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Transcranial magnetic stimulation as a therapeutic tool in psychiatry: what do we know about the neurobiological mechanisms?

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Abstract

Potential therapeutic properties of repetitive transcranial magnetic stimulation (rTMS) have been suggested in several psychiatric disorders such as depression, mania, obsessive-compulsive disorder, posttraumatic stress disorder and schizophrenia. By inducing electric currents in brain tissue via a time-varying strong magnetic field, rTMS has the potential to either directly or trans-synaptically modulate neuronal circuits thought to be dysfunctional in these psychiatric disorders. However, in order to optimize rTMS for therapeutic use, it is necessary to understand the neurobiological mechanisms involved, particularly the nature of the changes induced and the brain regions affected. Compared to the growing number of clinical studies on its putative therapeutic properties, the studies on the basic mechanisms of rTMS are surprisingly scarce. rTMS currently still awaits clinical routine administration although,there is compelling evidence that it causes changes in neuronal circuits as reflected by behavioural changes and decreases in the activity of the hypothalamic-pituitary-adrenocortical system. Both alterations suggest regional changes in neurotransmitter/neuromodulator release, transsynaptic efficiency, signaling pathways and in gene transcription. Together, these changes are, in part, reminiscent of those accompanying antidepressant drugs.

Keywords: Repetitive transcranial magnetic stimulation; Stress; Depression; Antidepressant; HPA system; ACTH; BDNF; Dopamine; Neuroprotection; Vasopressin

1. Introduction

1.1. Physical background and historical overview

Transcranial magnetic stimulation (TMS) was introduced in 1985 (Barker et al., 1985) as a neurological technique for non-invasively inducing motor movement by direct magnetic stimulation of the brain's motor cortex to measure connectivity and excitability (e.g. Curt et al., 1998; Keck et al., 1998; review: Rossini and Rossi, 1998; Hallett, 2000). It depends on the basic principle of mutual induction, discovered by Michael Faraday in 1831 (Faraday, 1831), whereby electrical fields E can be converted into magnetic fields B, and magnetic fields B can be converted into electrical energy. In the case of TMS, a brief surge of current flows through the stimulation coil to produce a transient magnetic field B. This field passes freely into the surrounding medium and induces an electric field E which impedes the magnetic field. If the electric field E falls in a conductor (i.e. brain tissue), then current will flow (Figs. 1 and 4). The ability of this current to painlessly excite nerve cells depends upon its time course, magnitude and direction. It is important to note that the effects obtained by use of TMS do not occur on the basis of the magnetic field applied but are achieved by the electric field induced that ultimately leeds to neuronal depolarization. Charge is moved across the excitable neuronal membranes, creating a transmembrane potential. If sufficient, this causes membrane depolarization and initiates an action potential, which then propagates along the nerve. In contrast to the direct transcranial electrical currents used in electroconvulsive therapy, magnetic fields are unaffected by the high impedance of the skull. Thus, TMS can stimulate the cerebral cortex relatively painlessly in awake patients (Barker et al., 1985).

The idea that nerve cells could be excited indirectly by magnetic fields via the principle of mutual induction is not new as already in 1896 d'Arsonval reported to the Société de Biologie in Paris that when a subject's head was placed in a strong time-varying magnetic field (110

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V, 30 A, 42 Hz), phosphenes (i.e. sensations of light), vertigo, and even syncope were perceived (d'Arsonval, 1896). During the latter half of the nineteenth century, there were numerous claims of cures with magnetic therapy, typically using one or more horsehoe magnets (Devinsky, 1993). However, many clinicians remained sceptical of the effects of constant weak magnetic fields outside the setting of hysteria. In the tradition of d'Arsonval, Beer in 1902 replicated the finding that phosphenes could be produced by applying an oscillating strong magnetic field to the head (Beer, 1902). Interestingly, as cited in George and Belmaker (2000), Beer and his coworker Pollacsek in 1902 filed a patent in Vienna regarding the use of an electromagnetic coil,

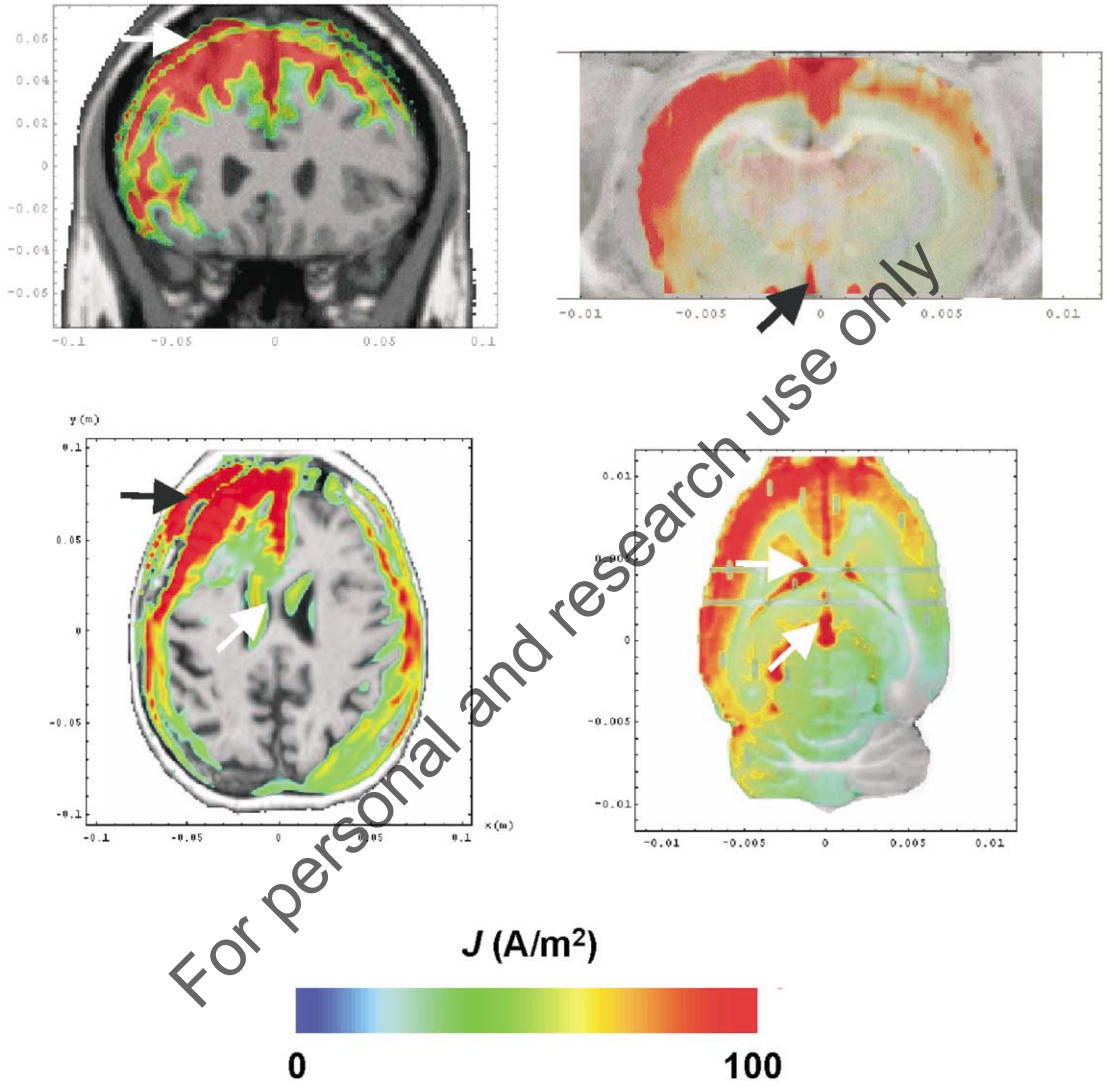

Fig. 1. Spatial distribution of current density (density plot) induced in one coronal layer (upper panel) and one transversal layer (lower panel) of human (left panel) and rat brain (right panel) by rTMS. The electrical characteristics of the brain are reconstructed from MRI images, whereby the conductivity distribution of the tissue is mapped onto the anatomical map of the brain. *Human:* Maximum coil current intensity $I_{max} = 4000$ A. Pulse rise time: approx. 60 μs. Commercial "figure 8" coil (DANTEC, Skovlunde, Denmark), inner diameter (ID): 20 mm, outer diameter (OD): 100 mm, 10 windings per coil. Resulting maximum magnetic induction modulus close to coil centre *B*: approximately 1.8 Tesla. Transversal/coronal section: 49 mm from vertex. Coil centre is at the same height as the section shown. Coil is tilted by 45° in the *xy* and *yz* planes (clinical use; see, e.g. Pascual-Leone et al. 1996; George et al. 1999). Contact point is the left dorsolateral prefrontal cortex. Average current density over red region: 92 ± 1.5 A/m^2. Arrows indicate cerebrospinal fluid (CSF) with highest conductivity value (1.6 A/Vm). *Rat:* $I_{max} = 6000$ A. Pulse rise time: approx. 60 μs. Prototype round coil, ID: 6 mm, OD: 57 mm, 21 windings, winding height: 7 mm; cable length: 1.40 m; encapsulation: min. 2 mm PVC (DANTEC). Resulting maximum magnetic induction modulus close to coil edge *B*: approx. 4.1 Tesla. Transversal section: 1.5 mm from vertex. Coronal section: 1.2 mm from vertex (bregma). The coil and stimulation parameters used in our studies (Post et al., 1999; Müller et al., 2000b; Keck et al. 2000b,c, 2001b; Czeh et al., 2000) were selected according to the exact characterization of the conductive phenomena elicited by rTMS in both human and rat brain. This was done to achieve a stimulation pattern which can be considered comparable with the situation during clinical treatment and resulted in a stimulation intensity of 4.1 T, i.e. 130% of rats' motor threshold. Coil is tilted by 45° in the *xy* and *yz* planes. Contact point is the left frontal cortex. Average current density over red region: 97 ± 0.6 A/m^2. Arrows indicate CSF. The stimulation device was kindly provided by DANTEC-Medtronic, Skovlunde, Denmark (Keck et al., 2000b,c, 2001b).

placed over the skull, to pass "vibrations" into the skull and treat "depression and neuroses". It is of note that the therapeutic concept of a use of electrical stimulation dates back to 46 A.D. when the Roman physician Scribonius Largus introduced the use of the torpedo fish (electric ray) to treat "headache, even if it is chronic and unbearable" (Kellaway, 1946). Subsequently, the therapeutic indications for "torpedo therapy" rapidly expanded to include gout, depression, and epilepsy (Devinsky, 1993).

Modern TMS began in 1985 when Barker and colleagues in Sheffield, UK, developed the first TMS device (Barker et al., 1985). However, the original commercially available stimulators were limited in the frequency with which they could produce stimuli by the recharging circuits therefore only allowing for the application of single-pulse TMS. To date, devices capable of stimulating the brain at frequencies up to 100 Hz have opened up new possibilities in magnetic stimulation research, as it had been known for many years that certain effects of brain stimulation were only seen if the brain area was repetitively stimulated, presumably because of cumulative excitatory and/or inhibitory effects. Such regularly repeated TMS delivered to a single scalp site is refered to as repetitive TMS (rTMS) and is usually used in the range of 1–30 Hz. The term fast rTMS is used to refer to stimulus rates of more than 1 Hz, and the term slow rTMS is used to refer to stimulus rates of 1 Hz or less. The investigation of perception, attention, learning, language, memory and awareness is now proceeding rapidly as rTMS can be used to investigate almost all areas of cognitive neuroscience (review: Walsh and Cowey, 2000). By use of rTMS neuronal activity can be disrupted transiently in restricted brain regions, allowing researchers to assess function on a millisecond scale due to its high temporal resolution (review: Hallett, 2000).

As a measure for the strength of TMS applied in preclinical and clinical studies, the biological efficacy of the stimulus in the individual subject rather than the output of a given stimulation device is critical (Wassermann, 1998). Therefore, the intensity of TMS is typically given as a multiple or percentage of the threshold intensity for evoking a small motor evoked potential (usually >50 μV) in a relaxed hand muscle in at least half of the trials via stimulation of the primary motor cortex (Rossini et al., 1994). It is of note that the strength of association between motor threshold reflecting motor cortex excitability and thresholds for neuronal depolarisation in other cortical regions is unknown. However, to date there is no method for determining stimulus strength in other brain areas more relevant for e.g. mood circuitries. The range of motor thresholds found in healthy subjects is wide (Cicinelli et al., 1997; Mills and Nithi, 1997), whereas in a given individual the motor threshold is very consistent (Ziemann et al., 1996; Cicinelli et al., 1997), with only a small interhemispheric difference. Motor threshold is usually tested during voluntary relaxation of the target muscle, because when measured during tonic activation it is significantly lowered (Rossini et al., 1994; Mills and Nithi, 1997). Motor threshold can also be determined in rodents and should be a prerequisite for conducting basic research in these animals (Jennum and Klitgaard, 1996; Linden et al., 1999; Müller et al., 2000b).

1.2. rTMS meets psychiatry

The pathophysiology of psychiatric disorders is conceptualized in terms of a dysfunction of neuronal circuits. Therefore, rTMS holds the potential of being able to selectively modulate activity in brain areas involved in pathological processes such as depression, mania, obsessive-compulsive disorder, posttraumatic stress disorder and schizophrenia (e.g. Höflich et al., 1993; Pascual-Leone et al., 1996; Greenberg et al., 1997; Grisaru et al., 1998a,b; McCann et al., 1998; Padberg et al., 1999; Cohen et al., 1999; George et al., 1999, 2000; Berman et al., 2000; Rollnik et al., 2000). Neuroimaging studies have shown that TMS is biologically active, both locally in tissue under the coil and at remote sites, presumably through transsynaptic connections (Ilmoniemi et al., 1997; Bohning et al., 1997, 1999; Paus et al., 1997; Wassermann et al., 1998; George et al., 1999; Siebner et al., 1999). The largest single area of TMS research in psychiatry has been the exploration of possible therapeutic effects of cortical, usually prefrontal, stimulation on symptoms of major depression (review: George et al., 1999; Sackeim, 2000). Although this technique is yet not sufficiently validated to be introduced in routine clinical use, there is sufficient evidence suggesting that rTMS of frontal brain regions exerts antidepressant effects, over and beyond placebo conditions (Reid et al., 1998; George et al., 1999; Sackeim, 2000). However, there are substantial discrepancies in the incidence and magnitude of antidepressant effects associated with rTMS in the current literature (review: George et al., 1999). The strong variety in clinical effects reported so far is most likely due to the treatment parameters that can be largely modified. These parameters include stimulus strength relative to motor threshold, total number of stimuli, frequency of stimulation, duration of stimulus trains and inter-train intervals, number of TMS sessions, anatomical location of stimulation, stimulation coil geometry, and sham stimulation condition, to number just a few.

So far, few satisfactory mechanisms to explain the clinical effects of rTMS have been put forward. To use rTMS optimally, it is most important to know how it is acting in brain tissue, i.e. knowledge concerning the putative neurobiological changes underlying the observed clinical effects. However, the limitations of

Table 1
Summary of TMS studies in rodents[a]

Reference	Animals/N	Site, coil	Intensity	Hz	Train duration	Intertrain interval	Trains/ session	No. of sessions	Total no. stimuli	Outcome measures
Ben-Shachar et al., 1997	Rat, $N=8$–10	Entire brain, circular stimulation coil (7 cm),	100% MO, 2.3 T	25	2 s	–	1	1	50	Monomanine concentrations
Ben-Shachar et al., 1999	Rat $N=8$–10	entire brain, circular stimulation coil (7 cm)	76% MO, 2 T	15	3.5 s	–	1	1 daily for 10 days	520	Monoamine concentrations; β-adrenergic, 5-HT_2- and BZD-receptor binding
Counter et al., 1993	Rabbit, $N=3$–4	Entire brain, circular stimulation coil (5 cm)	100% MO, 2 T	?	?	?	100 stimuli/ session	1 weekly for 4-12 month	1000	Histology, heart rate, respiration rate
Czeh et al., 2000	Rat, $N=6$–12	Left frontal, prototype stimulation coil (5.7 cm)	130% Motor threshold, 4.1 T, 120 A/μs	20	2.5 s	2 min	6	1 daily for 18 days	5400	Hippocampal neurogenesis, HPA system function
Ebert and Ziemann, 1999	Rat, $N=5$–7	Entire brain, circular stimulation coil (12.5 cm)	120 A/μs	20	3 s	–	1	1	60	Amygdala kindling
Fleischmann et al., 1995	Rat, $N=19$	Entire brain, circular stimulation coil (5 cm)	100% MO, 2 T	25	2 s	–	1	1 daily for 7–10 days	350–500	Apomorphine-induced stereotypy, seizure threshold
	Mice, $N=22$		100% MO, 2 T	25	2s	–	1	2	50	Porsolt swim test
Fleischmann et al., 1996	Rat, $N=1$–2	Entire brain Circular stimulation coil (9 cm)	?	25	2 s	–	1	1 daily for 9 days	450	β-adrenergic binding
Fleischmann et al., 1999	Rat, $N=9$–10	Entire brain, figure-8 coil (5 cm)	100% MO, 2.5 T	20	4 s	?	2	1 daily for 16 days	1280	seizure threshold
Fujiki and Steward, 1997	Mice, $N=2$–3	Entire brain, circular stimulation coil (5 cm)	70% MO, 1.63 T	25	10 s	3–5 min	1–30	1	250–7500	GFAP mRNA
Gur et al., 2000	Rat, $N=5$	Entire brain, figure-8 coil (2.5 cm)	75% MO, 1.12 T	15	13.3 s	40 s	3	1 daily for 10 days	6000	Activity of presynaptic 5-HT autoreceptors
Hausmann et al., 2000	Rat, $N=4$–5	Entire brain, figure-8 coil (2.5 cm)	75% MO	20	10 s	–	1	1 daily for 14 days	2800	c-fos-, GFAP-, BDNF-, FGF-2-mRNA, c-Fos
Jennum and Klitgaard, 1996	Rat, $N=8$–10	Entire brain, circular stimulation coil (12.5 cm)	90–180% Motor threshold, 167 A/μs	50	1 and 5 s	–	1	Acute:1 Chronic: 1 daily for 30 days	50–7500	Motor evoked potentials, seizures
Ji et al., 1998	Rat, $N=?$ Brain slices	Entire brain, circular stimulation coil (5 cm)	100% MO, 2 T	25	2 s	5 min	1 & 3	1	50–150	c-fos mRNA, c-Fos-, c-Jun-, pCREB
Keck et al., 2000b	Rat, $N=8$–12	Left frontal, prototype stimulation coil (5.7 cm)	130% Motor threshold, 4.1 T, 120 A/μs	20	2.5 s	2 min	3	1 daily for 33 days	4950	Forced swim test, EPM, social interaction, HPA-function, BZD-receptor binding, testosterone

Keck et al., 2000a	Rat, $N=5$–12	Left frontal, prototype stimulation coil (5.7 cm)	30% Motor threshold, 4.1 T, 120 A/μs	20	2.5 s	2 min	20	1	1000	Microdialysis: monoamines, amino acids, vasopressin
Keck et al., 2001b	Rat, (HAB/LAB) $N=6$–11	Left frontal, prototype stimulation coil (5.7 cm)	130% Motor threshold, 4.1 T, 120 A/μs	20	2.5 s	2 min	20	1 daily for 6 days	6000	Forced swim test, EPM, HPA system function
Kling et al., 1990	Rat, $N=12$	5 different areas of the head, circular stimulation coil (7.5 cm)	100% MO, 2.8 T	0.2	4 s	–	1	1	100	Memory for conditioned taste aversion, histology
Kole et al., 1999	Rat, $N=4$	Entire brain, circular stimulation coil (12.5 cm)	Above Motor threshold, 120 A/μs	20	3 s	–	1	1	60	5-HT_{1A} & NMDA binding sites
Levkovitz et al., 1999	Rat, $N=3$–5	Entire brain, teardrop shaped coil (5 cm)	100% MO, 2.2 T	1, 10, 25	2 s	–	1	Acute: 1, chronic: 1 daily for 7 days	2–350	Hippocampal reactivity to perforant path stimulation
Matsumiya et al., 1992	Rat, $N=52$	Entire brain, circular stimulation coil, (7.5 cm)	100–340% Motor threshold, 0.8–2.8 T	0.2	–	4 s	50–100 stimuli/ day	?	50–5381	Histology, motor evoked potentials
Müller et al., 2000b	Rat, $N=5$	Left frontal, prototype stimulation coil (5.7 cm)	130% Motor threshold, 4.1 T, 120 A/μs	20	2.5 s	2 min	3	1 daily for 55 days	8250	BDNF mRNA/ protein, CCK and NPY mRNA
Post et al., 1999	Rat, $N=8$–12, cell culture	Left frontal, prototype stimulation coil (5.7 cm)	130% Motor threshold, 4.1 T, 120 A/μs	20	2.5 s	2 min	3	1 daily for 55 days	8250	MWM, Social discrimination test, GFAP/B 50 protein, sAPP, cell viability
Ravnborg et al., 1990	Rat, N = 10	Entire brain, circular stimulation coil (14 cm)	1.9 T	0.1	?	?	1	Acute:1, chronic: 1 daily for 7 days	50–350	Blood brain barrier permeability
Sgro et al., 1991	Rat, $N=10$–11	Entire brain, circular stimulation coil (10.7 cm)	3.4 T	8	?	?	1	1	10 000	Histology (HE); electron microscopy
Wang et al., 1996	Gerbil, $N=?$	Left auditory cortex, prototype coil	3–4.8 T	1–10	0.1–2.5 s	5 s	1–30	1	2–240	Complex spike potentials in auditory cortex (LTP/LTD)
Zyss et al., 1997	Rat, $N=10$	Entire brain, prototype coil	0.1 T	50	5 min	–	1	1 daily for 10 days	15 000	Tail-flick test, locomotor activity, cAMP
Zyss et al., 1999	Rat, $N=8/16$	Entire brain, prototype coil	1.6 T	20, 30	5 min	–	1	9/18 sessions	54 000–108 000	Forced swim test

[a] *N*, number of animals per group; MO, machine output; T, Tesla (maximum magnetic induction modulus close to coil center/edge); BDNF, brain-derived neurotrophic factor; BZD, benzodiazepine; CCK, cholecystokinin; EPM, elevated plus-maze; FGF-2, fibroblast growth factor-2; GFAP, glial fibrillary acidic protein; HAB, high anxiety-related behaviour rats; HPA, hypothalamic-pituitary-adrenocortical; LAB, low anxiety-related behaviour rats; LTP/LTD, long-term potentiation/-depression; 5-HT, serotonin; MWM, Morris water maze; NPY, neuropeptide tyrosine; pCREB, phosphorylated cAMP response element binding protein; sAPP, soluble amyloid precursor protein.

human research necessitate preclinical studies in suitable animal models and basic studies at the cellular and molecular level to better understand how the induced intracerebral current density is regulated and which regulatory elements might serve as potential treatment targets. In this article, we will summarize the preclinical efforts, (1) to characterize the potential role of rTMS as a therapeutic tool in depression and (2) to document the effects of rTMS on the expression of potentially neuroprotective substances which lead to the more speculative conclusion that rTMS might find a role in the treatment of neurodegenerative disorders.

2. Current problems with rodent studies

To date, about 27 studies dealing with behavioural and neurochemical effects of TMS that might be related to psychiatric disorders are available (Table 1). However, the parameter space for rTMS is extraordinarily large and in most of the studies different stimulation conditions and treatment schedules were used herewith limiting comparability. For example, the frequency of stimulation is likely to be a crucial factor for the neurobiological effects. There is evidence that slow stimulation (< 1 Hz) has a net inhibitory effect whereas fast stimulation (> 1 Hz) increases cortical excitability, blood flow and metabolism (e.g. Pascual-Leone et al., 1994; Wang et al., 1996; Post et al., 1999; Kimbrell et al., 1999; Ziemann and Hallett, 2000). Moreover, in the vast majority of rodent studies the entire brain is likely to be stimulated due to the usage of commercially obtained stimulation coils (see also next paragraph; review: Belmaker and Grisaru, 1998). Therefore, it is difficult to relate the effects measured to specific neuronal circuits. As in clinical studies, another problem arises from the sham stimulation conditions used, which in some cases are likely to elicit biologically active conductive patterns (e.g. Loo et al., 2000). Further, the question of whether the animals were trained and handled (to exclude the possibility of being stressed due to the stimulation procedure per se or by the necessity to restrain them) is of importance especially for the interpretation of the neuroendocrine and behavioural data.

2.1. Relevance of studies in rats: brain size matters

The pioneering studies from the Belmaker group in rodents have demonstrated that chronic rTMS has an antidepressant-like effect in rats, e.g. on apomorphine-induced stereotypy and electroconvulsive shock thresholds (Fleischmann et al., 1995); the latter finding has been replicated recently (Ebert and Ziemann, 1999). However, in these studies, stimulation patterns used were not tested to be analogous to those used under clinical conditions and the effects observed were most probably due to a stimulation of the entire rat brain (review: Belmaker and Grisaru, 1998). In contrast, in clinical studies rTMS effects most probably relate to frontal forebrain stimulation (review: George et al., 1999). Consequently, to reliably investigate the underlying neurobiological effects in animal models, the adoption of equivalent stimulation conditions is indispensable. Based on calculations of the electrical field in a spherical head model (Roth et al., 1991), Weissman et al. suggested in 1992 that the efficiency of magnetic stimulation would be drastically reduced in small rodent brains (Weissman et al., 1992). The authors concluded that as the volume of the brain falls from that of a human to that of a rodent, the magnitude of the induced field drops by a ratio of at least 5 to 1. Therefore, the validity and usefulness of studies in rodents was questioned (Weissman et al., 1992) and the development of tiny stimulation coils that would truly model the ratio of coil to skull in human experiments (but are very difficult to develop because of overheating that occurs during rTMS) was requested (Belmaker et al., 2000; Lisanby et al. 2000).

Taken together, the major point raised is the question of whether it would be possible to relate the effects observed in rodent studies to frontal forebrain stimulation. Specifically, important methodological issues such as the determination of the magnetic flux and the characteristics of the elicited stimulation patterns are involved. In the following we will describe how we managed to overcome the apparant problem of rTMS in rats.

2.2. Intracerebral current density distribution in the rat

rTMS relies on the principle that a time-varying magnetic induction field will induce a current flow in any medium with non-zero conductivity, provided a portion of the magnetic flux is concatenated by the bound medium. In the case of rTMS, the medium is composed of biological tissue with highly inhomogeneous electrical characteristics, which under the influence of a dynamically varying magnetic induction field will give rise to inhomogeneous electrostatic field distributions. These contributions to the total electric field (and hence the induced current density distribution) resulting in the brain cannot be neglected, as they account for the influence of the brain's finite and inhomogeneous conductivity patterns. In this context, comparison parameters based on a spherical head model (such as head/coil ratio) contribute relatively little information to the question of comparability in real-life conditions. We therefore selected a theoretical and computational approach (Cerri et al., 1995; Ravazzani et al., 1996) which allows for all relevant electromagnetic effects to be taken into account, achieving an accurate reconstruction of the conductive phenomena elicited by rTMS both in the rat and the human brain.

The strong inhomogeneities of brain tissue and irregularities of head shape make such an exact characterization necessary, since these are the properties which predominantly determine the shape of charge and current density distributions arising during stimulation. We have accounted for these effects (hereby considering all—negative and positive—contributions to the resultant stimulation pattern) by reconstructing the electrical characteristics of the brain from MRI images of the human as well as of the rat brain. Conductivity values range from 0.01 A/Vm (bone) to 1.6 A/Vm (cerebrospinal fluid). In between are skin, gray matter and white matter. The problem is solved under consideration of all mutual influences of directly induced conductive effects and current/electric field corrections elicited by capacitative effects arising from the inhomogeneous conductivity distribution of the tissue. The magnetic induction field was calculated as a function of the coil geometry and the time evolution of the incoming current, after which discretized versions of Maxwell's equations in integral form were solved simultaneously for all meshes in the network. The coil (inner diameter: 6 mm; outer diameter: 57 mm; 21 windings; winding height: 7 mm; cable length: 1.40 m; encapsulation: min. 2 mm PVC) and stimulation parameters used in our studies (Post et al., 1999; Müller et al., 2000b; Keck et al., 2000b,c, 2001b; Czeh et al., 2000) were selected according to an exact characterization of the conductive phenomena elicited by rTMS in both human and rat brain as described above. For the first time, this enabled us to accurately adapt the experimental setup to achieve a stimulation pattern which is analogous to that used in patients during standard clinical treatment. The results of the above procedure show that our experimental setup allows to obtain a stimulation pattern which exhibits a definite peak in the left frontal region as desired (e.g. Keck et al., 2000b,c, 2001b; Fig. 1). It is therefore justified to interpret subsequently collected data as related to selective stimulation of this brain area.

2.3. Appropriate animal models

By use of the above-mentioned approach, we were able to demonstrate antidepressant-like effects such as changes in stress coping strategies and alterations in hypothalamic-pituitary-adrenocortical (HPA) system regulation of chronic rTMS of left frontal brain regions in commercially obtained rats (i.e. ''normal'' rats; Czeh et al., 2000; Keck et al., 2000b). However, to obtain predictions about the clinical condition in human depression, an animal model of depressive-like behaviour with face and predictive validity should be used (e.g. Geyer and Markou, 1995; Holsboer, 1999a). Accordingly, our experiments aimed at investigating the neuroendocrine and behavioural impact of rTMS of left frontal brain regions in an appropriate animal model that reflects significant psychopathological features of human depression. We therefore characterized the effects of rTMS on the regulation of HPA system activity, stress coping and anxiety-related behaviour in two Wistar rat lines selectively bred for high (HAB) and low (LAB) anxiety-related behaviour under a regimen adapted from clinical conditions. These two rat breeding lines differ not only in their inborn anxiety, but also in their stress coping strategies and their HPA system susceptibility to external stressors (Liebsch et al., 1998a; Landgraf et al., 1999; Henniger et al., 2000; Ohl et al., 2001). Moreover, HAB and LAB rats differ markedly in their reactivity to acute benzodiazepine treatment (Liebsch et al., 1998b), treatment with the high-affinity corticotropin releasing hormone (CRH) 1 receptor antagonist R121919 (Keck et al., 2001a) and chronic paroxetine treatment (M.E. Keck, unpublished observation).

3. Behavioural effects of rTMS: changes in stress coping

At the behavioural level, we were able to provide first evidence that chronic rTMS treatment in a psychopathological animal model under stimulation conditions adapted from hospital use (e.g. George et al., 1999) induces profound changes in acute stress coping strategies, as revealed by the forced swim test (Keck et al., 2001b; Fig. 2). This rTMS-induced shift in HAB animals towards active stress coping was markedly higher than has previously been reported in ''normal'' Wistar rats (Zyss et al., 1997; Keck et al., 2000b). Thus, we could demonstrate that rTMS-induced effects are not only present in the HAB rat line but are even amplified in the genetically predisposed animal model. In contrast, rTMS-treated LAB animals that innately display rather active stress coping abilities (Liebsch et al. 1998a, b) were unaffected. Our finding that chronic rTMS differentially affected the coping abilities of HAB and LAB rats indicates that these treatment-induced changes are determined by the rats' innate emotionality and coping strategy. Consequently, it is tempting to extrapolate the results obtained in the present study to the clinical condition. Indeed, it should be emphasized that antidepressant treatment strategies such as psychopharmacological agents exert marked beneficial actions in depressed individuals only, but have no mood elevating effects in healthy controls.

The occurrence of changes towards more active coping strategies during exposure to Porsolt's swim test has frequently been shown to predict the antidepressant efficacy of a drug when administered to patients suffering from depression (review: Borsini and Meli, 1988; Lucki, 1997). Therefore, the reported behavioural effects of rTMS support a potential antidepressant

efficacy of this treatment. As both the dopamine content in brain homogenates (Ben-Shachar et al., 1997) and in hippocampal microdialysates (Keck et al., 2000c) have been found to be elevated after acute rTMS, it is tempting to relate the decrease in rTMS-induced immobility time to these findings. Indeed, a number of dopamine agonists reduced floating time in rats in the forced swim paradigm (e.g. Borsini and Meli, 1988). Furthermore, we recently reported an increase in the expression of neuropeptide cholecystokinin (CCK) mRNA after chronic rTMS treatment in rats (Müller et al., 2000b). CCK, acting as a neuromodulator, increases the firing rate of dopaminergic neurons in the ventral tegmental area and in the substantia nigra, and the ability of CCK to directly affect local dopamine release has been demonstrated in numerous experiments (review: Crawley and Corwin, 1994). Therefore, the increase in CCK expression reported could possibly contribute to the behavioural effects of chronic rTMS observed in the forced swim test. A further explanation for the increase in active stress coping comes from our recent finding of a significant increase in BDNF mRNA and protein in specific areas of the rat brain after chronic rTMS (Müller et al., 2000b). In line with this finding is the observation that local infusion of high concentrations of BDNF into the midbrain exerts antidepressant-like effects in the forced swim test (Siuciak et al., 1997).

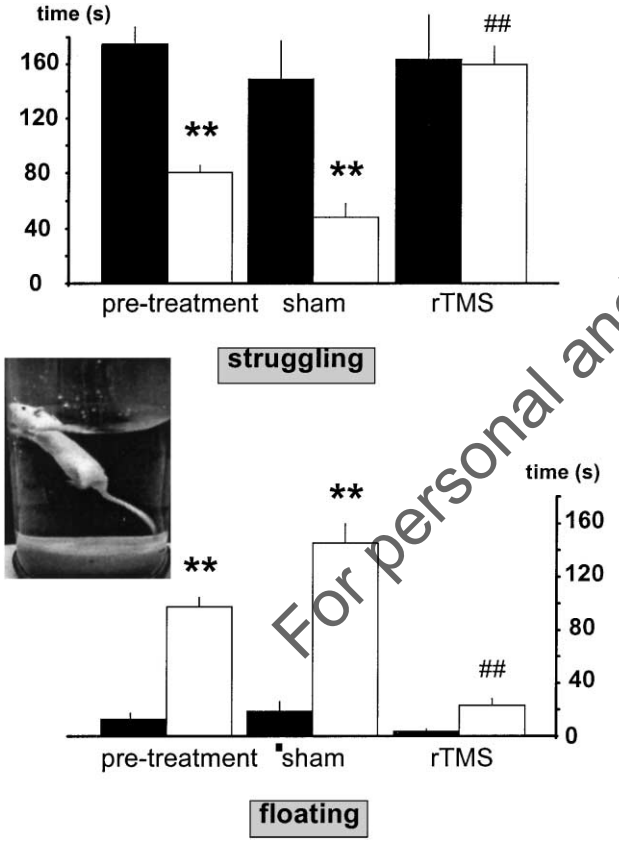

Fig. 2. Behavioural measures obtained in the forced swim test (5 min; 23 °C), performed prior to (pre-treatment) and after completion of the rTMS protocol in rats selectively bred for low anxiety-related behaviour (LAB; rTMS: $n=6$; sham: $n=6$; black bars) and rats selectively bred for high anxiety-related behaviour (HAB; rTMS: $n=6$; sham: $n=6$; open bars) rats. rTMS was applied for a total of six days (20 Hz for 2.5 s; 20 trains per session, i.e. 1000 stimuli per day; 130% of rats' motor threshold). Time during the 5-min testing session spent struggling and floating, respectively, and latency until the first floating reaction. ACTH data shown in Fig. 3 were measured simultaneously. Data are means±SEM. *$P<0.05$, ** $P<0.01$ vs. LAB; # $P<0.05$, ## $P<0.01$ vs. pre-treatment and sham in HAB rats (Keck et al., 2001b).

These findings extend earlier reports of reduced immobility in mice (Fleischmann et al. 1995) and rats (Zyss et al. 1997) following two sessions and two 5-day series of rTMS, respectively. However, in these pioneering studies the distribution pattern of intracerebral current density is unclear and most probably the whole brain has been electrically stimulated (Belmaker and Grisaru, 1998).

In a further experimental design it was shown that chronic rTMS had no effect on rats' behaviour in the elevated plus-maze and social interaction tests (Keck et al., 2000b). These tests have been validated for the detection of emotional responses to anxiogenic and anxiolytic substances (File, 1980; Pellow et al., 1985). The observed lack of an anxiolytic effect of rTMS is consistent with the finding that benzodiazepine-binding characteristics were found to be unchanged after chronic rTMS treatment (Ben-Shachar et al., 1999; Keck et al., 2000b), suggesting that rTMS might not be beneficial in treating anxiety-related behaviour.

4. Neuroendocrine effects of rTMS: attenuation of the stress-induced activity of the HPA system

Disinhibition of the HPA system regulation is a common feature in major depression, and clinical improvement after antidepressant treatment has been observed to be associated with a normalization of HPA system function (review: Holsboer and Barden, 1996; Keck and Holsboer, 1999b, 2001). Therefore, a hypothesis relating stress hormone dysregulation to causality of depression was submitted suggesting that antidepressants may act through normalization of these HPA changes (review: Holsboer, 2000). Indeed, findings of blunted hormone responses to stress have been obtained in rats after chronic treatment with various antidepressants (review: Reul et al., 2000). Thus, since pharmacologically different drugs similarly attenuate HPA system function, this neuroendocrine system was hypothesized to be a common denominator for clinically efficacious antidepressant treatments (Holsboer and Barden, 1996). In line with the above are the findings on rTMS-induced changes in stress-induced corticotropin (ACTH) and corticosterone plasma levels both in commercially obtained rats (Czeh et al., 2000; Keck et al., 2000b)

and—to a higher extent—in a psychopathological animal model (Keck et al., 2001b; Fig. 3) suggesting that chronic rTMS of frontal brain regions attenuates the stress-induced activity of the HPA system. Accordingly, changes in HPA system reactivity in human depression in response to rTMS have been suggested (Pridmore, 1999).

Within the limits of neuroendocrine HPA regulation it seems clear that corticosteroids restrain CRH and vasopressin expression (the main ACTH secretagogues at the level of the anterior pituitary) through activation of hypothalamic glucocorticoid receptors (review: de Kloet et al., 1998). The mechanism underlying HPA hyperdrive in depression is not yet firmly established, but clinical studies in patients and probands with high genetic risk are consistent with decreased glucocorticoid receptor and mineralocorticoid receptor function, rendering the cortisol-mediated negative feedback on CRH and vasopressin expression insufficient (Modell et al., 1997, 1998; Lopez et al., 1998; review: Holsboer, 2000; Fig. 4). It is currently still unclear whether the state of HPA hyperactivity is initially caused by an increased CRH/vasopressin drive resulting in mineralocorticoid receptor/glucocorticoid receptor dysfunction or by a primary defect in mineralocorticoid receptors and/or glucocorticoid receptors resulting in CRH and vasopressin hypersecretion (Holsboer et al., 2000; Reul et al., 2000). Several groups have shown that treatment of rats with various antidepressant drugs increases the binding capacity and gene expression of mineralocorticoid and glucocorticoid receptors in the hippocampus and other limbic and cortical brain areas (Brady et al., 1991; Seckl and Fink, 1992; Reul et al. 1993, 1994). Thus, the effects of antidepressants on these receptors may be a key phenomenon in the readjustment of HPA regulation in major depression. This readjustment has indeed been observed to be a prerequisite for stable remision of the disease (Zobel et al., 1999). To date, it is unclear if in the case of rTMS HPA system regulation is changed due to alterations in mineralocorticoid and glucocorticoid receptor function or if the blunted stress-induced HPA system activity is achieved via different mechanisms leading to a decrease in CRH and vasopressin gene expression. The virtually identical outcome of the CRH challenge test in rTMS-treated and control rats makes it unlikely that changes at the pituitary CRH-CRH 1 receptor-signaling pathway account for differences in neuroendocrine stress response (Keck et al., 2000b, 2001b). This observation suggests that rTMS-induced changes in neuroendocrine regulation are likely to occur at the hypothalamic level. Indeed, the finding of a specific activation in terms of immediate-early gene expression in the paraventricular nucleus of the hypothalamus in response to acute rTMS supports this notion (Ji et al., 1998). Similarly, changes in the dynamic release patterns of vasopressin and specific amino acids in this hypothalamic region have been reported (Keck et al., 2000c). The observation of an rTMS-induced blunted HPA activity is also interesting in light of findings suggesting that the prefrontal cortex may participate in the regulation of the neuroendocrine response to stressful stimuli and, in particular, can inhibit HPA system response to stress, i.e. CRH and vasopressin synthesis and release (e.g. Diorio et al., 1993). Accordingly, projections of the prefrontal cortex to the perinuclear area of the hypothalamic paraventricular nucleus have been demonstrated (Hurley et al. 1991; Takagishi and Chiba, 1991) and major depression is known to be frequently accompanied by frontal cortex dysfunction (review: George et

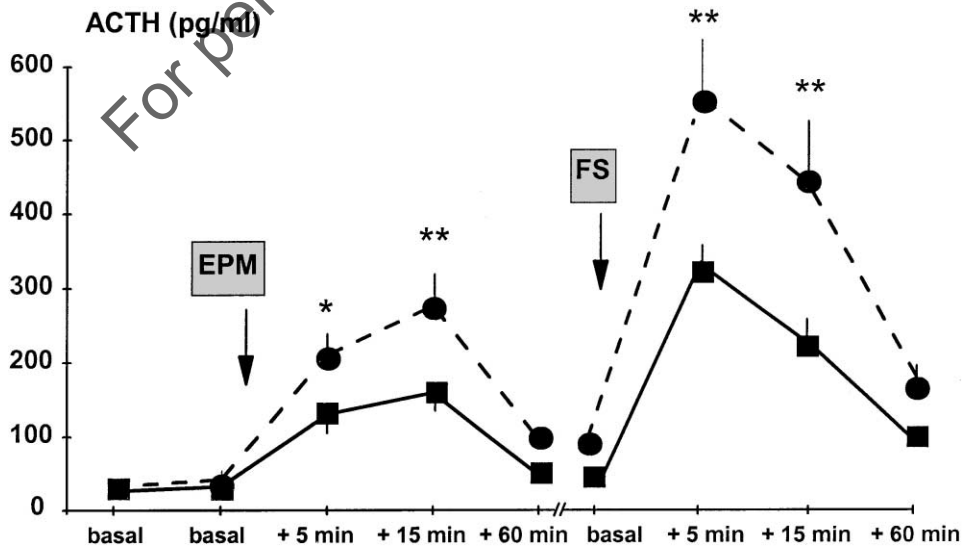

Fig. 3. (A) Effects of 5-min exposure to the elevated plus-maze (EPM) and forced swimming (FS; 23 °C) on plasma ACTH in rats selectively bred for high anxiety-related behaviour (HAB): rTMS-treated animals ($n=6$; squares) and sham-treated controls ($n=6$; circles; broken line). rTMS was applied for a total of 6 days (20 Hz for 2.5 s; 20 trains per session, i.e. 1000 stimuli per day; 130% of rats' motor threshold). Corresponding behavioural data are shown in Fig. 2. Data are means±S.E.M. ** $P< 0.01$; * $P< 0.05$ vs. control (Keck et al., 2001b).

al., 1994; Soares and Mann, 1997). Therefore, we hypothesize that rTMS-induced stimulation of frontal brain regions may normalize aberrant neuronal circuit functioning subsequently leading to a readjustment in hypothalamic CRH and vasopressin synthesis and release. Thus, in the case of antidepressant drug treatment and chronic rTMS, the neuroendocrine endpoint (i.e. normalization of HPA system function via regulation of CRH and vasopressin gene expression) might be reached through different pathways (Fig. 4).

5. Intracerebral neurochemical changes in response to rTMS

Direct non-invasive brain stimulation via rTMS causes changes in neuronal activity as reflected by behavioural alterations and changes in HPA system activity. These alterations are likely to be mediated through local changes in neurotransmitter, neuromodulator release and gene expression. Selected local neurotransmitter/neuromodulator systems might be particular candidates

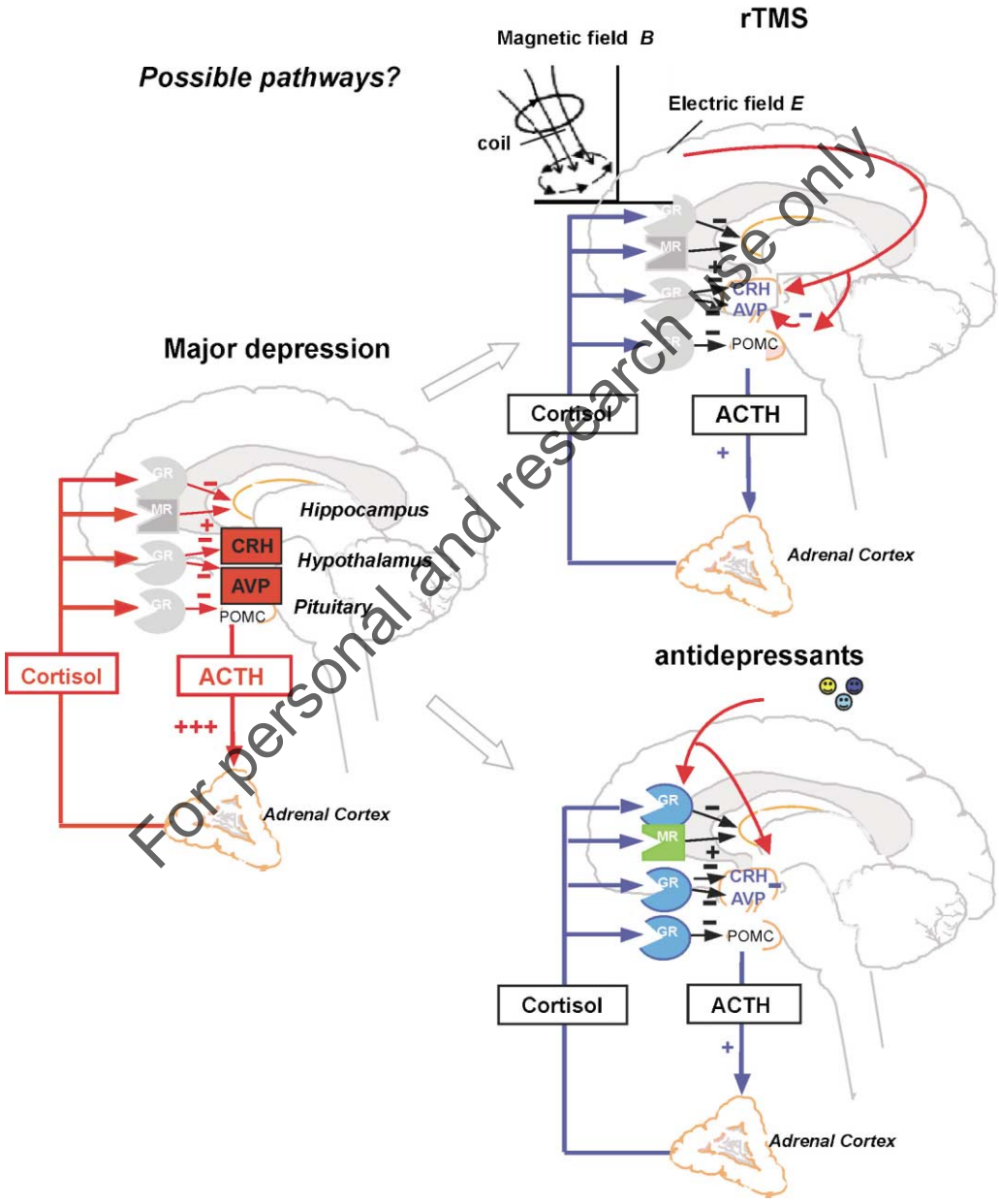

Fig. 4. Possible pathways of the effects of rTMS and antidepressant drugs according to the corticosteroid receptor hypothesis and dysregulation of HPA function in depression. CRH and vasopressin are hypersecreted in patients suffering from major depression whereby the corticosteroid receptor signaling is impaired. Long-term rTMS treatment of frontal brain regions is able to attenuate the stress-induced activity of the HPA system possibly via changes of the neuroendocrine regulation at the hypothalamic/hippocampal level. Antidepressant drugs increase the hippocampal levels of glucocorticoid-receptor (GR) and mineralocorticoid-receptor (MR), decrease the proopiomelanocortin (POMC) mRNA content in the anterior pituitary and diminish the level of ACTH and cortisol (Holsboer, 2000).

for rTMS-induced changes in interneuronal communication. In this context it is important to note that these substances become only biologically active after their release into the extracellular space (Landgraf, 1995). Microdialysis is a method with which changes in extracellular bioactive substances can be detected reliably in vivo (review: Benveniste and Hüttemeier, 1990). This technique is based on the passage of substances through a semipermeable membrane following the concentration gradient between outside and inside the probe and therefore allows for the measurement of dynamic changes in local release patterns.

Indeed, as outlined below, by use of the microdialysis technique, a differentiated modulatory effect of acute rTMS of left frontal brain regions on the dynamics of release patterns of selected neurotransmitter/neuromodulator systems could be demonstrated (Keck et al., 2000c).

5.1. Intracerebral release pattern of vasopressin

The neuropeptide vasopressin triggers a variety of central effects on neuroendocrine, autonomic, emotional and cognitive functions (Antoni, 1993; Landgraf et al., 1998; Raber, 1998). In addition, it is likely to play a key role in the disinhibition of the HPA system that occurs during the course of major depressive illness (Holsboer, 1995; Raber, 1998; Müller et al., 2000a). Vasopressin transported to the median eminence and released into the portal blood is well known to facilitate ACTH secretion (Antoni, 1993). In this context it is of interest to note that vasopressin released into the portal blood is likely to become the primary secretagogue of ACTH in affective disorders, herewith contributing markedly to HPA system dysregulation (von Bardeleben and Holsboer, 1989). Indeed, Purba et al. (1996) found indications of an enhanced vasopressinergic drive by showing an increased number of vasopressin-expressing neurons in the hypothalamic paraventricular nucleus of depressed patients. The observation that long-term rTMS of frontal brain regions in rats induced an attenuated HPA system response to stress, therefore, may be related to changes in intra-paraventricular nucleus release of vasopressin (Keck et al., 2000b, 2001b). Accordingly, a continuous decrease in vasopressin release of up to 50% in response to acute rTMS was reported recently to occur in this nucleus (Keck et al., 2000c; Fig. 5). Although the findings so far are not consistent (Heuser et al., 1998), additional indirect evidence for a role of vasopressin in affective disorders comes from the finding that fluoxetine treatment leads to a reduction in cerebrospinal fluid (CSF) concentrations of vasopressin in patients with major depression (De Bellis et al., 1993).

The changes in vasopressin release could be of interest also in another context: on the one hand rTMS has been reported to have the adverse effect of inducing headache, but on the other beneficial effects on migraine have been suggested (George et al., 1996). Interestingly, changes in intracerebral blood flow have been reported in response to acute rTMS (e.g. Bohning et al., 1999). Therefore, the observed changes in intra-paraventricular nucleus vasopressin release might be of interest in connection with the regulatory functions of vasopressin in cerebral blood flow (Takayasu et al., 1993) and its presumed role in the pathophysiology of migraine (review: Gupta, 1997).

5.2. Intracerebral release pattern of amino acids

Amino acids in the brain have a multitude of functions and may act as neurotransmitters and neuromodulators and have also been implicated in the metabolism and turnover rate of monoamines and in

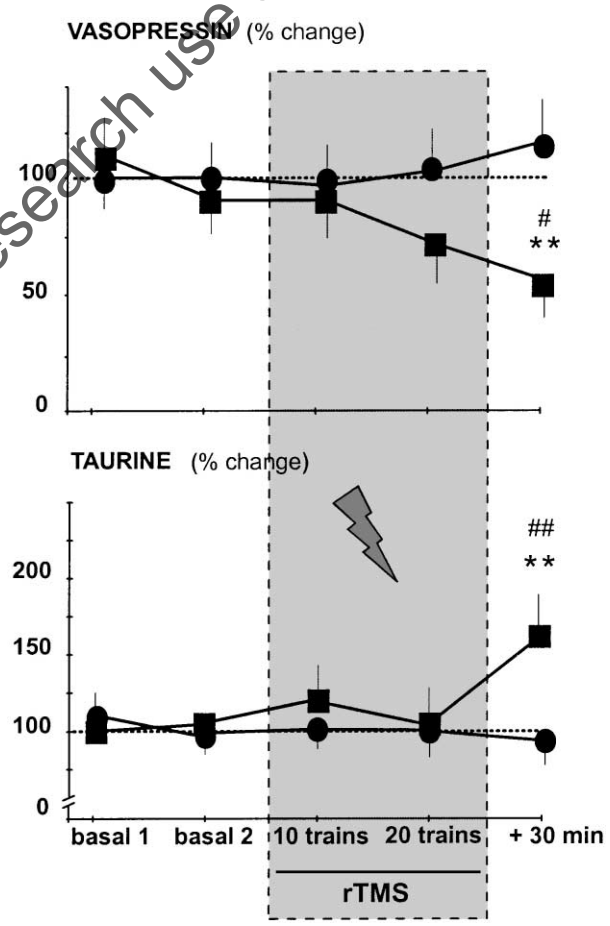

Fig. 5. Effects of acute repetitive transcranial magnetic stimulation on the vasopressin (rTMS; $n=12$; squares; sham stimulation; $n=9$; circles) and taurine (rTMS; $n=7$; squares; sham stimulation; $n=9$; circles) content of 30-min dialysates collected consecutively from the right paraventricular nucleus of urethane-anesthetized male Wistar rats before, during and after rTMS (20 Hz; 1000 stimuli; 130% of rats' motor threshold). Data are expressed as percentage of baseline ± S.E.M. $^{**}P<0.01$ vs. sham stimulation; $\#P<0.05$, $\#\#P<0.01$ vs. basal (Keck et al., 2000c).

HPA system dysregulation (e.g. Garcia de Yebenes Prous et al., 1978; Raber, 1998). In response to acute rTMS an increase of distinct amino acids in the hypothalamic paraventricular nucleus, which is likely to reflect specific biological effects, was reported (Keck et al., 2000c). The observed changes in amino acids level are substance-specific, as in the hypothalamic paraventricular nucleus only taurine (Fig. 5), serine and aspartate, but not γ-aminobutyric acid (GABA), glutamate, glutamine and arginine concentrations in the extracellular fluid were elevated in response to rTMS (Keck et al., 2000c).

In the hypothalamic supraoptic nucleus, taurine of glial origin is probably involved in the inhibition of vasopressinergic neurons through the activation of glycine receptors (Déleuze et al., 1998). Moreover, taurine has been shown to be released from glial cells in the neurohypophysis (posterior lobe), i.e. at the level of the axon terminals of supraoptic and paraventricular vasopressinergic neurons (Miyata et al., 1997). Hence, the increased extracellular concentration of the inhibitory amino acid taurine could have contributed to the decrease in intra-paraventricular vasopressin release after rTMS (Keck et al., 2000c). In contrast, the finding of an increase in intra-paraventricular serine and aspartate release is difficult to interpret and needs further investigation. In patients suffering from bipolar affective disorder (Fekkes et al., 1994) and in a subgroup of depressed patients that were non-responders to treatment with antidepressants (Maes et al., 1998), decreased plasma levels of aspartate and serine were described. Accordingly, serine has been reported to be elevated in CSF samples from patients receiving antidepressants (Pangalos et al., 1992). These findings indicate that mood disorders may be accompanied by perturbations in selected excitatory amino acids, and that antidepressant treatment might have a modulatory effect.

5.3. Intracerebral release patterns of monoamines

Several lines of evidence indicate that an enhancement of monoamine-mediated neurotransmission accompanies the therapeutic effects of most antidepressant treatments including electroconvulsive shock (e.g. Glue et al., 1990; Zis et al., 1992; McGarvey et al., 1993; Gur et al., 1997; for review: Blier and de Montigny, 1994; Holsboer, 1995). Release of monoamines in response to acute rTMS was first monitored in the hippocampus, which is believed to be highly involved in the pathophysiology of depression (Holsboer, 1995). Furthermore, specific effects of chronic rTMS in hippocampal areas have been observed (Müller et al., 2000b; Hausmann et al., 2000). Interestingly, with respect to the hippocampal monoaminergic system, we monitored a selective stimulation of dopamine release only (100% increase; Keck et al., 2000c). This finding suggests that acute rTMS increased the secretory activity of hippocampal dopaminergic axon terminals. The mechanism by which stimulation of frontal brain regions enhances dopamine efflux in terminal areas is likely to involve activation of the substantia nigra and the ventral tegmental area. Consistent with this assumption, it has been demonstrated that rat prefrontal cortex has dense efferent projections to these brain regions (Sesack and Pickel, 1992). Thus it is possible that prefrontal cortex stimulation activates the substantia nigra and ventral tegmental area leading to increased dopamine levels in terminal areas. In support of this assumption is our recent finding that rTMS applied under the same conditions increased dopamine release also in the striatum and the nucleus accumbens septi (Keck et al., unpublished observations), i.e. brain regions receiving dense dopaminergic projections from the substantia nigra and ventral tegmental area. The nucleus accumbens septi hereby is of particular interest as it is a major component of the neural circuitry of reward and incentive motivation, which most likely is dysfunctional not only in depression but also in schizophrenia leading to negative symptoms such as anhedonia and loss of interest (review: Fibiger, 1995). Indeed, preliminary clinical evidence suggests that rTMS might be able to improve negative symptoms in patients suffering from schizophrenia (Cohen et al., 1999; Nahas et al., 2000).

Taken together, the existence of psychiatric syndromes associated with impaired dopamine neurotransmission, i.e. depression, mania and schizophrenia (Holsboer, 1995) where a therapeutic effect of rTMS has been suggested (e.g. Pascual-Leone et al., 1996; Grisaru et al., 1998a,b; Nahas et al., 2000; Rollnik et al., 2000) indicates that the effect of rTMS on dopaminergic activity might be of particular relevance to elucidate its mechanism of action.

Accordingly, the substantia nigra and ventral tegmental area have been strongly implicated in cognitive functions and affective disorders and provide dopaminergic inputs to the hippocampus, striatum and nucleus accumbens (review: Fibiger, 1995; Feldman et al., 1997). In the case of hippocampal dopamine release, however, the possibility cannot be excluded that this effect might be mediated by local activation of the nerve terminals, because medial and lateral prefrontal cortex neurons project to the hippocampus (Groenewegen et al., 1997).

Similar albeit weaker effects of acute rTMS on the dopamine content of hippocampal homogenates (increase by 18%) were reported by Ben-Shachar et al. (1997). In addition, an increase in hippocampal concentrations of serotonin (5-HT) and its main metabolite 5-hydroxyindoleacetic acid (5-HIAA) was observed. In a subsequent study, however, under completely different stimulation conditions Ben-Shachar et al. (1999) were not able to replicate their findings on rTMS-induced changes in intracerebral monoamine concentrations.

Though, stimulation patterns applied were not tested to be analogous to those used under clinical conditions (Belmaker et al., 2000). Indirect evidence for a putative effect of acute rTMS on serotonergic activity comes from a study conducted by Juckel et al. (1999), where low current electrical stimulation via an electrode placed in the rats' medial prefrontal cortex poduced current-dependent increases in 5-HT release in the hippocampus and the amygdala. These effects were not observed when the lateral part of the prefrontal cortex was stimulated (Juckel et al., 1999). However, such anatomically precise electrical stimulation of a specific brain region is unlikely to occur with rTMS (Fig. 1).

Other studies also reported effects of rTMS on the brain serotonergic and noradrenergic systems: Levkovitz and coworkers (1999) demonstrated lasting effects of rTMS on reactivity of the rat hippocampus to electrode stimulation of its main excitatory afferent pathway, i.e. the perforant path. A long-lasting reduction in noradrenergic and serotonergic functions in the hippocampus of chronically treated rats was reported and animals showed significant changes in motility in an open field as well as an increase in pain sensitivity (Levkovitz et al., 1999). The behavioural changes described are likely not to be related to beneficial clinical effects in patients but are most probably due to the stimulation conditions applied, leading to a stimulation of the entire brain instead of a restricted region (Levkovitz et al., 1999). Under similar stimulation conditions Kole et al. (1999) monitored a selective increase in 5-HT_{1A} binding sites in the frontal cortex, the cingulate cortex, and the anterior olfactory nucleus in response to a single train of rTMS. As corticosteroids are well known to play an inhibitory role in 5-HT_{1A} mRNA and protein expression (Chalmers et al., 1993; Meijer and de Kloet, 1994; for review see also: Chaouloff, 1995), this finding is in line with the observation of an attenuated stress-induced HPA system activity in response to rTMS (Czeh et al., 2000; Keck et al., 2000b, 2001b). 5-HT uptake sites, however, showed no changes after a single train of rTMS (Kole et al., 1999). While most antidepressant drugs typically upregulate postsynaptic 5-HT_2 receptors, Ben-Shachar et al. found postsynaptic 5-HT_{2A} receptors to be downregulated in the frontal cortex and striatum after 10 days of rTMS (Ben-Shachar et al., 1999). By use of in vivo microdialysis of the prefrontal cortex combined with challenges with a 5-HT_{1A} receptor agonist or a 5-HT_{1B} receptor antagonist subsequent to 10 days of rTMS, subsensitivity of presynaptic serotonergic autoreceptor activity was demonstrated, herewith revealing parallels to other antidepressant treatments (Gur et al., 2000). However, like in the other studies showing an influence of rTMS on brain serotonergic systems, rats had to be restrained during stimulation (Kole et al., 1999; Belmaker et al., 2000; Gur et al., 2000). Therefore, it is difficult to distinguish between pure rTMS-related effects and effects secondary to the severe stress of restraint necessary for treatment. However, although the clinical significance remains unclear, these findings suggest that the serotonergic system might be influenced at various levels in response to rTMS.

6. Neurochemical effects: rTMS vs ECT

Both electroconvulsive shock and rTMS have been shown to exert similar effects at the behavioural level in rodent studies but have shown to have different clinical effectiveness in patients. In the latter, electroconvulsive therapy (ECT) has been demonstrated to be more efficient in the treatment of patients with delusional depression or depression refractory to antidepressant drug treatment (George et al., 1999; Grunhaus et al., 2000). However, rTMS has been suggested to be as effective as ECT in the treatment of nondelusional major depressive disorder (Grunhaus et al., 2000).

In rats, apart from changes in the Porsolt swim test, behavioural effects common to both electroconvulsive shocks and rTMS include enhancement in apomorphine-induced stereotypy and increases in seizure threshold for subsequent electroconvulsive stimulation (e.g. Fleischmann et al., 1995, 1999; Zyss et al., 1997; Ebert and Ziemann, 1999; Keck et al., 2000b, 2001b). Therefore, the possibility that rTMS might exert its putative antidepressant effects by mimicking some of the effects of ECT is under discussion (e.g. Zyss et al., 1994; Fleischmann et al., 1995, 1999). Both ECT and rTMS exert their therapeutic effects by inducing electric current in the brain tissue. Accordingly, it is appropriate to compare the neurochemical effects elicited by both treatment strategies. With respect to receptor binding and function, similarities in the downregulation of cortical β-adrenergic receptors have been described (Fleischmann et al., 1996; Zyss et al., 1997) in response to electroconvulsive shock and rTMS. However, using different stimulation frequencies and coils, this finding has not been replicated unequivocally (Ben-Shachar et al., 1999).

Concerning the intracerebral release pattern of neurotransmitters and neuromodulators, both similarities and discrepancies have been observed in response to acute electroconvulsive shocks and rTMS. In contrast to the finding of an increase in intra-paraventricular nucleus release of taurine, serine and aspartate in response to acute rTMS (Keck et al., 2000c), Korf and Venema (1985) reported that electroconvulsive shock decreased the extracellular concentration of taurine in the rat striatum, but had no effect on serine or aspartate. Undoubtedly, further studies are needed to elucidate whether the conflicting findings reflect (1) an activation

of different neurotransmitter/neuromodulator systems by rTMS and electroconvulsive shock, or (2) an activation of different brain regions (Ji et al., 1998), or (3) both.

Electroconvulsive shock in rats has been reported to induce a marked increase in extracellular serotonin concentrations in the hippocampus (Zis et al., 1992; McGarvey et al., 1993) and in dopamine concentrations in the striatum (Yoshida et al., 1997). In contrast to the latter finding, Glue et al. (1990) reported the striatal dopamine release to be unaltered after electroconvulsive shock. It is unclear whether the increased monoamine release is due to convulsions or to the passage of electroconvulsive shock current in brain tissue (McGarvey et al., 1993). In response to acute rTMS, marked increases in hippocampal, striatal and accumbal dopamine release have been observed (Keck et al., 2000c). Similarly, modest increases in dopamine content in the striatum and hippocampus have been monitored in brain homogenates (Ben-Shachar et al., 1997). The finding described by us and others (Ben-Shachar et al., 1997; Keck et al., 2000c) that acute rTMS did not affect intrahippocampal noradrenaline levels conflicts with data suggesting an increased noradrenaline release in the rat hippocampus following electroconvulsive shock (Thomas et al., 1992). Similarly, although previous studies reported a multitude of effects of electroconvulsive shock on hippocampal serotonergic neurotransmission (e.g. Zis et al., 1992; Gur et al., 1997) we were unable to detect changes in intrahippocampal serotonin release whilst others observed an increase in hippocampal serotonin and 5-HIAA content after acute rTMS (Ben-Shachar et al., 1997). However, the latter study has been conducted on tissue monoamine levels whilst in the other experiments extracellular, i.e. biologically active, monoamine concentrations were monitored.

Taken together, the discrepancies in neurochemical findings between electroconvulsive shock and rTMS can be taken as an indication that these two treatment strategies may differentially affect distinct neurotransmitter/neuromodulator systems. In support of this is the finding that rTMS induces different patterns of immediate-early gene expression in the rat brain than does electroconvulsive shock (Ji et al., 1998). The underlying physics support this assumption: the transcranial application of electricity is impeded by the scalp and skull, resulting in a substantial drop-off in amplitude and loss of focal precision. Therefore, to reach specific brain structures, high currents need to be applied that may elicit a general seizure as a "side effect" (Sackeim et al., 1993). In the case of rTMS, the transcranial induction of electricity using an alternating magnetic field avoids these drawbacks and may, at least in part, provide an explanation why these two modalities appear to exert different neurobiological effects.

7. Cognitive function and morphological outcome after rTMS treatment

The use of rTMS as a therapeutic tool in psychiatry requires repetitive and frequent use to be effective. So far, the use of rTMS in humans is regarded as safe (Wassermann, 1996; Kirkcaldie et al., 1997). Further, recent studies reported that rTMS might beneficially modulate learning and memory functions in patients with neurological disorders, e.g. Parkinson's disease (review: Grafman and Wassermann, 1999). Padberg et al. (1999) observed an improvement in verbal memory performance and Little et al. (2000) reported a better outcome on a list-recall test after rTMS treatment in patients suffering from major depression. In contrast, in cognitive neuroscience, the transient interruption of neuronal activity and the induction of transiently impaired brain functions play a role in the use of acute rTMS as an investigative tool (Grafman et al., 1994; Walsh and Cowey, 2000).

In rats, acute single pulse-TMS treatment has been suggested to impair retrograde memory function in a learned taste aversion test (Kling et al., 1990). However, long-term rTMS-treatment did not affect cognitive outcome as assessed in the Morris water-maze task, which is regarded as a good indicator of hippocampal function (Barnes, 1988), or in the social discrimination procedure. Hence, it is unlikely that chronic rTMS of left frontal brain regions impaired learning and memory performance (Post et al., 1999).

Concerning possible hazardous effects of rTMS at the structural and cellular level in the brain, Matsumiya et al. (1992) reported microvacuolar changes in the neuropil portion of cortical layers 2–6 in rats stimulated with 2.8 Tesla for at least 100 stimuli. In contrast, Sgro et al. (1991) did not detect significant morphological changes in the various rat brain regions after rTMS for a total of at least 10000 stimulations with 3.4 Tesla, nor did Counter et al. (1993) after chronic low frequency TMS (2.0 Tesla; 1000 stimuli) of rabbit brains. The effects of long-term rTMS treatment in rats similar to that used under clinical conditions have been examined in a study by Post et al. (1999). Here, the histopathological examination of cortical regions, amygdala and the hippocampus after long-term stimulation for 11 weeks, revealed no abnormal histological features or evidence for any cell loss. The absence of an increase in glial fibrillary acidic protein (GFAP; an indicator of reactive astrogliosis) after 11 weeks of rTMS treatment showed that the use of this technique under conditions comparable to clinical use does not result in significant structural brain alterations in rats (Post et al. 1999). Consistently, rTMS did not change the expression of cortical GFAP mRNA in rats that were treated for 14 days (Hausmann et al., 2000). In contrast, Fujiki and Steward (1997) found a profound but transient increase

in GFAP mRNA throughout the molecular layer of the dentate gyrus after acute application of 10–30 trains of 25 Hz frequency rTMS (1.63 Tesla) in mice. However, even without considering the marked differences in stimulation conditions and species used, this increase in GFAP mRNA confirms that acute rTMS can transiently activate gene expression, which does not necessarily result in reactive astrogliosis (Steward et al., 1993). We also failed to detect an increase in the expression of the neuron-specific phosphoprotein B-50 in the inner part of the molecular layer of the hippocampal dentate gyrus, which would be indicative of synaptic reorganization and dendritic sprouting of mossy fibers, as previously described in rats after kindling (Dalby et al. 1995). This indicates that long-term rTMS treatment (20 Hz) does not induce significant synaptic reorganization in the hippocampus (Post et al. 1999). Furthermore, this finding argues against the possibility that rTMS used under conditions comparable to those in clinical trials might induce kindling effects in rats as has been suggested by Jennum and Klitgaard (1996) by use of a stimulation frequency of 50 Hz. Similarly, Ebert and Ziemann (1999) found no effect of 20 Hz rTMS on the kindling process but could demonstrate that acute rTMS led to a decrease of seizure susceptibility in the amygdala of rats.

Taken together, there is no evidence that rTMS leads to structural alterations or impairment in cognitive functions even after long-term treatment in animals. In contrast, severe cognitive alterations, i.e. impairment of spatial learning and memory, retention of passive avoidance response have been reported repeatedly to occur after electroconvulsive shock in rats (Morgenson et al., 1994; Zupan et al., 1996) and after ECT in humans (anterograde and retrograde amnesia; Sackeim et al., 2000). The recent finding that chronic rTMS had virtually no influence on hippocampal neurogenesis further supports the notion that this technique can be considered as safe (Czeh et al., 2000). Accordingly, data of an in vitro study showed no detrimental effect of electromagnetic stimulation (analogous to rTMS) on the morphology or viability of mouse monoclonal hippocampal HT-22 cells (Post et al., 1999; Fig. 6).

8. Potential neuroprotective effect of rTMS: hypothesis and possible mechanisms

The results of recent rTMS-studies allow one to speculate about potential neuroprotective effects of this technique.

First, acute electromagnetical stimulation increased the viability of HT-22 cells and had a neuroprotective effect against oxidative stressors such as glutamate, hydrogen peroxide (H_2O_2) and amyloid beta; substances that are known to cause oxidative cell damage in these cells (Behl et al., 1995; Post et al., 1998, 1999). Moreover, the magnetic stimulation increased the release of the potentially neuroprotective secreted amyloid precursor protein (sAPP) into the supernatant of HT-22 cells and into cerebrospinal fluid of rats. Consistently, HT-22 cells preincubated with cerebrospinal fluid from long-term rTMS-treated rats were found to be protected against potent oxidative stressors (Post et al. 1999; Fig. 6). The amyloid precursor protein (APP), a type 1 transmembrane protein, is the precursor of the amyloid beta protein (Aβ) that is the main constituent of insoluble amyloid plaques and vascular deposits that are the pathological features in Alzheimer's disease (Haass and Selkoe, 1993; Selkoe, 1994; Yankner, 1996). Aβ generation depends on the processing of APP by endoproteases called β- and γ-secretases (Vassar et al., 1999). Cleavage by an α-secretase-pathway resulted in the release of a soluble form of APPα, secreted into extracellular milieu, which can be activated e.g. by electrical activity (Nitsch et al., 1993; review: Mattson, 1997). Although the biological functions of secreted APP (sAPPα) are still under investigation, the substance may play a role in neuroprotection against oxidative stressors such as Aβ and glutamate as well as in synaptic plasticity (Mattson et al., 1993; Schubert and Behl, 1993; Mucke et al., 1994; Masliah et al., 1997; White et al., 1998). Soluble APP derivatives are secreted by many types of cultured cells, and are also found in human cerebrospinal fluid and in the superfusates of brain slices. Cerebrospinal fluid levels of sAPP have been demonstrated to be decreased in patients with Alzheimer's disease (Van Nostrand et al. 1992), a finding which is in line with the proposed neuroprotective role of this protein. The electrical field, induced by rTMS seems to be able to stimulate the release of sAPP as it was shown also by direct electrical depolarization in hippocampal slices (Nitsch et al., 1993). Further, the activity of the transcription factor NF-κB was found to be unchanged in HT-22 cells and in rat cortex after electromagnetical stimulation (Fig. 6). The role of NF-κB in oxidative stress and cell survival/apoptosis is well established (Schreck et al., 1991; Schmidt et al., 1995; Baichwal and Bäuerle, 1997; Lezoualc'h and Behl, 1998; Foo and Nolan, 1999) and the suppression of the NF-κB activity has been shown to be neuroprotective depending on the experimental and cellular paradigm and on the mode and kinetics of activation (Post et al., 1998, 2000; Lezoualc'h et al., 2000). Secondly, not only the increase of sAPP release but also changes of other factors like the increased expression of brain-derived neurotrophic factor (BDNF) at the mRNA and protein level in cortical regions and hippocampus may play a role in explaining the potential neuroprotective effect of rTMS (Müller et al., 2000b; Fig. 7). BDNF belongs to the family of neurotrophins and was shown to be involved in survival and differentiation in specific areas of the central nervous system as well as in regulating

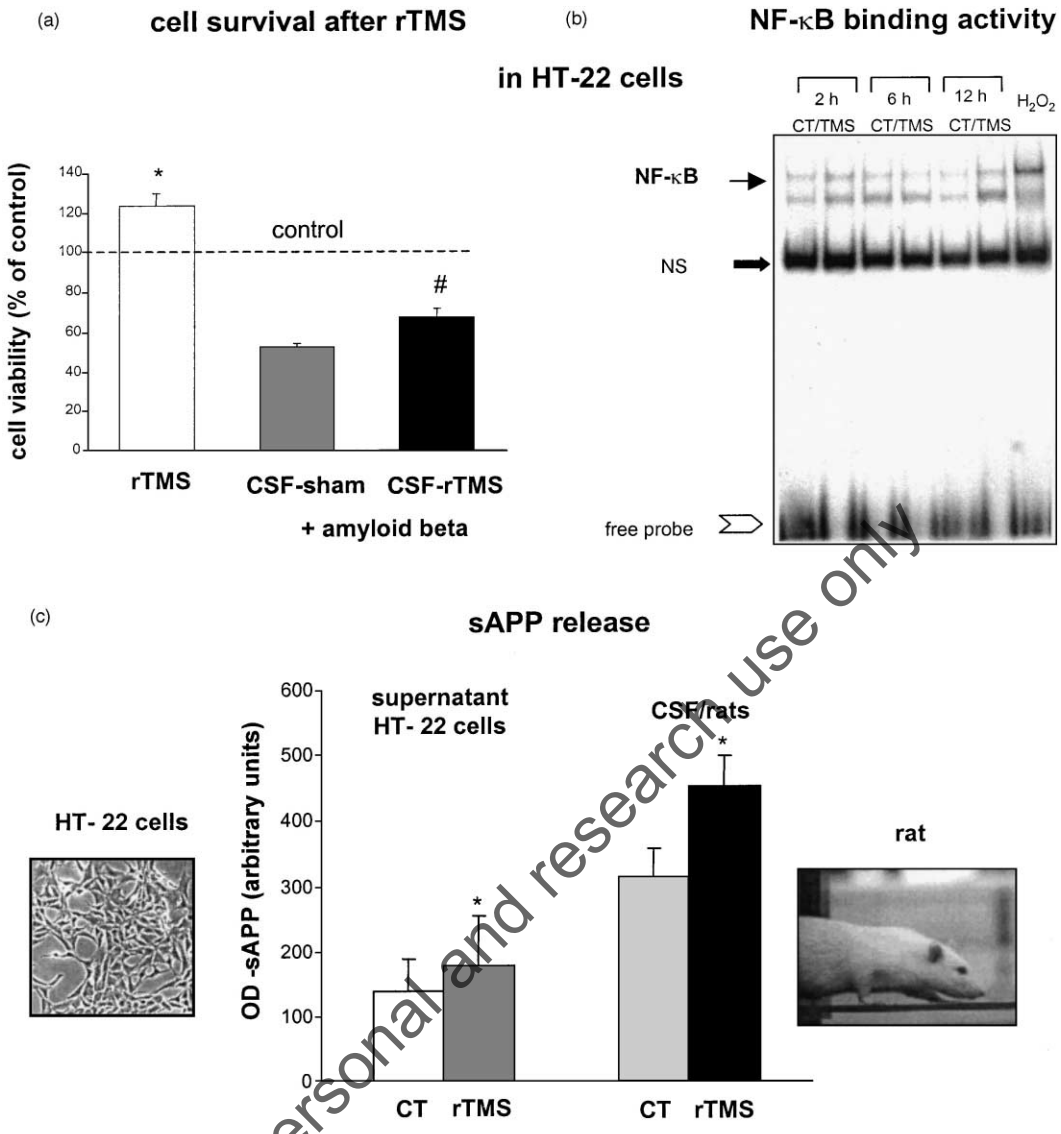

Fig. 6. (a) Effects of rTMS treatment on cell survival of HT-22 cells and on HT-22 cells incubated with cerebrospinal fluid (CSF) of rTMS-treated rats. Cell survival after electromagnetic stimulation, as determined by the MTT assay (% of control) is shown in the left bar. Values are expressed as mean±S.E.M. (n = 20) of three independent experiments. *$P < 0.001$ vs. control. In the right panels, the effect of rat CSF on the survival of HT-22 cells challenged with Aβ is shown. HT-22 cells were preincubated with CSF from rTMS-treated (rTMS + Aβ) or sham-stimulated rats (sham + Aβ) for 8 h, after which 20 μM Aβ was added and the cells were incubated for 16 h. Thereafter, cell viability was determined using the MTT assay. Data are means (% of control)±SEM for triplicate cultures. #$P < 0.01$ vs. sham-. (b) DNA binding activities of NF-κB in HT-22 cells were analyzed after rTMS challenge for 1 h and incubation for different time points. Treatment with 120 μM H_2O_2 was used as a positive control. Nuclear extracts were prepared and EMSAs were performed. The autoradiograph of the native gel is shown. The *small arrow* indicates the position of specific NF-κB/DNA complexes; the *bold arrow* shows the position of non-specific complexes (NS); *the arrowhead* depicts the position of the free DNA probe. The specificity of the detected NF-κB band has been demonstrated previously in HT-22 cells by supershift analysis (Post et al., 1998, 2000). The binding activity of NF-κB (arbitrary optical density units) was quantified by scanning the autoradiographies and showed no significant differences between groups. (c) A semi-quantitative analysis of data from both HT-22 cells and CSF of rats after rTMS treatment is shown. Supernatant of HT-22 cells and CSF from rats were subjected to immunoblot analysis using an antibodies against APP. *Left panel*. Cell morphology of HT-22 cells treated with rTMS. Cultures were photographed using phase contrast with magnification ×200. *Left columns*. HT-22 cells were treated with rTMS (1000 stimuli, 120 A/μs, 20 Hz) or left untreated (control, CT). After 6 h, supernatants of HT-22 cells were harvested and subjected to western blot analysis. Densitometric quantitation of sAPP released from the cell cultures is shown. *Right panel*. Rats were treated with rTMS (150 stimuli per day, 120 A/μs, 20 Hz, 130% of motor threshold) for 11 weeks or received stimulations of the low lumbar spine region (sham). After the long-term/sham stimulation paradigm, CSF was withdrawn from the cisterna magna and assayed using western blot analysis for sAPP.

neuronal connectivity and synaptic plasticity (Lewin and Barde, 1996). Further, BDNF was shown to rescue neurons from cell death after excitotoxic, hypoglycaemic or ischaemic insults (Lindholm et al., 1993; Kiprianova, 1999; Frechilla et al., 2000). BDNF which is expressed at high levels in the adult hippocampus, can be upregulated by electrical stimulation (Balkowiec and Katz, 2000) and plays a role in hippocampal long-term

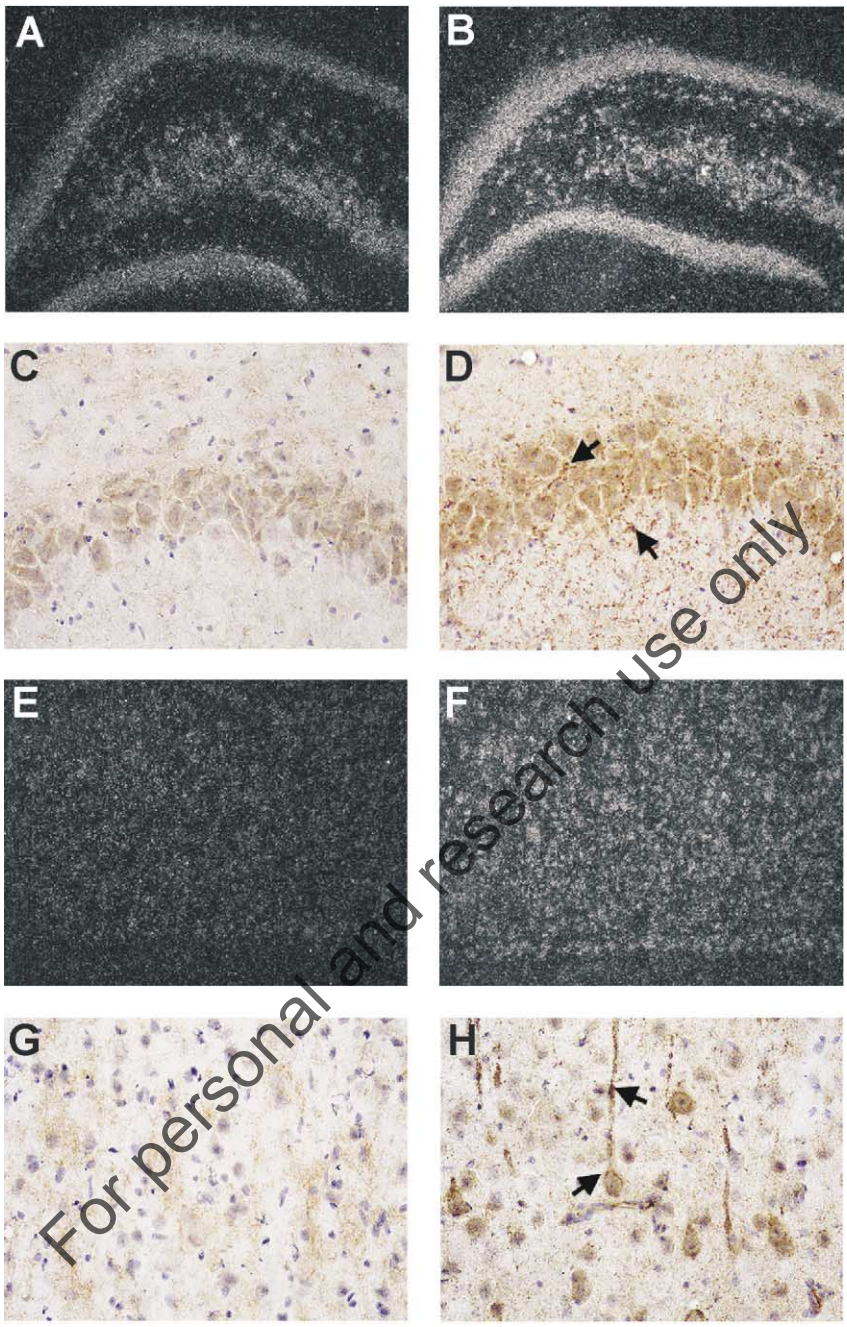

Fig. 7. Long-term rTMS increases the expression of BDNF mRNA and BDNF-like immunoreactivity in specific regions of the rat brain (B,D,F,H). rTMS was applied for a total of 11 weeks (20 Hz for 2.5 s; 3 trains per day, i.e. 150 stimuli per day; 130% of rats' motor threshold; $n=5$). The control sections (sham-treated animals; $n=5$) are shown in A, C, E, and G. Representative coronal sections of hippocampal areas (A,B) and the parietal cortex (E,F) of in situ hybridization analysis using an α-^{35}S-dATP labeled oligonucleotide probe are shown. Darkfield photomicrographs reveal a marked increase in BDNF mRNA expression in hippocampal areas CA3 and dentate gyrus (B) and in the parietal cortex (F) in response to rTMS. Consistently, in these regions also the BDNF-like immunoreactivity is increased: in granule neurons of the dentate gyrus (D), where many large immunoreactive granules can be observed (arrows), and in the parietal cortex (H). In the parietal cortex rTMS induces not only an increase in cytoplasmic immunoreactivity, but also a prominent staining of cell membranes and dendritic processes (arrows; Müller et al., 2000b).

potentiation (Chen et al., 1999). Interestingly, Wang et al. (1996) observed both long-term potentiation and long-term depression-like changes after rTMS in the gerbil auditory cortex. Chronic rTMS treatment increased BDNF mRNA and protein level in specific areas of rat brains, namely in the CA3 region of the hippocampal pyramidal cell layer and in the granule cell layer of the dentate gyrus (Müller et al., 2000b). Therefore, rTMS might be a stimulus for the release of endogenous BDNF comparable to the effect of direct electrical stimulation in neuronal cells (Balkowiec and Katz, 2000; Du et al., 2000).

Furthermore, it is noteworthy that after chronic rTMS treatment BDNF mRNA and protein expression are increased in exactly the same brain regions as observed after ECT and antidepressant drug treatment (Nibuya et al., 1995, 1996) suggesting that a common molecular mechanism may underlie different antidepressant treatment strategies. This might be achieved via attenuation of HPA system activity that occurs both in response to long-term rTMS and antidepressant drug treatment (Reul et al. 1993, 1994; Keck et al. 2000b, 2001b) as it has been shown that glucocorticoid and mineralocorticoid receptors participate in the control of neurotrophic factor gene expression (Hansson et al., 2000). Interestingly, rTMS seems to be useful in minimizing ischemic brain damage after transient occlusion of the middle cerebral artery in rats and to improve the neurological outcome in these animals (M.E. Keck, unpublished observations).

9. Conclusion and outlook

In accordance with clinical studies (review: Wassermann, 1998), the rodent studies available so far suport the notion that rTMS is a safe technique even when used chronically, i.e. up to 11 weeks in rats (Post et al., 1999; Müller et al., 2000b). Currently, there is no evidence that rTMS causes structural brain damage or detrimental cellular alterations, but additional studies are necessary to further support this aspect. It is further important to note that single-pulse TMS failed to induce changes of the blood–brain barrier in rats (Ravnborg et al., 1990).

Taken together, the preclinical findings provide, at least in part, an explanation for the possible neurobiological mechanisms underlying the therapeutic effects reported in numerous clinical trials. However, based on current validation studies it seems premature for rTMS to be approved for routine clinical use (review: George et al., 1999; Sackeim, 2000). Notwithstanding, further studies systematically investigating the influence of varying stimulation parameters (e.g. the duration of treatment, the total number of magnetic stimuli applied, the stimulation frequency and precise localization of the stimulation coil) are necessary to better characterize the neurobiological effects of TMS responsible for its efficacy in the treatment of different neurological and psychiatric disease conditions.

The fact that rTMS is able to increase the expression and release of potential neuroprotective substances such as sAPP and BDNF deserves further attention. So far, several findings from both in vitro and in vivo experiments support the proposal that neurotrophic factors might help in the treatment of neurodegenerative disorders by protecting against neuronal cell loss and by increasing the function of surviving neuronal populations (e.g. Conner et al., 1997). To date, neurodegenerative diseases leading to dementia such as Alzheimer's disease, Parkinson's disease or focal brain atrophies represent one of the greatest therapeutic challenges in medicine. Although their underlying causes are probably different in nature, they have at least one major point in common: the selective loss by cell death of specific neuronal populations in the brain. There is thus a serious need for therapeutic strategies that can specifically protect neurons against oxidative cell death in these devastating pathological conditions. In this context, much work has been done on endogenous neuroprotective and neurotrophic factors, such as sAPP and BDNF that show strong survival-promoting effects on many neuronal populations (e.g. Lindholm et al., 1993; Shimohama et al., 1993; Conner et al., 1997). Although these are potentially fruitful therapeutic candidates, their administration is fraught with restricted penetration of the blood-brain barrier and fast degradation. Therefore, we hypothesize that the stimulation and the expression of endogenous neuroprotective substances, i.e. sAPP and BDNF, directly within the brain by use of rTMS is a worthwhile approach which is currently under investigation at the Max Planck Institute of Psychiatry.

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