Exp Brain Res (1997) 116:375–380 © Springer-Verlag 1997

RESEARCH NOTE

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Presynaptic inhibition compared with homosynaptic depression as an explanation for soleus H-reflex depression in humans

Received: 16 October 1996 / Accepted: 7 April 1997

Abstract The H-reflex is depressed for seconds if elicited following a single H-reflex or train of H-reflexes. Presynaptic inhibition from flexor afferents (tibialis anterior) onto soleus Ia afferents elicited by either single or trains of stimuli had no effect on the soleus H-reflex on a time scale of seconds. Postsynaptic inhibition was also excluded by magnetic stimulation tests that showed that the excitability of the motoneuron pool was not changed at latencies within a range of seconds. Homosynaptic depression localized at the presynaptic terminal seems to be the mechanism behind the H-reflex depression in humans.

Key words H-reflex depression · Homosynaptic depression · Presynaptic inhibition · Spinal cord · Human

Introduction

The amplitude of the H-reflex depends on the history of previous activations even when all other variables are kept constant. For example, with paired stimulation to elicit H-reflexes, the amplitude of the second soleus H-reflex depends on its latency with respect to the previous stimulus to the posterior tibial nerve (PTN; Taborikova and Sax 1969; Pierrot-Deseilligny et al. 1981; Crone and Nielsen 1989). Distinct factors contribute to changes in amplitude at different intervals of paired stimulation. In the first 150–200 ms following the conditioning stimulus, there are changes in the excitability of the peripheral nerve and the muscle tissue (Morita et al. 1993) that add to spinal cord changes. At longer latencies, peripheral effects have no influence and only spinal cord mechanisms limit the size of the second H-reflex. At intervals from about 300 to 500 ms, there is a depression of the H-reflex, of spinal cord origin, that slowly recovers back to normal after several seconds, both in humans (e.g., Crone and Nielsen 1989) and in cats (e.g., Eccles and Rall 1951). When a slow train of H-reflexes is elicited, there is a gradual fall in the reflex amplitudes toward a plateau. This low-frequency depression, seen both in humans (e.g., Ishikawa et al. 1966, for lower limb; Rothwell et al. 1986, for upper limb) and cats (e.g., Lloyd and Wilson 1957), increases with the frequency of the train, but even slow trains such as at frequencies of 0.5 Hz and 1 Hz cause significant depression.

Low-frequency H-reflex depression has frequently been attributed to presynaptic inhibition of Ia afferents (e.g., Calancie et al. 1993). This has been ascribed to the inhibition of soleus Ia afferent terminals by Ia afferents themselves through one or more interneurons. This same mechanism has been proposed to explain the phenomenon of inhibition of the soleus H-reflex by vibration of the Achilles tendon (e.g., Delwaide 1973, 1993, in humans; Gillies et al. 1969, in cat). This autogenetic presynaptic inhibition in Ia terminals is still an apparently unsettled issue in the cat (Decandia et al. 1967; Barnes and Pompeiano 1970; Fu et al. 1978), and it is certainly controversial in humans, as the possible experimental manipulations are much more restricted. Nevertheless, data on soleus H-reflex depression by a tendon tap to the biceps femoris tendon in humans suggest that in this pathway presynaptic inhibition would not last more than about 400 ms (Nielsen et al. 1995), which suggests that longer duration H-reflex depressions should be attributed to other mechanisms. An explanation is that synaptic activity itself (from Ia to motoneuron) leads to diminished capacity for synaptic transmission in subsequent activations, i.e., a homosynaptic depression (Curtis and Eccles 1960; Burke et al. 1989; Crone and Nielsen 1989; Nielsen et al. 1995; Hultborn et al. 1996).

To be able to analyze more directly the depressing effects of presynaptic inhibition on the soleus H-reflex, we have to stimulate a nerve that presumably only acts on

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the soleus Ia-motoneuron linkage by presynaptic inhibition. It is well known that flexors are a major source of presynaptic inhibition, and indeed a short duration vibration applied to the tibialis anterior tendon causes a decrease in soleus H-reflex amplitude at a latency around 40–60 ms, which is attributed to presynaptic inhibition (Ashby et al. 1987; Hultborn et al. 1987). This last finding is used in the present work to elicit presynaptic inhibition on soleus Ia afferents from a nonsoleus origin (from an antagonist flexor muscle). Instead of using a tibialis anterior tendon vibration, we employed electrical stimulation (a brief tetanus) to the common peroneal nerve (CPN) to avoid the possibility of the vibration being picked up by the soleus spindles.

By comparing the recovery of soleus H-reflex from depression with the effects on soleus H-reflex of a similar conditioning to the common peroneal nerve, we shall be testing directly the hypothesis that presynaptic inhibition is the mechanism behind H-reflex depression in humans, with the basic assumption that autogenetic or homosynaptic presynaptic inhibition should have properties similar to presynaptic inhibition from other origins.

Materials and methods

The experiments were done on 14 healthy subjects, ranging in age from 26 to 61 years. All subjects gave their written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Institutional Review Board. In most experiments the subject stayed relaxed in a reclining position in a comfortable armchair, while in a few the subject was lying prone. In some experiments the foot was restrained so that no movement (or very little) could be noticed after each stimulus to the tibialis anterior or to the soleus. In a few subjects both legs were tested.

Electromyographic recordings and data analysis

Bipolar electromyographic (EMG) recordings were obtained using 9-mm disk surface electrodes of stainless steel placed on the soleus muscle and the Achilles tendon. The waveforms were filtered from 2 Hz to 10 kHz and sampled at 10 kHz (there is no aliasing because there is very little energy in frequencies above 5 kHz). At the beginning of each session, the curves of H and M amplitudes as a function of stimulus intensity were obtained. From this the value M_{max} was found, i.e., the maximum possible value for M. Peak-to-peak values of each H-reflex waveform were computed on-line (area of rectified H-reflexes gave qualitatively similar conclusions) and waveforms were saved for further analysis. Means and standard deviations were computed from at least ten trials, each trial being comprised of a conditioning stimulation (single or train) and a test H-reflex obtained after a specified delay. Normalized values of H-reflexes were computed with respect to the first H-reflex when trains of H-reflexes were elicited, or in the case of conditioning stimulation to the CPN, the amplitude of the test reflex was normalized to the amplitude of the first H-reflex obtained from the immediately preceding train.

Electrical stimulation

Rectangular constant-current pulse stimulation was used throughout, with a duration of 1 ms. The PTN was stimulated at the popliteal fossa using monopolar stimulation delivered via a conventional surface electrode or a locally built ball electrode. A remote anode was placed on the patella. For each subject a stimulus intensity that caused an H-reflex of about 20% M_{max} on the ascending limb of the recruitment curve was routinely used. The CPN was stimulated with a rigid bipolar electrode at the head of the fibula, with current pulses at an intensity at the threshold for a 100-μV (peak-to-peak) M-wave from the tibialis anterior muscle. Testing for the existence of presynaptic inhibition in each subject was done with a brief tetanus consisting of four current pulses at 250 Hz to the CPN applied about 50 ms before the stimulation of the PTN. Subjects that did not show a clear presynaptic inhibitory effect at this latency were not tested for H-reflex depression.

Stimulation paradigms

For all experiments, a conditioning stimulation was followed by a test H-reflex, and subsequent conditioning trials were at least 1 min apart. Four types of conditioning stimuli were used in the various experiments: (1) conditioning stimulation of the PTN nerve consisted of either single stimulation pulses or (2) a train of ten pulses at frequencies of 0.5 Hz or 1.0 Hz. (3) Conditioning stimulation of the CPN nerve consisted of either a single tetanus of four pulses at 250 Hz or (4) a train of ten such tetani at frequencies of 0.5 Hz or 1 Hz. Test reflexes were evoked by a single pulse to the PTN after a delay of 1–5 s after the last conditioning stimulus pulse. For most experiments, trials with conditioning stimulation of the PTN and CPN were alternated.

Magnetic stimulation

In three subjects, magnetic evoked potentials (MEP) in the relaxed soleus were obtained by stimulating the scalp with a Cadwell electromagnetic stimulator (coil diameter 10 cm). For each subject the threshold for MEP was found and the test stimuli were 130% threshold, except for the third subject for which this was larger than the maximal stimulator output (hence this latter intensity was used). An MEP1 was obtained 1 s prior to the 1.0-Hz train of ten conditioning stimuli applied to the PTN, and an MEP2 at 1.2 s after the last H-reflex. The control MEP amplitudes were less than 5% M_{max} and were not larger than 30% the control H-values. Mean MEP values were computed for each subject based on ten trials. The purpose of this test was to check the motoneuron excitability after the conditioning stimuli at a latency similar to that for which reflex depression has been studied.

Results

Following a single conditioning stimulus to the PTN, a second stimulus to elicit a test H-reflex was given at intervals from 1 to 5 s to determine the characteristics of the recovery. For nine subjects (Fig. 1A), the normalized mean amplitude of the test H-reflexes at 1 s was 0.53 (normalized with respect to the control amplitude). Slow recovery was seen at subsequent intervals and by 5 s the mean amplitude recovered to 0.85 of the control value.

To test whether the time course of recovery of H-reflexes is compatible with presynaptic inhibition, we compared the time course of soleus H-reflex after tibial nerve stimulation to that of presynaptic inhibition produced by stimulation of the antagonist muscle nerve. Since the magnitude of presynaptic inhibition of soleus H-reflexes from the tibialis anterior varies considerably in different subjects, we first screened subjects for the presence of reciprocal inhibition at latencies consistent with presynaptic inhibition (40–80 ms). Six subjects (from nine tested) showed a clear presynaptic inhibition

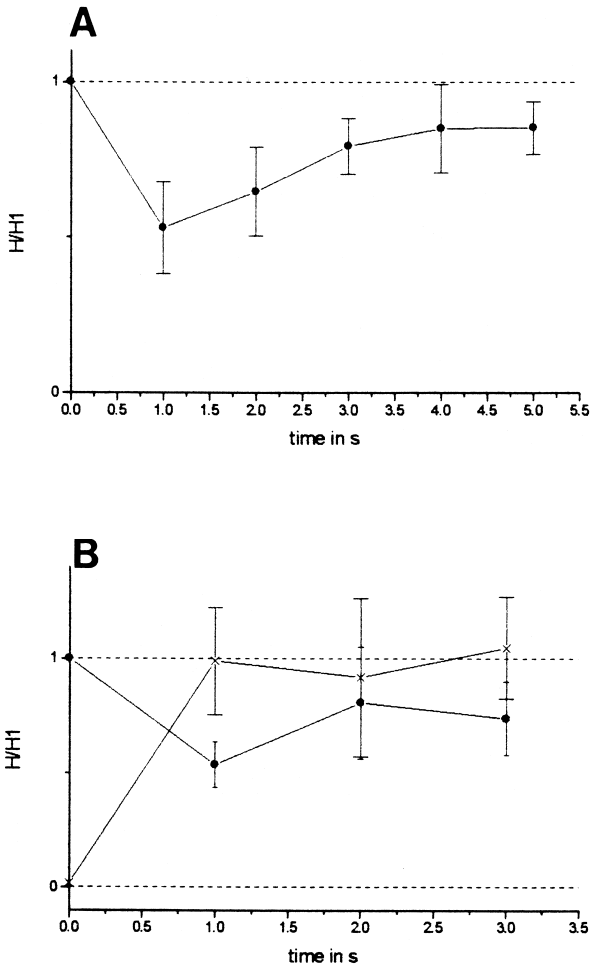

Fig. 1A, B Time course of the soleus H-reflex recovery from depression following a single H-reflex. **A** Overall mean from nine subjects. The peak-to-peak reflex sizes were referred to the peak-to-peak amplitude of a control H. For each subject a data point was the mean of ten trials and means from all subjects are shown. In some subjects not all intervals were tested: at 1 s, 2 s, 3 s, 4 s, and 5 s the data are the means from nine, ten, nine, six, and five cases, respectively, the total number of cases being ten at 2 s because one subject was analyzed twice on different days. The *vertical lines above and below the data points* indicate the standard deviation of each set of mean values from which each overall mean was computed (e.g., the overall mean at 1 s, equal to 0.5304, and the respective standard deviation 0.1489 were computed from nine individual mean values). **B** Data comparing the effects of posterior tibial nerve (PTN; *dots*) and common peroneal nerve (CPN; *crosses*) conditioning on H-reflexes at different latencies in one subject. For the *crosses*, the first response at the soleus had zero amplitude, because the stimulus was at the CPN, while the amplitudes of the test reflexes (elicited by PTN stimulation) at latencies of 1.0 s, 2.0 s, and 3.0 s were practically equal to the control values. The *vertical bars* indicate the SD. The *bars* for the PTN case have *short horizontal ticks* at either end, while for the CPN the ticks are longer. These same conventions are used in Fig. 2B

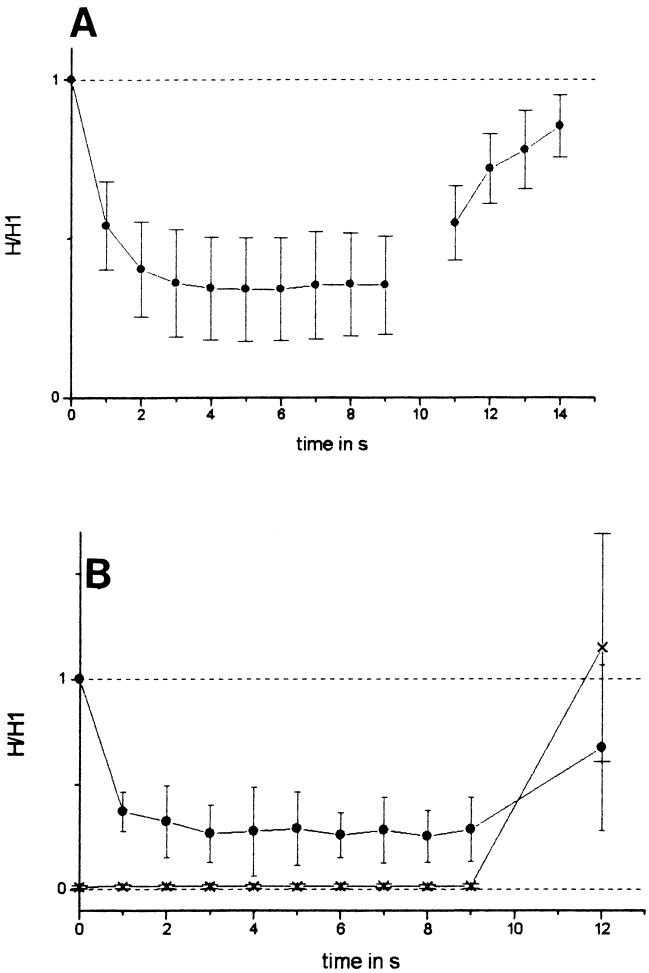

Fig. 2 **A** Depression of soleus H-reflexes during a 1-Hz train of ten stimuli applied to the PTN and ensuing recovery measured at four different latencies (2 s, 3 s, 4 s, and 5 s). The overall depression data shown were computed as the means of 38 cases originating from seven subjects. Each case was the mean of ten trials. The four recovery points at delays 2 s, 3 s, 4 s, and 5 s from the last depressed H-reflex (i.e., at instants 11–14 s) were computed as the means from ten, ten, nine, and eight cases, respectively. The *vertical bars* are the SDs. **B** Depression and recovery at a 3-s delay, for PTN (*dots*) and CPN (*crosses*) conditioning trains of ten stimuli at 1 Hz for the same subject as in Fig. 1B. Reflex amplitudes are with respect to first H-reflex elicited by a train to the PTN. *Vertical bars* are the SDs

from a brief tetanus to the antagonist muscle nerve at 50 ms, which ranged from 14 to 57%. The recovery of the soleus H-reflex was further analyzed in these subjects, using a single conditioning tetanus to the CPN with test H-reflexes at the same latencies as used for the PTN-conditioned experiments to assess recovery. Figure 1B shows the results from one subject with presynaptic inhibition of 42.5% (i.e., conditioned soleus H-reflex was 57.5% of the control H-reflex size) when tested at the 50 ms screening latency. At the earliest test stimulus at a latency of 1 s, the amplitude of the H-reflex had fully recovered. This was a general finding whenever we could assure good experimental conditions, meaning a large enough presynaptic inhibition at 50 ms and no dorsiflexion twitch at the ankle for each CPN conditioning stimulus (each dorsiflexion stretches the soleus and therefore activates its Ia afferents, and therefore presynaptic inhibition is not the sole mechanism in action).

When a train of ten pulses at 1 Hz was applied to the PTN, most of the H-reflex depression usually occurred

within the first three pulses and a plateau was maintained during subsequent pulses, as shown in Fig. 2A for seven subjects. The pooled data shows that the depression follows a monotonic decay and that in a few seconds it reaches a plateau. However, in different subjects the decay profiles to the depression plateau may be different, in one the plateau being reached at the second H-reflex, while in another at the fourth, for example. Following the train of stimuli, recovery was monotonic and did not reach control values even at 5 s after the last H-reflex in the train. The recovery phase had time constants ranging from 1.8 s to about 5 s for different subjects.

The recoveries of the H-reflex after PTN and CPN conditioning trains were compared by testing reflexes elicited at similar latencies. Figure 2B shows the recoveries of the test reflex at 3 s from the same subject shown in Fig. 1B. At this delay, the mean amplitude of the recovered H-reflex was about 1.15 for CPN conditioning, in comparison with the mean amplitude of 0.67 following PTN conditioning at the same latency. The importance of fixing the foot was shown in experiments where the foot was allowed to dorsiflex after each CPN stimulus, with the result that there was a clear H-reflex depression after the conditioning stimuli. This depression following CPN stimulation with the foot unrestrained is likely to reflect a contribution induced by stretch of the soleus muscle and its spindle receptors.

The monotonic decay of H-reflexes toward a depressed plateau followed by a slow recovery also occured for 0.5-Hz trains of stimuli to the PTN, although the depressed plateau levels were higher than those seen for 1-Hz trains. In eight subjects for which both the 1-Hz and 0.5-Hz trains were used, the results were: (1) mean plateau amplitude values of 0.28 and 0.53 (percentage of control H), respectively; (2) depressed plateaus reached at the third H-reflex on the average, for both stimulus frequencies. When the conditioning train was to the CPN, the recovery was complete at all delays tested.

Transcranial magnetic stimulation to evoke soleus MEPs was used to test the excitability of the soleus motoneurons, since this pathway does not use the Ia afferent pathway to excite motoneurons. MEPs were evoked approximately 1 s before (MEP1) and after (MEP2) a 1.0-Hz train of ten conditioning stimuli to the PTN. For three subjects, mean ± SD of MEP1 and MEP2 amplitudes prior to and after the conditioning train, respectively, were 4.55 ± 0.26 (%M_{max}) and 3.43 ± 0.98 (%M_{max}), without any consideration for outliers. There was no statistically significant difference between the two means (paired *t*-test, $P>0.20$). The corresponding means of the control H amplitudes and of the plateau values of depressed H-reflexes were 26.86 (%M_{max}) and 10.71 (%M_{max}), respectively. The MEPs were also quantified as means of ratios and ratios of means. For the first subject, mean (MEP2/MEP1) = 1.087 and mean (MEP2)/mean(MEP1) = 0.923; for the second subject, the respective values were 1.029 and 0.890; while, for the third subject, 0.850 and 0.803 if some outliers were removed (criterion for an outlier: peaks at very different times to those obtained from the same trial), but 1.094 and 0.480 if no outliers were removed. The first measure [mean(MEP2/MEP1)] had standard deviations 0.843, 0.448, and 0.243 (1.707 if no outliers were removed in the latter) for the first, second, and third subjects, respectively. As there was no statistical difference between the two means of the pooled MEPs and also the ratio measures were all close to 1, the results above suggest that the there are no changes in the excitability of the motoneuron pool involved in the range of H-reflex sizes used in this work. This would rule out postsynaptic inhibition of motoneurons as a possible cause for the depressed H-reflexes.

In three subjects, the effect of a passive dorsiflexion at the ankle preceding a train of H-reflexes was investigated. Slow passive dorsiflexion (40°) over 4 s with the foot returned in 1 s to the natural position caused a marked depression of the ensuing 1-Hz train of H-reflexes as compared to depression occurring without the conditioning dorsiflexion. In fact, the amplitude of H-reflexes in the 1-Hz train of stimuli following passive dorsiflexion showed very little further depression and was similar to the plateau level attained when using a train of PTN stimuli alone.

Discussion

The rationale behind our experiments was that if presynaptic inhibition is the main factor contributing to the depression and to the ensuing recovery of H-reflexes for stimuli applied to the PTN, then similar effects should be expected when stimuli are applied to the CPN because this is a well-accepted source of presynaptic inhibition on the soleus Ia connections to homonymous motoneurons (Morin et al. 1984; Hultborn et al. 1987). For example, in Fig. 1B, if we interpret the depression/recovery from PTN conditioning as being caused by presynaptic inhibition, it seems reasonable to assume that stimulation of the CPN, which caused a decrease in the normalized H-reflex to 0.575 at a latency of 50 ms, would also have a similarly slow return to normal. But this was not observed in our data. Similarly, for a train of conditioning stimuli to the PTN, one notices a progressive decrease toward a plateau (Fig. 2A), indicating an accumulation of effects during this depression phase. If this were caused by presynaptic inhibition, then it should probably also happen when a train of conditioning stimuli were applied to the CPN. For example, for the data in Fig. 2B, the first stimulus (a tetanus of four pulses) to the CPN would cause a decrease in the normalized H-reflex at 50 ms latency to 0.575. The accumulation of effects with the next stimuli in the train would presumably cause an attenuation of the H-reflex amplitude in excess of the 42.5% found for a single CPN tetanus; let us say, the normalized H-reflex amplitude would be around 0.500 (assuming a similar ratio of H at 2 s over H at 1 s for PTN stimulation), and so on. In this and other cases the assumed depressed reflexes caused by presynaptic inhi-

bition from the CPN should have been followed by recovery trajectories similar to those found for PTN conditioning, but these were not found. Instead we found the test reflex amplitudes at different latencies from the end of the train fluctuating around the normalized value 1.0, indicating that the presynaptic inhibition effect had a much shorter time course. Similar findings were associated with trains of 0.5 Hz. As there is no basis to assume that a presumed homonynous presynaptic inhibition of the Ia-motoneuron pathway in humans would respond quite differently from heteronynous presynaptic inhibition originating from the antagonist flexor, the results suggest that homosynaptic depression is a phenomenon distinct from classical presynaptic inhibition.

The general findings of this work are in accordance with the results of Nielsen et al. (1995) and Hultborn et al. (1996) that presynaptic inhibition is shorter-lived than homonymous H-reflex depression. Nevertheless, the experiments used to reach this conclusion were different from their studies. Hultborn et al. (1996) compared the effects of homonymous conditioning (soleus) on heteronymous (femoral) afferents, whereas in our series of experiments the effects of homonymous activation, heteronymous activation, and transcranial magnetic stimulation were always evaluated on the same set of test afferents and motoneurons. The study of Hultborn et al. (1996) also investigated monosynaptic reflex depression in cats and was able to rule out explicitly presynaptic and postsynaptic inhibition at intervals comparable with those used in human studies. These findings uphold our interpretation of the human data. A very recent work on humans and cats by Wood et al. (1996) also concluded that H-reflex depression following muscle length changes was not caused by presynaptic inhibition.

Among the possible mechanisms behind H-reflex depression in humans, prolonged postsynaptic inhibitory effects on soleus motoneurons caused by the activation of spinal cord interneurons (Renshaw, Ib, and others) or by motoneuron dynamics (e.g., after-hyperpolarization) can be considered. But these effects have a short duration and were also ruled out here by the lack of changes in the motoneurons' excitability as tested by magnetic stimulation of the brain. The strong depression of the H-reflex trains following a slow passive dorsiflexion argues against possible involvement of Ib afferents, as it is well accepted that such slow passive flexions do not activate Ib Golgi tendon organs (Jami 1992). The remaining postsynaptic mechanism that could explain homosynaptic H-reflex depression would be desensitization of the postsynaptic receptors or a mechanism similar to that causing homosynaptic long-term depression (Linden and Connor 1995). Kuno (1964) tested this type of hypothesis in cat Ia synapses on motoneurons and found no evidence of receptor desensitization. Receptor desensitization and LTD (long-term-depression) require a long period to build up, contrary to the H-reflex depression which occurs following a single stimulus.

For these reasons, presynaptic phenomena seem the most likely explanation for H-reflex depression. Excluding presynaptic inhibition based on the above discussion, one possibility is that there is an activity-dependent action potential propagation failure at Ia axonal branch points, but, at least in frog spinal cord, this does not seem to happen (Dityatev and Clamann 1996). Finally, an additional hypothesis could be a failure of Ia axons in following repetitive stimulation. But data from Morita et al. (1993) show that, for the interstimulus intervals that we employed (not less than 1 s), the compound nerve action potentials have no change in their amplitudes. Therefore, it seems that a depression of neurotransmitter release is the most probable mechanism behind human H-reflex depression.

Short-term homosynaptic depression is found in neonatal rat spinal cord (Lev-Tov and Pinco 1992) and has been attributed to a decrease in transmitter (glutamate) release. Kuno (1964) showed in cats that subsequent motoneuron Ia excitatory postsynaptic potentials (EPSPs) in a low-frequency train (e.g., 3/s) show depression that is associated with a decrease in the probability of release of quanta and without change in quantal size. This means that there is a progressive decrease in the amount of released neurotransmitter following successive stimuli in a train, because less packets of quanta are released. However, the mechanisms responsible for the depression are still an open issue (neurotransmitter depletion, Ca channel inactivation, etc.).

Quite clearly, the mechanisms behind homosynaptic depression in humans are even more elusive. In this respect it might be that the interplay of animal and human experimentation with modeling approaches will enrich future research. For example, a very speculative model (Kohn et al. 1995) on H-reflex depression is compatible with the finding that both the 0.5-Hz and 1-Hz train responses reach the plateau after approximately the same number of stimuli (simulation done with typical values obtained from experimental data). Certainly future research will suggest improvements in the modeling effort and elucidate the involved mechanisms.

Finally, H-reflex depression following electrical or mechanical (e.g., vibration or muscle length changes) stimuli seems to be due to homosynaptic depression. This has an impact both on motor control studies and on the understanding and treatment of a number of neurological conditions such as spasticity.

Acknowledgements We thank Drs. Eric Wassermann and Ali Samii for their help with the magnetic stimulation and Nguyet Dang for technical support. During his stay at the NIH, A. F. Kohn was a recipient of a fellowship from CNPq (Brazil).

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