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CASE REPORT

Opioid receptor binding in parahippocampus of patients with temporal lobe epilepsy: Its association with the antiepileptic effects of subacute electrical stimulation

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Summary Opioid receptor binding was evaluated in parahippocampal cortex (PHC) obtained from patients with intractable mesial temporal lobe epilepsy (MTLE) with and without subacute high frequency electrical stimulation (HFS) in this brain area. Mu, delta and nociceptin receptor binding was determined by autoradiography in PHC of five patients (ESAE group) with MTLE history of 14.8 ± 2.5 years and seizure frequency of 11 ± 2.9 per month, two of them (40%) with mesial sclerosis. This group demonstrated antiepileptic effects following subacute HFS (130 Hz, 450 μs, 200—400 μA), applied continuously during 16—20 days in PHC. Values were compared with those obtained from patients with severe MTLE (history of 21.7 ± 2.8 years and seizure frequency of 28.2 ± 14 per month) in whom electrical stimulation did not induce antiepileptic effects (ESWAE group, $n = 4$), patients with MTLE in whom no electrical stimulation was applied (MTLE group, $n = 4$) and autopsy material acquired from subjects without epilepsy ($n = 4$ obtained from three subjects). Enhanced 3H-DAMGO (MTLE, 755%; ESAE, 375%; ESWAE, 693%), 3H-DPDPE (MTLE, 242%; ESAE, 80%; ESWAE, 346%) and 3H-nociceptin (MTLE, 424%; ESAE, 217%; ESWAE, 451%) binding was detected in the PHC of all epileptic groups. However, tissue obtained from ESAE group demonstrated lower opioid receptor binding (3H-DAMGO, 44.5%, $p < 0.05$; 3H-DPDPE,

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47%, $p < 0.05$; 3H-nociceptin, 39.3%, $p < 0.5$) when compared with MTLE group. The present results indicate that a high effectiveness to the antiepileptic effects induced by HFS is associated with reduced opioid peptide binding.

Introduction

We previously reported that subacute high frequency electrical stimulation (HFS) of the parahippocampal cortex (PHC) significantly decreases the number of interictal spikes at focus and abolished clinical seizures in patients with intractable mesial temporal lobe epilepsy (MTLE).[1] Blockage of temporal lobe epilepsy by PHC stimulation seems to be due, at least in part, to an inhibitory process of the stimulated area according with the following effects observed in the patients receiving HFS: (a) an increased threshold and decreased duration of the PHC afterdischarge and depression of the PHC evoked response recovery cycles, comparing the same patients before versus after PHC stimulation; (b) a single photon emission computed tomography (SPECT) hypoperfusion of the hippocampal region comparing the epileptic and stimulated side versus the normal and non-stimulated side in the same patient.[1,2] We described that subacute electrical stimulation of PHC is more effective in producing antiepileptic effects in patients with less severe epilepsy, an effect associated with higher GABA tissue content and a low rate of cell loss, but without changes in $GABA_A$ and benzodiazepine receptor binding in PHC.[3]

Experimental evidences support the involvement of opioid peptides in ictal, postictal and interictal activity.[4–10] Positron Emission Tomography (PET) studies revealed that the epileptogenic hippocampus from patients with MTLE shows reduced mu and delta receptor binding whereas the lateral temporal cortex of these patients, an area proposed to play an important role in the seizure expression and propagation, demonstrates an increase and non-significant changes of mu and delta receptors, respectively.[11,12]

The major purpose of the present study was the characterization of mu, delta and nociceptin receptor binding in PHC of patients with MTLE who showed antiepileptic effects after receiving subacute HFS in this brain area. Clinical and electrophysiological results obtained from these patients displaying antiepileptic effects during the HFS were previously reported.[1,2] Opioid receptor binding characterization may improve the understanding of the pathophysiology of a number of antiepileptic conditions associated with electrical stimulation, and it may greatly enhance the safety and efficacy of this therapy.

Material and methods

Subject selection and brain samples

PHC tissue was obtained from patients with intractable MTLE history who underwent extensive preoperative phased evaluation in order to define focal areas of maximal epileptogenesis. None of the patients involved in the present study demonstrated gross structural lesions, such as tumors or vascular malformations. Table 1 provides a summary of the relevant clinical data and side of the epileptic focus for each patient.

HFS was applied in patients who, on the basis of history and neurological examination, were felt to be potential candidates, i.e. patients suffering from intractable complex partial seizures in whom invasive and non-invasive diagnostic procedures allowed to localize unilateral MTLE. Further details about the criteria for patient selection, electrode implantation, clinical characteristics and temporal lobectomy were previously reported.[1,2] This study was approved by the scientific committees of the institutions involved in the present research and informed consent was obtained from each patient.

Patients were divided into four groups as follows:

a) MTLE without HFS (MTLE group): four patients (mean age 29.5 ± 1.7 years old) with intractable temporal lobe epilepsy history of 17.2 ± 1.3 years and seizure frequency of 63 ± 45 per month had "en block" anterior lobectomy, ipsilateral to the epileptic focus. Magnetic resonance imaging (MRI) demonstrated mesial sclerosis in every one of these patients (Table 1).
b) MTLE plus HFS with antiepileptic effects (ESAE group): five patients (mean age 27.8 ± 1.9 years old) with intractable temporal lobe epilepsy history of 14.8 ± 2.5 years and seizure frequency of 11 ± 2.9 per month underwent electrode implantation which was performed as follows: multicontact electrode grids were unilaterally