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Physiology & Behavior 84 (2005) 379–386

PHYSIOLOGY & BEHAVIOR

The role of the environment on the development of spike-wave discharges in two strains of rats

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Received 8 June 2004; received in revised form 17 December 2004; accepted 22 December 2004

Abstract

Recently, we demonstrated that Type 1 and 2 spike-wave discharges (SWD) in the EEG of juvenile WAG/Rij rats were affected differently by housing before the period at which SWD start to occur. Here we consider possible sensitive periods by analyzing strain and housing influences before and after age of SWD onset. The effects of environment in WAG/Rij and ACI rats were investigated by manipulating housing during the period in which SWD become fully manifested in WAG/Rij rats. Rats were first housed from weaning in either an impoverished or enriched environment. Housing changed for half of the rats at three months, while for the other half housing stayed the same. EEG recordings at six months showed that enriched housing led to a worsening of seizure activity. The occurrence, number and mean duration of both types of discharges were influenced differently by strain, housing and age. Our data strengthen the strong genetic dependence of Type 1 SWD, but the mean duration seems to remain sensitive to housing during development. Type 2 SWD are more sensitive to environmental influences, especially in WAG/Rij rats. Moreover, the period after three months seems a sensitive period for housing effects on Type 2 SWD in this strain. Finally, our data further support the idea that Type 1 and 2 SWD are different phenomena, with their number and mean duration controlled by distinct mechanisms.

Keywords: Absence epilepsy; ACI rat; Environment; Housing; Spike-wave discharges; Strain; WAG/Rij rat

1. Introduction

The WAG/Rij rat is a well established model for absence epilepsy [1,2]. In the EEG, the seizures are characterized by generalized 7–11 Hz spike-wave discharges (SWD), lasting on average 5 s. Behaviorally, seizures are accompanied by decreased consciousness and immobility [3].

Cross breeding epileptic WAG/Rij rats with ACI rats, a strain nearly devoid of SWD [4,5], revealed an autosomal dominant monogenetic inheritance for the occurrence of SWD [6,7]. The number and duration of SWD showed complex inheritance patterns, implying that SWD are influenced by more than one gene. Comparable results were also reported for other rat strains [8–10] and were recently supported by outcomes of linkage analysis [11].

The onset and course of SWD is age related [12]. Around two to three months of age, SWD begin to appear sporadically in the EEG of some WAG/Rij rats. Thereafter, SWD increase in number and duration during development, until SWD are fully matured at six months of age, when SWD are frequently present in all WAG/Rij rats. An age-dependent increase was also observed in other rat strains [8,13,14]. Although in WAG/Rij rats SWD are virtually absent before three months of age, some variation in age of onset exists between rats during the course of development. In addition substantial variation exists in number and duration of SWD between individual subjects. This suggests that next to genetic, environmental factors might also play a role. Indeed, Vadász et al. proposed that developmental–environmental factors are, next to genetic factors, involved in the development of SWD [10]; and in EL mice environmental factors were shown to alter seizure susceptibility [15].

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0031-9384/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.physbeh.2004.12.015

In addition to the generalized SWD (Type 1 SWD), WAG/Rij rats show a second, more localized, type of SWD (Type 2 SWD). Compared to Type 1 SWD, Type 2 SWD have a lower amplitude of opposite polarity, a shorter duration (~1 s), a slightly lower (~6 Hz) frequency, different cortical spatial distribution, are not accompanied by behavioral signs and have opposite sensitivity to dopaminergic agents such as haloperidol and apomorphine [3,16].

The presence of Type 2 SWD was recently reported for ACI rats, a strain commonly used as non-epileptic control, as well [17,18]. Although most ACI rats are almost free of Type 1 SWD [5], at least some ACI rats develop absence seizures when they become older [4]. The fact that both, WAG/Rij and ACI rats, demonstrate Type 1 and 2 SWD, albeit to a different degree, make them appropriate for studying possible influences of strain and environment on both types of discharges.

Recently, we demonstrated that environmental influences play a role in the development of both types of SWD even before they are fully developed in the EEG [18]. In that study, WAG/Rij and ACI rats were housed from the time of weaning in either an impoverished or enriched environment for 60 days. EEG recordings at three months of age revealed that enriched housing led to a worsening of Type 1 and 2 SWD.

However, in WAG/Rij rats Type 1 SWD just start to appear at three months of age [12] and in ACI rats they show up for the first time around six months of age [4]. This issue has not been addressed so far for Type 2 SWD. Regarding the progress of seizure development with age, the question remains whether strain and housing influences in older rats would reveal similar effects. Data from induced convulsive seizure models revealed that environmental manipulations during different periods in life affect seizures differently [19–21]. Hence, the question is whether there might be a sensitive period for environmental effects on the two types of SWD and whether such a period is different for the two strains. Therefore, the aim of the present experiment was to study the effects of strain and housing on both types of SWD before and after their age of onset.

2. Materials and methods

2.1. Animals and course of the experiment

Seventy-five WAG/Rij and 80 ACI rats, bred and born in our laboratory, were used. All experimental procedures were approved by the local animal ethics committee of Nijmegen University and performed according to local guidelines and the European Communities Council Directive of 24 November 1986 (86/609/EEC).

A schematic overview of the experimental protocol is given in Fig. 1. A split-litter design was used for the division of the animals across groups. Male WAG/Rij or ACI rats were housed for 60 days in an impoverished housing (IC) or an enriched housing (EC) condition from weaning until three months of age. At three months of age the housing condition changed for half of the animals from impoverished to enriched or vice versa, the others remained in their original housing condition. Rats were then housed differently for another 60 days.

At three months of age, half of the rats of each strain and housing condition underwent surgery for permanent electrode implantation; the other half underwent a sham operation. For the operated rats, EEG recordings were performed at three months of age, and again at six months of age. The sham-operated rats underwent real surgery and subsequent EEG recordings at six months of age only. During surgery and EEG recordings all rats were temporarily single housed.

Strain		Housing before 3 months of age	Measurements at 3 months of age*	Housing after 3 months of age	Measurements at 6 months of age
WAG/Rij rats (n = 75)	Weaning, Split-litter design	Impoverished (IC) (n = 19)	Surgery	Impoverished (IC) (n = 15)	EEG/SWD recordings
		Enriched (EC) (n = 20)	EEG/SWD recordings	Impoverished (IC) (n =18)	
		Impoverished (IC) (n = 18)	Sham operation	Enriched (EC) (n = 18)	Surgery
		Enriched (EC) (n =18)		Enriched (EC) (n = 18)	EEG/SWD recordings
ACI rats (n = 80)		Impoverished (IC) (n = 20)	Surgery	Impoverished (IC) (n = 19)	EEG/SWD recordings
		Enriched (EC) (n = 20)	EEG/SWD recordings	Impoverished (IC) (n = 20)	
		Impoverished (IC) (n = 20)	Sham operation	Enriched (EC) (n = 18)	Surgery
		Enriched (EC) (n = 20)		Enriched (EC) (n = 20)	EEG/SWD recordings

Fig. 1. Schematic overview of the experimental protocol used. Male WAG/Rij or ACI rats were housed in an impoverished (IC) or an enriched housing (EC) condition from the time of weaning. At three months of age housing changed for half of the rats from IC to EC or vice versa. For the other half, housing stayed the same over the entire period. Hence, there are four housing groups (IC/IC, EC/IC, IC/EC, EC/EC) for each strain. At weaning a split-litter design was used to divide animals across groups. EEG recordings were performed at three and six months of age. *Data not shown (see Ref. [18]).