris et al. 1957). The Hoffmann (H) reflex is enhanced after cramp (Ross et al. 1976) and transcutaneous nerve stimulation at sites remote from the cramped muscle are reported to relieve severe, long-lasting, and widespread muscle cramp (Mills et al. 1982).

Muscle stretching is reported to abruptly interrupt cramp induced by voluntary contraction or high-frequency stimulation of peripheral nerve (Baldissera et al. 1991; Denny-Brown 1945).
The surface electromyogram (EMG) was recorded with disposable bipolar silver–silver chloride electrodes, attached 3 cm above the muscle tendon junction over the central belly of the lateral and medial heads of GA. Careful attention to skin degreasing allowed low interelectrode impedance. An earth electrode was also placed over the heads of GA. Careful attention to skin degreasing allowed low interelectrode impedance. An earth electrode was also placed over the heads of GA. Careful attention to skin degreasing allowed low interelectrode impedance. An earth electrode was also placed over the heads of GA.

Tendon stimulation
A stimulus intensity of 60 mA was used for all experiments because it was found to produce maximal inhibition in previous experiments (Khan and Burne, unpublished observations). Small metal plates served as stimulating electrodes. The cathode was positioned centrally on the GA tendon, about 1 cm below the musculotendinous junction and the anode medially on the anterior calf adjacent to the cathode. The technique for obtaining tendon inhibition from GA is described in more detail in Khan and Burne (unpublished observations).

Electrical recording
The surface electromyogram (EMG) was recorded with disposable bipolar silver–silver chloride electrodes, attached 3 cm above the muscle tendon junction over the central belly of the lateral and medial heads of GA. Careful attention to skin degreasing allowed low interelectrode impedance. An earth electrode was also placed over the tibia. Amlab (Amlab International, Sydney, Australia) hardware was used to record and filter the EMG (band-pass 5–400 Hz), digitize it (1 kHz), and display the raw signals and mean root-mean-square (RMS) values in real time on a computer screen. The RMS display was available to subjects to match their isometric contractions to target levels. The digitized raw data were saved to computer hard disk and then further processed and analyzed off-line (Matlab v. 7, The MathWorks, Natick, MA). The raw EMG signals were digitally detrended, filtered (10- to 80-Hz pass), and full-wave rectified; average curves were computed from a minimum of 30 successive trials. The area of inhibitory and excitatory response components was then calculated by software as previously described (Blanch and Burne 2001). The mean value and the SD of 100 ms of prestimulus data were calculated and points less than the SD were regarded as inhibitory points. The sum of these points estimated the area of inhibition.

Protocol
Subjects were positioned on their right side on a stretcher adjustable for height. The right knee was fully extended and the right foot was fitted to a footplate and stabilized to a supporting frame. The footplate was designed to rotate in the horizontal plane, allowing the foot to be fixed in its maximally plantarflexed position with GA in its shortened position. The ankle joint was fixed to prevent muscle lengthening, which could subsequently break the cramp. Subjects notified the onset, perceived location, and relative intensity of the induced cramp, which was attended by visible knotting. Subjects were instructed to attempt maximal relaxation of voluntary drive once cramp was present so that the activity present could be attributed to cramp. The typical occurrence of cramp in one head of GA permitted voluntary relaxation to be assessed by confirming the absence of EMG in the noncramping head. In the testing position, no subjects were able to voluntarily produce EMG in one head of GA only. Induction of cramp was attempted several times in each session, each attempt being followed by 15–20 min of rest, unless a persisting cramp was obtained.

Statistics
Comparison of the inhibitory areas of cramp-related EMG and voluntary EMG were made by one-way repeated-measures ANOVA. Simple linear regression was used to relate inhibitory area to the mean background contraction. Both analyses were performed using Statistica (StatSoft, Tulsa, OK). The level set for statistical significance was $P < 0.05$.

RESULTS

Inhibition of voluntary contraction
Figure 1, A and B illustrates the simultaneous inhibition of a normal voluntary contraction [20% of maximum voluntary contraction (MVC)] in the medial and lateral heads of GA following tendon stimulation (60 mA, 1 ms). The features of the reflex response and the timing of inhibitory and excitatory phases were as described by Khan and Burne (unpublished observations). The first and larger inhibitory component ($I_1$) commenced $55 \pm 0.57$ ms (SD) after the stimulus onset and its duration was $69.5 \pm 11.0$ ms. This was followed by a smaller inhibitory phase ($I_2$) of latency $193 \pm 10.8$ ms and duration $39 \pm 14.7$ ms. $I_1$ was followed by the excitatory peak ($E_1$) of latency $142.2 \pm 8.4$ ms and $I_2$ was followed by the excitatory peak ($E_2$) of latency $240 \pm 11.8$ ms (mean $\pm$ SD).

Effect of mean background contraction
For all subjects, the strength of reflex inhibition, $I_1$ and $I_2$, after tendon stimulation was negatively correlated with the mean background contraction. The relationship was approximately linear as shown for one subject in Fig. 2, A and B. It can be seen that the amount of reflex inhibition and the mean background contraction were strongly correlated in this subject.
Fig. 1. Simultaneous inhibition of a normal voluntary contraction at 20% of maximum voluntary contraction (MVC) in the medial (A) and lateral (B) heads of gastrocnemius muscle (GA) after tendon stimulation (60 mA, 1 ms). Effects of the same stimulus on the cramping medial head (C) and relaxed noncramping lateral head (D) of GA are also shown. I₁ and I₂ denote the first and second inhibitory periods. E₁ and E₂ denote the peaks of the first and second excitation that followed the electromyographic (EMG) inhibition. Stimulus commenced at 300 ms, as indicated by the arrow on timescale.

Effect of tendon stimulation on cramp

Of the thirteen subjects, eight successfully produced cramp in one head of GA. Relaxation of voluntary contraction was confirmed by inspection of the EMG from the noncramping head of GA. In all subjects, reflex inhibition of cramp EMG

(P = 0.014, r² = 0.97, linear regression). Figure 2, C and D shows the pooled data for the reflex inhibition I₁ (P = 0.0001 and r² = 0.7809) and I₂ (P = 0.7538 and r² = 0.0001) after tendon electrical stimulation. These data confirm an approximately linear inverse relation between strength of reflex inhibition and the mean background contraction in the subject population.
activity was observed after tendon stimulation and the subjects reported relief of cramp during or after 30 shocks had been delivered to the tendon. Figure 1, C and D shows the inhibition of cramp (I1, I2) after tendon electrical stimulation in the same subject. The onset latency of I1 was found to be 55 ± 0.58 (SD) ms, similar to that reported earlier for the voluntary contraction and previously in upper limb muscles (Burne et al. 1996a). The onset latency of I2 was found to be 193 ± 10.8 (SD) ms, which was again similar to that reported earlier for the voluntary contraction. The timing of I2 has not previously been reported in the literature.

Comparison of inhibition of voluntary contraction and cramp

Because the magnitude of voluntary inhibition varied with the mean background level, we fitted the cramp inhibitory data (I1, I2) to the regression plot relating voluntary inhibition to mean background contraction level in the same subject (Fig. 2, A and B). It was thus shown that the area of cramp inhibition lay within the 95% confidence intervals for voluntary inhibition in all subjects. Table 1 summarizes the group data comparing the magnitude of inhibition of voluntary EMG and cramp-related EMG in the same subjects and at the same level of background contraction. There was no statistically significant difference in latency or area of inhibition (P > 0.05, repeated-measures ANOVA). In fact, the areas of I1 (P < 0.01, r² = 0.93) measured during cramp and voluntary contraction were strongly correlated in the same subjects. This result is illustrated in Fig. 3.

Comparison of tendon inhibition in cramping and noncramping subjects

The magnitude of reflex inhibition of voluntary contraction following tendon stimulation was compared in subjects that subsequently produced cramp during the experiment and subjects that could not be induced to cramp during the experiment. It was found that I1 (group mean 2,360 μV·ms for cramping subjects, 2,720 μV·ms for noncramping subjects, P = 0.09) and I2 (group mean 640 μV·ms for cramping subjects, 1,120 μV·ms for noncramping subjects, P = 0.017, repeated-measures ANOVA) were smaller in the cramping subjects (Fig. 4B). This difference was highly significant for I2 but failed to be significant for I1.

TABLE 1. Inhibitory reflex responses during voluntary contraction and cramp

<table>
<thead>
<tr>
<th>Inhibition (I1)</th>
<th>Inhibition (I2)</th>
<th>Average EMG, μV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voluntary</td>
<td>Cramp</td>
<td>Voluntary</td>
</tr>
<tr>
<td>3,600</td>
<td>3,400</td>
<td>1,175</td>
</tr>
<tr>
<td>1,600</td>
<td>1,500</td>
<td>641</td>
</tr>
<tr>
<td>4,900</td>
<td>4,800</td>
<td>2,431</td>
</tr>
<tr>
<td>2,500</td>
<td>2,300</td>
<td>203</td>
</tr>
<tr>
<td>1,500</td>
<td>1,000</td>
<td>184</td>
</tr>
<tr>
<td>1,100</td>
<td>800</td>
<td>107</td>
</tr>
<tr>
<td>4,500</td>
<td>3,600</td>
<td>1,173</td>
</tr>
<tr>
<td>3,000</td>
<td>3,400</td>
<td>1,150</td>
</tr>
<tr>
<td>Mean</td>
<td>2,533.4</td>
<td>2,322.3</td>
</tr>
<tr>
<td>SD</td>
<td>1,609.9</td>
<td>1,572.1</td>
</tr>
</tbody>
</table>

Voluntary and cramp inhibitions following tendon electrical stimulation with the same level of mean background contraction (last column) are compared. I1 and I2 represent the first and secondary inhibitory components of the reflex response following tendon stimulation. The reflex response was clearly distinguished in all experiments. Population mean and SD values are shown.

FIG. 3. Data from 8 cramped subjects showing the correlation between the areas of inhibition of voluntary and cramp EMG. Solid line is the linear regression line and the broken lines are 95% confidence intervals for the data shown.

DISCUSSION

Cramp in GA was painful, involuntary, and localized. In half of the subjects it was absent or incomplete and did not persist long enough to do the experiment. Induction of cramp was indicated electrically by the presence of EMG activity in one head of GA while the other head remained silent. In contrast, no subject was able to voluntarily contract one head of GA and relax the other in the testing position. These findings confirm that cramp was localized and involuntary in nature.

Our observations clearly show that muscle cramp can be inhibited by stimulation of tendon afferents in the cramped muscle. When the inhibition of cramp-generated EMG and voluntary EMG was compared at similar mean background EMG levels, the area and timing of the inhibition did not differ significantly. This strongly suggests that the same reflex pathway was the source of the inhibition in both cases. Thus the cramp-generated EMG is also likely to be driven by spinal synaptic input to the motorneurons.

It is well documented that tendon electrical stimulation produces strong inhibition of the ongoing voluntary EMG activity and this inhibition arises from tendon afferents by reflex inhibitory pathway (Burne et al. 1996). Muscle stretching causes a sudden interruption of cramp induced by either voluntary contraction or electrical stimulation of the peripheral nerve (Bertolasi et al. 1992; Denny-Brown et al. 1948; Fowler 1973; Layzer et al. 1982; Schwellnus et al. 1996). Passive stretch of a contracting muscle effectively activates autogenic inhibitory Ib afferents in the tendon (Granit 1950). However, it has been proposed that the inhibition following electrical stimulation arises from group III tendon afferents that presynaptically inhibit the terminals of 1a stretch reflex afferents (Priori et al. 1998). It is thus possible that these afferents are responsible for inhibition of cramp, although little is known about their response to passive stretch.

Regardless of the species of afferent involved, we have shown in parallel experiments that tendon electrical inhibition is approximately linearly related to the length of the contracting muscle and maximal when the muscle is fully stretched.
III afferents produce presynaptic inhibition of 1a terminals. This is further supported by the observation from the current experiments that electrical tendon stimulation less effectively inhibits larger than small voluntary contractions. In summary, the muscle conditions that appear necessary to facilitate cramp, a near maximal contraction of the shortened muscle, are also the conditions that render the inhibition generated by tendon afferents ineffective. It is thus likely that reduced inhibitory feedback from the tendon may have an important role in generating cramp (see also discussion by Schwellnus et al. 1997). This conclusion is further supported by our observation that "noncrampers" produced significantly stronger inhibition than those that were subsequently induced to cramp on the same day.

It was previously shown that stimulation of the nerve supplying the cramp muscle was effective in blocking cramp activity (Lanari et al. 1973). Our findings support the proposal of these authors that the inhibition they observed was due to stimulation of tendon afferents.

It is well documented that the muscles most prone to cramping are those that span two joints (Manjra 1991; Nicol 1996). Contraction in the shortened position would result in decreased tension in the tendons of the muscle during contraction. Tendon activity would therefore be decreased in plantarflexion compared with dorsiflexion.

The common observation that the intensity of cramp tends to increase progressively over time can be interpreted as evidence of a positive feedback mechanism. There is also much evidence that intramuscular mechanisms facilitate cramp (Joeskes 1982; Layzer et al. 1971; Mills et al. 1982). It is possible that intramuscular changes, such as those associated with fatigue, stimulate chemically sensitive intramuscular afferents, such as group III afferents that are also stretch sensitive. These may play a role in facilitating motoneuron activity in the absence of negative feedback from tendon afferents. This imbalance in positive and negative feedback signals can result in abnormal, sustained motoneuron activity. Also Nelson and Hutton (1985) found an increase in resting discharge frequency of type Ia and type II afferents as well as a dramatic decrease in Golgi tendon organ (type Ib) firing rates to slow stretches during fatigue.

Our observation that voluntary inhibition was inversely related to the mean background contraction level is consistent with the proposal (Priori et al. 1998) that the stimulated group III afferents produce presynaptic inhibition of 1a terminals.

The 1a stretch afferents are reported to contribute a decreasing proportion of the total synaptic drive to motoneurons as the contraction level increases toward maximum (Harrison and Taylor 1981). The effects of tendon inhibition on the total synaptic drive should thus also decrease with contraction level.

The central origin of cramp is also supported by studies of motor unit properties, which report no marked changes in their profiles during voluntary contraction and cramp (Ross et al. 1995). This contrasts with studies of fasciculation (Baldissera et al. 1991; Denny-Brown 1984). In summary: first, the inhibition of the voluntary EMG activity recorded after tendon stimulation decreased with increased mean background contraction in an approximately linear fashion. Second, cramp-related EMG was inhibited after tendon electrical stimulation and the strength of inhibition was strongly correlated with the strength of voluntary EMG inhibition at a similar level of mean background contraction in the same subject. This result suggests that the cramp-generated EMG is driven by spinal synaptic mechanisms rather than by a generator within the motoneurones or by intramuscular mechanisms.

The recordings from both heads of gastrocnemius were particularly important to determine the true onset of cramp. Once cramp was induced in one head of gastrocnemius after a sustained maximal voluntary contraction, the EMG activity in the other head remained silent. These data thus provided an objective measure of the involuntary and localized nature of cramp (Norris et al. 1957).

REFERENCES


