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RESEARCH ARTICLE

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The effect of lorazepam on the motor cortical excitability in man

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Abstract The effect of the short-acting benzodiazepine lorazepam on motor cortex excitability was investigated in 11 healthy volunteers using the technique of focal transcranial magnetic stimulation. The threshold intensity for evoking an electromyographic response in the resting and active abductor digiti minimi muscle, the size of the motor evoked potential, the duration of the cortical and peripheral silent periods, the corticocortical inhibition and facilitation after paired magnetic stimuli, and the transcallosal inhibition were used as parameters to assess various aspects of motor system excitability. Baseline values were compared with data obtained 2, 5 and 24 h after a single oral dose of 2.5 mg lorazepam. Resting and active motor thresholds and the size of the motor evoked potential remained unchanged. The duration of the cortical silent period was prolonged with a maximum effect 5 h after drug intake, while the peripheral silent period did not show any lengthening at that time. The corticocortical inhibition showed a tendency toward more inhibition, while the corticocortical facilitation was almost completely suppressed. The transcallosal inhibition showed an inconsistent trend to less inhibition. In parallel to the pharmacokinetics of lorazepam, all effects peaked at 2 h and 5 h, and were (partially) reversible after 24 h. It is hypothesized that most of these findings are due to the reinforcement of GABA action by lorazepam at the level of the motor cortex. The lack of effect on motor threshold and on the size of the motor evoked potential may indicate that these parameters are physiologically distinct from corticocortical excitability and the cortical silent period. The relevance of the present data in clinical epileptology is discussed.

Key words Transcranial magnetic brain stimulation · Motor cortex excitability · Lorazepam · Benzodiazepine · Human

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Introduction

Transcranial magnetic stimulation of the human motor cortex conducted in a conditioning-test paired pulse paradigm allows to study selectively and noninvasively corticocortical excitability (Kujirai et al. 1993) and interhemispheric inhibition (Ferbert et al. 1992; Netz et al. 1995). The very low intensity conditioning stimulus in the paradigm of Kujirai et al. (1993) is too weak to produce a corticospinal response. The inhibition of the test response by the conditioning shock at short interstimulus intervals and the facilitation at longer intervals is probably due to the activation of local inhibitory and excitatory cortical circuits projecting onto the population of corticospinal neurons. The interhemispheric inhibition in the paradigm of Ferbert et al. (1992) is very probably produced via a transcallosal route. Since these double stimulation techniques are not confounded by effects at the level of the spinal cord, they may prove to be a major extension of the conventional single-pulse stimulation (Barker et al. 1985). So far, except from a few recent double stimulation studies (Ridding et al. 1995; Terao et al. 1995) data on excitability changes of the motor system in neurological disorders have been reported only by using the single-pulse stimulation to evaluate the motor threshold and the duration of the silent period (Hufnagel et al. 1990; Cantello et al. 1991; Reutens et al. 1993; von Giesen et al. 1994; Haug and Kukowski 1994; Priori et al. 1994a, b; Valls-Solé et al. 1994). The same is true for the reported studies on the effect of drugs on motor excitability (e.g., Schönle et al. 1989, Hufnagel et al. 1990, Kofler et al. 1992, Mavroudakis et al. 1994, Priori et al. 1994b). The present study extends these investigations, since, to our best knowledge, this was the first time that the paired-pulse stimulation had been applied to investigate the effect of an anticonvulsant drug on the excitability of the motor cortex. The short-acting benzodiazepine lorazepam (7-chloro-5-(2-cholorophenyl)-1,3-dihydro-3-hydroxy-2*H*-1,4-benzodiazepine-2-one) was chosen as the study drug because of its well-defined mechanism of action.

Materials and methods

Studies were performed on 11 healthy volunteers (8 men, 3 women; mean age 26.9±3.2 years) who all gave their written informed consent. All experimental procedures were approved by the local ethical committee. According to the Oldfield questionnaire for handedness, eight subjects were right-handed, three were left-handed. Subjects were seated in a comfortable reclining chair. Surface electromyographic (EMG) recordings were made from the right abductor digiti minimi (ADM) and, in the case of transcallosal inhibition, also from the left ADM. The raw signal was amplified and filtered with a time constant of 10 ms and a low-pass filter of 2.5 kHz. Signals were then fed into an IBM-PC/486 AT-compatible laboratory computer, using the NEUROSCAN (version 3.0) data collection (sampling rate 5 kHz) and conditional averaging software. The transcranial magnetic stimulation (TMS) was applied to the hand area of the left motor cortex and, in the case of transcallosal inhibition, also to the hand area of the right motor cortex, using Magstim 200 magnetic stimulators (Magstim Company, Whitland, Dyfed, UK) and figure-of-eight magnetic coils (diameter of one winding 70 mm, peak magnetic field 2.2 T). Corticocortical excitability was studied by paired stimulation, using a bistim module (Magstim) to connect two stimulators to one coil.

Measurements

Motor threshold

To measure the motor threshold, the optimal position of the magnetic coil was determined by moving the coil in 1-cm steps around the presumed area over the left motor cortex. The coil was always held tangentially to the scull with the handle pointing backward and laterally at 45° from the midline. Thus, the current induced in the brain pointed forward in an approximately perpendicular direction to the assumed line of the central sulcus. The optimal position was defined as the site of stimulation which consistently yielded the largest motor evoked potential (MEP) of the right ADM at a moderately suprathreshold stimulation intensity. This position was marked on the scalp by a red pencil so that the coil could be placed at exactly the same site during subsequent sessions. The threshold intensity, expressed as percentage of maximum stimulator output, was appoached from slightly suprathreshold intensities by reducing the stimulus intensity in steps of 1% and was defined as the first stimulus intensity which did not produce a MEP of more than 50 μV in five consecutive trials. Motor thresholds were determined in the resting and in the isometrically moderately active ADM.

Size of the MEP and duration of the cortical silent period and peripheral silent period

MEP and cortical silent period (CSP) were obtained in the tonically active ADM performing ten trials each at TMS intensities of 10, 20, 30, and 40% above active motor threshold. The single-trial peak-to-peak MEP size was determined in the nonrectified recordings and from this data conditional means were calculated. The end of the CSP was defined in the rectified single trials as the time when the voluntary EMG activity started to return continuously. The duration of the CSP was then calculated by subtraction of the time which corresponded to the end of the preceding MEP. From the single-trial data, the conditional means were calculated. Since it has been shown that the early part of the CSP might at least in part be due to inhibition at the level of the spinal cord (Fuhr et al. 1991; Ziemann et al. 1993), the peripheral silent period (PSP) was also obtained in the tonically active ADM of five subjects by supramaximal electrical stimulation of the ulnar nerve at the wrist (square-wave, constant-current pulses of 0.2 ms duration (Tönnies Erben, D-79108 Freiburg, Germany) in order to differentiate between possible effects of lorazepam on the spinal and supraspinal level. PSP duration was determined in the single-trial rectified recordings as has been described above for the CSP.

Corticocortical excitability curve

In the resting ADM, the corticocortical excitability curve was measured, largely following the procedure described by Kujirai et al. (1993). Briefly, paired stimuli were applied through the same coil. The second stimulus, which is referred to as the test stimulus, was moderately suprathreshold so as to produce an EMG response of 0.5–1.5 mV mean peak-to-peak amplitude. The conditioning shock preceded the test shock by 1 of 12 different interstimulus intervals (range 1–30 ms) and was set to the very low intensity of 5% below active motor threshold. It has been shown previously that a conditioning stimulus which was set below resting threshold had no effect on the size of the H-reflex (Kujirai et al. 1993), so that any effect of the conditioning shock on the size of the test response in the present experiments is even more unlikely to occur at the spinal level. Four blocks of trials were performed, each consisting of four randomly intermixed conditions (ten trials each): the test stimulus given alone, and three conditions with the conditioning shock occuring at different intervals prior to the test shock. The time elapse between consecutive trials was 5 s. The single-trial peak-to-peak amplitudes of the EMG response were measured and from these the conditional means were calculated. Changes in the amplitude of the test response were expressed as percentages of the unconditoned mean.

Transcallosal inhibition

The measurement of transcallosal inhibition followed in all details the procedure given by Ferbert et al. (1992). The conditioning stimulus was delivered through a second coil placed at the optimal position over the hand area of the right motor cortex at various intervals (range 4–20 ms) prior to the test stimulus given to the left motor cortex. The intensity of the conditioning shock was set to 15% above resting motor threshold of the left ADM. Otherwise, arrangement of blocks of trials and calculation of the conditioning effect were as for the corticocortical excitability curves above.

One experimental session lasted, on average, 60 min and was performed before (baseline) and 2, 5, and 24 h after a single oral dose of 2.5 mg lorazepam. The drug induced mild to moderate side effects, including tiredness in all subjects, slight ataxia in six subjects, impaired concentration in six subjects, headache in one subject, and nausea and vomiting in one subject. Side effects peaked at 2 h after drug intake, were less prominent at 5 h, and fully reversible at 24 h. Sleep was not induced in any of the subjects during the experimental sessions and the side effects in no case interfered with the subject's ability to fully comply with the experimental protocol.

Statistical procedures

The effect of lorazepam on motor system excitability was assessed for all parameters from above by the two-tailed, paired Student's *t*-test ($P<0.05$). Always, group means were compared before and at the different times after administration of lorazepam.

Results

Motor thresholds

The mean thresholds ($n=11$) in the resting and active ADM under baseline conditions were 42.8±5.2% and 32.6±4,5%, respectively. These motor thresholds remained unaffected by lorazepam throughout (thick lines in Fig. 1). It is also shown in Fig. 1 (thin solid and dashed lines) that the individual thresholds in no case changed by more than 3% and, in 8 relaxed and 10 active ADM remained stable within a 2% range.

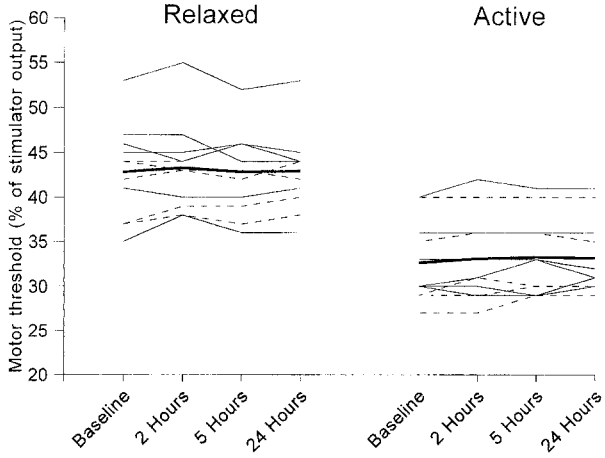

Fig. 1 Course of individual (*thin solid and thin dashed lines*) and mean (*thick solid line*) relaxed and active motor thresholds of 11 subjects before (*Baseline*), and 2, 5, and 24 h after a single oral dose of 2.5 mg lorazepam. Thresholds are given as a percentage of maximum stimulator output. Note that in no case did threshold change by more than 3%

Duration of the CSP and PSP, and size of the MEP

EMG recordings of the CSP and PSP from a single subject are shown in Fig. 2A. From top to bottom, recordings were obtained before, and 5 h and 24 h after the intake of lorazepam, respectively. The stimulus intensity for the CSP was 20% above active motor threshold. Each trace is the single-trial rectified mean of ten trials. After 5 h (middle trace) the CSP was prolonged by 57 ms in comparison with baseline (upper trace), while no lengthening effect could be detected for the PSP. After 24 h (lower trace) the lengthening of the CSP was fully reversible. Since the level of muscle preactivation and the MEP size might influence the duration of the CSP (e.g., Cantello et al. 1992; Wilson et al. 1993), these parameters were also determined. The mean levels of muscle contraction (measured over the first 50 ms from sweep onset to the time of cortical stimulation) were 56, 50, and 49 μV at baseline, 5 h and 24 h, respectively. The corresponding peak-to-peak sizes of the MEP in the non-rectified recordings were 4.8, 5.1, and 5.1 mV. Thus, in this particular case the level of sustained muscle contraction and the MEP size could be excluded as major sources of the CSP prolongation.

The mean baseline CSP durations (n=11) at stimulus intensities of 10, 20, 30, and 40% above active motor threshold were 42, 89, 147, and 174 ms, respectively (thick line in Fig. 2B). Lorazepam increased the mean duration of the CSP by up to 26 ms at the lower three stimulus intensities, with the strongest effect 5 h after drug intake (Fig. 2B). The single and double asterisks in Fig. 2B indicate the level of significance (P<0.05 or P<0.01, respectively). The mean peak-to-peak amplitude of the MEP (n=11) preceding the CSP remained unchanged by lorazepam throughout and at all stimulation intensities (Fig. 2C). This excludes a major contribution of MEP size to the observed prolongation of the mean CSP duration.

Figure 2D shows the effect of lorazepam on the mean duration of the CSP of those five subjects which also have been tested for effects of lorazepam on the duration of the PSP. These data are similar to the grand mean in Fig. 2B. The individual CSP data of these subjects are again displayed in Fig. 2E (thin lines) at stimulation intensities of 10% and 20% above active motor threshold. Apart from single exceptions, all subjects showed a lengthening of the CSP at 2 h and 5 h after lorazepam intake. Changes of the mean data were significant at both times (mean lengthening of 35 ms and 33 ms, respectively) for a stimulation intensity of 10% above threshold, and at 5 h (mean lengthening of 38 ms) for a stimulation intensitiy of 20% above threshold (P<0.05). In contrast, the duration of the PSP after electrical ulnar nerve stimulation was slightly lengthened (on average by 10 ms) in all subjects at 2 h, but none of the subjects showed a prolongation at 5 h any more (right column in Fig. 2E). Thus, while lorazepam had its maximum lengthening effect on the CSP after 5 h, there was no lengthening effect on the PSP at this time.

Corticocortical excitability

MEPs of the same subject as in Fig. 2A are shown before, and 2, 5, and 24 h after the intake of lorazepam in Fig. 3A. Each trace is the mean of ten single trials. EMG responses to the test stimulus alone (top records) had a peak-to-peak amplitude of about 1 mV in all sessions. The middle and bottom records display the EMG response when conditioned by a low-intensity magnetic pulse delivered through the same coil 7 ms or 20 ms prior to the test pulse, respectively. During the baseline con-

Fig. 2 **A** From *top to bottom* the EMG recordings from the tonically active abductor digiti minimi muscle of a single subject show on the *left* the cortical silent period to 20% suprathreshold transcranial magnetic stimulation before, and 5 h and 24 h after a single oral dose of 2.5 mg lorazepam, and on the *right* the corresponding peripheral silent period to supramaximal electrical ulnar nerve stimulation. Each display is the single-trial rectified mean of ten trials. *Arrows* indicate the end of the silent periods. Horizontal calibration is 100 ms, vertical calibration 0.25 mV. Maximum M-waves are truncated at the top. Note that lorazepam lengthened the duration of the cortical silent period by some 50 ms 5 h after lorazepam intake, while the peripheral silent period remained unchanged. **B** Effect of lorazepam on the mean cortical silent period duration of 11 subjects at stimulation intensities of 10, 20, 30, and 40% above active motor threshold. Baseline data are shown by the *thick line*. Data obtained 2, 5, and 24 h after lorazepam are given as *thin lines with: solid triangles, stippled circles, and open triangles*, respectively. *Asterisks* indicate significant changes in silent period duration (*P<0.05, **P<0.01; two-tailed, paired t-test). **C** Effect of lorazepam on the mean peak-to-peak amplitude of the motor evoked potential (*MEP*) preceding the cortical silent period. Otherwise, same conventions as in **B**. **D** Effect of lorazepam on the mean cortical silent period duration of those five subjects who also were tested for peripheral silent period duration. **E** Time course of individual (*thin lines*) and mean (*thick line*) cortical silent period durations (*CSP*) at stimulus intensities of 10% and 20% above active motor threshold in comparison with the corresponding course of peripheral silent period durations (*PSP*). *Asterisks* indicate significant changes in mean silent period duration (*P<0.05, **P<0.01; two-tailed, paired t-test)

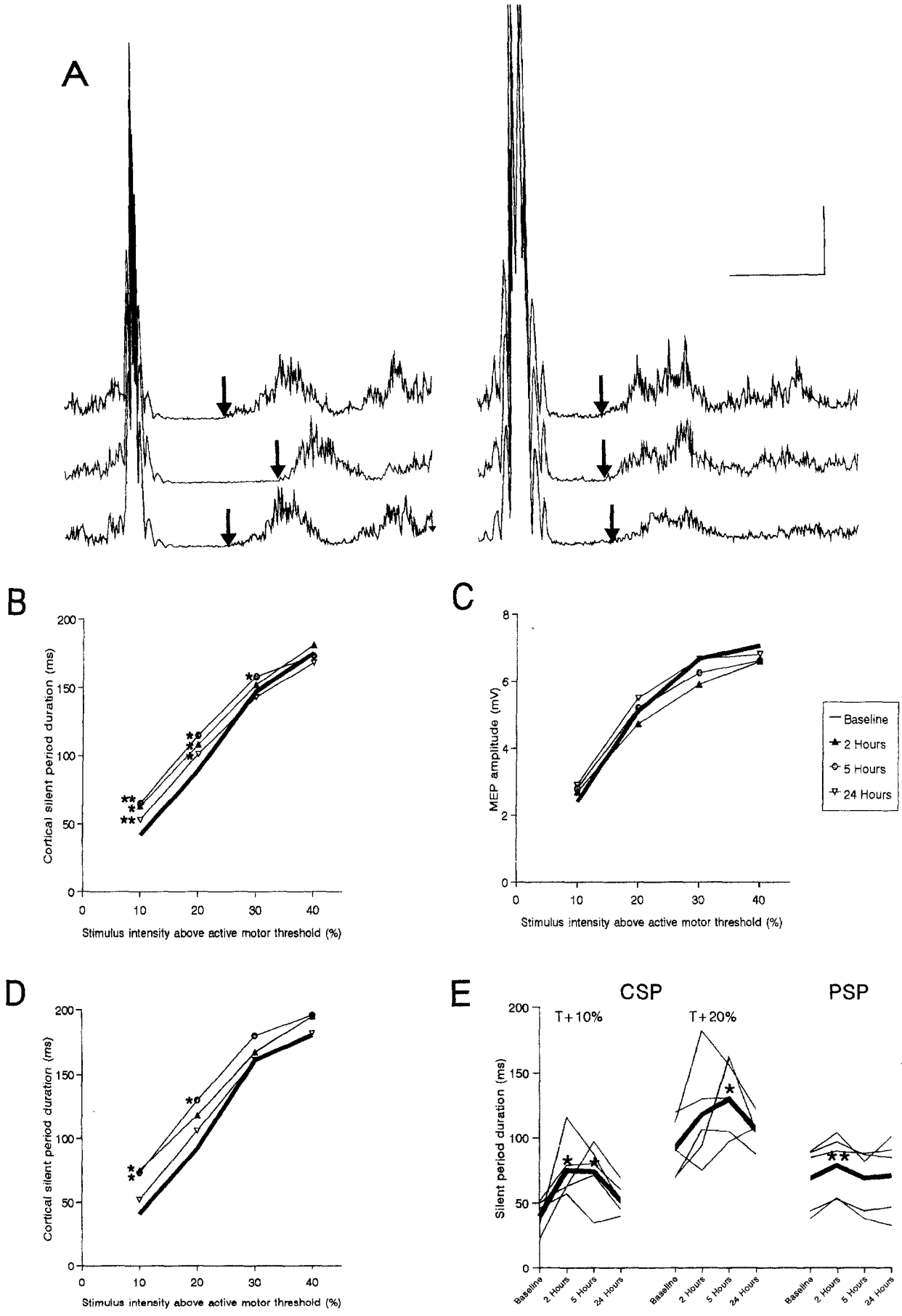
A
B
Cortical silent period duration (ms)
Stimulus intensity above active motor threshold (%)
C
MEP amplitude (mV)
Stimulus intensity above active motor threshold (%)
Baseline
2 Hours
5 Hours
24 Hours
D
Cortical silent period duration (ms)
Stimulus intensity above active motor threshold (%)
E
CSP
PSP
T+10%
T+20%
Silent period duration (ms)
Baseline
2 Hours
5 Hours
24 Hours

Fig. 2A–E

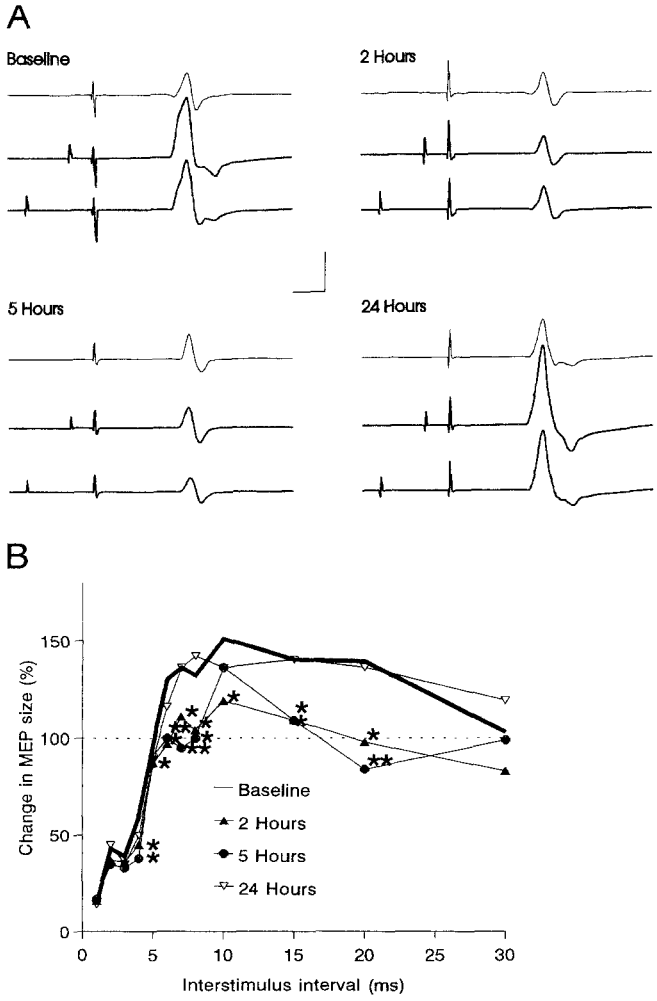

Fig. 3 **A** EMG recordings of the motor evoked potential from the relaxed abductor digiti minimi muscle of the same subject as in Fig. 2A before and 2, 5, and 24 h after a single oral dose of 2.5 mg lorazepam. Responses are shown to the test stimulus alone (*top*) and to the test preceded by the subthreshold conditioning shock at 7 ms and 20 ms (*middle and bottom traces*, respectively). The intensity of the conditioning shock was set to 28% of maximum stimulator output, while the active motor threshold in this subject was 33%. Active threshold did not change throughout. Each trace is the mean of ten single trials. Horizontal calibration is 10 ms, vertical calibration 1 mV. Note that lorazepam completely and reversibly suppressed corticocortical facilitation 2 h and 5 h after baseline. **B** Effect of lorazepam on the mean corticocortical excitability of 11 subjects before (*thick line*) and 2, 5, and 24 h after a single oral dose of 2.5 mg lorazepam (*thin lines with: solid triangles, solid circles, and open triangles*, respectively). Interstimulus intervals between conditioning and test stimuli are given on the abscissa, the effect of the conditioning stimulus on the size of the motor evoked potential (*MEP*) on the ordinate. The *dotted line* represents the size of the unconditioned MEP (100%). *Asterisks* denote significant changes in mean MEP size (*$P<0.05$, **$P<0.01$; two-tailed, paired *t*-test)

dition this subject showed a clear facilitation at both interstimulus intervals (207% and 173%, respectively). Two hours after lorazepam intake, this facilitation was completely abolished at both intervals (88% and 99%, respectively). At 5 h this suppressive effect was still present (97% and 73%), while at 24 h the baseline facilitation was largely restored (207% and 147%). The base-

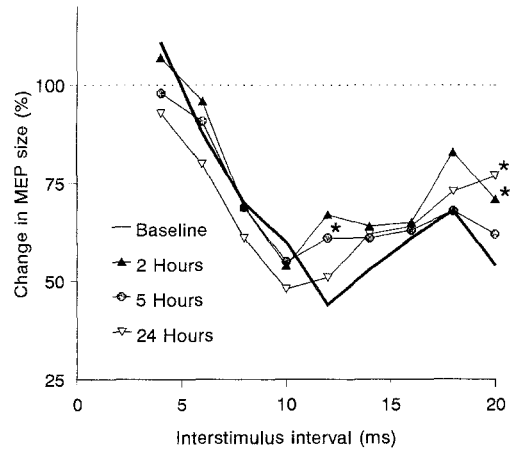

Fig. 4 Effect of lorazepam on the mean transcallosal inhibition of 11 subjects. Same conventions as in Fig. 3B

line curve of the mean excitability data (thick line in Fig. 3B; $n=11$) resembles closely the curve reported previously by Kujirai et al. (1993). Short interstimulus intervals (1–4 ms) resulted in an inhibition of the test response, while longer intervals (6–30 ms) produced a test response facilitation. Lorazepam caused a significant enhancement of inhibition at 4 ms and an even more conspicuous reduction of facilitation at interstimulus intervals of 6–20 ms. The single and double asterisks indicate significant excitability changes ($P<0.05$ and $P<0.01$, respectively). These effects occurred almost equally at 2 h and 5 h after drug intake (filled triangles and gray circles in Fig. 3B, respectively), while at 24 h the corticocortical excitability was back to baseline values at all interstimulus intervals (open triangles in Fig. 3B).

Transcallosal inhibition

The mean baseline curve ($n=11$) was similar to the curve obtained by Ferbert et al. (1992). The test response started to be inhibited at an interstimulus interval of 6 ms, was maximally inhibited at 12 ms, and then gradually recovered at longer interstimulus intervals (thick line in Fig. 4). Lorazepam produced no significant effect at the intervals of 4–10 ms and an inconsistent trend to less transcallosal inhibition at the longer intervals, which became significant only at a few intervals (see asterisks in Fig. 4).

Discussion

To the best of our knowledge, this is the first time that the technique of paired-pulse TMS has been applied to investigate human motor cortex excitability under the influence of an antiepileptic drug. From an epileptological point of view, one would be interested in a measure which allows a selective evaluation of cortex excitability. For the two conditioning-test, double-pulse techniques which have been established recently in order to measure

corticocortical excitability (Kujirai et al. 1993) and transcallosal inhibition (Ferbert et al. 1992; Netz et al. 1995), it has been shown by means of H-reflex studies that the effect of the conditioning stimulus is due to supraspinal mechanisms. This may prove to be a major advantage over the conventional single-pulse measurements (motor threshold, silent period), which are confounded by interactions at the level of the spinal cord (Fuhr et al. 1991; Cantello et al. 1992; Inghilleri et al. 1993; Ziemann et al. 1993). Since benzodiazepine receptors are densely distributed in the human cerebral cortex (e.g., Abadie et al. 1992) but occur only sparsely in the ventral horn of the spinal gray matter (Faull and Villinger 1986; Waldvogel et al. 1990), we were interested to know whether benzodiazepines induce changes in motor system excitability at a predominantly cortical level and whether it is possible to show this by means of paired shock stimulation. This was the reason to select for investigation the short-acting benzodiazepine lorazepam, which acts selectively through the reinforcement of γ-aminobutyric acid (GABA) action on the Cl^- ionophor by increasing channel opening frequency (e.g., Olsen 1987).

The following novel findings are presented in this study:

1. With various transcranial magnetic stimulation experiments it was possible to detect significant changes in motor system excitability in healthy human volunteers after a single, medium oral dose of lorazepam. These changes peaked 2–5 h after drug intake and were largely reversible after 24 h. This time course parallels the pharmacokinetics of lorazepam in humans, with a peak in plasma concentration about 2 h after a single oral dose and an elimination half-time of 12–15 h (e.g., Knowles et al. 1971)
2. Lorazepam had no effect on motor threshold and the size of the MEP. The cortical silent period was lengthened (peak at 5 h), while the peripheral silent period was only slightly prolonged at 2 h and not affected any longer at 5 h. The corticocortical inhibition showed a tendency toward more inhibition, while the corticocortical facilitation was almost completely suppressed. The transcallosal inhibition showed an inconsistent trend to less inhibition.

In addition to the notion that lorazepam has a specific mode of action through the reinforcement of GABA action without any known direct effect on the conductivity of membrane ion channels, the discussion on the physiological basis of the observed drug effects first has to reflect some general issues before the present results will be discussed in detail: Which properties of the motor cortex determine its excitability? Two factors are thought to be of principal importance (e.g., Engel 1989): first, the excitability of neuronal membranes, which is regulated by passive membrane characteristics (such as resting membrane potential, membrane input resistance, ion channel conductance). Second, the firing pattern of the network of cortical interneurons which temporally and spatially summates on the population of corticospinal neurons. Of course, these mechanisms also apply to the population of motoneurons in the spinal cord.

Which structures are activated by TMS? Extensive evidence has been provided that focal magnetic stimulation at low or moderate intensity, with the current induced in the brain directed perpendicularly toward the central sulcus, mainly activates corticospinal neurons transsynaptically, probably through horizontally oriented interneuronal fibers (Day et al. 1989; Brasil-Neto et al. 1992; Werhahn et al. 1994). However, this is still a matter of debate, since good evidence also exists for the hypothesis that TMS can activate corticospinal neurons directly at or near the initial axonal segment (Amassian et al. 1990; Edgley et al. 1990, Baker et al. 1994). No matter which hypothesis turns out to be true, both modes of activation should be critically dependent on the cortical excitability in the sense dicussed above.

It is expected that the GABA-enhancing properties of lorazepam should affect the pattern of firing probabilities within the cortical interneuronal network, while the threshold for excitation of neuronal membranes should remain unchanged.

The present findings probably meet these expectations:

1. A single oral dose of lorazepam had no effect on the resting and active motor threshold. In view of the clear effect of lorazepam on other parameters of motor excitability, this at first sight is rather surprising. A low sensitivity of the motor threshold to excitability changes would be the simplest explanation for this lack of effect. However, it could also be hypothesized that the motor threshold after single-pulse magnetic stimulation tests the excitability of cell and fiber membranes and not the excitability of the neuronal network connected to the corticospinal system, thus remaining unaffected by the GABA-enhancing action of lorazepam. In accord with this view, reports now exist that the anticonvulsant drugs valproic acid and diphenylhydantoin, which modulate ion channel conductivity, increase motor threshold (Reutens et al. 1993; Mavroudakis et al. 1994).
2. Although the early part of the CSP is at least in part due to spinal inhibitory mechanisms, the late part is probably due to inhibition at the cortical level (Fuhr et al. 1991; Cantello et al. 1992; Inghilleri et al. 1993; Roick et al. 1993; Wilson et al. 1993; Ziemann et al. 1993). This view is supported by the present results, which show that the GABA-enhancing action of lorazepam induces a prolongation of the CSP duration. In order to be more confident that this lengthening of the CSP was really due to an enhancement of inhibition at the cortical level, the PSP after electrical nerve stimulation was also obtained. The slight lengthening of the PSP 2 h after drug intake indicates a significant increase in spinal inhibition by lorazepam. However, in favor of a mainly cortical action of lorazepam, at 5 h, when the lengthening effect on the CSP reached the maximum, no lengthening of the PSP was seen any longer. The size of the MEP preceding the CSP and the level of sustained target

muscle contraction remained unaffected by lorazepam. This excludes these parameters as possible sources of changes in CSP duration (Cantello et al. 1992; Wilson et al. 1993) and further substantiates the view that the prolongation of the CSP is specifically due to the GABA-enhancing action of lorazepam. A reduction in MEP size by a short-acting benzodiazepine (midazolam) was reported by another group (Schönle et al. 1989). However, it is unclear how this finding relates to our data because of differences in the experimental procedure (midazolam was applied intravenously over 30 min and measurements were taken during the infusion only). Finally, despite its clear increasing effect on motor threshold, the anticonvulsant diphenylhydantoin has no effect on the duration of the CSP (Mavroudakis et al. 1994). Since diphenylhydantoin has no known GABAergic properties, this negative result is also in accord with the concept that the CSP is mainly due to cortical GABAergic mechanisms.

3. Further credit to the data on the CSP is given by the finding that in the paired shock paradigm the GABA-enhancing action of lorazepam showed a trend to increase corticocortical inhibition and, which is the more important effect, suppresses almost completely corticocortical facilitation. This is thought to be good evidence for a GABAergic effect occurring specifically on the level of the motor cortex for the following reasons: first, it has been shown that the very low intensity conditioning stimulus has no effect in the spinal cord and probably exerts its suppressing effect on the size of the test response by activation of inhibitory interneuronal circuits in the motor cortex which project onto the population of corticospinal neurons (Kujirai et al. 1993). These authors did not pay much attention to the facilitatory effect of the conditioning shock on the test response at longer interstimulus intervals. They speculated on a possible spinal contribution to this effect. However, some recent work from the same labaratory (U. Ziemann, M. C. Ridding, and J. Rothwell, unpublished observations) provided evidence in favor of a mainly cortical excitatory mechanism, so that it is now thought that the low intensity conditioning shock is capable of activating separate populations of inhibitory and excitatory interneurons in the motor cortex. Thus, inhibitory and facilitatory excitability changes in the interneuronal network of the motor cortex can be probed by the paired shock paradigm. Second, the GABA-enhancing action of lorazepam should increase the gain of the inhibitory circuits, leading to more corticocortical inhibition and less excitation. This largely meets the present findings. We can only speculate on the observation of a weaker effect of lorazepam on corticocortical inhibition compared with facilitation. One reason might be the occurrence of a "floor effect," assuming that the conditioning stimulus, before lorazepam intake, has already fully activated those inhibitory interneuronal circuits which mediate the corticocortical inhibition so that lorazepam cannot enhance this system any further. Some supporting evidence for this view comes from the paper by Kujirai et al. (1993), who have shown that maximum corticocortical inhibition can be obtained by a conditioning stimulus intensity of 0.8 times relaxed motor threshold, which on average is equivalent to the stimulus intensity used here. Lower or higher intensities induced less inhibition. The more conspicuous suppressive effect of lorazepam on corticocortical facilitation supports the concept that the facilitation is not merely a rebound but a separate phenomenon from corticocortical inhibition, and that this excitatory circuit is controlled by another inhibitory system, which can be driven by GABA. Finally, the prediction can be made that anticonvulsant drugs without GABAergic or any other neurotransmitter properties should not affect the corticocortical excitability but this has not been tested yet by means of the paired shock paradigm.

4. Lorazepam showed an inconsistent trend on transcallosal inhibition toward less inhibition. It can only be speculated why a clear effect was not seen. The nature of interhemispheric transfer along the corpus callosum is still a matter of controversy. Animal experiments have shown point-to-point facilitation between homotopic areas of the right and left motor cortices and inhibition in a wide area of surrounding cortex (Asanuma and Okuda 1962). Evidence for transcallosal facilitation in man was given by the experiments of Cracco et al. (1989) and Ugawa et al. (1993). In contrast to the latter study, by using the same paradigm of bilateral conditioning-test magnetic stimulation of the motor cortex but a higher intensity of the conditioning shock, other authors reported on a predominantly inhibitory transcallosal effect (Ferbert et al. 1992; Netz et al. 1995). It has been suggested that the peak-to-peak facilitation was overwhelmed by strong surround inhibition in the "test cortex" induced by the large conditioning stimulus (Ferbert et al. 1992; Ugawa et al. 1993). If so, the true nature of callosal transfer would be mainly facilitatory and the final result of transcallosal stimulation would depend on the amount of lateral inhibition. It is, however, practically impossible to predict the net effect of an increased GABA gain on lateral inhibition in this diffusely stimulated "test cortex." For instance, animal experiments have shown that the firing properties of sensory and motor neurons can be "broadened" if the GABA-antagonist bicuculline is applied in the direct vicinity of these neurons (e.g., Sillito 1975; Matsumara et al. 1992). From this it has been hypothesized that "sharp" neuronal response properties depend on local GABAergic inhibitory mechanisms. In contrast, "broadening" is also possible if GABA is applied to remote lateral inhibitory neurons (e.g., Crook and Eysel 1992). This dichotomy of coexistent increments and decrements in lateral inhibition may be the reason for the absence of any clear net effect by lorazepam in the present experiments on transcallosal inhibition.

The combination of distinct effects on motor system excitability presented here for lorazepam is compatible with a very recent study which, in a similar experimental setup, has investigated the effect of ethanol (Ziemann et

al. 1995). In the absence of any effect on motor threshold, ethanol lengthens the CSP and strongly suppresses corticocortical excitability. These effects were explained by the known GABAergic properties of ethanol in the central nervous system.

In summary, the present study introduces the possibility of measuring noninvasively the effect of single oral doses of antiepileptic drugs on human motor system excitability in vivo. The extension of the present data to various other antiepileptic drugs may provide a more detailed insight into their physiological effects on a systemic level in man. This may have major implications in clinical epileptology, since it is also possible with the various techniques used here to obtain abnormal excitability data in patients with epilepsy (J. Rothwell, personal communication). In the future, this knowlegde may facilitate a more reliable prediction than presently possible of whether a given antiepileptic drug is effective in the treatment of a given epileptic patient who has been shown by TMS to have an abnormal motor cortex excitability.

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