J Neural Transm (1997) 104: 191–197

Journal of Neural Transmission

Transcranial magnetic stimulation induces alterations in brain monoamines

Short Communication

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Accepted December 18, 1996

Summary. Transcranial magnetic stimulation has been suggested as a possible therapeutic tool in depression. In behavioral models of depression, magnetic stimulation induced similar effects to those of electroconvulsive shock. This study demonstrates the effect of a single session of rapid TMS on tissue monoamines in rat brain. Alterations in monoamines were selective and specific in relation to brain areas and type of monoamine. The results imply on a biochemical basis to the suggested ECT-like treatment potential of TMS.

Keywords: Transcranial magnetic stimulation (TMS), brain monoamines, electroconvulsive shock (ECS), depression, rat.

Introduction

Transcranial magnetic stimulation (TMS) is a new non-invasive, safe and painless method (Baker, 1991) for the stimulation of the brain. Magnetic stimulation of the human brain is increasingly being used for functional cortical mapping of primary motor pathways and speech areas and the investigation of cortical function related to cognition in both health and disease states. (Barker et al., 1986; Baker, 1991; Gates, 1995). It is used also as a contributing diagnostic tool in multiple sclerosis, motor neurone disease, facial spasm, stroke, epilepsy and peripheral nerve lesions (Jarratt, 1987; Mazziotta, 1994).

TMS has been recently suggested for the treatment of patients with Parkinson's disease (Pascual-Leone et al., 1994a,b) and psychiatric diseases especially those of mood and emotional disfunction. It is possible that magnetic pulses may work by mimicking some of the effects of electroconvulsive therapy (ECT), which is currently the most effective treatment in severe depressive states and to a certain extent in other psychiatric disorders such as

acute mania and schizophrenia. Unlike ECT, TMS (in the limit of safety) does not cause seizures and convulsions and is conducted on conscious subjects.

Preliminary clinical studies suggested an antidepressant potential for low and high frequency successive TMS in depressed patients (Hoflich et al., 1993; George et al., 1995; Grisaru et al., 1994; Kolbinger et al., 1995). The neurochemical basis for TMS effects has not been studied. However, it has been reported that TMS reduces immobility in the forced swimming test model of depression similar to electroconvulsive shock (ECS) and most antidepressant drugs. Moreover, similar to ECS, repetitive rate TMS enhanced apomorphine induced stereotypy (Grahame-Smith et al., 1978; Green, 1984; Fleischman et al., 1995), which may suggest that both treatments affect the dopaminergic system. Magnetic stimulation also inhibited seizure activity in animals in a similar way to the post seizure anticonvulsant effect of electric stimulation. TMS as well as ECS decreased duration and increased threshold for a subsequent ECS induced seizure (Fleischmann et al., 1994, 1995), which may be related to the inhibition of the short-latency motor-evoked potentials following cortical stimulation (Rothwell, 1993; Nakamura et al., 1995).

The role of monoamines in the pathophysiology of depression and the mechanism of action of antidepressant treatments has been investigated in numerous studies (for reviews see Salmon et al., 1993; Halbreich and Lumley, 1993; Brown and Gershon, 1993). Given the behavioral effects of TMS in rats and the suggested therapeutic effect in some depressed patients, its effects on brain monoamines are of high interest and are the focus of this study.

Methods

Experimental procedure

TMS of 1 msec pulses from a Cadwell Rapid Stimulator, field intensity of 2.3 Tesla (100% intensity) with a 5 cm coil, producing 50 stimuli at a rate of 25 Hz for 2 sec was administered to male Sprague-Dawley rats (200–230 g). The coil was placed above the rat's head without direct contact. Control rats received sham treatment by placing the coil in a perpendicular position to the rat's head. Ten seconds after the stimulation rats were sacrificed by decapitation, their brain rapidly removed on to ice and the following brain area dissected; frontal cortex, striatum, hippocampus and midbrain. Tissues were immediately placed in liquid nitrogen, then weighed and homogenized with 0.1N $HClO_4$. After centrifugation the supernatant was collected and stored at −70°C until used. Two separate experiments were performed with 8–10 rats in each group in each experiment. All animal procedures were approved by the local Laboratory Animal Care and Use Committee.

HPLC analysis

Concentrations of norepinephrine (NE), dopamine (DA), dihydroxyphenyl-alanine (DOPA), dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), serotonin (5-HT) and 5-hydroxyindolacetic acid (5-HIAA) were determined by HPLC with electrochemical detector, equipped with a column of 5 μm spherical C_{18} particles. The dual electrode analytical cell operates in a redox mode with 0.3 V oxidation potential and −0.35 V reduction potential. The mobile phase consists of 0.1 M phosphate buffer pH 2.6 containing 0.2 mM EDTA, 0.2 mM octane sulfonic acid, 2.5% methanol and 4.5% acetonitrile.

Results

Acute r-TMS produced region specific changes in the concentrations of monoamines in rat brain (Fig. 1). Dopamine content in the frontal cortex of

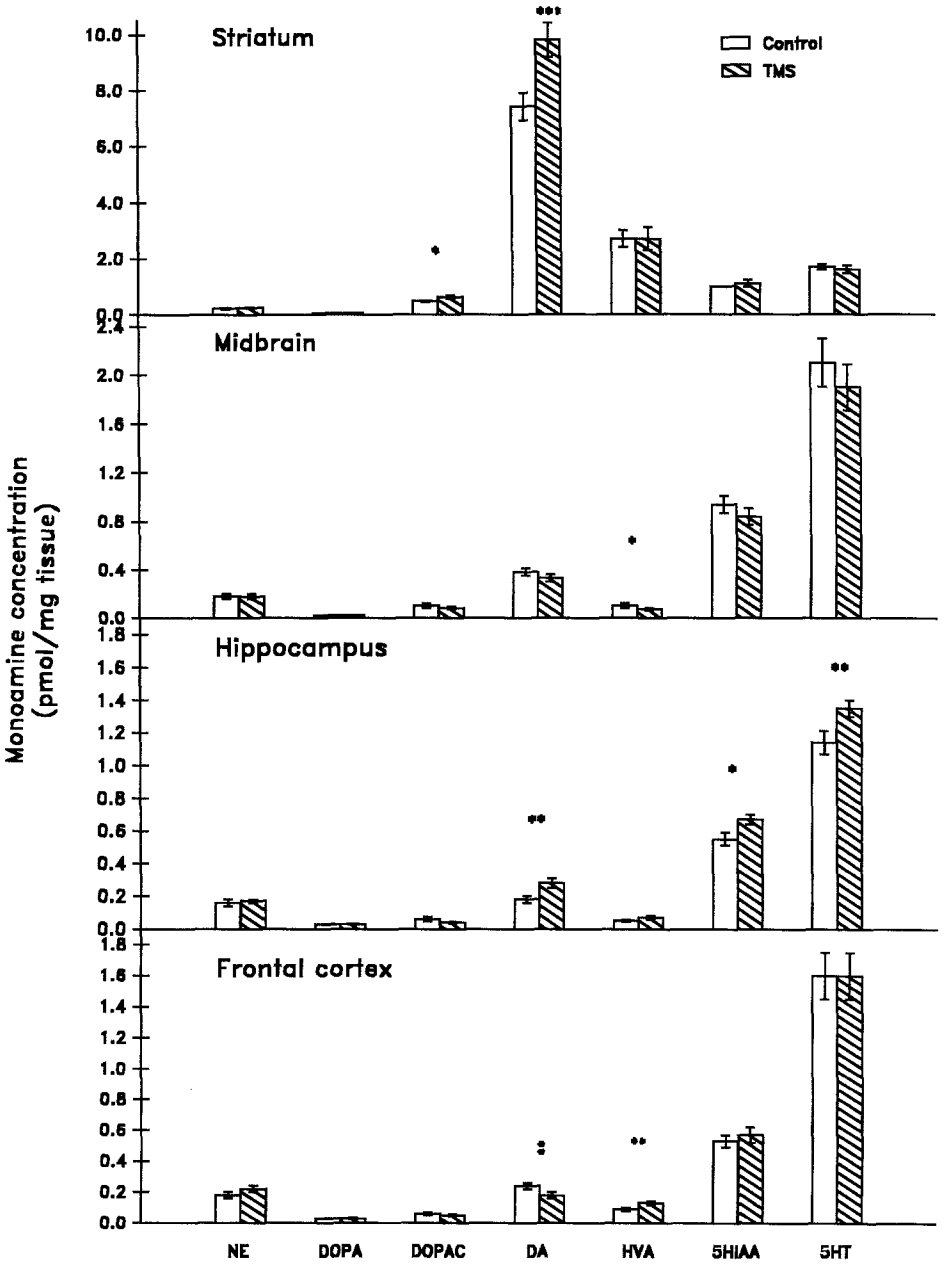

Fig. 1. The effect of a single session of rapid TMS on norepinephrine, dopamine, serotonin and their metabolites in various brain regions. Rats were sacrificed 10 sec after the magnetic stimulation and tissue monoamines levels were detected. Data are means ± SEM of two separate experiments with 16–20 rats in each group. A significant difference between TMS and sham treated rats obtained by two ways ANOVA was defined as $p < 0.001$. Subsequent comparison was carried out by Bonferoni: *$p < 0.05$, **$p < 0.02$, ⁂$p < 0.01$ ***$p < 0.001$

Table 1. TMS induced turnover rates of monoamines in various brain regions

Area		DOPAC + HVA / DA
Frontal cortex	TMS	1.00 ± 0.07*
	Control	0.62 ± 0.06
Striatum	TMS	0.33 ± 0.02**
	Control	0.43 ± 0.03
Midbrain	TMS	0.45 ± 0.02
	Control	0.52 ± 0.03
Hippocampus	TMS	0.39 ± 0.01*
	Control	0.61 ± 0.04

Rats were treated as described in Method section. Data are mean ± SEM values of two experiments and 16–20 rats. Comparison between TMS and sham treated groups was carried out by two-tailed Student's t test of the ratio. *$p < 0.001$, **$p < 0.02$

the r-TMS treated rats was reduced by 26 ± 2.8% while in the striatum and the hippocampus the levels of dopamine were increased by 25 ± 1.5% and 18 ± 0.8%, respectively. Dopamine concentrations in the midbrain were not affected by r-TMS. Turnover rates of dopamine, as expressed by the ratio of (DOPAC + HVA)/DA, increased in the frontal cortex and decreased in the striatum and hippocampus in the r-TMS treated rats with no change in the midbrain (Table 1).

r-TMS caused an increase in serotonin and 5HIAA levels in the hippocampus but not in any other brain region examined in this study. Unlike dopamine, serotonin turnover rate, as expressed by 5-HIAA/5-HT, was similar in r-TMS treated rats to that of controls.

Norepinephrine concentrations were not affected by r-TMS in any of the brain regions examined in this study.

Discussion

The results of this study show that r-TMS induces specific alterations in brain monoamines' steady state concentrations and turnover rates. Dopamine concentrations increased significantly in the striatum and hippocampus but decreased in the frontal cortex 10sec after r-TMS. These changes were accompanied by a significant decrease in turnover rates of dopamine in the striatum and hippocampus and an increase in the frontal cortex. Unlike dopamine, serotonin and 5-HIAA concentrations were affected by magnetic stimulation only in the hippocampus, without a change in turnover rate. Monoamines concentrations in midbrain did not change following magnetic stimulation with a minor change in HVA concentrations. The reasons for this regional and neurotransmitter specific pattern are still not clear. It is interesting that following a single ECS, a change in a similar order of magnitude in

tissue monoamines concentrations is detected (Ebert et al., 1973; Nimgaonkar et al., 1986). In extracellular DA concentrations in the striatum (Zis et al., 1991) and 5-HT concentrations in the hippocampus (Zis et al., 1992; McGarvey et al., 1993) ECS induced a marked increase. However, the pattern of regional changes in interstitial monoamine concentrations induced by acute ECS (Glue et al., 1990) parallels that of TMS. r-TMS had no effect on NE levels, which is in agreement with previous findings on ECS effects in whole brain and slices from frontal cortex (Nimgaonkar et al., 1986; Green et al., 1987).

Significant alterations in the metabolism of cerebral monoamines in several brain regions following stress were previously reported (Stone, 1975; Dunn, 1988). These changes in monoamines are in the same order of magnitude as those induced by r-TMS but exhibit a different regional and transmitter pattern. Furthermore, in the current study the control and the experimental groups were subjected to the same conditions of handling and r-TMS noise. Thus, the alterations in brain monoamine levels and turnover rates in the r-TMS group are probably not a result of stress effects.

Monoamines especially NE and 5-HT, are believed to play an important role in the biochemical events related to depression. ECT, which is highly effective in depression, induces specific changes in monoamine mediated responses, which have been correlated with the effects of ECS in animals. It has recently been reported that TMS has antidepressant properties which might mimic those of ECT. The ability of TMS to induce in rats similar biochemical alterations to those of ECS may further support the potential role of TMS as an antidepressant treatment, and bring us closer to the understanding of the mechanism of action of TMS.

Acknowledgment

Work was supported by The Ernst and Anna Lachman fund of the Technion Israel Institute of Technology.

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Received November 11, 1996