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Chronic administration of selective serotonin reuptake inhibitor (SSRI) paroxetine modulates human motor cortex excitability in healthy subjects

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The aim of the study was to investigate the effect of chronic administration of paroxetine (selective serotonin reuptake inhibitor: SSRI) on motor cortex excitability in healthy subjects by means of transcranial magnetic stimulation (TMS), functional magnetic resonance imaging (fMRI) and behavioral motor tests. In a randomized, double-blind, crossover study, twenty-one right-handed subjects received 20 mg daily of either paroxetine or a placebo over a period of 30 days separated by a period of 3 months wash-out. The TMS study is presented here correlated with some results of the motor behavior study (finger tapping test) and the fMRI study (primary sensorimotor cortex (S1M1) volume of activation). TMS was used to test motor threshold (MT), motor evoked potential recruitment curve (RC), cortical silent period (CSP) and paired-pulse intracortical inhibition and facilitation (ICI, ICF). Chronic administration of paroxetine did not modulate ICI or CSP but induced a significant enhancement of mean ICF (ANOVA $P = 0.04$), which significantly correlated with increase of speed in a finger tapping test ($P = 0.02$). This suggests a modulation of cortical interneuronal excitatory pathways without changes in the excitability of cortical inhibitory GABAergic interneurons. A decrease of RC (ANOVA $P = 0.05$) was also observed after 30 days intake of paroxetine in comparison with placebo and was associated with changes of fMRI activation intensity (left S1M1 hypoactivation, Loubinoux, I., Tombari, D., Pariente, J., Gerdelat, A., Pastor, J., Cassol, E., Rascol, O. and Chollet, F., Modulation of behavior and cortical motor activity in healthy subjects by a chronic administration of a serotonin enhancer. NeuroImage (in press)), without changes of S1M1 activation volume. Finally, the different modulation of RC and ICF after chronic administration of paroxetine compared to single dose (opposite effects) emphasizes the different pharmacological action of the drug at cortical level depending on its acute or long-term administration.

Keywords: Transcranial magnetic stimulation; Cortical excitability; Motor performance; SSRI; Chronic treatment

Introduction

Pharmacological modulation of motor cortex excitability has been the subject of extensive investigation in the past in the intention of finding drugs which can selectively stimulate motor function and improve motor recovery after brain lesions. Beneficial effects of noradrenergic modulation by amphetamine administration have been observed on motor recovery in animals (Boyeson and Feeney, 1990; Feeney et al., 1982; Stroemer et al., 1998) and in stroke patients (Crisostomo et al., 1988). The selective drug-induced increase of cortical excitability might play a role in synaptic plasticity (Butefisch et al., 2002; Ziemann et al., 2002) and then improve functional recovery after brain lesions. In this way, the noradrenergic modulation of human cortex excitability by the presynaptic alpha 2-antagonist yohimbine (Plewnia et al., 2001) or selective norepinephrine reuptake inhibitor reboxetine (Plewnia et al., 2002) has been studied recently in healthy subjects with transcranial magnetic stimulation (TMS), and it has been proposed that the neuroplasticity induced by the combination of drugs and motor training may have a possible relevance for strategies to enhance recovery after stroke.

There is considerable evidence that serotonin is also involved in motor function in animals and humans (Geyer, 1996; Hasbroucq et al., 1997; Hindmarch, 1995; Jacobs and Fornal, 1997), and we have shown recently that a single dose of selective serotonin reuptake inhibitor (SSRI, fluoxetine or paroxetine), which enhances central 5-HT neurotransmission and postsynaptic serotonin

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receptor stimulation, modulates motor performance and fMRI cerebral activation in healthy subjects and post-stroke patients (Loubinoux et al., 1999, 2002; Pariente et al., 2001). The positive correlation between the increase in executive motor area activation and the increase in motor performance observed in these groups of post-stroke patients, as in other studies, suggests that serotonin could be a good candidate to promote functional motor recovery in stroke patients in association with physical rehabilitation (Dam et al., 1996).

In a TMS study, Ilic et al. (2002) showed that, in healthy subjects, a single dose of sertraline, another SSRI, induced a complex modulation of motor cortex excitability with an increase in the recruitment curve and a decrease in paired-pulse intracortical facilitation. Pleger et al. reported recently a change in cortical excitability (enlargement of hand muscles motor map) after a single dose of 20 mg of fluoxetine, without a change in motor performance (motor learning; Pleger et al., 2004). Most of the TMS or fMRI studies of drug-induced cortical modulation are conducted separately using the single dose drug intake paradigm. Because an SSRI treatment for post-stroke rehabilitation would last at least 1 month, we decided to study the effect of a 1-month administration of paroxetine on the motor cortex excitability of healthy subjects by means of a TMS, fMRI and motor performance-coupled study. Only results of the TMS study are presented here, correlated with some results of the behavioral motor study (finger tapping test). In order to shed some light on the TMS measurements and especially the recruitment curve, the volume of left primary sensorimotor (SIMI) activation during a voluntary right hand movement was assessed with fMRI. The complete set of fMRI and behavioral results are presented in a separate paper (Loubinoux et al., in press). Our hypothesis was that chronic administration of paroxetine should, like the single dose, induce a modulation of paired-pulse intracortical motor excitability and/or of the single shock recruitment curve without a change of motor threshold.

Methods

Subjects

Experiments were performed on 21 healthy subjects (11 men and 10 women), aged 42–68 years (mean 57.5 ± 6.5 years), recruited by the clinical investigation center of Toulouse. They had a normal neurological examination and no history of neurological or psychiatric disease. Exclusion criteria were depression (MADRS scale), hypertension or the presence of cardiac dysrhythmia, contra-indication to MRI, pregnancy, use of antidepressants or drugs that were incompatible with antidepressants (stimulants, vasodilators, β blockers, anxiolytics), alcoholism, drug-addiction, allergy to SSRI or to other related drugs. All subjects were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). The protocol was approved by the local Ethics Committees (Toulouse I), and all subjects included gave their written informed consent prior to the study.

Experimental protocol

In the present randomized, double blind, crossover study, the subjects received 20 mg daily of either paroxetine or placebo over a period of 30 days separated by a period of 3 months wash-out. After each treatment, the subjects underwent in a random order, TMS, fMRI examinations and a behavioral motor assessment on the same day. Thus, each subject served as his or her own control. The paroxetine and placebo were indiscernible and prepared by a hospital pharmacist independently of the investigators. Neither the patients nor the investigators were aware of which treatment had been administered. The randomization code was kept by the clinical investigation center of Toulouse and was broken at the end of the study (May 2003).

Transcranial magnetic stimulation (TMS)

Recording technique

EMG activity was recorded from silver/silver-chloride surface electrodes secured to the skin over the muscle belly of the right first dorsal interosseus (FDI). The EMG signals were amplified, filtered (bandpass 100 Hz–1 kHz), rectified and digitized at a frequency of 5 kHz using an A/D converter (computerized data acquisition system built with the Labview graphical programming language, Elitek system) and stored for later off-line analysis on a personal computer. During the experiments, EMG activity was continuously monitored with visual (oscilloscope) and auditory (speakers) feedback to ensure either complete relaxation at rest or a constant level of EMG activity during tonic contraction.

Stimulation

Transcranial magnetic stimulation was done using a figure-of eight shaped magnetic coil (diameter of each wing: seven cm) connected to two Magstim 200 stimulators linked by a Bistim unit (Magstim, Dyfed, UK). The coil was applied to the hand area of the left motor cortex, tangentially to the skull with the handle pointing backwards and laterally at an angle of 45° to the sagittal plane. Subjects were seated in a comfortable reclining chair with a tightly fitting swimming cap place over the head, their forearm pronated and supported by an armrest. Special care was taken to avoid variance in TMS responses due to differences in coil and electrodes placement from one session to the other. We used three marks on the coil matching three other marks on the cap by means of an optical targeting system in order to keep constant the position of the coil over the scalp during the session and for the second session performed 4 months later in exactly similar conditions. Distances between the edge of the swimming cap and eyebrows and forehead wrinkles were measured, allowing, as much as possible, exact replacement of the swimming cap at the second TMS. The optimal position (hotspot) of the magnetic coil for eliciting motor evoked potentials (MEP) in resting right FDI was determined by moving the coil around the presumed representation of FDI in the left motor cortex (2 cm forward and 4 cm laterally from the vertex). The optimal position was defined as the site of stimulation which consistently yielded the largest MEP and produced contraction of FDI alone at a moderately suprathreshold stimulation intensity. The coil was tightly fixed on a tripod device.

Measurement of intracortical and spinal excitability

Resting and active motor thresholds. The resting motor threshold (rMT) was defined as the minimum TMS intensity (measured to the nearest 1% of the maximum output of the magnetic stimulator) required to elicit an MEP of at least 50 μV in the relaxed FDI in at least five out of ten consecutive trials (intertrial