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C. R. Biologies 328 (2005) 143–153
COMPTES RENDUS BIOLOGIES
http://france.elsevier.com/direct/CRASS3/

Neurosciences

The neurobiology of temporal lobe epilepsy: too much information, not enough knowledge

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Received 1 July 2004; accepted after revision 19 October 2004

Available online 19 December 2004

Presented by Nicole Le Douarin & Henri Korn

Abstract

Although there are many types of epilepsy of both genetic and acquired forms, temporal lobe epilepsy (TLE) with hippocampal sclerosis is probably the single most common human epilepsy, and the one most intensely studied. Despite a wealth of descriptive data obtained from patient histories, imaging techniques, electroencephalographic recording, and histological studies, the epileptogenic process remains poorly understood. Progress toward understanding the etiology of an acquired neurological disorder is largely dependent on the degree to which experimental animal models reflect the human condition. Recent observations suggest that significant disparities exist between the features of human TLE with hippocampal sclerosis and those of animal models that involve prolonged *status epilepticus* to initiate the epileptogenic process. TLE most commonly involves patients with focal seizures who exhibit limited and often asymmetrical brain damage, did not experience *status epilepticus* prior to the onset of epilepsy, and who appear relatively normal on neurological examination. Conversely, animals subjected to prolonged *status epilepticus* exhibit severe brain damage, behavioral abnormalities, and frequent generalized seizures. In addition, although many TLE patients exhibit an atrophic hippocampus that may, or may not, be a source of spontaneous seizures, hippocampal damage in animals subjected to *status epilepticus* is an inconsistent and often minor part of a much greater constellation of damage to other brain structures. Furthermore, many patients exhibit developmental structural abnormalities that presumably play a role in the clinical etiology, whereas most animal models involve severe insults in initially normal laboratory rats. Although much has been learned using the current animal models, the available data suggest the need for a critical reappraisal of the assumptions underlying their use, and the need to develop experimental preparations that may more closely model the human epileptic state. ***To cite this article: R.S. Sloviter, C. R. Biologies 328 (2005).***

Résumé

Bien qu'il y ait de nombreuses épilepsies, à la fois de formes génétique et acquise, l'épilepsie du lobe temporal (ELT) avec sclérose hippocampique est probablement l'épilepsie humaine la plus commune, et celle qui est étudiée le plus intensément. Malgré une abondance de données descriptives obtenues d'après l'historique des patients, par des techniques d'imagerie, d'en-

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1631-0691/$ – see front matter
doi:10.1016/j.crvi.2004.10.010

registrement électroencéphalographiques et par des études histologiques, le processus épileptogène demeure mal connu. Les progrès dans la compréhension de l'étiologie d'un désordre neurologique acquis dépendent largement du degré auquel les modèles expérimentaux animaux reproduisent les conditions du patient. Des observations récentes suggèrent que des différences significatives existent entre les caractéristiques de l'ELT humaine avec sclérose hippocampique et celles observées sur les modèles animaux qui exigent un *status epilepticus* pour créer le processus épileptogène. L'ELT concerne le plus communément des patients développant des crises focales traduisant une lésion cérébrale limitée et souvent asymétrique, qui n'ont pas traversé de *status epilepticus* avant que ne se déclare leur épilepsie, et qui apparaissent relativement normaux à l'examen neurologique. Inversement, des animaux soumis à un *status* prolongé montrent de sévères lésions cérébrales, des anomalies comportementales ainsi que de fréquentes crises généralisées. De plus, bien que de nombreux malades atteints d'ELT montrent un hippocampe atrophique qui peut, ou non, être une source d'attaques spontanées, des lésions hippocampiques chez des animaux présentant un *status* ne sont en revanche qu'une partie souvent mineure d'une constellation beaucoup plus grande de lésions impliquant d'autres structures cérébrales. De plus, nombre de patients montrent des anomalies structurales du développement, qui jouent probablement un rôle dans l'étiologie clinique, alors qu'un grand nombre modèles animaux impliquent des lésions sévères réalisées chez des rats de laboratoire initialement normaux. Quoiqu'on ait appris beaucoup en utilisant les modèles animaux courants, les données disponibles suggèrent qu'un réexamen critique des hypothèses sous-jacentes à leur usage doit être effectué, et qu'on doit développer des protocoles expérimentaux qui puissent modéliser de manière plus fidèle l'état épileptique humain. ***Pour citer cet article : R.S. Sloviter, C. R. Biologies 328 (2005).***

Keywords: Epilepsy; Seizures; *Status epilepticus*; Excitotoxicity; Ischemia

Mots-clés : Épilepsie ; Attaques ; *Status epilepticus* ; Excitotoxicité ; Ischémie

1. Introduction

Temporal lobe epilepsy (TLE) is a common and often medically intractable neurological disorder that is possibly unique in terms of the wealth of descriptive data that have been obtained from historical anatomical studies, electroencephalographic recording methods, modern imaging techniques, depth recording before and during surgery, and from histological study of surgical and autopsy tissues [1]. The sheer mass of data now available on the subject of temporal lobe epilepsy is emblematic of the modern problem of having so much information on any given subject that it is a significant conceptual challenge to separate facts from notions, associations from causes, and to discriminate between the possibly important and the probably unimportant. The enormous amount of information now available to us, taken together with the natural desire we have to get clear and unambiguous answers to all of the questions we ask, makes simple answers appealing, and may explain, in part, the general hesitancy we have to admit that we may know far less than we actually do.

In the search for real understanding of the epileptic process, it may be useful conceptually to contrast TLE, a neurological disorder in which the nature of the network defect is largely unknown, with Parkinson's disease, a disorder in which the loss of identified dopaminergic neurons disinhibits a known network, resulting in the clinical behavioral signs of the disorder [2]. Like patients with Parkinson's disease, those with TLE exhibit neuronal loss and a network imbalance that presumably causes the clinical condition. Unlike the identified network defect of Parkinson's disease, however, the neuronal loss that presumably produces a network imbalance in the temporal lobe remains unidentified. We do not really know precisely which cell populations, when lost, cause the network imbalance in TLE, or which cells generate the seizure discharges. Nor do we have an effective drug treatment, like levodopa, that both points to the identity of the defective component and corrects the network imbalance to an extent that produces symptomatic improvement. Thus, in TLE, both the cause and the cure remain unknown, and we primarily utilize drugs that suppress the clinical manifestations, but probably do not directly target the underlying network defect.

A logical assumption that we can make about the etiology of temporal lobe epilepsy is that there is a derangement of excitatory and inhibitory mechanisms that, in some way, causes abnormal network discharges that define the clinical epileptic state. Un-