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Research Report

Neuronal activity in the parietal cortex of EL and DDY mice

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ABSTRACT

To elucidate the mechanism of epileptogenesis, seizures were investigated in the EL mouse, which is an excellent model for epilepsy. In these mice, epileptic seizures initiate in the parietal cortex, where markers of GABA-mediated inhibition are reduced compared with the parietal cortex of DDY mice (the parent strain). This is the first report on units of neuronal activity in the parietal cortex of EL and DDY mice (14 each) using an extracellular microelectrode in vivo under moderate pentobarbital anesthesia. The parietal cortex neurons of the EL mice were less active at rest than those of the DDY mice, but they responded more actively to proprioceptive afferent input from muscle stimulation than the DDY neurons. Three types of spontaneous firing were classified in both EL and DDY cortical neurons: periodically firing, Type A; continuously firing, Type B; and random firing, Type C. The proportions of these three types of neurons were almost the same in the EL mice as in the DDY mice. The peak frequency of the periodical cycle of Type A neurons in the EL mice (375 ms) was longer than that of the Type A neurons in the DDY mice (225 ms). Four patterns of responses to stimulation were observed in the parietal cortex neurons. More excitatory patterns were observed in the EL mice than in the DDY mice. The trans-laminar distribution of cells with different response patterns was also different between the EL and DDY mice. These characteristics of parietal cortex neurons may help determine the seizure susceptibility or ictogenesis in EL mice because the mechanisms underlying these patterns could provide the basis for hypersynchronized discharges in epileptic seizures.

1. Introduction

Epileptic seizures have two essential physiological mechanisms: abnormality of cellular excitability and abnormal network function. The EL mouse is a genetic animal model of epilepsy that has been maintained in our animal center as an inbred strain with the back-crossing procedure onto the parent strain. The mode of inheritance is autosomal dominant (Suzuki, 1976), and the parent strain of the EL mouse is the DDY/hydrocephalus type II (DDY). Seyfried and his colleagues proposed that the seizure susceptibility of the EL mouse was polygenic (Rise et al., 1991) and later presented environmental risk factors for seizure occurrence and hypothesized that quantitative trait loci (QTL) were linked to a polygenic background (Todorova et al., 1999, 2006). However, the details of the genetic aspects of seizure susceptibility remain unclear (Leussis and Heinrichs, 2007).

The seizures of an EL mouse arise from the parietal cortex (PCX) (Suzuki and Nakamoto, 1977) and are augmented in the

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hippocampus (Ishida et al., 1987), as shown electrophysiologically and confirmed by the local glucose utilization method using 2-deoxy glucose (Nakamoto et al., 1992; Suzuki et al., 1983b). The seizures of an EL mouse are induced by abrupt accelerating movements (e.g., tossing an animal into the air—Suzuki and Nakamoto, 1977; or rotating movements—Fueta et al., 1983) beginning at an early stage of development (4 to 5 weeks of age). The effective mode of stimulation is proprioceptive, not vestibular, because these stimuli induce seizures even after unilateral or bilateral destruction of the whole labyrinths (Suzuki and Nakamoto, 1987). After seizure-provoking stimuli have been repeated, seizures can be easily induced, eventually occurring almost spontaneously. We (Suzuki and Nakamoto, 1982) have named this phenomenon "abnormal plasticity", which they have considered to be one of underlying processes of the development of seizures in the EL mouse. The abnormal plasticity is represented by growing electroencephalographic discharges (Suzuki and Nakamoto, 1982) and by decreasing GABA-related inhibitory activity (Mita et al., 1991; Murashima et al., 1990).

In this paper, single-unit firing patterns of neurons in the parietal cortex of EL and DDY mice (14 each) recorded in vivo with an extracellular microelectrode under moderate pentobarbital anesthesia are described for the first time. Here, we describe the patterns of neuronal activity in the parietal cortex (PCX) of EL and DDY mice using an extracellular microelectrode recording approach. The receptive fields for deep somatosensory or proprioceptive sensation are localized in this cortical region, and the PCX should therefore be involved in some of the abnormal mechanisms underlying the seizures triggered by this type of stimulation. While the seizures of EL mice initiate in the PCX, no significantly abnormal cytoarchitecture has been found in this region (Suzuki et al., 1983a). However, GABA concentrations and GAD activity in the PCX—in an area of approximately 500 μm×400 μm—is lower in EL mice than in DDY mice (Murashima, et al., 1990). Other, non-localized biochemical findings have also been reported in the EL mouse brain (Hiramatsu et al., 1990; Mita et al., 1991). We have therefore tried to examine the neurophysiological characteristics of this localized PCX area and report some features that may contribute to seizure activity and ictogenesis in EL mice.

2. Results

2.1. *Spontaneous activity*

Even under moderate anesthesia, many neurons in the PCX of both the EL and DDY mice fired spontaneously at frequencies ranging from 1 to 40 Hz. In the DDY mice, most of the neurons fired at frequencies >10 Hz, while in the EL mice, most of the neurons fired at a lower frequency (Fig. 1). The average firing frequency of the EL units was 2.74 (SD 3.45) Hz, which was significantly lower than that of the DDY units 7.77(SD 10.31) Hz ($p<0.001$).

When the firing features of all the neurons were inspected one-by-one, three patterns of neuronal discharge were found: Type A neurons fired cyclically or periodically; Type B neurons fired continuously; and Type C neurons were very inactive. All

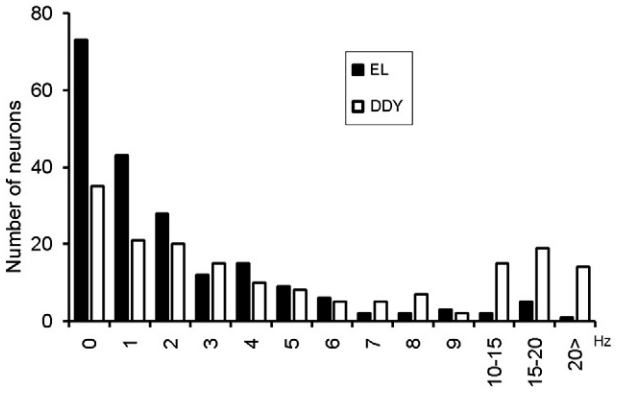

Fig. 1 – The frequencies of the spontaneous firing of the PCX neurons. The filled bars indicate the firing frequency of the EL neurons and the blank bars indicate that of the DDY neurons. The mean frequency, 2.74 (SD 3.45) Hz, of the EL neurons was significantly lower than that of the DDY neurons (7.77 (SD 10.3) Hz, $p<0.001$). Ordinates: no. of cells. Abscissa: Hz.

the neurons were classified into the three types (Table 1), and the Type C neurons were observed more often in the EL mice. However, no significant difference was found in the proportion of the three types of neurons between the EL and DDY mice. The autocorrelation method was performed on the histograms of inter-spike intervals (ISI) of the spontaneous activities of the first two neuronal groups (Fig. 2A), while in the neurons of the Type C type, no discrete ISI pattern was found.

Further analysis of the ISI of Type A neurons in the DDY mice (Fig. 2B4) revealed a high peak at 175 msec. This means that many neurons fire cyclically with an ISI of approximately 175 ms. In contrast, a similar but lower peak was observed at 375 ms in the Type A neurons of the EL mice (Fig. 2A4). This means that many EL neurons cyclically fire at approximately 375 ms, which is slower than the DDY neurons. In neurons exhibiting the Type B pattern of firing, the ISI decreased exponentially in the DDY neurons (Figs. 2B3, B5) but decreased more gradually in the EL neurons (Figs. 2A3, A5). These observations of different cycles of neuronal firing should be considered along with the difference in the average spontaneous discharge rates between the DDY neurons (higher frequency) and the EL neurons (lower frequency). In other words, the spontaneous firing patterns of the EL PCX neurons showed quite different features from those of the DDY neurons. Besides analyzing the interval histogram, the spike durations among the different neuron types in the EL and DDY mice were examined, however, no differences were found.

The laminar distribution of the three types of neurons in the PCX is shown in Table 2 and Fig. 3. Here, we divided the

Table 1 – The number of the PCX neurons classified by ISI type. No statistically significant differences were found.

	Type A Cyclic	Type B Continuous	Type C Inactive	Total
EL	42	66	93	201
DDY	45	72	61	178
Total	87	138	154	379