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Research report

Absence epileptic activity in Wistar Albino Glaxo Rijswijk rat mothers

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ABSTRACT

Absence epileptic activity was analyzed during pregnancy, the postpartum period and after weaning to establish alterations of seizures throughout the reproductive cycle. Wistar Albino Glaxo Rijswijk (WAG/Rij) rats were used in the study as a model of absence epilepsy and because their seizures do not interfere with rearing offspring. The number of spike-wave discharges (SWDs) was gradually elevated from the 19th pregnancy day to delivery. Meanwhile, the characteristics of individual SWDs did not change suggesting that SWD generation remained the same. In the postpartum and postweaning periods, the number of SWDs was not increased in the absence of pups. However, returning the pups to mothers resulted in a markedly elevated number of SWDs for 1 h. If pups were taken away after 30 min, the number of SWDs dropped immediately suggesting that the presence of pups increased the SWD number. The time mothers spent with the litter and in kyphosis suckling posture were in correlation with their SWD number further suggesting the importance of interaction with pups in SWD induction. Suckling elevates prolactin levels but surprisingly, its intracerebroventricular injection markedly reduced SWD number in suckled WAG/Rij mothers suggesting that the SWD-inducing effect of suckling is not mediated by prolactin. Rather, the elevated prolactin level may provide some protection against pro-epileptic effects of suckling. In conclusion, we first identified periods within the reproductive cycle with increased absence epileptic activity, implying that more attention should be devoted to epileptic activity changes in mothers.

1. Introduction

There is a practical interest in epilepsy during pregnancy and lactation as most women with epilepsy can conceive and bear healthy children (McCormick, 1987). About a third of mothers experience an increase in seizure frequency (Yerby, 1996; Steinhoff, 2008), but the interpretation of this finding is complicated by various changes in the metabolism of different anti-epileptic drugs in mothers (Fotopoulou et al., 2009; Rapcencu et al., 2012). Animal models typically indicated a protective effect of pregnancy and lactation as the seizure frequency declined in the pilocarpine- as well as the kainic acid-induced rat model of epilepsy during these periods in mother rats (Berzaghi Mda et al., 1987; Amado and Cavalheiro, 1998). Pregnancy and lactation are accompanied by complex hormonal changes and also new behavioral phenotypes in mothers (Bridges, 2015). Estrogen and progesterone levels increase during pregnancy with the latter one showing a sharp drop in its plasma concentration in the last days before parturition. While the levels of both steroid hormones are low in the postpartum period of lactational anoestrus (Tsukamura and Maeda, 2001), prolactin levels induced by suckling are markedly elevated during lactation (Nagy et al., 2005; Cservenak et al., 2010). Prolactin is a pituitary protein hormone with numerous physiological functions such as milk production, induction of maternal behavior, and effects on the maternal immune system (Torner, 2016). These hormonal changes but also

Abbreviations: ACSF, artificial cerebrospinal fluid; EEG, electroencephalogram; FFT, Fast Fourier Transform; i.c.v., intracerebroventricular; PD, pregnancy day; PPD, postpartum day; PWD, postweaning day; S.E.M., standard error of the mean; SWD, spike-wave discharge; WAG/Rij, Wistar Albino Glaxo/Rijswijk.

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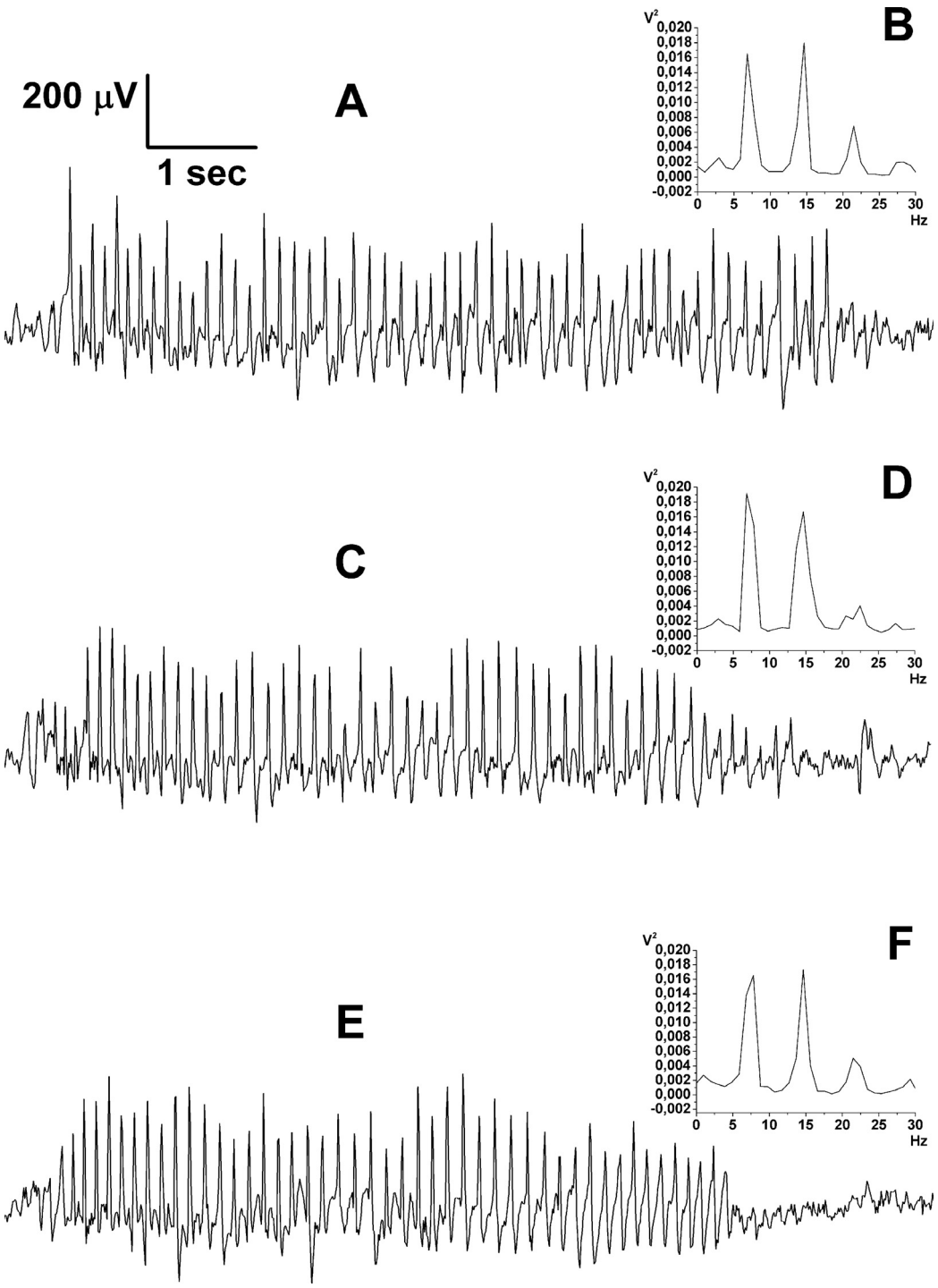

Fig. 1. Representative examples of spike-wave discharges (SWDs) recorded from female WAG/Rij rats. SWDs show similar features (morphology, duration and discharge frequency) in before mating control (A, B), on the 21th day of pregnancy (C,D), and in response to suckling on the 12nd postpartum day (E,F).

direct neuronal inputs from the pups are responsible for a frequency of behavioral changes that occur in mothers to take care of the offspring (Dobolyi et al., 2014). In rats, mothers build a nest, retrieve pups to the nest where they feed their litter (Bridges, 2015). The most effective form of nursing (upright crouched nursing) is in the kyphosis posture, which is characterized by the legs of females being in extension position and the body showing a dorsal (kyphotic) arch (Stern et al., 2002). However, most pharmacologically induced animal models of epilepsy interfere with delivery, lactation and maternal behaviors (Mellanby et al., 1993) preventing the study of their different specific components on the occurrence of epileptic seizures. In that regard, genetically epilepsy-prone strains provide useful models. Previous studies indicate that a well validated model of idiopathic, non-convulsive types of epilepsy, the Wistar Albino Glaxo/Rijswijk (WAG/Rij) rats demonstrate normal pregnancy and maternal behaviors, and are able to rear their offspring whose development shows no defects (Coenen and Van Luijtelaar, 2003; Tolmacheva et al., 2004; Bazyan and van Luijtelaar, 2013; van Luijtelaar et al., 2014). For these reasons, we choose this strain to study the effects of