Corticospinal potentials after transcranial stimulation in humans

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SUMMARY The descending volley evoked in humans by transcranial electrical stimulation of the scalp was recorded with epidural and spinal electrodes. It consisted of an early wave, which increased in amplitude and decreased in latency when the strength of the stimulus was increased. The mean conduction velocity of the early wave was 66, SD 2.5 m/s. At high stimulus intensity this wave was followed by later and smaller waves, which travel at the same speed as the initial potential. The recovery cycle of the descending volley was studied by delivering paired cortical stimuli at time intervals ranging from 0.5 to 10 ms. The early wave evoked by the test stimulus recovered to about 50% at a 1 ms interval and to 100% at a 3.5 ms interval. The later waves could not be tested at short time intervals but with time intervals longer than 3.5 ms they recovered to 100%. It is suggested that the initial and later waves after scalp stimulation are equivalent to the D and I waves seen in animal experiments.

Electrical stimulation of the exposed motor cortex in animals produces a complex response, which can be recorded from the pyramidal tract at the level of the bulbary pyramid or lateral column of the cervical spinal cord. The response consists of an initial wave, called D wave, followed by later waves, called I waves. The origin of D and I waves and their possible role in controlling movements are still unclear. In humans, transcranial stimulation (TCS) elicits a contralateral muscle potential with activation of fast corticospinal axons. The muscular events produced in humans by single transcranial stimuli are similar to those seen in animals after stimulation of the exposed motor cortex; in addition, recordings from the spinal epidural space after TCS have shown descending volleys in humans, similar to the D and I waves seen in animal experiments.

Using epidural and spinal electrodes, we have measured the conduction velocity and recovery cycle of the descending volleys evoked by TCS in humans.

Subjects and methods

The study was performed on ten subjects ranging in age from 23 to 67 years. Five subjects, with pain in the legs due to chronic arthropathy, were being submitted to implantation of epidural electrodes for stimulation for pain relief. Five subjects, with tumours of the thoracic spinal cord, were undergoing surgery involving opening of the dura mater and exposure of the spinal cord. All subjects were anaesthetised (70% nitrous oxide, fentanyl 1–3 μg/kg/h) and curarised (pancuronium 0.04 mg/kg). The study was approved by the local ethical committee.

Stimulation Transcranial stimulation was performed with a prototype low-impedance electrical stimulator, delivering high-voltage stimuli (600 V maximum voltage, 100 μs time constant) at short time intervals (minimum interval 0.5 ms). Silver/silver-chloride electrodes were fixed with collodium to the scalp, with the anode on, and the cathode 7 cm anterior, to the vertex, over the leg motor area. In some recordings the cathode was on, and the anode 7 cm lateral, to the vertex, over the hand motor area. The intensity of stimulation is expressed as a percentage of maximal stimulator output.

Recordings Signals were recorded bipolarly by means of Sigma Medtronic 3483 epidural electrodes, inserted percutaneously into the lumbar epidural space or placed on the spinal cord between the dura and the lateral surface of the cord. The proximal electrode was connected to the inverting input of the amplifier (negativity upward). In some subjects, a unipolar recording was also performed with a reference electrode placed subcutaneously near the recording electrodes. The stimulus artifact, however, was larger than that seen with bipolar electrodes. In both epidural and spinal recordings, the electrodes were moved rostrally under...
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radiographic guidance to the upper thoracic or cervical level. Signals were amplified (filter band-pass 2 Hz–5 KHz), averaged (16 trials) and stored on floppy discs by means of a BASIS (OTE) signal analyser.

The latency of the potentials was measured at the negative peak. The amplitude was measured peak-to-peak. The conduction velocity was measured to peak rather than onset because the stimulus artifact sometimes made measurement of onset-latency difficult. The potential did not change in duration or shape at higher stimulation intensity. Measurements of conduction velocity would have been the same if either peak or onset latencies were measured. This way of measuring was also used by Boyd et al.

To calculate conduction velocity (in five subjects with epidural and four with spinal electrodes), recordings were taken at two different sites along the cord and the distance between the two sites was measured on radiographs.

To study the recovery cycle (in two subjects with epidural and two with spinal electrodes) transcranial shocks were delivered in pairs (conditioning and test shock) at inter-stimulus time intervals ranging from 0.5 to 10 ms (averaging 16 trials for each time interval) and the amplitude of the test wave (evoked by the second shock) was expressed as a percentage of the conditioning wave (evoked by the first shock).

Monitoring showed that the current passed in the first and second stimulus was similar.

Results

In all subjects a sequence of potentials was recorded from the spinal cord after transcranial stimulation of the motor cortex. The sequence consisted of an initial large negative wave, followed by a series of smaller negative waves (figs 1, 2). The duration of the entire sequence was 4.9, 0.6 ms (mean, SD) (range 4.3 to 5.4 ms) with epidural, and 7.1, 0.8 ms (mean, SD) (range 6 to 8 ms) with spinal electrodes; the amplitude of the potentials was smaller in epidural than in spinal recordings. In both types of recordings, the amplitude of the initial wave was larger and the latency shorter in the cervical with respect to the thoracic region. In unipolar recording, performed in some patients, the amplitude of the potential was larger than that seen with bipolar recordings but the latency was similar, and the stimulus artifact decidedly larger.

The effect of a progressive increase in stimulation intensity was examined in two subjects. When the stimulation was increased in intensity from 20% to 70%, in the first subject with epidural electrodes, the amplitude of the initial wave rose from 16 to 80 μV and the latency decreased by an average of 0.8 ms. In the second subject, who had spinal electrodes, increasing the stimulation intensity from 20% to 100% caused the amplitude of the initial wave to pass from 42 to 230 μV and the latency to decrease by an average of 0.5 ms.

The increase in amplitude and decrease in latency with different stimulation intensities, is probably as Boyd et al. suggest, due to stimulus spread to more distal parts of the cortical axons. In three subjects with epidural and in all subjects with spinal electrodes placed in the cervical region, the initial wave was followed by later waves. These appeared at high

Fig 1 Descending volley after scalp stimulation recorded by epidural electrodes. When the recording electrodes were moved caudally from C7 to T5, the peak of the negative wave shifted progressively. The conduction velocity is plotted on the horizontal axis. The dashed line represents the regression line between distance and latency and corresponds to a conduction velocity of 62 m/s. Each trace is the average of 16 trials (horizontal calibration 2 ms, vertical calibration 15 μV).

Fig 2 Descending volley after scalp stimulation recorded with spinal electrodes in the cervical region. An initial wave is followed by a number of later waves (indicated by the arrows). Superimposition of two averages of 16 trials (horizontal calibration 2 ms, vertical 40 μV).
stimulation intensity. In one subject, two distinct waves could be identified (fig 2), but we were not able to see whether the increase in stimulus strength affected each wave differently. In five subjects with epidural (fig 1) and four subjects with spinal electrodes, the electrodes were moved along the spinal cord, to calculate the conduction velocity of the initial wave. It ranged from 55 to 71 m/s (mean, SD 63.0, 7.9) in epidural and from 58–65 m/s (mean, SD 62.0, 2.5) in the spinal recordings. In two subjects with spinal electrodes, we also compared the latency of the early and later waves at two different sites (fig 3). When the electrode was moved caudally the peak latency increased but the latency interval between early and later waves remained constant (fig 3). The conduction velocity of the initial and the two main later waves was 60.0, 3.1 m/s (mean, SD).

Figure 4 shows the recovery cycle of the initial wave in two subjects with epidural electrodes. With a time interval of 0.5 ms, no test response was recorded in either subject. At 1 ms interval the test response appeared with an amplitude of 40% of the conditioning response and at a latency of 1 ms longer than the conditioning response. From intervals of 1.5 ms on, the test response began to recover and reached the unconditioned values of amplitude and latency at intervals of 3.5 ms in both subjects. The recovery cycle of the later waves was studied in two subjects with spinal electrodes, at intervals from 3.5 to 10 ms. With shorter intervals, conditioning and test responses overlap, making a proper measurement impossible. Similarly to initial waves, however, at intervals of 3.5 ms, the test responses had already recovered, showing no difference from conditioning responses in either subjects (fig 5).
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Discussion

In humans electrical stimulation of the scalp produces a short latency contraction of the contralateral limb muscles. The stimulation site appears to be at or near the motor cortex and the muscle contraction is probably due to activation of the fast conducting axons of the cortico-spinal tract.4,7 Boyd et al 4 and Inghilleri et al 9 have recorded from the epidural space, the descending volley evoked by transcranial stimulation. In their recordings the volley was composed of initial and later waves. In this paper we recorded the descending volley both from the epidural space and the surface of the spinal cord. Initial and later waves were recorded and the conduction velocity was similar to the two methods. This suggests that epidural and spinal electrodes record activity from the same descending tracts. In spinal recordings the initial wave is larger in amplitude, the later waves are more easily recorded and the position of the recording electrodes can be more accurately identified.

The descending volleys recorded in humans bear close resemblance and can be considered equivalent to the potentials observed in primates and humans by direct stimulation of the exposed cortex. Patton and Amassian 1 and Amassian et al 2 stimulated the somatosensory cortex and recorded the responses with electrodes inserted into the bulbar pyramid or lateral column of the cervical spinal cord. They observed an early stable response at short latency, which they called D (direct) wave, because its latency was too short to have involved a synapse, followed at higher stimulation intensity by later responses, called I (indirect) waves. Katayama, et al 10 have reported a similar sequence in humans, after stimulation of restricted areas of the exposed cerebral cortex.

In this study the conduction velocity of the initial wave was approximately 70 m/s, being similar to that of the D wave measured in animals and in humans with an exposed cortex. 1,3,7,10 The conduction velocity also coincides with values obtained by Boyd et al 4 and Inghilleri et al 9 in epidural recordings and with indirect measurements derived from percutaneous stimulation of the scalp and cervical region 16 and of the spinal cord. 11 On the other hand, Levy and York 12 by direct stimulation of the lateral quadrant of the cord surface, found conduction velocities well over 100 m/s, which may have been due to the recruitment of faster conducting axons by the stimulus. 13,14 However, their method has been questioned because it was liable to overestimate the conduction velocity. 9

We have also measured the conduction velocity of the later waves, which was equal to that of the initial component, both ranging from 64 to 71 m/s. A similar value has been obtained by Kernels and Wu. 3 They stimulated the baboon's precentral motor cortex and recorded the discharge of the corticospinal tract from the cervical spinal cord and found that the conduction velocity of the three first later waves was similar to that of the D wave. In spinal recordings, the two later waves, for which the conduction velocity was calculated, were intermingled with other less synchronous waves of smaller amplitude. For this reason, it was not possible to make reliable measurements. This activity may therefore be produced by other neuronal structures.

Paired stimuli applied to the scalp at various intervals have shown that amplitude and latency of initial wave recover completely in 3-5 ms, thus showing a behaviour similar to that seen in peripheral axons. 13 At the same interval the later waves are also present. The effect of paired cortical stimuli on the D wave was studied by Patton and Amassian 1 and Amassian et al 2 in animal experiments and by Katayama et al 10 in humans with an exposed cortex. The D wave was present but attenuated in the cat at conditioning test intervals of 1-3 ms. 1 In humans this occurred at interstimulus interval of less than 2 ms. 10 In a more recent paper Amassian et al 2 have also studied the effect of repetitive stimulation on the I waves and have shown that the I waves can follow a high frequency cortical train of 300 Hz stimulation.

Patton and Amassian 1 observed that I waves were more affected than D waves by cortical injury, asphyxia and anaesthesia; in addition, deep stimulation of the white matter only evoked D waves, I waves appearing after stimulation of the grey matter. In this study we were not able to make recordings at different levels of anaesthesia. However, Katayama et al 10 using different doses of barbiturate observed a progressive decrease in later waves. Patton and Amassian 1 suggested that the D wave probably results from excitation of the initial segment of the pyramidal neurons whereas I waves result from indirect excitation of pyramidal neurons through interneurons. This view was shared by Kernels and Wu, 3 who concluded that I waves are mainly evoked by a semi-synchronous repetitive dis- charge of the identical corticospinal fibres responsible for D waves. Amassian et al 2 suggest that the I waves may be generated by combined excitation of (1) specific thalamo-cortical projection from VL-VA nuclei, (2) cortico-cortical projections from the post-central and premotor cortex, and (3) intrinsic tangentially orientated fibre systems located deep in the perikarya of the lamina V giant pyramids. The first I wave is attributed to monosynaptic excitation of pyramidal tract neurons, successive I waves probably reflecting single delays in synaptic discharge.

With the technique of scalp stimulation the results observed in animals can be reproduced in the human corticospinal system. The descending volley recorded
in humans seems to be equivalent to that seen in animals. On the basis of conduction velocity and recovery cycle we agree with Day et al that the D wave after transcranial stimulation is due to activation of pyramidal axons.

The conduction velocity of the I waves supports the hypothesis that they travel along the same pyramidal axons as the D wave. I waves show a rapid recovery cycle and completely recover at intervals of 3.5 ms, as does the D wave. At first glance, this suggests that I waves as well as the D wave are activated postsynaptically. However, they could be generated through synapses with a short refractory period or alternatively the conditioning and test stimulus may excite different cortical cells.

References

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