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Research Report

Differential seizure response in two models of cortical heterotopia

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ABSTRACT

Malformations of cortical development (MCD) are linked to epilepsy in humans. MCD encompass a broad spectrum of malformations, which occur as the principal pathology or a secondary disruption. Recently, Rosen et al. (2012) reported that BXD29-*Tyrl4*$^{lps-2J}$/J mice have subcortical nodular heterotopias with partial agenesis of the corpus callosum (p-ACC). Additionally Ramos et al. (2008) demonstrated that C57BL/10J mice exhibit cortical heterotopias with no additional cortical abnormalities. We examined the seizure susceptibility of these mice to determine if the presence (BXD29-*Tyrl4*$^{lps-2J}$/J) or absence (C57BL/10J) of p-ACC, in strains with MCD, confers a differential response to chemi-convulsive treatment. Our results indicate that C57BL/10J mice with layer I heterotopia are more susceptible, whereas BXD29-*Tyrl4*$^{lps-2J}$/J mice with more severe subcortical nodular heterotopia and p-ACC are more resistant to seizure behavior induced by pentylenetetrazole. These data suggest that p-ACC may confer seizure resistance in models of MCD.

1. Introduction

Malformations of cortical development (MCD), including disordered neuronal proliferation, migration and cortical organization, can result in focal or global abnormalities affecting both structure and function. MCD have been linked to both epilepsy and developmental delay in humans. Focal cortical dysplasia (FCD), are the most common group of MCD in patients presenting with intractable epilepsy and epilepsy in children (Blümcke et al., 2009). FCD encompass a broad spectrum of malformations, including cortical dyslamination, cytoarchitectural lesions and underlying abnormalities of white matter, and can occur as the principal pathology or as a secondary disruption (for review see Blümcke et al., 2011). Understanding the role these malformations play in epileptogenesis is necessary in order to develop new therapies for MCD-related epilepsies. Examination of animal models of the various types of MCD can provide valuable insight into the mechanisms which lead to altered cortical excitability.

Recently FCD have been reported in BXD29-*Tyrl4*$^{lps-2J}$/J (Rosen et al., 2012) and a large percentage of C57BL/10J mice

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(Ramos et al., 2008). The BXD29-*Trl4*$^{lps-2J}$/J strain exhibits bilateral subcortical nodular heterotopias as well as partial agenesis of the corpus callosum (pACC), whereas the C57BL/10J mice display layer I cortical heterotopia without a callosal defect. Examination of the seizure susceptibility of these two related strains could elucidate whether the presence (BXD29-*Trl4*$^{lps-2J}$/J) or absence (C57BL/10J) of p-ACC, in strains with MCD, confers a differential response to chemi-convulsive treatment.

The BXD strain family was generated by creating F2 mice from a cross of C57BL/6J and DBA/2J strains, and then subsequent inbreeding to create ~80 different BXD recombinant inbred strains (Peirce et al., 2004; Taylor, 1989). Since their creation, several of these original lines have accumulated new mutations, including the BXD29/TyJ strain. A subset of the BXD29/TyJ strain suffered a mutation in the Toll-like receptor 4 gene (Tlr4) rendering them insensitive to inhalation of lipopolysaccharide [lps] (Cook et al., 2006). These mutant mice were renamed BXD29-*Trl4*$^{lps-2J}$/J mice, and the BXD29/Ty (wildtype) strain was rederived from embryos frozen in 1978. It was recently discovered that the BXD29-*Trl4*$^{lps-2J}$/J mice exhibit MCD, whereas the wildtype BXD29/Ty strain does not (Rosen et al., 2012). It is important to note that the Trl4 mutation was ruled out as the cause of the FCD identified in the BXD29-*Trl4*$^{lps-2J}$/J strain (Rosen et al., 2012).

Examination of the seizure susceptibility of the parental lines, C57BL/6J and DBA/2J, as well as the majority of the first cohort of BXD strains demonstrated the variable resistance to the chemi-convulsant pentylenetetrazole (PTZ) (Wakana et al., 2000). Wakana et al. (2000) confirmed that the C57BL/6J strain is relatively resistant to PTZ treatment, whereas the DBA/2J line is more susceptible to seizure, and the F2 derived recombinant inbred strain, BXD line, displays a range of responses to PTZ. More specifically, these data demonstrate that the BXD29/Ty strain exhibits a similar resistance to PTZ induced seizure behavior to the C57BL/6J parental line. In contrast, another BXD recombinant inbred line, BXD9/Ty, and DBA/2J mice were more susceptible to chemi-convulsant induced seizure behavior. However, it is unclear how the BXD29 mutant mice, BXD29-*Trl4*$^{lps-2J}$/J, would respond to PTZ treatment in light of the presence of bilateral subcortical nodular heterotopia, known to increase seizure susceptibility to chemi-convulsant treatment (Croquelois et al., 2009), but which also have partial callosal agenesis.

The C57BL family is probably the most widely used of all inbred strains, which consists of four major substrains, including C57BL6 and C57BL10. C57BL6 and C57BL10 mice possess a very close genetic relationship; differing at just three loci on chromosome 4 (McClive et al., 1994). Recently Ramos et al. (2008) reported that C57BL6 and C57BL10 mice exhibit layer I neocortical heterotopia, similar to those identified postmortem analysis of patients with developmental dyslexia (Galaburda and Kemper, 1979; Galaburda et al., 1985). These malformations have also been identified in several inbred strains of mice which exhibit cognitive impairments (Denenberg et al., 1991; Boehm et al., 1996; Balogh et al., 1998), as well as increased cortical excitability *invitro* (Gabel and LoTurco, 2001) and increased seizure susceptibility *in vivo* (Gabel and LoTurco, 2002). Based on previous studies, it is likely that C57BL mice with heterotopia will also exhibit an increased susceptibility to PTZ induced seizure behavior in comparison to C57BL mice without heterotopia; however this hypothesis has yet to be confirmed.

In this study we examined the PTZ induced seizure behavior of BXD29 and C57BL strains to determine if the different neuroanatomical phenotypes influenced the seizure susceptibility of these models of MCD. Based on the higher incidence of heterotopia reported in C57BL10/J mice compared to the C57BL6/J strain (Ramos et al., 2008), we examined endpoint seizure behavior of C57BL/10J mice with and without layer I neocortical heterotopias, but which do not exhibit other cortical defects. Based on previous research examining the seizure susceptibility of mice with similar MCD, we hypothesized that C57BL/10J mice with heterotopia will exhibit seizure behaviors at lower doses of PTZ than mice without heterotopia. However, it was unclear whether the p-ACC would influence seizure susceptibility in the BXD29 mutant mice, BXD29-*Trl4*$^{lps-2J}$/J, that have large bilateral nodular heterotopias known to increase seizure susceptibility (Croquelois et al., 2009).

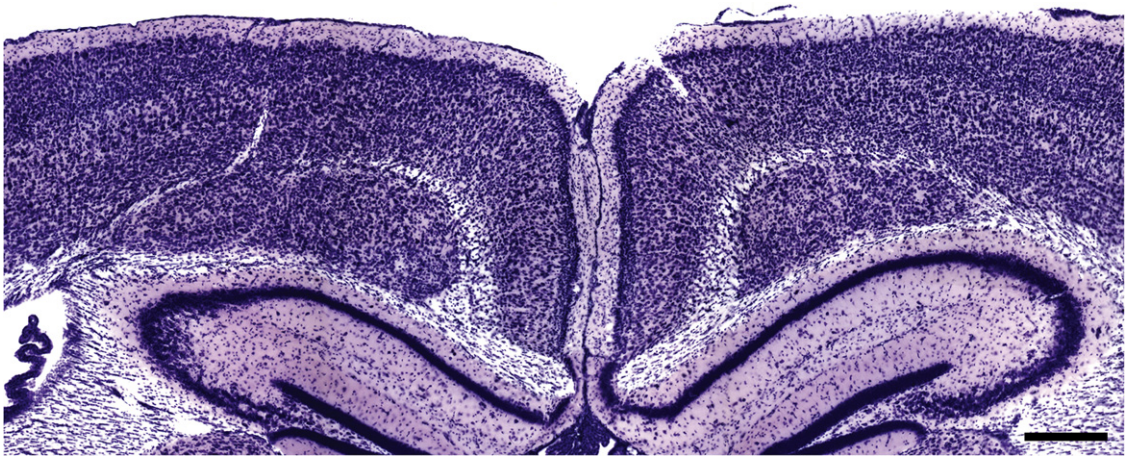

Fig. 1 – BXD29-*Tlr4*$^{lps-2J}$/J mutant mice have bilateral heterotopia and partial agenesis of the corpus callosum. Nissl stain of section in the coronal plane with bilateral midline neocortical nodular heterotopias. Scale bar = 500 μm.