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Electrophysiological mechanisms of action of electroconvulsive therapy

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In spite of the guidelines and consensus on its indications and application, electroconvulsive therapy (ECT) continues to be one of the therapeutic procedures with less knowledge on its mechanism of action. It is interesting to evaluate the way in which the factors that modulate the convulsant activity can be modified by this therapy and its relation with the therapeutic effect.

The aim of the present article is to review, in the context of neurobiological theories, the bibliography regarding the electrophysiological mechanisms of action of ECT, mainly the anticonvulsant hypothesis. Having better knowledge about these mechanisms can achieve an improvement in the clinical practice and provide a starting point to search for alternative treatments based on the same physical bases.

After doing a study of all the papers and reference books, those works which, according to their methodology and design, provide relevant scientific information with regard to the principal topic of this review and that have been published between 1993 and 2007 were selected. In order to provide better consistency to the text, a series of articles prior to 1993 that were considered important within the setting studied have been included, since they establish the theoretical bases of ECT and have been frequently mentioned after their publication.

The scientific evidence obtained is systematized into three sections: basic concepts, neurophysiological hypotheses and electrophysiological findings.

Key words:
Electroconvulsive therapy. Anticonvulsant hypothesis. Electrophysiology. Mechanism of action.

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Mecanismos de acción electrofisiológicos de la terapia electroconvulsiva

Pese a la elaboración de guías y consensos sobre sus indicaciones y aplicación, la terapia electroconvulsiva (TEC) sigue siendo uno de los procedimientos terapéuticos con menor certeza en su mecanismo de acción. Es interesante evaluar la manera en la que los factores que modulan la actividad convulsiva pueden ser modificados por esta terapia y su relación con el efecto terapéutico.

El objetivo del presente artículo es revisar, en el contexto de las teorías neurobiológicas, la bibliografía existente sobre los mecanismos de acción electrofisiológicos de la TEC, principalmente la hipótesis anticonvulsiva. El mayor conocimiento sobre dichos mecanismos, puede conseguir una optimización en la práctica asistencial, así como un punto de partida para buscar tratamientos alternativos basados en las mismas bases físicas.

Entre todos los artículos y libros de texto, se han seleccionado aquellos trabajos que, por su metodología y diseño, aportan datos científicamente relevantes respecto al tema principal de esta revisión y que hayan sido publicados entre 1993 y 2007. A fin de aportar mayor consistencia al texto, también se han incluido una serie de artículos, previos a 1993, considerados importantes en el ámbito que se trata, puesto que establecen las bases teóricas de la TEC y han sido citados con frecuencia tras su publicación.

Las evidencias científicas obtenidas se sistematizan en tres apartados: conceptos básicos, hipótesis neurofisiológicas y hallazgos electrofisiológicos.

Palabras clave:
Terapia electroconvulsiva. Hipótesis anticonvulsiva. Electrofisiología. Mecanismo de acción.

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INTRODUCTION

Since the introduction of electroconvulsive therapy (ECT) almost 70 years ago, it has been shown to have constant effectiveness in the treatment of depression, mania and schizophrenia.[1] Knowledge on the limitations of the drug treat-

ment in the therapeutic approach of the psychiatric disorders gave rise to a renewed desire to investigate on ECT, which was initiated in the 1970's and has continued up to date.

Even though guidelines and consensuses have been elaborated on its indications and application,[2,3] it continues to be one of the therapeutic procedures with the least certainty in its mechanism of action (up to date, more than 100 theories have been proposed[4]) with great variability in the opinions regarding its safety and efficacy by the general population and the health care professionals. On the other hand, it has often been criticized, based on biased information, basically regarding its side effects, principally on the mnesic level.

Regarding its mechanisms of action, it is interesting to evaluate how the factors that modulate convulsant activity can be modified by ECT and its relationship with the therapeutic effect. The anticonvulsant hypothesis has the greatest support. [5,6]

During the treatment cycle, ECT gives rise to an increase in the seizure threshold and decrease of the seizure duration, so that the magnitude of increase in the seizure threshold is correlated with clinical response.[5,7] This observation supports the anticonvulsant hypothesis,[8] that defines ECT-induced seizure as an active process in which substances are released into the CNS that decrease brain excitability, suppress seizure and are essential for the therapeutic effect.

Having better knowledge on the ECT mechanism of action can achieve optimization in the care practice and be a starting point to search for alternative treatments based on the same physical basis. [9]

OBJECTIVE

The purpose of this article is to review, within the context of neurobiological theories,[10] the electrophysiological mechanisms of action of ECT, mainly the anticonvulsant hypothesis.

METHODOLOGY

The bibliographic sources were obtained using two methods: 1) Consulting reference textbooks in the field of ECT and the American and Spanish consensuses on the use of this therapy. 2) Electronic search for articles in the data bases PUBMED and EMBASE, using different combinations of the following terms in English: *electroconvulsive, therapy, anticonvulsant, hypothesis, neurobiological, neurophysiological, long-term potentiation, electroencephalography, seizure and threshold,* as well as a search with the same terms in Spanish in the database IME.

Among all the results obtained, those works which, due to their methodology and design contributed scientifically relevant data regarding the principal subject of this review and that had been published between 1993 and 2007 were selected. The Jadad scale[11] was used for the selection of original articles and the Cochrane criteria[12] for the review articles. Those articles that did not fulfill the previously described criteria and/or whose content was not directly related with the purpose were excluded.

In order to provide better consistency to the text, a series of articles prior to 1993 that were considered important within the setting studied have been included, since they established the theoretical bases of ECT and have been frequently mentioned after their publication.

In all, the following were consulted: 7 textbooks, 2 online documents, 27 original articles and 18 review articles. Nine of these publications were prior to 1993. Even though they met the previously described selection criteria, 8 articles were excluded due to their methodology.

REVIEW

Basic concepts

In this first section, the essential theoretical aspects on which the neurophysiological hypotheses are supported and the electrophysiological changes related with ECT are presented.

Neuronal physiology during seizures

Nerve signals are transmitted by action potentials, which are fast changes in membrane potential. In order to conduct a nerve signal, this potential is moved over the nerve fiber until reaching its tip. Each action potential begins with a sudden change of the normal negative resting potential, which is approximately -90 millivolts, to a positive membrane potential (at the expense of the opening of the ion channels and massive sodium entry into the intracellular space). The process ends with a return, almost equally fast, to the negative potential thanks to a rapid diffusion of potassium ions towards the extracellular space. Thus, the three action potential phases are: resting phase, depolarization phase and repolarization.[13,14]

The potential change may occur if direct stimulation is applied with electric current, basically depending on three parameters: electric current intensity, temporal dynamics and direction of the current flow. [14]

The purpose of electroconvulsive stimulation is to provide electrical stimulation with the sufficient potential so that an elevated percentage of neurons would be discharged at the same time and thus induce adequate seizure. It is initiated by the massive synchronic recruitment of some in-

tracerebral neuronal sites, such as occurs in the major spontaneous type motor seizure.[1] Due to the complex structural and electrophysical properties of the skull and brain, electrical stimulation during ECT requires much higher doses of current than those used to stimulate the nerve fibers or nerve tissues under experimental conditions.[14]

Adequate seizure and intensity of the stimulus

In the recommendations for treatment with ECT, it is considered that if an adequate generalized seizure is induced in each session (a seizure lasting between 15 and 20 seconds on the electroencephalographic level is currently accepted[2]), the patient has received an optimal and effective treatment.

A subconvulsive electrical stimulus is that which is not able to induce seizure, while an aborted or short seizure is that whose duration is less than that mentioned. Age, initial seizure threshold, absolute doses of anesthetics, and number of previous ECT sessions are the principal factors inversely related with seizure time.[7,9]

At present, it is stated that the duration by itself is not sufficient to establish whether a seizure has been adequate, the electroencephalographic characteristics of it becoming increasingly important (recruitment phase, typical spike-and-wave complexes and post-ictal suppression). Thus, duration is incomplete as a measure of the convulsant activity, since it does not express the intensity, uniformity or its distribution through the brain.[15,16]

Seizure threshold

It is defined as the smallest amount of electrical energy needed to induce an adequate seizure.[9] This parameter is influenced by all those factors that may affect electrical impedance and neuronal excitability.

Many studies have related the increase of the seizure threshold with clinical response to ECT. As a general rule, this increase generally has a range of 40 to 100% during the course of the therapy. In two different clinical trials (1987 and 1993)[17,18] with a total of 145 patients, the Sackeim group demonstrated that the percentage of increase in the seizure threshold is greater in the group of patients that can be considered responders to ECT than in the group of patients with limited response.[7] It should be taken into account that this parameter is affected by all of the variables mentioned in the following and that are summarized in table 1:

- Age and gender.
- Location of the electrodes: bilateral bifrontotemporal placement has a greater seizure threshold than the right unilateral one proposed by D'Elia. A total of 40% of the patients have a seizure threshold under 50 mC when right unilateral ECT is applied, while this percentage decreases to 7% when bilateral ECT is applied. The cause of this is not clear but it may be because in the unilateral ECT, the current passes through the brain structures with lower seizure thresholds. In spite of this, the application of right unilateral ECT requires higher doses to be effective.[7,9,19,20]
- Anesthetic agents: an excessive dose of this group of drugs produces short and aborted seizures, prolongs post-ictal recovery, increases the risk of anesthetic complications and intensifies amnesic effects. [21,22] The influence of methohexital and propofol in convulsive activity and in the recovery profiles were analyzed by Fredman at al. (1994) in a cross-sectional randomized study.[23] Although the use of propofol was associated with shorter seizure durations on both the motor and electroencephalographic levels, in comparison with methohexital, this difference was not clinically significant since the durations exceeded 30 seconds in both groups.
- Psychotropic drugs: in general, no systemic research studies in humans have been done. Most of the information comes from research in animals and clinical experience. [9,20,22]
- Sleep deprivation: Gilabert et al. (2004)[24] observed that sleep deprivation during treatment with ECT produces a decrease in the seizure threshold (from 190.4 mC in the first session to 176.4 mC in the last one) in regards to those patients who were not sleep deprived (in these, they found an increase in the threshold from 190.4 mC to 321.91 mC). In this context, they question whether the progressive increase of the threshold is the cause of the efficacy.

Table 1 Factors that affect the seizure threshold[7,9,19-22,24]

Parameter	Seizure threshold	Observations
Age	↑	Loss of cerebral plasticity in the elderly
Gender	↑	Men (greater cranial thickness and neuronal mass)
	↓	Women
Electrode position	↑	BL ECT
	↓	RU ECT
Anesthetics	↑	Propofol > methohexital
Drugs	↑	Benzodiazepines and anticonvulsants
	↓	Adenosine antagonists (caffeine and theophylline), lithium carbonate, neuroleptics and clozapine
Sleep deprivation	↓	

↑: increase; ↓: decrease; TBL ECT: bilateral ECT; RU ECT: right unilateral ECT.

Neurophysiological hypotheses

The two main neurobiological hypotheses of the mechanism of action of the antidepressant effect of ECT are anticonvulsant hypothesis and the seizure generalization hypothesis; the hypothesis of diencephalic stimulation has evolved towards a subtype of the latter.[25] Both hypotheses are described in the next section, together with the prefrontal model and anatomico-ictal theory.

Anticonvulsant hypothesis

Seizure is necessary for efficacy of the ECT, however, it is not sufficient to explain it. Thus, the events that occur during and after the seizure must be taken into account. This is why the hypothesis was proposed that seizure provocation precipitates a self-limited endogenous process.[26,27] Seizures do not end due to an inadequate supply of carbohydrates or neuronal exhaustion, or due to other passive processes (epileptic status indicates that the brain is able of maintaining the convulsive activity for days). The termination of the episode is an active inhibitory process essential for the efficacy of ECT. [28,29]

As we have already seen, it has been established that ECT has potent anticonvulsant properties, [7,17,18,30] as demonstrated by 1) the progressive increase of the seizure threshold and decrease of the seizure duration, that we would designate as a tolerance phenomenon during the treatment with ECT; 2) the regional and/or global reductions of the cerebral blood flow and cerebral metabolic index; 3) the induction of a slow wave activity in the electroencephalogram (EEG) and 4) the increase of the functional activity of the neuropeptides and neurotransmitter inhibitors that occurs with the ECT. [7,9,31]

These findings have been principally described by Sackeim et al. in different studies conducted in the 1980's and 1990's. However, there has not been any independent confirmation of these results. Subsequent investigations have not been able to conclude that the absolute value of the threshold or the magnitude of its increase during a course of ECT is useful to predict clinical outcome. On the contrary, most of the studies show the opposite relationship: the greater the increase of the seizure threshold, the worse the clinical response. In spite of this, only isolation and identification of an endogenous anticonvulsant substance (specifically associated with ECT-induced seizures in humans) followed by the demonstration that its blockade does not influence clinical improvement, could invalidate the anticonvulsant hypothesis. [25]

Seizure generalization hypothesis

This hypothesis is different from the others regarding the ECT mechanism of action because it does not invoke neurochemical mechanisms but rather neurophysiological ones. It proposes that the more extensive (and in some way more efficient) the ECT-induced brain seizure activity is, the better the antidepressant clinical response will be. The hypothetical construct of seizure generalization integrates several findings regarding the complex relationships between the technical aspects of the ECT administration and therapeutic impact.[25]

Sackeim et al. (1996) found that the greater antidepressant activity of the ECT was associated to an increase of the inter-ictal suppression in the anterior prefrontal regions.[32] Along these same lines, previous findings related the reduction of cerebral blood flow induced by ECT (in the same anatomical areas) with clinical response. [33] The reduction of the regional glucose metabolism produced in the frontal lobes after the application of bitemporal ECT also agrees with these results.[34-36]

The electroencephalographic findings related with this hypothesis will be described further on.

The diencephalic hypothesis of ECT is currently included within the seizure generalization hypothesis, as a special form of it. It postulates that for the complete development of the therapeutic effect of the ECT, the seizures induced should be sufficiently generalized to include those diencephalic centers involved in the regulation and modulation of the appetitive behaviors, daytime rhythms, hormone release and physiological homeostasis.[25] The most easily demonstrable prediction of this hypothesis is that the ECT-induced seizures that are not associated to tachycardia reflect good development and a peak in the cardiac output rate (result of the stimulation of the cardioaccelerator center on the diencephalic level) will be translated into a limited antidepressant clinical response. [37-39]

Although the seizure generalization hypothesis in ECT is based on a powerful combination of ictal and inter-ictal events, its confirmation requires the demonstration that these mechanisms are necessary requirements for the improvement in the depressive systems to take place after the application of the ECT. [25]

Prefrontal model

On the bases of the differences existing in regards to dose and efficacy when unilateral and bilateral ECT are compared, the importance of the spatial distribution of the low density and the initiation of the resulting seizure activity has been proposed. While the unilateral ECT concentrates the low density in the anterior two thirds of the hemisphere stimulated, the bilateral one concentrates the effects in the prefrontal regions.[25]

The magnitude of the reductions in the cerebral blood flow (CBF) in the specific prefrontal regions is related with the efficacy of ECT, and the responders to this therapy have more likelihood of post-ictal suppression and of developing

slow wave activity on the EEG than the nonresponders. Thanks to the improvement of the techniques, the possibility of identifying specific functional networks associated to efficacy has increased.[40]

It has been postulated that the right unilateral ECT at high doses implies significant reductions of the CBF in the anterior prefrontal cortex. Bilateral ECT is characterized by a marked anteroposterior gradient, concentrated near the prefrontal pole where it is more likely that the seizures are initiated. These observations are important to clarify the critical brain regions for the treatment efficacy and to understand the dose-response ratio of the electrical stimulation.[34-36,40]

The prefrontal model is the simplest and most pragmatic of those previously described, so that some of the clinical characteristics associated to the response, that require more complex models (for example of the relationship between the post-ictal suppression in the EEG and the clinical improvement with ECT) cannot be explained with it. Combining the different models makes it possible to give more meaning to the neurophysiological hypotheses, since these represent different phases of the ECT-induced seizures: the prefrontal model specifies the critical anatomical regions for the initiation of the seizure and the generalization model specifies the different characteristics of the expansion of the episode and the diencephalic participation.[25]

Anatomico-ictal theory

The anatomico-ictal theory is a unification of the neurophysiological hypotheses of ECT. Its heuristic value gives it more possibilities of being correct then the individual components separately.

It postulates that the seizure episodes precipitated by ECT will have a better antidepressant clinical effect if they are initiated in the prefrontal regions of the brain and widely extend towards the cortex and subcortex, involving the diencephalic centers. [25]

Electrophysiological findings

In this section, the electroencephalographic changes that occur, the mechanisms involved in the termination of the seizure and, finally, some aspects related with the long-term potentiation and neurogenesis are described.

Electroencephalographic changes

1. Ictal Electroencephalogram

During treatment with ECT, we can observe some typical electroencephalographic phases (see Figure 1): [1,41]

- Baseline. The baseline EEG before the stimulus can be significantly different from the baseline EEG of an awake patient, due to the anesthetics administered. It often consists in a mixture of fast and slow activity that may have greater amplitude than that observed while awake. The effect varies depending on the depth of anesthesia.
- Electrical stimulation. During this period, the EEG activity is blocked by interference of the stimulus current.
- Pre-ictal stimulation. After electrical stimulus, a short pre-ictal period of low amplitude fast activity can sometimes be observed.
- Epilepsy recruitment rhythm. It is a brief period of very rhythmic activity, of low to moderate alpha or beta amplitude, that appears after the pre-ictal activity. It is believed that this phenomenon is associated to the synchronizing effects of the thalamocortical projections during the early phases of the seizure generalization.
- Polyspike activity. The earliest phase that can be observed in the seizure is frequently characterized by a high frequency polyspike activity. This phase coincides with the early tonic and clonic components of the motor response and generally lasts from 10 to 15 seconds.
- Slow waves and polyspike complexes. During the clonic phase of the ictal motor response, the polyspikes activity evolves to repetitive slow waves and polyspike complexes, that are synchronic with the clonic movements and that decrease in frequency as the clonic phase progresses.
- Termination phase (post-ictal suppression). Amplitude and regularity of the polyspike and slow waves pattern gradually decrease. In some cases, the polyspikes and slow waves can terminate suddenly.
- Post-ictal phase. It begins immediately after the termination of the seizure on the EEG, producing a slow increase in amplitude and in frequency, and thus, an approach to the preanesthetic baseline.

2. Inter-ictal electroencephalogram

ECT gives rise to global and topographic changes in the functional activity of the brain. During the post-ictal period, a considerable amount of slow wave activity (delta and theta) is produced that reflects the spatial extension of the neuron populations subject to inhibition.[42,43] That is why the inter-ictal EEG tends to become slower and has greater amplitude with the administration of successive sessions of ECT, returning to normality 1 to 12 months after treatment termination. Acetylcholine is involved in the development of these electroencephalographic changes, which are a sign that the seizures and persistence of their effects have been produced.[44,45]

Sackeim et al. (1996),[32] in a randomized study for different conditions of the application of ECT to 62 patients with major depressive disorder, concluded that induction of slow wave activity in the cortex is associated with the ECT efficacy. They emphasized the anteroposterior gradient and the

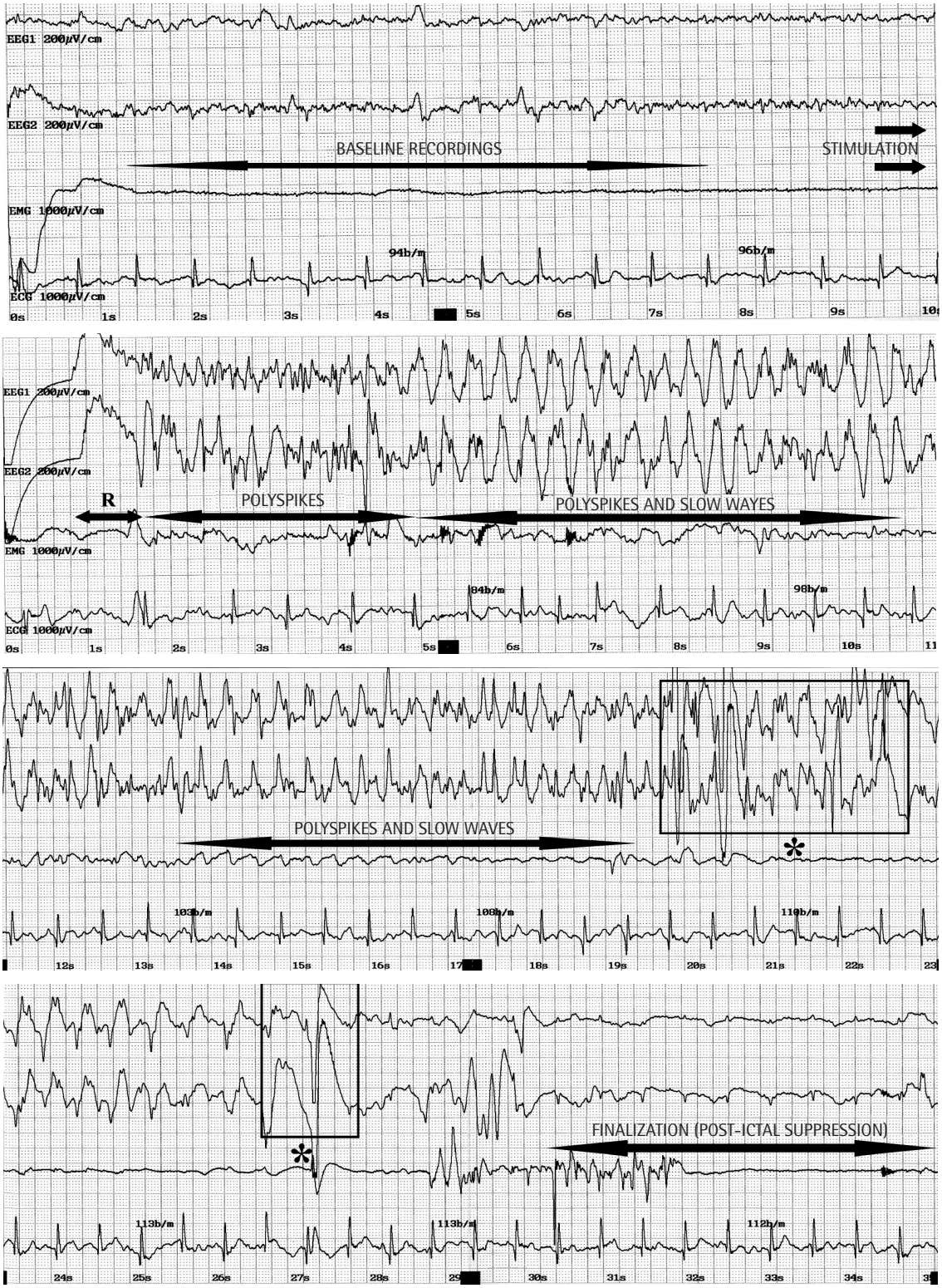

Figura 1 *Electroencephalographic recordings of different phases of the typical convulsion of the ECT. EEG: electroencephalogram; EMG: electromyogram; ECG: electrocardiogram; R: recruitment phase. The asterisks are artifacts in the recording provoked by the movement.*

Source: own production.

fact that both the reduction of the cerebral blood flow (CBF) in the prefrontal cortex and the increase of the delta activity are related with clinical efficacy.

There are other important findings described by different research groups:[7,9,46] post-ictal suppression is deeper with bilateral ECT than with unilateral; seizures with bilateral ECT have greater ictal EEG amplitude, symmetry, coherence, morphological regularity and post-ictal suppression than with unilateral ECT; the increase of the electrical dose and bilateral position of the electrodes correlates both positively with greater voltage and regularity of the ictal EEG and greater post-ictal suppression of the EEG activity is associated to a more positive treatment outcome.

Mechanisms of seizure termination

The mechanisms involved in the seizure episode termination have been described based on studies on epilepsy and in experimental animals. Those having the greatest importance involve the potassium channels, zinc and the gabaergic system.

- ATP dependent potassium channels (KATP). They are expressed on the pre- and post-synaptic level in many brain regions. Their function is controlled by the metabolic status of the neuron. A decrease in the ATP:ADP ratio activates these channels, limiting the cellular excitability and release of transmitters during the metabolite stress phases. Recent studies show the importance of the KATP in the control of neuron excitability, propagation of the seizure and control of seizure threshold.[47]
- Potassium channels activated by G. proteins. Their activation represents an important mechanism by which the neurotransmitters and neuropeptides regulate the neuron excitability. They are located on the pre-and postsynaptic level and their activation reduces the release of transmitters and the response to this synaptic inputs. [47]
- Gamma-aminobutyric acid (GABA). It is the main inhibitory neurotransmitter in the brain. Because multiple experiments have demonstrated that the gabaergic neurotransmission blocker substances generate seizures in the control tissues and that different gabaergic system potentiators have antepileptic actions in human patients, it has been suggested that gabaergic activity prevents the seizures. In the same way, it has also been widely observed that activation of the glutamatergic synapses generates seizures. [48,49] It is postulated that the neural hypometabolic state that follows the ECT is associated and perhaps is produced by an increase in the gabaergic transmission.[26]
- Zinc. It is concentrated in certain excitatory pathways of the CNS, especially in the mossy fibers of the hippocampus, where it has been suggested that it modulates transmission and synaptic plasticity. Bancila et al. (2004), using rat mossy fiber synaptosomesm, applied zinc in microsomal concentrations during a short anoxic-hypoglycemic episode. They found that through the activation of the presynaptic KATP channels, zinc protects the neurons against hyperexcitation, excessive release of transmitters and excitotoxicity. They postulated that zinc probably acts as an endogenous neuroprotector during pathological conditions such as epilepsy or stroke.[50]

Changes in synaptic plasticity and long term potentiation

In recent years, many investigations on neurobiology of the memory have focused on the electrophysiological phenomenon known as long-term potentiation (LTP). This is an experimentally induced form of synaptic plasticity, easily demonstrable in the hippocampus, that constitutes a lasting increase of the excitatory synaptic force. It has been proposed as a plausible mechanism of the neural substrate of learning. Several experiments have demonstrated that the repeated application of electroconvulsive stimulation (ECS) in rats produces a marked block of the LTP in the hippocampus and neocortex.[51,52] This mechanism has been proposed as the possible causing factor of cognitive and mnesic conditions that appear after an ECT cycle.[53]

On the other hand, it has been postulated that the beneficial effect of ECT in the treatment of acute depressive disorders[54] may be related with changes in synaptic plasticity and blockade of the long term depression processes (LTD) on the striatal level.[55]

DISCUSSION AND CONCLUSIONS

There are several aspects that limit the empirical validity of the electrophysiological mechanisms of action, both theoretical and methodological. The substantial increase of the seizure threshold is a necessary, but not sufficient, condition for response to ECT. Patients in whom the physiopathology of the disorder is not related with the excessive disinhibition or excitation may not respond to treatment.[9] As has already been seen, during the course of the treatment, a series of dynamic changes occur. The accumulated anticonvulsant effect may directly affect the expression of a seizure, independently of the effects produced by the intensity of the electrical stimulus.[7]

After reviewing the literature on the electrophysiological mechanisms of action of electroconvulsive therapy, we can draw the following general conclusions: 1) There are data that support electrophysiological changes, but the different neurobiological series cannot be contemplated independently due to the complexity of the brain function that involves the interaction of biochemical, hormonal and electrophysiological systems. 2) ECT has anticonvulsant properties, the termination of the episode needing an active and essential inhibitory process for its efficacy, bringing about a complete series of neuronal mechanisms. 3) The seizure threshold is a filter for many of the neurobiological effects

of the electrical stimulus and consistent relationships exist between the electrical dose and the behavioral effects only after it has been exceeded.[9] 4) It is postulated that the LTP blockage that appears after the electroconvulsive stimulation can be the underlying mechanism to the cognitive and mnesic alterations that appear after the application of ECT. 5) The many findings published on ECT and electroconvulsive stimulation should be replicated to be able to differentiate the effects that are primary from those that are secondary and discover which are really therapeutic. 6) More experiments are needed to increase or block the anticonvulsant properties of ECT and determine the effects that are produced in its efficacy.[7] 7) Having better knowledge of the mechanisms of action will make it possible to develop other more effective techniques based on them.

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