Dopa-responsive dystonia and normalization of soleus H-reflex test results with treatment

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Abstract

We studied the maximal H-reflex to maximal direct muscle potential (H/M ratio), late facilitation and late inhibition in the recovery curve, and vibratory inhibition of the soleus H-reflex in three consecutive patients with hereditary dopa-responsive dystonia, before and during treatment with levodopa. In one patient, we repeated the H-reflex tests twice after withdrawal of levodopa. The results were compared with those in a group of 48 healthy subjects. In the patients before treatment, the soleus H-reflex recovery curve showed increased late facilitation and depressed late inhibition, reflecting alterations in postsynaptic interneuronal activity. Vibratory inhibition, predominantly reflecting presynaptic inhibitory action, was depressed. Normalization of these test results occurred during levodopa treatment, concurrent with a clear clinical response. The H/M ratio, reflecting the excitability state of the motoneuron pool, was similar during and without levodopa treatment. In the one patient tested after levodopa withdrawal, enhancement of late facilitation and decrease of vibratory inhibition paralleled the reoccurrence of dystonia most clearly. Since soleus H-reflex tests mainly reflect mechanisms operating at the spinal level, spinal aminergic or dopaminergic systems are probably involved in dopa-responsive dystonia.
Introduction

Dopa-responsive dystonia (DRD) dramatically responds to levodopa therapy (Nygaard et al. 1991). Benefits from treatment are lasting, and the problems associated with long-term levodopa therapy in patients with Parkinson's disease are generally absent. With H-reflex tests, various spinal reflex activities that may contribute to the origin of dystonia can be studied, but to our knowledge they have not been performed in patients with DRD. H-reflex tests in patients with idiopathic generalized dystonia show a decrease in the reciprocal inhibition of the H-reflex in the forearm and enhancement of the H-reflex recovery curve in the arm and in the leg (Sax et al. 1976; Panizza et al. 1990; Bour et al. 1991). In addition, vibratory inhibition of the soleus H-reflex in the leg is depressed (Bour et al. 1991). These findings suggest hyperexcitability of oligosynaptic and polysynaptic pathways and a disturbance of presynaptic inhibitory mechanisms. DRD offers a unique opportunity to analyze different neurophysiological mechanisms that may be involved in dystonia in the same subject in the symptomatic and asymptomatic state. In this study, we report on results of soleus H-reflex tests before and during levodopa treatment in three consecutive patients with a hereditary DRD.

Methods

Soleus H-reflex tests

Recording and stimulation techniques for the soleus H-reflex have been described previously (Hugon 1973; Ongerboer de Visser et al. 1989). During all tests, subjects were seated in a reclining chair in a standardized position. Soleus H-reflexes were elicited only in the absence of triceps surae EMG activity, which was noted on the oscilloscope at the beginning and end of each reflex study. In addition, EMG activity was monitored aurally during the investigation. The H-reflex was discarded, if there was any soleus activity prior to tibial nerve stimulation. Soleus H-reflex responses elicited by 1 ms square constant current pulses to the posterior tibial nerve in the popliteal fossa were amplified with a band-pass filter of -3 dB at 2 Hz and 10kHz (6dB/octave) and digitally stored with a sample frequency of 10 kHz in a mini-computer (PDP 11/73, Digital, USA). The time interval between successive trials during the determination was at least 30 seconds. For the construction of an H-reflex recruitment
curve as a function of stimulus intensity, intensity increment of successive stimuli was
chosen small at low intensity levels, while it was gradually enlarged at higher intensity.
Each recruitment curve consisted of 12 or more H-reflex responses at different
intensities. Simultaneously with the H-reflex recruitment curve, a recruitment curve
of direct soleus M potentials was constructed also as a function of intensity. Peak-
peak values of the maximal H-reflex response and maximal M-potential were used
for the H/M ratio (Bour et al. 1991).

Vibration of the Achilles tendon with a frequency of 100 Hz and an undamped
amplitude of 1 mm was applied by vibrator (Brüell and Kjaer 4809, Denmark). The
cumulative vibratory index (CVI) was used as a quantitative measure for the vibratory
effects on the H-reflex (Ongerboer de Visser et al. 1989). This CVI is defined as the
ratio between the surface under the recruitment curves obtained during and without
vibration at the stimulus intensity up to which integration is carried out. The CVI at
the stimulus intensity level yielding the maximal H-reflex response was used only
(Bour et al. 1991).

H-reflex recovery curves were constructed by application of paired pulses of equal
intensity. The stimulus intensity level where the H-reflex reached half its maximum
value was used (Bour et al. 1991). Time-intervals between conditioning and test stimulus
were 100, 200, 250, 300, 400 and 500 ms and at 1, 3, 10 and 30 seconds. Early facilitation
and inhibition were not examined. The recovery curves were plotted as the ratio in
percentage between the area values of the test and the conditioning H-reflex response
against time-interval between the two stimuli. The two following characteristic values
were used for statistical analysis: the local maximum of the test H-reflex occurring in
the late facilitatory phase at a stimulus time-interval ranging from 50 to 320 ms, and
the local minimum of the test H-reflex found in the late inhibitory phase of the
recovery curve at a stimulus time-interval ranging from 320 to 1000 ms.

Control subjects

The neurophysiological results were compared with those found in a control group
of 48 healthy subjects aged 20-70 years (mean 38 years). The latter have been published
earlier (Koelman et al. 1993).
Statistical methods

In patients with measurements on both legs the mean value of both measurements was used. Soleus H-reflex test results of patients before levodopa treatment were compared with those of controls using unpaired two-tailed two-sample Student's t tests. Soleus H-reflex test results of patients with and without therapy were compared with paired t tests.

Case reports

Patient 1 is a 53-years-old man who developed slowly progressive dystonia, at the age of seven, firstly localized in the left leg and subsequently in the left shoulder. In the following years, the disease slowly progressed to a generalized dystonia and at the age of 13 the patient was unable to stand, to sit and to eat independently. Mental development was normal. He was treated with anticholinergic drugs with no beneficial effect. At the age of 18, the signs subsided and consisted of slight generalized dystonic movements increasing with fatigue or anxiety but not interfering with daily life activities. At the age of 51, dystonia was present in both arms and cramps were frequent in the right leg. On treatment with 50 mg of levodopa (with carbidopa) three times a day, all dystonic movements disappeared within 2 weeks. Soleus H-reflex investigations were performed on the right leg before treatment and after 3 months of levodopa treatment, when all dystonic signs had disappeared.

Patient 2 is a 22-years-old woman, daughter of patient 1, who developed slowly progressive generalized dystonia at the age of 5 years. Dystonia was at first localized in the legs in a mild form, which worsened during walking. Subsequently, dystonic movements were also present at rest and involved the arms and neck muscles as well. Mental function was normal and she remained fully independent. With 50 mg levodopa (with carbidopa) twice a day, all dystonic movements disappeared within two weeks. Soleus H-reflex tests were performed on both legs before treatment and after 4 months of levodopa treatment, when no dystonic signs were present. In addition soleus H-reflex tests were performed twice after discontinuation of the levodopa treatment. The first examination was 3 days after discontinuation of treatment. At that time, no dystonic signs were found although the patient experienced some restlessness in the arms. The second examination was 2 days later when she developed a severe torsion dystonia of the neck and the right leg.

Patient 3 is a 35-years-old man, the nephew of patient 1, who experienced dystonic
movements and cramps since the age of 12, more severe on the right side, increasing with fatigue and anxiety. He remained fully independent and dystonic movements did not interfere with daily life. With 50 mg of levodopa (with carbidopa) three times a day all complaints disappeared within two weeks. The soleus H-reflex investigations were performed on both legs before treatment and when on levodopa treatment for 4 months.

Figure 1a and b. Recruitment curves of soleus M response and H-reflex of the right leg in patient 3 without levodopa treatment (a) and during levodopa treatment (b), showing an increased H/M ratio and increased H-reflex inhibition with vibration during treatment.

**Results**

The individual soleus H-reflex tests of patient 3 before and during levodopa treatment are presented in figures 1a and b and 2. The combined soleus H-reflex test results of the different patients are presented in the table. Without levodopa treatment in the patients the mean H/M ratio was 44% (range 23-65%) and was similar to the H/M ratio in controls (mean value 48%, range 6-100%). In the patients no uniform influence of levodopa treatment on the H/M ratio was seen (mean value 47%, range
15-80%). Contrarily, without levodopa treatment recovery and vibratory features of the soleus H-reflex were clearly abnormal in the patients. The most prominent alterations were found in the soleus H-reflex recovery curve. In the patients late facilitation was significantly increased with a mean value of 145% (range 120-200%), whereas in controls the mean value was 42% (range 9-92%, p<0.001). During treatment with levodopa late facilitation fell to a mean value of 44% (range 25-110%, p<0.01).

Figure 2. Recovery curves of soleus H-reflex of the right leg in patient 3 without levodopa treatment (square) and during levodopa treatment (circle), showing decreased late facilitation and increased late inhibition of soleus H-reflex to the test stimuli during levodopa treatment.

With discontinuation of treatment in patient 2 after 3 days late facilitation increased, even when no signs of dystonia were present. After 5 days, late facilitation was most significantly disturbed in the leg clinically most affected. In the patients without levodopa treatment, late inhibition of the recovery curve was decreased with a mean value of 57% (range 25-90%), whereas in controls the mean value was 17% (range 2-44%, p<0.001). With treatment late inhibition increased and returned to normal with a mean value of 8% (range 4-11%). After discontinuation of levodopa treatment in patient 2 late inhibition did not deteriorate again, not even when dystonia reappeared.

In the patients, pretreatment vibratory inhibition was diminished with a mean value of 43% (range 24-82%), whereas in controls the mean value was 19% (range 0% to 60%, p=0.02). With treatment suppression of the H-reflex during vibration increased in the patients and had a mean value of 12% (range 4-23%). After discontinuation of levodopa treatment in patient 2, inhibition of the H-reflex during vibration deteriorated only slightly again in the clinically most affected leg after 5 days.
Discussion

We demonstrated a clear relationship between changes in soleus H-reflex recovery and vibratory test results and the disappearance and reoccurrence of dystonia, providing further evidence that alterations in these soleus H-reflex tests are linked with dystonia.

Without levodopa treatment, there was a marked potentiation of late facilitation and a clear decrease of late inhibition of the soleus H-reflex recovery curve in our patients. The late facilitatory phase of the soleus H-reflex recovery curve is present around a time interval of 200 ms between the conditioning and test stimuli and is speculated to be mediated by cutaneous afferents (Gassel 1970; Pierrot-Deseilligny et al. 1973). Our results of potentiation of late facilitation in DRD are in agreement with earlier findings in groups of patients with idiopathic generalized dystonia (Panizza et al. 1990; Sax et al. 1976). Potentiation of late facilitation is present in the upper motoneuron syndrome and in parkinsonian rigidity as well (Zander Olsen and Diamantopoulos 1967; Yap 1967; Sax et al. 1980), and probably reflects alterations in descending control mechanisms on spinal interneuronal activity (Masland 1972).

The late inhibitory phase of the soleus H-reflex recovery curve is present at a time interval of 300 msec up to 3 seconds between the conditioning and test stimuli and may be caused by the inhibitory action of the afferent impulses from secondary endings in the muscle spindles (Granit et al. 1966). In patients with the upper motoneuron syndrome, a decrease of late inhibition is also present (Koelman et al. 1993). In our patients, both abnormalities in the recovery curve responded dramatically to treatment with levodopa coupled with a dramatic clinical improvement of dystonia.

Although the absolute values of vibratory inhibition of the soleus H-reflex were less strikingly abnormal, improvement in vibratory inhibition was induced by the application of levodopa in our patients. H-reflex suppression during Achilles tendon vibration, which strongly activates primary muscle spindle endings, is presumed to be caused by an autogenic axo-axonal presynaptic inhibition of Ia terminals (De Gail et al. 1966; Gillies et al. 1969; Burke and Ashby 1972). However, other mechanisms, such as neurotransmitter depletion and post activation depression, are possible as well (Hultborn et al. 1987; Crone and Nielsen 1989). In spasticity, vibratory inhibition is markedly decreased (Delwaide 1973; Taylor et al. 1984; Ongerboer de Visser et al. 1989), whereas in parkinsonian rigidity vibratory inhibition is normal (Delwaide 1985). In spastic subjects, different drugs reinforce vibratory inhibition, but this action may
Table. Soleus H-reflex test results in controls and patients with and without levodopa treatment

<table>
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<tr>
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<th>Patient 1</th>
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<th>Patient 3</th>
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<td></td>
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<td>Left leg</td>
<td>Right leg</td>
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<td>65</td>
<td>35</td>
<td>44</td>
<td>23</td>
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<tr>
<td>L-DOPA +</td>
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<td>73</td>
<td>80</td>
<td>41</td>
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<tr>
<td>DAY 3 -</td>
<td></td>
<td>68</td>
<td>49</td>
<td>68</td>
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<tr>
<td>DAY 5 -</td>
<td></td>
<td>66</td>
<td>27</td>
<td>70</td>
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**Late Facilitation of recovery curve (%)** 42 (20)

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<td>32</td>
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<td>110</td>
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<tr>
<td>DAY 5 -</td>
<td>50</td>
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**Late Inhibition of recovery curve (%)** 17 (11)

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<td>60</td>
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<td>9</td>
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<td>DAY 5 -</td>
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**Cumulative vibratory inhibition (%)** 19 (16)

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<td>50</td>
<td>24</td>
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<td>DAY 3 -</td>
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<td>DAY 5 -</td>
<td>2</td>
<td>27</td>
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In patient 2, test results after 3 days (DAY 3 -) and after 5 days (DAY 5 -) of discontinuation of levodopa treatment are shown.

be limited to the pathologic situation with disturbed vibratory inhibition only (Delwaide et al. 1983). An action of levodopa upon presynaptic inhibition, seen in our patients with DRD, has not been reported previously.

In our patients, the H/M ratio was unaltered compared to control subjects and may
indicate that in dystonia excitability of soleus motoneurones is not affected. The normal 
H/M ratio is probably related to the enhancement of tendon jerks not being a 
characteristic feature in dystonia as the upper motorneuron syndrome, in which H/M 
ratio increases with increase of tendon reflex activity (Rothwell et al. 1983; Koelman 
et al. 1993).

In the patient tested twice after discontinuation of levodopa, abnormalities in the 
different H-reflex tests did not all reoccur at the same time. Potentiation of late 
facilitation was already present after 3 days whereas there was only a slight decrease in 
vibratory inhibition in the clinically most affected leg after 5 days and late inhibition 
even remained normal. Thus, as in spasticity the abnormalities in the different 
mechanisms tested, may occur independently (Delwaide 1985). Moreover, the different 
abnormalities in the soleus H-reflex test results may be of different clinical significance. 
If so, the combination of abnormalities in the late facilitatory period and vibratory 
inhibition appear to be linked to the clinical signs of dystonia most clearly.

Although 6-fluorodopa positron emission tomography (PET) scans are normal in 
DRD, a dysfunction of nigro-striatal dopaminergic pathways is thought to be 
responsible for the clinical signs in DRD (Nygaard et al. 1992; Snow et al. 1993) 
However, the results of our soleus H-reflex tests suggests that spinal aminergic or 
dopaminergic mechanisms contribute to the clinical signs of DRD. In spinal or 
decerebrated animals, a modulatory effect of aminergic and dopaminergic mechanisms 
at the spinal level is suggested by the action of various drugs on reflexly induced 
motor responses (Barasi and Roberts 1977; Commissiong and Sedgwick 1979; Dupelj 
and Geber 1981; Gentleman et al. 1981; Carp and Anderson 1982; Lindvall et al. 
1983; Jankowska 1993). There are reports of both inhibitory and facilitatory effects 
of dopamine (Barasi and Roberts 1977; Commissiong and Sedgwick 1979; Carp and 
Anderson 1982; Jankowska 1993). Dopaminergic endings that may influence motor 
functions are found in the dorsal horn (Lindvall et al. 1983). The recent discovery of 
existence of dopaminergic terminals in the vicinity of motoneurons in the ventral 
horn of rat lumbar spinal cord provides further support to the functional role of 
dopamine in the spinal motor control mechanisms (Shirouzu et al. 1990). In the 
normal human spinal cord, dopamine levels are similar to those found in animals 
suggesting the existence of spinal dopamine projections in humans (Lindvall et al. 
1983; Commissiong and Sedgwick 1975). Dysfunction of the spinal aminergic or 
dopaminergic system may be involved in the restless legs syndrome (Guilleminault et
A dopaminergic deficit on different levels in DRD and Parkinson’s disease might render an alternative explanation for the clinical differences between the two diseases and the observation that 6-fluorodopa PET studies are normal in DRD (Snow et al. 1993). Our findings underscore the necessity to consider dysfunction of spinal dopaminergic mechanisms in the pathophysiology of DRD.

Acknowledgments

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References


