Paliperidon mediated modification of cortical inhibition

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Abstract
Transcranial magnetic stimulation is a neurophysiological method which enables direct quantitative in vivo assessment of cortical excitability and inhibition. The aim of the study was to assess the impact of paliperidone on the motor threshold and cortical silent period, in a drug-naive patient, with first episode schizophrenia using this technique. Paliperidone monotherapy caused a significant reduction of severity of schizophrenic symptomatology in the patient. At the same time, a significant prolongation of the cortical silent period, from 118.68 ms before to 185.13 ms after therapy, occurred. Because the cortical silent period is a function of GABA\textsubscript{B} receptors, we can assume that paliperidone may have the ability to enhance GABA\textsubscript{B} receptor-mediated neurotransmission.

INTRODUCTION
Transcranial magnetic stimulation (TMS) is a neurophysiological method that can non-invasively affect brain activity (Barker et al. 1985). It induces electric currents in the brain cortex by means of a time-variable magnetic field (Barker et al. 1987). Using special application protocols, TMS can provide diagnostic and qualitative measurements of specific neurophysiological brain parameters such as intracortical excitation and inhibition (Pascual-Leone et al. 2002), mapping cortical representation of motor, sensory or cognitive functions (Wassermann 1998) or investigation of functional brain connectivity (Hoffman et al. 2007) possible.

The studies to evaluate pathophysiological mechanisms in schizophrenia often focus specifically on cortical excitability and inhibition. They are based on the view that the characteristic symptoms of schizophrenia, such as auditory hallucinations, delusions or a concept of negative symptoms or cognitive deficits, reflect “activation” or “inhibition” of the relevant brain areas or an imbalance of their mutual neuronal connections and circuits. These hypotheses are supported by findings of functional neuroimaging methods. Functional magnetic resonance (fMRI) has found that auditory hallucinations are associated with activation of neuronal cortical and subcortical network areas including Broca’s area and the bilateral temporal cortex (Shergill et al. 2000). Studies with single photon emission tomography (SPECT) have found increased perfusion of the left temporal cortex, an area which has been related to delusions (Puri et al. 2001). Results from electrophysiological studies have found that the cerebral cortex, in patients with schizophrenia, is less capable or unable to manage its responses to stimuli, which supports the hypothesis of impaired cortical inhibition or facilitation (Alder et al. 1982; Swerdlow and Koob 1987).
The principle of impaired dynamics of the cerebral cortex in schizophrenia has not been satisfactorily clarified. In vivo receptor studies (SPECT) have documented a negative correlation between the occupancy of benzodiazepine receptors and the positive symptoms of schizophrenia (Busatto et al. 1997). Due to the fact that occupancy of benzodiazepine receptors corresponds to the functional status of the type A subunit of the gamma-aminobutyric acid (GABA_A) inhibition receptor, we can assume that the brain inhibition system in schizophrenia is impaired. In accordance with this finding, postmortem studies have found a reduced number of GABA neurons in the brain cortex of schizophrenic patients compared to controls or patients with depression (Volk et al. 2002). Because GABA neurons have a significant position among the brain’s inhibition interneurons, it is clear that schizophrenia is characterized by impairment of the cortical inhibition.

Transcranial magnetic stimulation (TMS) is a neurophysiological noninvasive method which enables direct quantitative assessment of cortical excitability and inhibition in vivo. Because of technical limitations of the chosen method, it was only possible to target the investigation on the area of the motor cortex. However, the functional alterations of cortical dynamics which reflect typical symptoms of schizophrenia, such as auditory hallucinations or delusions may also be generalized in the area of the motor cortex. Therefore TMS is a very useful neurophysiological technique which can detect qualitative and quantitative pathophysiological alterations of the brain in schizophrenia through measurements of motor threshold, pair pulse inhibition or facilitation, and induction of the cortical silent period (CSP).

The aim of the study was to assess the impact of paliperidone on motor thresholds and the cortical silent period, in a drug-naïve, first episode schizophrenia patient and to evaluate changes associated with 28-days of monotherapy with this particular antipsychotic agent.

METHODOLOGY

Clinical characteristics

A male-patient with a diagnosis of schizophrenia according to the DSM-IV (American Psychiatric Association 1994) was included in the study (N = 1). It was the patient’s first episode of schizophrenia and the patient had never received any antipsychotic agents prior to study participation. The diagnosis was confirmed by two experienced psychiatrists. The patient had a negative urine toxicological examination and underwent neurological examination and brain MRI with negative findings. The absence of somatic diseases was confirmed with a standard clinical examination. The patient was right-handed, per the Edinburgh Handedness Inventory (Oldfield 1971). Prior to inclusion in the study and 28 days after paliperidone monotherapy, his clinical status was assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987); TMS measurements were performed at the same time. The study was approved by the local ethics committee and complies with the requirements of the Declaration of Helsinki. The patient signed an informed consent prior to participation in the study.

Experimental TMS protocol

For TMS measurements, two magnetic stimulators (Magstim 200) were used which were interconnected using a Bistimu module (Magstim, Dyfed, UK) and a figure-eight stimulation coil with a diameter of 70 mm. The stimulation coil was placed on the surface of the patient’s head, relative to the motor cortex of the left brain hemisphere, and oriented in such a way as to produce motor evoked potentials (MEP) of maximum peak to peak amplitude on the contralateral target muscle (musculus abductor digiti minimi). The optimal position of the stimulation coil was defined and fixed using recommended standards (Rossini & Rossi 1998). The stimulation coil, which was attached to the scalp, was directed occipitally and it formed an angle of approximately 45 degrees relative to the sagittal axis (i.e. approximately at a right angle to the central sulcus) (Brasil-Neto et al. 1992). With the stimulation coil in this position, the induced electrical current spread in an anteromedial to posteriolateral direction, approximately perpendicular to the direction of the central sulcus and preferentially activated transsynaptic corticospinal neurons (Werhahn et al. 1994).

Determination of the motor threshold (MT)

Motor thresholds (MTs) were registered using electromyography (EMG) on the musculus abductor digiti minimi lat. dx. MT was defined as the lowest stimulation activity, which out of 10 single impulses, caused at least 5 motor potentials with a peak to peak amplitude of at least 50 μV. The interval between the single stimulation thresholds was at least 10 seconds; this was done to reliably exclude possible effects of subsequent TMS stimuli on corticospinal excitability (Chen et al. 1997). During determinations of MTs, the target muscle had to have been completely relaxed for a period of at least 100 ms before stimulation was initiated. Application of TMS pulses were initiated with a stimulation intensity of 90% of the maximum device output and gradually reduced, in 2% increments, until a stimulation intensity capable of producing at least 5 out of 10 MEPs with peak to peak amplitudes of at least 50 μV was achieved. The EMG recording was registered on a EMG (Medelec Synergy) using a pair of superficial electrodes attached to the ball and tendon of musculus abductor digitii minimi of the right hand by means of medical adhesive tape. The ground-electrode was placed on the wrist of the same hand.

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Measurement of the induced cortical silent period (CSP)
The induced cortical silent period was acquired using the application of single TMS pulses above the area of the motor cortex with an intensity of 150% of the rest MT of the musculus abductor digiti minimi during a willful, weak tonic contraction. Duration of the CSP was defined as a time between the initiation of MEP and return of willful EMG activity. This is referred to as the absolute CSP and is ended by any deviation of the EMG wave (Wu et al. 2000). In total, ten measurements were performed and then the CSP was acquired using automatic analysis performed with EMG Medelec Synergy software.

RESULTS
The subject of the study was a 24-year-old male who was diagnosed with first episode paranoid schizophrenia and had been admitted to the Psychiatric clinic, Faculty of Medicine, Masaryk University, Brono, Czech Republic. He had had mental problems for the previous six months. The patient had never been treated by a psychiatrist before and he had never used antipsychotic drugs or any other psychopharmaceuticals. After his diagnosis was confirmed he was given paliperidone, as a monotherapy, at an initial dose of 3 mg with subsequent incremental increases of 3 mg per day for three days until the final daily dose of 12 mg per day was achieved. Before initiation of antipsychotic therapy, the total PANSS score was 101 (positive subscale PANSS 26, negative subscale PANSS 28), the total PANSS score, after 28 days of therapy, fell to 65 (positive subscale PANSS 13, negative subscale PANSS 22) representing an overall reduction of 36% (50% relative to the positive subscale PANSS and 21% for the negative subscale PANSS). Individual rest MT before the therapy was 38%, the average CSP latency achieved was 118.68 ms, median 117.15 ms (SD = 16.84). Individual rest MTs after therapy were 36%, the average CSP latency achieved was 185.13 ms, median 184.95 ms (SD = 16.84). Individual rest MTs after therapy was 38%, the average CSP latency achieved was 118.68 ms, median 117.15 ms (SD = 16.84). Individual rest MTs after therapy were 36%, the average CSP latency achieved was 185.13 ms, median 184.95 ms (SD = 16.84). Individual rest MTs after therapy was 38%, the average CSP latency achieved was 118.68 ms, median 117.15 ms (SD = 16.84). Individual rest MTs after therapy were 36%, the average CSP latency achieved was 185.13 ms, median 184.95 ms (SD = 16.84). Individual rest MTs after therapy was 38%, the average CSP latency achieved was 118.68 ms, median 117.15 ms (SD = 16.84). Individual rest MTs after therapy were 36%, the average CSP latency achieved was 185.13 ms, median 184.95 ms (SD = 16.84). Individual rest MTs after therapy was 38%, the average CSP latency achieved was 118.68 ms, median 117.15 ms (SD = 16.84). Individual rest MTs after therapy were 36%, the average CSP latency achieved was 185.13 ms, median 184.95 ms (SD = 16.84). Individual rest MTs after therapy was 38%, the average CSP latency achieved was 118.68 ms, median 117.15 ms (SD = 16.84). Individual rest MTs after therapy were 36%, the average CSP latency achieved was 185.13 ms, median 184.95 ms (SD = 16.84). Individual rest MTs after therapy was 38%, the average CSP latency achieved was 118.68 ms, median 117.15 ms (SD = 16.84). Individual rest MTs after therapy were 36%, the average CSP latency achieved was 185.13 ms, median 184.95 ms (SD = 16.84). Individual rest MTs after therapy was 38%, the average CSP latency achieved was 118.68 ms, median 117.15 ms (SD = 16.84). Individual rest MTs after therapy were 36%, the average CSP latency achieved was 185.13 ms, median 184.95 ms (SD = 16.84). Individual rest MTs after therapy was 38%, the average CSP latency achieved was 118.68 ms, median 117.15 ms (SD = 16.84).

DISCUSSION
Paliperidone monotherapy caused a significant reduction in the severity of schizophrenic symptomatology in a patient presenting with first episode paranoid schizophrenia. A significant prolongation of the CSP interval occurred at the same time. This can be interpreted as an adjustment of cortical inhibition, which is impaired in schizophrenia (Daskalakis et al. 2002). CSP is thought to reflect the degree of inhibitory mechanisms mainly within the cortical-striatal-pallidal-thalamic-cortical loop (Moll et al. 2006) and changes in thalamocortical modulation (Faig & Busse 1996; Munchau et al. 2002). A prolongation of the CSP has been reported in healthy controls after intake of quetiapine (Langguth et al. 2008). Similar to patients with schizophrenia, prolongation of CSP duration was documented in patients with Tourette’s disorder under neuroleptic treatment (Ziemann et al. 1997). Also based on the findings, that medicated schizophrenic patients have a higher CSP than unmedicated patients (Daskalakis et al. 2002; Fitzgerald et al. 2002), it has already been repeatedly suggested that the lengthening of CSP may reflect part of the antipsychotic properties of neuroleptic agents. Reduced CSP duration is a marker of impaired cortical inhibition. The CSP duration is invariably found to be shortened in patients with schizophrenia either without or with the use of antipsychotics compared to controls (Fitzgerald et al. 2002). Antipsychotic therapy extends the CSP and therefore causes changes in abnormal cortical inhibition processes (Daskalakis et al. 2002).

A deficit of cortical inhibition in schizophrenia reflects the pathology of the cortical and subcortical brain areas. Abnormalities of motor functions in schizophrenia result from increased activity of subcortical dopaminergic neurons which cause disinhibition of cortical inhibitory neurotransmissions (Walker et al. 1994). It is assumed that a reduced number of GABA interneurons in the prefrontal cortex, anterior cingulum and hippocampus cause the deficit of inhibitory functions in schizophrenia (Benes et al. 1999). Inhibition deficits of sensomotor gating also results from excessive activation of subcortical dopaminergic neurotransmission, which leads to reduced activation of cortical inhibition pathways (Swerdlow & Koob 1987). However, in schizophrenia, it is not clear whether a single impaired inhibitory mechanism reflects the fractional brain pathologies or if they are part of a more uniform deficit of inhibitory brain mechanisms.

Patients with schizophrenia who are taking antipsychotics have generally longer CSPs than patients not on medication. While olanzapine or clozapine cause prolongation of cortical inhibition in patients with schizophrenia (Boroojerdi et al. 1999), haloperidol caused reduction of cortical inhibition in healthy volunteers. A possible explanation is differences in dopaminergic tone between schizophrenic patients and healthy volunteers (Laruelle et al. 1996).

It is known from neurophysiological studies that the CSP is a function of GABA_B receptors. These are metabotropic receptors which increase potassium concentrations and lead to hyperpolarization of postsynaptic neurons (Franek 2004). Based on our results, it can be assumed that, as with clozapine, paliperidone can enhance GABA_B receptor-mediated neurotransmission as well. Clozapine increases suppression of the P50 wave which provides evidence of potentiation of GABA_B receptors by clozapine. Inhibition of the P50 wave is mediated by GABA_B receptors on glutamate terminations (Freedman et al. 2000). Prolongation of
the CSP, by influencing GABA neurotransmission, is not only a property of clozapine but possibly of paliperidone as well.

The main concern of our result there is limited data from only one single subject. So it is very difficult to draw general conclusion. It is well known that the cortical silent period may be influenced by several unspecific confounding factors. Thus the observed result can be related to the antipsychotic effect, but it can also be due to unspecific confounding factors, or it can be a side effect of the drug unrelated to antipsychotic efficacy. These issues should be resolved by investigating a larger patient sample in further studies.

CONCLUSION

Paliperidone produced a therapeutic response in a patient with first episode schizophrenia with a subsequent change of impaired cortical inhibition, as expressed by prolongation of the CSP interval. Paliperidone can therefore be assumed to enhance GABAB receptors-mediated neurotransmission.

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