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ORIGINAL INVESTIGATION

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Intracortical excitability is modulated by a norepinephrine-reuptake inhibitor as measured with paired-pulse transcranial magnetic stimulation

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Abstract *Objective:* Paired-pulse transcranial magnetic stimulation (ppTMS) of the motor cortex can be used to measure intracortical inhibition and facilitation of evoked motor potentials dependent on different interstimulus intervals (ISI). The reuptake-inhibition of norepinephrine, known as an excitatory neuromodulator and neurotransmitter, was postulated to enhance cortical excitability through increased facilitation and reduced inhibition as measured with ppTMS. *Methods:* Eight healthy subjects were examined with ppTMS at ISIs of 2, 3, 4, 5, 6, 7, 8, 10, 15 and 20 ms before and approximately 1.5 h after ingestion of 8 mg reboxetine. The group effects at the different ISIs pre/post reboxetine intake were analysed. *Results:* Post-reboxetine ppTMS showed an enhanced intracortical facilitation effect at ISIs of 8, 10, 15 and 20 ms. A decreased inhibition was found at an ISI of 3 ms. *Conclusions:* Reboxetine-induced higher postsynaptic norepinephrine level enhances intracortical excitability as measured with ppTMS. This finding provides new perspectives for evaluating neurophysiological properties of antidepressive medication and for investigating the pathophysiology of depression.

Keywords Paired-pulse transcranial magnetic stimulation · Norepinephrine reuptake inhibition · Reboxetine · Depression · Cortical excitability

Introduction

A better understanding of the neurophysiology of psychiatric medication effects and of psychiatric disorders may open new perspectives for more differentiated treatment strategies. Norepinephrine is a major modulating neurotransmitter in the human brain, and it is involved in the pathophysiology of psychiatric diseases such as major depression (Ressler and Nemeroff 1999). The norepinephrine-reuptake inhibitor reboxetine has antidepressant effects (Nelson 1999).

Paired-pulse transcranial magnetic stimulation (ppTMS) can be used to measure intracortical excitability (Kujirai et al. 1993). It consists of an initial conditioning pulse (CP) below motor threshold and a subsequent suprathreshold test pulse (TP) with a variable interstimulus interval (ISI) in the range of milliseconds. The CP has an effect on the intracortical neural network without eliciting a motor response. The characteristics of this effect are measured by the TP, which accordingly evokes a motor potential (MEP) that is modulated compared to a single TP. The paired-pulse MEP is inhibited compared to the single TP when applying a short ISI of 1–4 ms, whereas it is facilitated with longer ISIs of about 6–20 ms (Ziemann 1999). This inhibitory or excitatory influence of the CP on the intracortical neurons can be modulated by altering the neurotransmitter state and points to characteristics of applied neuropsychiatric drugs (Ziemann 1999). Agonists of the serotonergic, dopaminergic and GABAergic systems were reported to increase intracortical inhibition (ICI) and to decrease intracortical facilitation (ICF), (Ziemann et al. 1996a, 1996b, 1996c; Werhahn et al. 1999; Manganotti et al. 2001). Some of their antagonists, as well as glutamatergic and noradrenergic agonists, have been shown to cause the opposite effects (Ziemann et al. 1998; Schwenkreis et al. 1999, 2000; Plewnia et al. 2001a).

There is further evidence of altered cortical excitability in psychiatric diseases. An interhemispheric difference with lower excitability on the left side was shown in depressed patients (Maeda et al. 2000). Obsessive-compulsive and schizophrenic patients were reported to have reduced intracortical inhibition (Greenberg et al. 2000; Maeda et al. 2000; Daskalakis et al. 2001; Fitzgerald 2001). Since neurotransmitter altering medication is a major treatment strategy, these first findings are of particular interest for future investigations of transmitter

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systems in psychiatric diseases using ppTMS. Testing the influence of a psychotropic substance in a psychiatric disorder may reveal pathophysiological markers of the disorder, or predict therapy response. This could be realized by correlating the influence of a psychiatric drug on cortical excitability before treatment. Effects of antidepressant medication on cortical excitability as measured with ppTMS have been shown after IV application of clomipramine (Manganotti et al. 2001), after ingestion of sertraline (Ilic et al. 2002), and preliminarily after reboxetine (Plewnia et al. 2001b, conference abstract). The aim of this study was to evaluate the effects of reboxetine as a selective norepinephrine-reuptake inhibitor and excitatory neurotransmitter on cortical excitability, using a wide range of ISIs. Our hypothesis was that reboxetine would increase intracortical excitability, reflected by reduced inhibition at short ISIs at 2–4 ms and increased facilitation at longer ISIs of 6–20 ms.

Materials and methods

Subjects

Ten healthy subjects were initially included. Eight of them completed the study. The study was approved by the local institutional review board. The procedures and purposes of the study were explained to the subjects and written informed consent was obtained. Inclusion criteria were right-handedness, and no history of severe neuropsychiatric disorder, epilepsy, brain injury or brain surgery, or a cardiac pacemaker. Subjects should not have consumed any medication, illegal drugs, nicotine or alcohol in the 3 days before the study, and they were asked not to drink coffee in the morning before ppTMS or during the study.

Paired-pulse stimulation

Subjects were seated in a comfortable chair. Their head was placed on a self-constructed chin and forehead rest in order to prevent head movements. The magnetic coil was held by a tripod to avoid coil movements during the paired-pulse session. Stimulation was applied with a combined TwinTop and MagLite25 stimulator (Dantec/Medtronic) using a figure-8 coil (MC-B70). The optimal coil position for stimulation was defined as the position above the left motor cortex where the most prominent motor answer was obtained with a slightly suprathreshold stimulus. The coil was held tangentially to the skull with the handle pointing about 45° dorsolaterally. Prior to each ppTMS session (pre- and post-reboxetine), resting motor threshold (RMT) was determined as the lowest stimulation intensity that evoked in at least three out of six stimulations a MEP of at least 50 μV peak to base, as recorded by a surface EMG (Keypoint Portable, Medtronic) from the relaxed right M. abductor pollicis brevis (APB) (Rossini et al. 1994).

Intracortical excitability was tested using the paired-pulse paradigm (Kujirai et al. 1993) consisting in a first subthreshold conditioning pulse (CP) followed by a second suprathreshold test pulse (TP). The intensity of the CP for each session (before and after drug intake) was set to be about 5% below the RMT revealed before the session. This intensity should evoke more prominent facilitatory effects compared to a CP of 20% below RMT (Kujirai et al. 1993; Ziemann et al. 1996d). The intensity of the TP was adjusted to induce a MEP in the range of 0.5–2 mV (peak-to-base) amplitude, when applied as single evaluating test pulse prior to the corresponding session.

The ppTMS was performed with ten different ISIs: 2, 3, 4, 5, 6, 7, 8, 10, 15, 20 ms. In each session, two blocks of paired pulses were applied. Each block consisted of five paired pulses of each ISI, making 50 paired pulses, and ten single TPs serving as control MEPs. The order of the paired pulses with the different ISIs and the control MEPs were randomized for each block. The paired pulses and control MEPs were applied with a delay of at least 5 s between each other, in order to avoid possible interference with the effects of the previous pulses.

The mean of the ten control MEPs of each block served as a reference for the relative changes of the amplitudes of the different ISIs. Thus, the size of the mean amplitude of each ISI condition was calculated as a percentage relative to the mean of the corresponding control MEPs in the same block.

Drug application

After completing the first two blocks, subjects were asked to take reboxetine 8 mg (two tablets of 4 mg). Reboxetine is a selective norepinephrine-reuptake inhibitor and is used as an antidepressant (Nelson 1999). Because of its plasma half-life of about 12–16 h, this drug is often taken in two doses per day of 4 mg per dose. After the paired-pulse session prior to medication, the next session started with a delay of 70 min. Because the exact repositioning of the coil and evaluating RMT and stimulus intensity took time, the post-reboxetine ppTMS measurements began about 1.5 h after drug intake and ended about 30 min later.

Statistical procedures

In order to determine a drug effect comparing pre-reboxetine ppTMS and post-reboxetine ppTMS, in a first step the median of the values for the five ISIs in each block were calculated as a percentage of the median of the ten control MEPs of the same block. The median was chosen because the absolute values of the amplitudes are not normally distributed. To confirm the results, we calculated the data using the mean as well and further after a removal of all values exceeding 2 SD within an ISI block. Because there were two blocks per session, the means of the percentages of both blocks were calculated for further analysis. The percentage values of each subject were pooled in a pre-reboxetine-group for each ISI and a post-reboxetine-group for each ISI in order to analyse the pre-post group effect. Effects of reboxetine on inhibition and facilitation comparing pre- and post-reboxetine intake were tested using a MANOVA for repeated measures by means of multivariate single comparisons for each ISI. Wilcoxon test was performed as well, to test non-parametrically pre-post effects of each ISI. The group effect of the motor thresholds pre- and post reboxetine were also compared using the Wilcoxon test. In order to test if an effect of different pre-/post-values might be accounted to different absolute reference test MEP amplitudes from which the relative values for each ISI were calculated, test amplitudes were compared using Student's *t*-test and Wilcoxon test. Statistics were done using the Statistica 5.5 software package (Statsoft, Tulsa, USA).

Results

The subjects (five female, age 24–35, all right-handed) did not complain serious side effects of stimulation. Two subjects had to be excluded, one because no stable control MEP amplitudes were obtained after reboxetine intake, and the other because of an inability to sit quietly as well as sleepiness during the post-reboxetine measurements. Of the initial ten subjects seven experienced medication side effects (some multiple): insomnia (n=2), fatigue (4),

Table 1 Means and SDs as percentages of the paired-pulse test amplitudes at the different interstimulus intervals (*ISI*) in relation to the control amplitudes (*MEP*). Mentioned are the measurements obtained by ppTMS before reboxetine intake (*pre-rbx*) and after reboxetine intake (*post-rbx*), and the results of the statistics comparing the pre/post-rbx results

	MEP	ISI 2	3	4	5	6	7	8	10	15	20
Mean pre-rbx	100%	31	68	58	97	168	249	252	255	255	205
SD pre-rbx		29	22	27	52	125	140	135	105	97	120
Mean post-rbx	100%	27	103	59	110	163	272	341	400	379	335
SD post-rbx		16	41	39	52	135	169	130	159	169	192
MANOVA *P*=		0.93	0.003	0.46	0.32	0.10	0.18	0.01	0.002	0.03	0.04
Wilcoxon *P*=		0.89	0.01	0.48	0.16	0.16	0.12	0.04	0.02	0.02	0.04

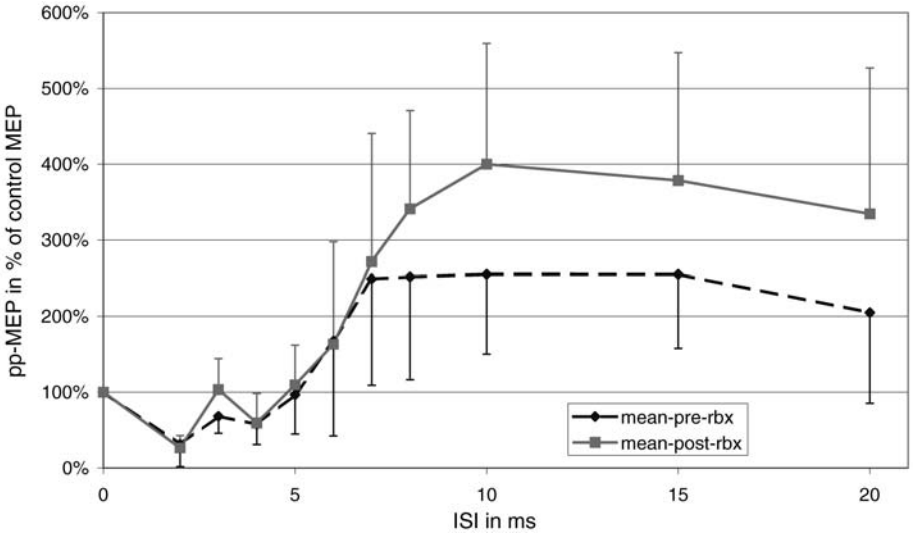

Fig. 1 The graph shows the data of Table 1 are means and standard deviations (SD) as a percentage of the eight subjects of the paired-pulse test amplitudes at the different interstimulus intervals (*ISI*) in relation to the according control amplitudes (*MEP*); *pre-rbx* measurements before reboxetine intake, *post-rbx* measurements after reboxetine intake

nervousness and restlessness (3), aggressive feelings (1), piloerection and cold feelings (4). Three subjects did not report side effects. The observed side effects are in accordance with previous reports (Siepmann et al. 2001).

The comparison of the RMTs pre- and post-reboxetine revealed a significant lower RMT after reboxetine intake (Wilcoxon $P<0.05$).

The paired-pulse curve for the different ISIs without reboxetine showed an inhibition for the short ISIs of 2, 3 and 4 ms and a facilitation for 7, 8, 10, 15 and 20 ms, in trend for 6 ms. The turning point from inhibition to facilitation was in mean closest to the ISI of 5 ms.

The effects of reboxetine intake on the different ISIs were tested within a MANOVA for repeated measures by means of multivariate single comparisons for each ISI (Table 1, Fig. 1). We observed significant differences on motor amplitudes for ISI 3 [$F(1,7)=18.9$, $P=0.003$], which no longer showed an inhibition (103%) after administration of reboxetine (before 68%). Increased facilitation was observed at the following ISIs: 8 [$F(1,7)=12.8$, $P=0.01$], 10 ms [$F(1,7)=$, $P=0.002$], 15 ms [$F(1,7)=8.1$, $P=0.03$], 20 ms [$F(1,7)=6.1$, $P=0.04$]. The data are presented in Fig. 1 showing two graphs of MEP over varying ISIs with standard deviations. The analysis using the means of the ISIs of each block and after elimination of exceeding values provided the same results as when the medians were used.

Discussion

The main finding of this study is increased intracortical excitability following enhanced postsynaptic norepinephrine levels, as measured with ppTMS in the motor cortex. The norepinephrine reuptake inhibitor reboxetine increased intracortical facilitation at ISIs of 8, 10, 15 and 20 ms. It further reduced intracortical inhibition at an ISI of 3 ms. Additionally, reboxetine lowered the resting motor threshold. These findings are in line with Plewnia et al. (2001a, 2001b and unpublished data), who reported an increase of intracortical facilitation after the intake of the presynaptic alpha$_2$-inhibitor yohimbine and after reboxetine as well.

The paired-pulse curve for the different ISIs without reboxetine showed an inhibition for the short ISIs of 2, 3 and 4 ms and a facilitation for 7, 8, 10, 15 and 20 ms. These are similar characteristics to those reported in the literature (Kujirai et al. 1993; Ziemann 1999). The percentage values for the facilitation already in the pre-reboxetine curve are relatively high compared to reports where a conditioning pulse with an intensity of 80% RMT was used. However, they are in accordance with reports of stronger facilitation using conditioning pulses with higher intensities below RMT, as in our study, or CPs at 80% of the active motor threshold (Kujirai et al. 1993; Ziemann et al. 1996d).

Innervation with noradrenergic fibres appears to be widespread in the neocortex, as demonstrated in rats (Levitt and Moore 1978). Unilateral ablation of the nucleus coeruleus diminishes ipsilateral cortical noradrenaline content and fibre innervation. The nucleus coeruleus in the ventral tegmentum is known to modulate the noradrenergic system (Aston-Jones et al. 1999). Drugs such as reboxetine may enhance the excitatory effect of this system, resulting in increased intracortical facilitation and reduced intracortical inhibition.

It has been suggested that intracortical inhibition may be mediated by activation of GABAergic interneurons by the conditioning pulse, resulting in the suppression of late descending volleys (I-waves) that are generated by trans-synaptic activation of pyramidal tract neurons (Ziemann 1999). Another mechanism could be related to the refractory period of the pyramidal tract neurons. The subthreshold conditioning pulse may cause depolarization of some pyramid neurons, but not enough to evoke a muscle sum action potential. When a few milliseconds later the suprathreshold test pulse is given, the initially depolarized neurons are still in their refractory period, and cannot contribute to the action potential, which then appears to be inhibited.

The mechanism of intracortical facilitation is thought to be different from that of ICI and not to be just a rebound phenomenon following previous inhibition (Ziemann 1999). However, its exact mechanism has not yet been clarified. Possible mechanisms are the induction of slow excitatory postsynaptic potentials and/or induced intracellular signalling cascades enhancing excitability of pyramidal tract neurons by trans-synaptic activation of metabotrope receptors. On an electrophysiological basis, fibres in cortical layers I and II that project to such receptors on pyramidal tract neurons may be depolarized because of an intra/extracellular membrane potential shift when lying in the electric field, resulting in saltatory conduction towards the pyramidal tract neurons.

There is evidence that ppTMS can detect modulatory influence of several psycho-/neurotropic substances on the excitability of the cortical network, as demonstrated in the motor cortex (Ziemann 1999).

Concerning antidepressant medication, clomipramine 25 mg IV, which has major serotonergic, minor acetylcholinergic and, after metabolism, also noradrenergic effects, was found to decrease ICF, and to increase ICI in depressed patients (Manganotti et al. 2001). A decreased ICF in healthy subjects was reported after an oral dose of 100 mg sertraline as a specific serotonin reuptake inhibitor (Ilic et al. 2002). These findings of opposite effects of serotonergic and noradrenergic antidepressants on intracortical excitability point toward a dissociation between their electrophysiological influence and their mediation of an antidepressive effect, which requires further study.

An examination of ppTMS studies suggests excitatory influences of the glutamatergic (Ziemann et al. 1998; Schwenkreis et al. 1999, 2000) and noradrenergic systems on the motor cortex, whereas stimulation of the dopami-

Table 2 Overview of studies investigating the effect of ppTMS on several transmitter systems. *ICI* intracortical inhibition, *ICF* intracortical facilitation

Transmitter system	ICI	ICF	Remarks
Dopamine	↑	↓	Agonists (pergolide, bromocriptin) ICF only trend, antagonist haloperidol reverse effects both significant (Ziemann et al. 1996a, 1997)
GABA	↑	↓	Shown with lorazepam, ethanol, antiepileptic drugs (Ziemann et al. 1996b, 1996c, Werhan et al. 1999)
Serotonin	↑	↓	Clomipramine 25 mg IV (Manganotti et al. 2001), sertraline 100 mg oral dose (reduced ICF; Ilic et al. 2002)
Glutamate	↔	↑	Antagonists riluzole, memantine, dextrometorphane (Ziemann et al. 1998; Schwenkreis et al. 1999, 2000)
Norepinephrine	↓	↑	Yohimbine, reboxetine (Plewnia et al. 2001a, b)
Acetylcholine	↔	↔	Muscarinic receptor blockade, scopolamin, 4 subjects (Di Lazarro et al. 2001)

Table 3 Overview of studies investigating the effect of ppTMS in psychiatric disorders. *ICI* intracortical inhibition, *ICF* intracortical facilitation, *MT* motor threshold, *ISI* interstimulus interval

Psychiatric disorder	ICI	ICF	Remarks
Depression	(↑) Left	(↓) Left	Interhemispheric difference in ICI in depression, left-sided lower excitability, *n*=8, off medication (Maeda et al. 2000)
OCD	↑	↔	Less ICI in ISI 2–5 ms, lower MT, independent of SSRI medication, *n*=16, (Greenberg et al. 2000)
Schizophrenia	↓	↔	Less ICI in schizophrenic patients compared to controls (Daskalakis et al. 2002; Fitzgerald et al. 2002)
Anxiety-related personality/ neuroticism	(↓)	(↑)	Personality inventory in 46 healthy, correlation with neuroticism in men, not anxiety, mean of all ISI (Wassermann et al. 2001)

nergic (Ziemann et al. 1996a, 1997), serotonergic and GABAergic (Ziemann et al. 1995, 1996c; Werhahn et al. 1999) systems showed inhibitory effects (Table 2).

Only a few studies have been presented to date investigating the intracortical excitability state using ppTMS in psychiatric disorders. In OCD patients, decreased ICI was found, independently of SSRI medication, reflecting a higher excitation level (Greenberg, et al. 2000). A comparable result was reported for unmedicated schizophrenic patients, showing less ICI than medicated patients and controls (Fitzgerald et al. 2002; Daskalakis et al. 2002). In unmedicated depressed patients, an interhemispheric difference in ICI was reported, with lower excitability of the left motor cortex than of the right. However, this difference was not significant compared with healthy controls (Maeda et al. 2000). A personality inventory of 46 healthy subjects was correlated to the mean of the ISI values of the paired-pulse curve and a correlation between the item neuroticism, but not anxiety, and higher ISI values reflecting higher excitability was found in men (Wassermann et al. 2001) (Table 3).

The above-mentioned studies indicate that the ppTMS effects are not specific for a certain neurotransmitter system or are typical for a neuropsychiatric disorder. However, ppTMS may serve to characterize the influence of certain transmitter system-specific neuropsychiatric drugs on cortical excitability, and to characterize further the general excitability state in psychiatric disorders.

In conclusion, ppTMS has been shown to be a useful tool for examining the excitatory state of the cerebral cortex. Reboxetine as a norepinephrine reuptake inhibiting antidepressant enhances cortical excitability in healthy subjects. It may be of special interest to investigate the influence of psychiatric medication in psychiatric disorders in order to reveal pathophysiological aspects or response predictors for treatment.

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