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Research paper

Fear-conditioned alterations of motor cortex excitability: The role of amygdala

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ABSTRACT

Background and objective: We hypothesized that fear-conditioning may increase motor cortical excitability in preparation for response to fear. We tested our hypothesis in healthy subjects and in the second step, to determine the role of amygdala in alterations of motor cortex excitability, we included a group of patients who previously underwent unilateral amygdalo-hippocampectomy for temporal lobe epilepsy.

Patients and methods: In the first step, we included 16 healthy volunteers. In the second step, 14 patients who previously underwent unilateral amygdalo-hippocampectomy for temporal lobe epilepsy and who were seizure-free were included in the study. Motor evoked potentials (MEPs) recorded over right hand were recorded twice before and after the observation of fearful faces (fear-conditioning). Auditory startle response (ASR) was also recorded.

Results: Comparisons of before and after fear-conditioning MEP parameters within the healthy subjects group showed MEP amplitude was higher after fear-conditioning ($p = 0.019$). Same comparison in patients with unilateral amygdalo-hippocampectomy demonstrated shorter MEP latency ($p = 0.036$) and higher MEP amplitudes after fear-conditioning ($p = 0.046$). CSPs did not show any change after this paradigm in both groups. Comparisons of ASR findings before and after fear-conditioning demonstrated enhanced responses after fear-conditioning in both healthy subjects and in patients with unilateral amygdalo-hippocampectomy. For MEPs or ASRs, there was a similar enhancement in patients with left- or right-sided operation.

Conclusions: Fear-potentiation of both corticospinal and reticulospinal pathways occurs in healthy humans and bilateral potentiation of ASR and potentiation of MEPs are maintained even after resection of unilateral amygdala regardless of its side.

1. Introduction

Fear is a behavioral response in which humans or animals present with freezing of gait, exaggerated startle and autonomic symptoms like sweating. The most important brain structure which is engaged in the acquisition of conditioned fear responses is the basolateral amygdala [1,2]. Amygdala projects to various hypothalamic and brainstem areas known to be involved in specific signs and symptoms of fear and anxiety [3].

The relationship of fear and the startle response has been relatively well-defined and most of the studies covering fear behavior have used auditory startle response (ASR) in their paradigm. A direct pathway between amygdala and pontine reticular nucleus was shown and was considered a critical pathway for the generation of ASR [4]. After fear-conditioning, magnitudes of ASR get bigger or latencies shorten, indicating hyperexcitable ASR and suggesting the excitatory role of amygdala on the generator of ASR in the reticular formation. Fight or flight reaction is a continuation of behavioral response probably requiring a high motor preparation. Limited studies in healthy subjects demonstrated an increased size of motor evoked potentials (MEPs) after fear-related music or fearful images [5,6].

Therefore, we hypothesized that fear-conditioning may also increase motor cortical excitability in preparation of response to fear. We tested our hypothesis in healthy subjects using magnitudes of MEPs before and after fear-conditioning and we also analyzed the findings of a relatively well-known method in the field, ASR. In the second step, to determine the role of amygdala in the alterations of motor cortex excitability, we included a group of patients who previously underwent unilateral amygdalo-hippocampectomy for temporal lobe epilepsy.

2. Subjects and methods

2.1. Subjects

In the first step, we included 16 healthy volunteers. In the second

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step, 14 patients who previously underwent unilateral amygdalo-hippocampectomy for temporal lobe epilepsy and who were seizure free after the operation were included in the study. The age and gender was similar in both groups. The surgery had been performed according to the previous descriptions [7]. In all patients, unilateral amygdala and hippocampus resection was done. In seven patients, superior temporal gyrus and temporal pole were also resected along with amygdala and hippocampal structures whereas the resection was confined to amygdala and hippocampus in the others (selective amygdalo- hippocampectomy). Operation side was right in five patients. They were not using antiepileptic medications. None of the participants had anxiety or depression. Participants with any disorders which may change the results of electrophysiological investigations (e.g. hearing loss or drugs which may potentially affect cortical excitability) or in which electrophysiological investigations are contraindicated were excluded from the study.

Age at onset, seizure semiology, duration of epilepsy, detailed clinical history and detailed neuropsychological assessments were noted as parts of the clinical assessment. Patients with psychosis, anxiety or depression at the time of electrophysiological investigations were also excluded from the analysis because these disorders may have confounding effects on electrophysiological results.

This study was approved by the local ethical committee. All participants provided informed consent.

2.2. Methods

All electrophysiological recordings were done with surface silver–-silver chloride electrodes using Neuropack Sigma MEB-5504k, Nihon Kohden Medical, Tokyo, Japan while subjects were sitting comfortably in a chair in a dark, quiet laboratory room. All recordings were repeated twice, before and just after the observation of fearful faces. After-recordings were done 500 ms after the observation of fearful faces.

2.2.1. Transcranial magnetic stimulation

We applied single-pulse transcranial magnetic stimulation (TMS) with 40–100% of maximal output intensity using a MagStim Model 200 (Magstim Co, Dyffed, UK) stimulator and a circular coil over vertex. Monophasic current was applied in PA direction [8]. Briefly, surface electrodes were placed over abductor pollicis brevis (APB) on dominant side in a belly-tendon fashion and ground electrode was on the forearm. The coil center was localized on the vertex since we used a circular coil. The filter settings were 3 kHz high-cut and 20 Hz low-cut. The amplitude sensitivity was 200–500 μV.

First, we determined resting motor threshold (rMT) and active motor threshold (aMT) for each subject. rMT was defined as the minimal intensity required to elicit a response with 50 μV of minimal amplitude in the target muscle in at least five out of 10 recordings. For aMT, participant performed submaximal (approximately 10–25% of maximal level) contraction of the specific muscle, as shown by the investigator and the level of contraction was adjusted by audiovisual feedback. The minimal intensity of motor cortex stimulation which elicited a reliable response with minimal amplitude which were distinguished from the ongoing EMG activity in at least five out of 10 recordings was accepted as aMT. During motor threshold determination, we started with slightly higher intensities and approached to motor threshold by 1% reductions. After determination of motor thresholds, we recorded 20 MEPs during rest using 120% rMT and 20 traces of cortical silent period (CSP) by stimulating with 120% aMT while subjects continued submaximal contraction.

We performed recordings of a second block of 20 MEPs during rest and 20 traces of cortical silent period (CSP) 500 ms after observation of fearful faces. For these recordings, we used the same motor thresholds as in the first block.

2.2.2. Auditory startle response

We placed bipolar surface electrodes on bilateral orbicularis oculi (O.oc), sternocleidomastoid (SCM), biceps brachii (BB) and APB muscles. Ground electrode was placed over the sternum. The electrodes were placed in a belly-tendon fashion except O.oc for which the recording electrode was placed on the lower eyelid with a reference electrode located on the lateral orbital margin. First, hearing thresholds were determined and subsequently a monophasic 105 dB HL auditory tone burst stimulus was applied bilaterally through headphones. The recordings were repeated eight times. To prevent habituation, stimuli were given unexpectedly at approximately every 2–5 min and stimulus duration was 100 ms at onset which was increased by 50 ms every two stimuli. Single sweeps of 500 ms were recorded with filters at 10 and 10.000 Hz. The amplitude sensitivity was 200–500 μV.

The recordings were done in two blocks before and after observation of fearful faces similar to MEP recordings.

2.2.3. Observation of fearful facial expressions

Recordings which included actors displaying fearful expressions Karolinska Directed Emotional Faces database (Lundqvist, Flykt, & Ohman, 1998) were shown using 13.1 inch Toshiba R211 model laptop under maximal luminance measurements. The distance between the eyes of participants and the screen was 1 m.

2.3 Statistical analysis

For TMS investigation, peak-to-peak amplitude and onset latency of MEPs and CSP duration were measured using cursors and mean values were calculated.

- For ASR, onset latencies, durations and amplitudes of responses on each muscle were measured using cursors and mean values were calculated. Response probability of each muscle and total ASR probability were calculated as follows: Number of responses of muscle (O.oc, etc)/Number of total recordings (8) × 100.

The following comparisons were performed:

1. Between before and after observation of fearful faces in the group of healthy subjects using Wilcoxon test.
2. Between before and after observation of fearful faces in the group of patients with amygdalo-hippocampectomy using Wilcoxon test.
3. Between before- observation of fearful faces in healthy subjects and patients using Mann Whitney-U test.
4. Between after- observation of fearful faces in healthy subjects and patients using Mann Whitney-U test.
5. To understand the impact of the operation side (left vs right), as well as the operation type (selective amygdalohippocampectomy vs anterior temporal lobectomy) in the patient group, two-way ANOVA was used.

Data analyses were performed using the SPSS 15 software statistical package (SPSS Inc., Chicago, IL, USA). p value < 0.050 accepted as significant.

3 Results

Mean age of healthy subjects was 30.1 ± 8.7 years whereas mean age of the patient group was 36.8 ± 8.5 years ($p = 0.052$). Male-to-female ratios were 10/6 and 8/6, respectively ($p = 0.765$). The mean duration after operation was 11.8 ± 2.9 years. All patients were right-handed and had focal-onset seizures. Table 1 shows detailed clinical findings of each patient with epilepsy surgery. There was no difference of resting or active motor thresholds recorded between groups (46.7 ± 2.7% for patients and 47.3 ± 2.5% for healthy subjects, $p = 0.497$; 39.6 ± 2.1% for patients and 40.3 ± 1.8% for healthy

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