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Loudness Dependence of Auditory Evoked Potentials as Indicator of Central Serotonergic Neurotransmission: Simultaneous Electrophysiological Recordings and *In Vivo* Microdialysis in the Rat Primary Auditory Cortex

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Serotonin released in synapsis is one of the key neurotransmitters in psychiatry and psychopharmacology. The loudness dependence of auditory evoked potentials (LDAEP) has been proposed as a marker for central serotonergic neurotransmission. Several findings in animals and humans support this hypothesis. However, the *in vivo* measurement of cortical extracellular serotonin levels has never been performed simultaneously with the recording of auditory evoked potentials. The interrelationship between low cortical serotonergic activity and strong LDAEP is yet to be proven. The auditory evoked potentials were recorded in the epidura above the primary auditory cortex of male Wistar rats whereas extracellular serotonin levels in the primary auditory cortex were measured by *in vivo* microdialysis before and after i.p. application of the selective serotonin reuptake inhibitor citalopram. At baseline, the correlation of coefficients between the LDAEP, especially of the N1 component, and extracellular serotonin levels in the primary auditory cortex was negative. The increase of serotonin levels after citalopram application was significantly related to a decrease of LDAEP of the N1 component ($r = -0.86$, $p = 0.003$). These data support the view that the LDAEP is closely modulated by cortical serotonergic activity. Thus, the LDAEP might serve as an inversely related marker of synaptically released serotonin in the CNS.
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INTRODUCTION

Today, several lines of evidence suggest that the central serotonergic neurotransmission, especially the synaptically released serotonin, plays a major role in the pathophysiology of a number of psychiatric disorders such as major depression (Heninger *et al*, 1996), alcoholism, seasonal affective disorder, bulimia (Malison *et al*, 1998; Willeit *et al*, 2000; Tauscher *et al*, 2001), and obsessive-compulsive disorder (Pogarell *et al*, 2003). Unfortunately, progress in diagnosis and therapy of mental disorders ascribed to a disturbed serotonergic neurotransmission is slowed down by the fact that no reliable indicator of the serotonergic system is yet available (Nash and Meltzer, 1991; Yatham and Steiner, 1993). Only indirect markers for central serotonergic function such as monoamine or monoamine metabolite levels in serum and CSF have been measured. The diagnostic value of peripheral functional measures is limited because they are nonspecific and only partially reflect central serotonergic activity (Murphy, 1990; Moret and Briley, 1991; Potter and Manji, 1993).

The *in vivo* assessment of serotonergic neurotransmission is therefore an important field of research. Auditory evoked potentials (AEP) are averaged event-related encephalographic potentials linked to acoustic stimuli. Although other neurotransmitters such as glutamate and GABA are involved in generating the AEP (Zheng *et al*, 2007; Javitt *et al*, 1995), the parameter stimulus intensity dependence or loudness dependence of auditory evoked potentials (LDAEP) is most likely a consequence of different activity levels in the serotonergic system (synaptically released serotonin at the auditory cortex): a strong LDAEP reflects a low serotonergic activity and a weak LDAEP reflects a high serotonergic activity (Hegerl and Juckel, 1993; Juckel *et al*, 1999). Here, the LDAEP of the primary auditory cortex is the relevant parameter because the serotonergic innervation of the primary auditory cortex is stronger than that of the secondary auditory cortex (Azmitia and Gannon, 1986; Lewis *et al*, 1986). A strong LDAEP is found in patients with neurological or psychiatric disorders with an assumed deficiency of serotonin, such as depression (James *et al*,

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1990), borderline personality disorder (Norra *et al*, 1998), anorexia nervosa (Rothenberger *et al*, 1991), migraines (Wang *et al*, 1996), long-term ecstasy abuse (Tuchtenhagen *et al*, 2000; Croft *et al*, 2001), or obsessive-compulsive disorder (Juckel *et al*, submitted). A number of clinical and experimental findings in humans suggest a correlation between the synaptical release of serotonin and the LD of the N1/N2 component. A weak LDAEP has been observed after pharmacological treatment with serotonin-agonistic drugs such as zimelidine, sertraline, and lithium (Buchsbaum and Pfefferbaum, 1971; Hubbard *et al*, 1980; Von Knorring, 1982) or, in contrast, a strong LDAEP in schizophrenic patients after long-term use of serotonin-antagonistic substances (5-HT2A receptor) such as clozapine and olanzapine (Juckel *et al*, 2003). Furthermore, patients with a low serotonergic activity show a favorable response to serotonergic medication (Gallinat *et al*, 2000; Juckel *et al*, 2007).

Animal research supports the view of the LDAEP being related to serotonergic neurotransmission. Juckel *et al* (1999) reported that microinjection of a 5-HT1A agonist into the dorsal raphe nucleus of cats, which reduces the firing rate of serotonergic neurons and the synaptic release of serotonin, resulted in an increased LDAEP in the primary auditory cortex but not in the secondary auditory cortex, whereas injection of a 5-HT1A antagonist was followed by a decreased LDAEP. Intravenous administration of a serotonin-agonistic substance was followed by an increase in LDAEP of the primary but not secondary auditory cortex, and an antagonist led to a decrease (Juckel *et al*, 1997). Altogether, these findings imply a strong relationship between the LDAEP and the serotonergic system and support the hypothesis that the LDAEP can indicate central serotonergic function in the human brain. In animal studies, the measurement of AEP, including LDAEP, has already been described (Arezzo *et al*, 1986; Molnar *et al*, 1986; Juckel *et al*, 1996). AEP and N1/P2 components in rats provide reliable measurement (Barth *et al*, 1993). Direct comparison between rat and human AEP was performed by Sambeth *et al* (2003): the first four components depend on sensory processes and can serve as a model of human AEP. The polarity of the components in rats shows the same order as in humans, but the latency of the components is usually 1.82 times shorter, because the electrophysiological signal is conducted faster in the small skull and brain of rats.

The *in vivo* relationship between the LDAEP and the synaptical serotonin release has not been analyzed before. Simultaneous measurement of both parameters would allow direct access to the relation between evoked potentials and serotonergic function. Therefore, the LDAEP was recorded epidurally above the primary auditory cortex in anesthetized male Wistar rats. Simultaneously, extracellular serotonin levels were measured in the primary auditory cortex by *in vivo* microdialysis. Furthermore, dialysate samples were taken before and after intraperitoneal injection of the selective serotonin reuptake inhibitor citalopram or vehicle. The aim of the study was to prove the hypotheses that (1) there is a negative correlation between LDAEP and serotonin levels in the primary auditory cortex and (2) there is a suppressive effect of systemic application of citalopram on the functional states of the local serotonergic system.

MATERIALS AND METHODS

Animals

Male Wistar rats weighing 280–380 g were used. Before experimentation, animals were housed 4–5 per cage under conditions of constant temperature (21–23°C) and maintained on a 12-h light/dark cycle with food and water available *ad libitum*. Principles of laboratory animal care and all procedures were approved by the Animal Care Committee of the Charité—Universitätsmedizin Berlin, Berlin, Germany. Additionally, all efforts were made to minimize the number of animals used and their suffering.

Experimental Procedure

Animals ($n = 18$) were divided into two subgroups, an experimental group ($n = 9$) and a control group ($n = 9$). Before surgery, animals were deeply anesthetized with chloral hydrate (400 mg/kg i.p.) and placed in a stereotaxic apparatus (TSE Systems, Bad Homburg, Germany). The level of anesthesia was periodically verified via the hind limb compression reflex or the tail picking test and maintained using supplemental administration of chloral hydrate (60 mg/kg i.p.). The temperature was monitored using a rectal probe and maintained at 36–37°C with a heating pad (TSE Systems).

Microdialysis. A burr hole of 2 mm diameter was drilled over the primary auditory cortex (AP –4.3; ML 7.0). After resection of the dura and exposure of the cortical surface, a guide cannula was brought in position through the burr hole (DV 3.2) with a micromanipulator (TSE Systems). A microdialysis probe (Microbiotech/se AB microdialysis probe MAB 2.20.2, exposed membrane 0.6×2 mm, cutoff 35 kDa, Microbiotech, Stockholm, Sweden) was placed through the guide cannula in the primary auditory cortex (coordinates of probe tip: AP –4.3; ML 7.0; DV 5.2). The guide cannula was fixed on the skull surface with dental cement. The microdialysis probe was perfused with artificial CSF (in mM: NaCl 125, $CaCl_2$ dehydrate 1, $MgCl_2 \cdot 6H_2O$ 1, Na_2So_4 5, KCl 2.5, $NaH_2PO_4 \cdot H_2O$ 0.5, Na_2HPO_4 dehydrate 2, $NaHCO_3$ 27 with pH adjusted to 7.25–7.35 with phosphoric acid) for 1 h before insertion of the probe using a microinjection pump and with flow rate 10 µl/min. After insertion, the flow rate was adjusted to 1.5 µl/min and the first dialysate sample was collected after 2 h. During these 2 h, the probe was perfused with artificial CSF to wash out operation debris. The extracellular samples were then collected every 20 min for 4 h. The samples were collected in microcentrifuge tubes. The microcentrifuge tubes were kept in an icebox while collecting the samples. The aliquots were analyzed in high-performance liquid chromatography (HPLC) columns.

Measurement of serotonin. HPLC was performed using a Shimadzu HPLC system equipped with an LC 10AD pump, degasser DGU-14A, an autoinjector SIL-10AD, and a Decade electrochemical detector (Antec Leyden, The Netherlands) with a VT-03 electrochemical flow cell with 2.0 mm diameter glassy carbon electrode against *in situ* Ag/AgCl reference electrode. A reverse-phase 100×2.00 mm Prontosil 120-3-C18 analytical column (Bischoff Chromatography,

Germany) was used at room temperature with a flow rate of 0.300 ml/min. The mobile phase consisted of 50 mM sodium dihydrogen phosphate (NaH_2PO_4), 0.78 mM octyl sodium sulfate, 0.1 mM Na_2EDTA, 2 mM NaCl, and 6% isopropanol. The pH of the mobile phase was adjusted with sodium hydroxide to 5.4. For the electrochemical detection of serotonin levels, the potential was set at 750 mV. Quantification of the compound concentrations was based on the chromatographic peak height using the external standard method (Shimadzu Chromatography data system Class-VP version 6.1).

AEP recordings. A tripolar stainless-steel screw-electrode was used to record the AEP. Electrodes were screwed into the skull. The tip of each electrode stayed epidural. The active lead was implanted over the primary auditory cortex (AP −5.6; ML 7.0 related to bregma). The reference and the ground electrodes were placed on the skull anterior to the frontal cortex and over the cerebellum. Electrical brain activity was transmitted to high-impedance preamplifiers through a light low-noise cable (GRASS Instruments). The EEG was filtered between 3 and 1000 Hz and sampled at 500 Hz. EEG was recorded 100 ms anterior to stimulus and 1000 ms poststimulus. EEG was recorded and analyzed by a commercial software (Brain Vision Recorder, Brain Vision Analyzer). After fixation of the electrodes and implantation and fixation of the microdialysis probe, the earplugs of the stereotaxic frame were removed and two speakers were placed 3 cm lateral to each ear. Acoustic stimulation was performed by commercial software (Neurobehavioral Systems Presentation 0.81). The binaural acoustic stimuli consisted of sinus tones of 4 ms duration and with 1000 Hz frequency. Tones were presented in four different intensity levels: 87, 96, 104, and 111 dB SPL. Seventy stimuli of each intensity level were presented in a random order with a randomized interstimulus interval of 1.8–2.2 s. Animals were stimulated and AEP were recorded parallel to each microdialysis sample.

Experimental procedure. Experiments were performed in each group as follows: the first three dialysate samples were defined as baseline serotonin levels and their AEP were collected. After collecting the baseline, animals of the experimental group ($n=9$) were injected with the SSRI citalopram (10 mg/kg i.p.). The animals of the control group ($n=9$) were injected with 0.3 ml NaCl i.p. After injection, samples were collected as described above.

Data Analysis

Microdialysis. Concentration of serotonin was measured by reversed-phase high-performance liquid chromatography with electrochemical detection. Peak height was determined using the external standard method.

LDAEP. All data were corrected for technical and other artifacts by visual analysis of the single sweeps. Amplitudes of the components were determined as highest positive or negative values in the latency windows according to Sambeth *et al* (2003): P1, 10–30 ms; N1, 41–80 ms; P2, 80–130 ms; N2, 130–200 ms. The loudness dependence of each component was calculated as the median slope of all possible straight lines connecting the different amplitude values to each intensity level. The median slope indicates the amplitude change due to increasing stimulus intensity, that is, LDAEP.

RESULTS

The AEP of all animals showed a clear loudness dependence. As hypothesized, we found significant Pearson correlation coefficients between serotonin levels in primary auditory cortex at baseline before intervention and the LDAEP of the N1 and P2 components, epidurally recorded above the primary auditory cortex (Table 1). The correlation coefficient for the P1 component tended to be significant, whereas no significant effects were found for the N2 component.

In the experimental group ($n=9$), we found a significant correlation coefficient between the change of LDAEP of the N1 component due to citalopram and the corresponding changes of the extracellular serotonin levels. When serotonin levels increased, the LDAEP decreased ($r=-0.86$, $p=0.003$; Figures 1 and 2). (experimental group—change in serotonin level/change of LDAEP of N1 component (pg/μV/8 dB): 0.02/−0.45; 0.06/0.26; 0.07/0.26; 0.02/−0.75; 0.08/1.95; 0.04/0.74; −0.01/−1.89; 0.04/−1.43; 0.02/−1.38). For the P1, P2, and N2, no such effects were seen at significant levels. In the control group, no significant correlation coefficient between the LDAEP of AEP components and extracellular serotonin levels was found (control group—change in serotonin level/change of LDAEP of N1 component: (pg/μV/8 dB): −0.01/2.14; −0.03/2.68; −0.01/1.27; −0.02/1.04; −0.03/−10.54; 0.02/2.04; −0.03/−0.11; −0.01/0.63). There was a significant interaction effect of serotonin level changes (baseline/follow-up) and group condition (citalopram/NaCl) (ANOVA with repeated measurements: $F(1/16)=17.7$, $p=0.001$), whereas such an effect was not found for the LDAEP of the N1 component ($F(1/16)=0.9$, NS).

DISCUSSION

The aim of this study was to investigate the relationship in rats between the LDAEP and the extracellular serotonin levels in the primary auditory cortex. The extracellular serotonin levels consist of serotonin released from cortical neurons. Several studies in humans and animals propose a negative correlation between the parameters LDAEP and serotonin levels, that is, weak LDAEP is related to high serotonin activity and vice versa (Von Knorring and Perris, 1981; Hegerl and Juckel, 1993; Juckel *et al*, 1999; Croft *et al*,

Table 1 Correlation Coefficients between Serotonin Levels in Primary Auditory Cortex at Baseline before Intervention and the Loudness Dependence of the AEP Components ($n=18$)

LDAEP	P1 component	N1 component	P2 component	N2 component
Serotonin levels	−0.446 ($p=0.064$)	0.654 ($p=0.004$)	−0.491 ($p=0.045$)	0.207 ($p=0.442$)

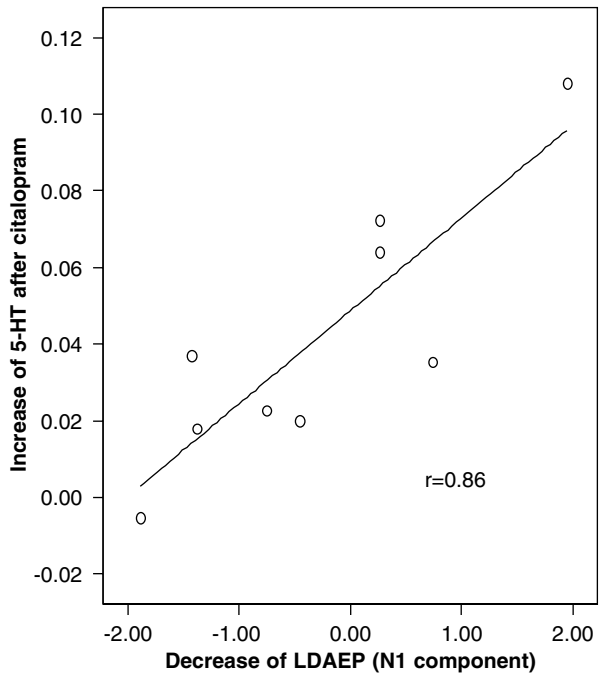

Figure 1 In the citalopram group, an increase of extracellular serotonin levels in the primary auditory cortex was associated with LDAEP recorded there ($n = 9$).

2001). However, this relationship has only been investigated indirectly, for example, by recording AEP before and after serotonin agonistic medication. In this study, LDAEP as well as extracellular serotonin levels in the primary auditory cortex were measured simultaneously using epidural electrophysiological recording and *in vivo* microdialysis before and after i.p. application of the SSRI citalopram *vs* placebo. The main results of the study were (1) there were significant negative correlations between the LDAEP of the N1 as well as that of the P2 component and the serotonin levels in the primary auditory cortex of male Wistar rats and (2) the increase of local serotonin levels induced by systemic citalopram application was intraindividually related to a decrease of LDAEP of the N1 component. These results support the assumption that the LDAEP is closely modulated by cortical serotonergic activity, and therefore the LDAEP might serve as a marker for the synaptically released serotonin in CNS.

The LDAEP is very suitable for monitoring central serotonergic activity as individual differences in LDAEP result from variations in the cortical mechanisms involved in the generation of these waves because they do not covary with peripheral or subcortical changes of neuronal activity caused by increases in stimulus intensity (Lukas and Siegel, 1977; Lukas, 1987a, b). Such nonspecific modulation of the LDAEP is considered to be dependent on extrathalamic

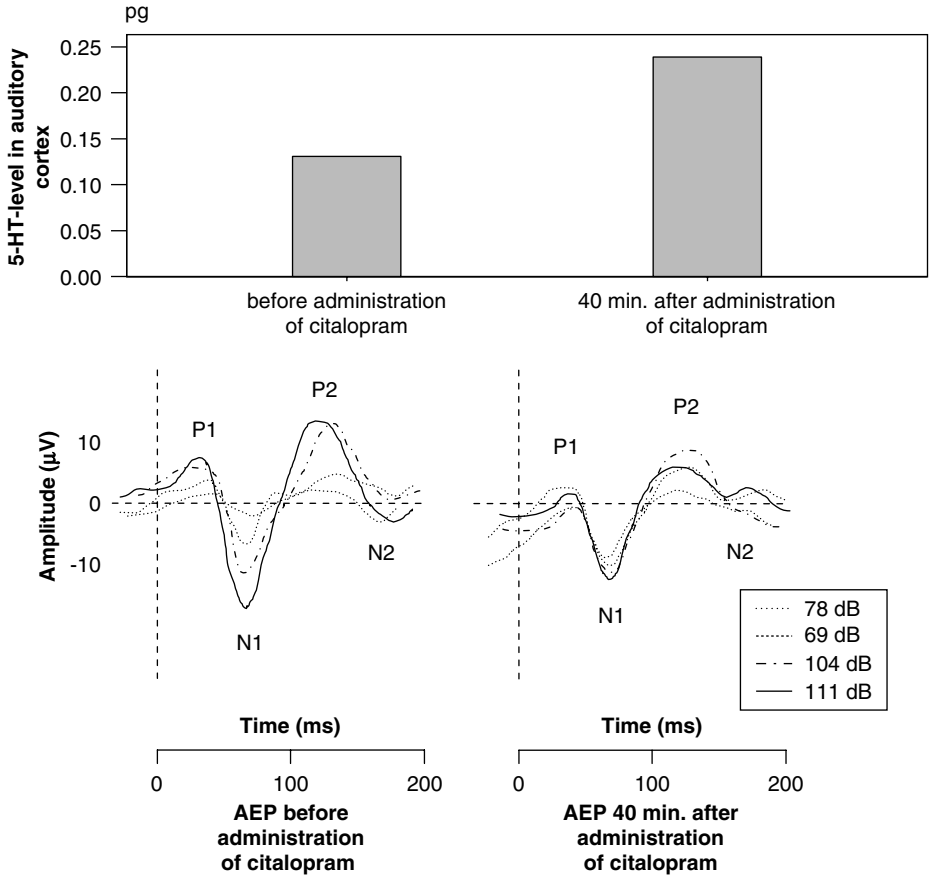

Figure 2 Serotonin levels in primary auditory cortex and AEP waveform pattern before and after the administration of citalopram (rat 2).

monaminergic systems projecting from the brainstem to the cortex (Foote and Morrison, 1987; Morrison and Hof, 1992), especially the serotonergic system (Hegerl and Juckel, 1993). Serotonergic innervation of primary sensory cortices is focused on layer IV, where thalamacortical sensory input is received and processed on to layers III and V of the pyramidal cells, the generators of the LDAEP.

A possible explanation for why we did not find a significant effect for the LDAEP of the P2 component in our experiments is that the mean amplitude of the P2 component is lower in rats than in humans (Sambeth *et al*, 2003). Furthermore, anesthesia reduces the AEP amplitudes, probably through a concomitant inhibition of the excitatory postsynaptic potentials of cortical pyramidal cells (Maclver *et al*, 1996; Schwender *et al*, 1997; Thornton and Sharpe, 1998; Antunes *et al*, 2003). As the animals in our study were anesthetized, the amplitude of the P2 component might have been decreased to a level at which differences were not significantly measurable whereas the naturally higher N1 component still showed a pronounced LDAEP.

Care is warranted in the interpretation of these results. The first limitation of the study is that the number of subjects ($n = 9$ per group) is relatively small. Secondly, there is no doubt about the involvement of other monoamines and neurotransmitters in generating and modifying AEP and the LDAEP, but in this study we wanted to concentrate on the role of serotonin because of its important clinical impact. Thirdly, experiments were performed with anesthetized animals. Anesthesia is known to affect temporal processing in rat auditory cortex. Rennaker *et al* (2007) showed a suppression of neural responses to broadband clicks after the administration of ketamine. Nevertheless, we used anesthesia to reduce artifacts. The implantation of the microdialysis probe in addition to the fixation of three electrodes in the skull was a complex procedure and the fixation on the skull was difficult. In previous experiments, we found disturbances in serotonin measurements due to probe dislocation after head movements. Furthermore, we wanted the auditory stimulus to be stable throughout the whole experiment. In a freely moving animal, head position and angle toward the loudspeakers would change continuously. Besides, sounds of animal movements might interfere with the acoustic stimuli. By performing experiments in anesthetized animals, we ensured the same head position toward the speakers and the same loudness of stimuli without other sound sources in the experimental chamber throughout the whole experiment in all animals. Furthermore, differences remain between the generation of AEP in rats and humans. Obviously, a single rat model is unlikely to reflect all pathways that generate an evoked potential in human subjects. However, anatomical findings correspond in both species: granular cells in layer IV of the auditory cortex of rats and humans receive direct projections from the thalamus (McCormick and Prince, 1985; Di and Barth, 1993). Changes in serotonergic and noradrenergic neurotransmission precipitate changes in AEP in both species (Manjarrez *et al*, 2001, 2005; Keedy *et al*, 2007). The AEP of rats shows similarities to that of humans in terms of latency, waveform, and duration (Sambeth *et al*, 2003). In particular, similarities of rat and human AEP were shown for P1, N1, P2, and N2 components (Sambeth *et al*, 2003; Keedy *et al*, 2007). Rat P1 component (P13) showed an amplitude reduction in response to rapidly presented stimuli, which was similar to that seen in human P1 (P50) (Miyazato *et al*, 1995). In a stimulus repetition experiment, the amplitude decrements were similar in both species (Sambeth *et al*, 2004). Therefore, the LDAEP of the rat seems to be a promising animal model.

Detecting the correlation coefficient between LDAEP and serotonin levels in this study allows for the first time an evaluation based on empiric data about how closely the two parameters are connected. This is of utmost importance for the clinical use of LDAEP in psychiatry. Altogether, the results support the hypothesis that the LDAEP is modulated by cortical serotonin levels and might serve as a marker for the serotonergic activity.

DISCLOSURE/CONFLICT OF INTEREST

The authors declare that, except for income received from the primary employer, no financial support or compensation has been received from any individual or corporate entity over the past 3 years for research or professional service and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest.

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