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# Why is the developing brain more susceptible to status epilepticus?

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Early in life, the brain is unusually susceptible to seizures and especially status epilepticus (SE) (DeLorenzo et al., 1992; Chin et al., 2006). This can be due to different factors: intrinsic factors including increases in local excitability and receptor function; inability of specific brain circuits to contain seizures [such as immaturity of intrinsic endogenous networks that lead to seizure termination, e.g., the substantia nigra pars reticulata (SNR)–based system]; age-specific triggers such as fever, hypoxic–ischemic insults, apoptosis; underlying brain pathology; genetic predisposition; hormonal influences; inflammation-related effects; and epigenetic contributors. Indeed, extensive apoptosis was reported as the only possible contributing factor in a case of intractable infantile SE (Cherian et al., 2009).

Our laboratory has been extensively studying the role of the SNR in the control of SE as a function of age. The SNR is a structure crucially involved in cognition (Zaghloul et al., 2009), retention memory and working memory processes (O'Reilly, 2006), coordination of motor functions, as well as in the control of seizures (Depaulis et al., 1994).

The ability of the SNR to control seizures in rats is age- and sex-dependent. In the adult SNR, there are two distinct regions—$SNR_{anterior}$ and $SNR_{posterior}$—that have different roles in seizure propagation and control. Metabolic data show that prior to the seizure onset, there is increased uptake in $SNR_{posterior}$, which could act as a ''gateway'' for seizure propagation (Veliskova & Moshé, 2006). After clonic seizures occur, there is increased deoxyglucose (DG) uptake in $SNR_{anterior}$. This may reflect an attempt of the SNR to curtail the seizure; during a clonic seizure there is increased γ-aminobutyric acid (GABA) release from the striatonigral terminals, silencing SNR neurons, leading to disinhibition of SNR output systems and the arrest



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of the ongoing seizure. This is consistent with anticonvulsant effects of bilateral, strictly local injections of $GABA_A$ receptor agonists in the $SNR_{anterior}$, and nigral lesions. Therefore, a key feature of the mature phenotype is the presence of an anticonvulsant region located in the $SNR_{anterior}$. In the immature brain, the SNR does not show any increases in DG uptake during seizures. Furthermore, infusions of $GABA_A$ agonists in post natal day 15 (PN15) male rats have proconvulsant effects and are ineffective in PN15 female rats (Veliskova & Moshé, 2001). The seizure-controlling effects of $SNR_{anterior}$ on clonic seizures are observed in both male and female rats at least from PN25 (female) and PN30 (male). The maturation of the $GABA_A$-sensitive SNR may depend on $GABA_A$-receptor signaling. Early in life, the relative abundance of the sodium potassium chloride cotransporter NKCC1 favors the intracellular accumulation of chloride, and a $GABA_A$-receptor activation depolarizes neurons, activates voltage sensitive calcium channels, increases intracellular calcium, and activates calcium-sensitive signaling processes that are important for neuronal differentiation, function, and survival (Galanopoulou, 2008b). Later on, the developmental increase in potassium chloride cotransporters that extrude Cl ion to the extracellular space (KCC2) dominate, and $GABA_A$ receptors assume their classical hyperpolarizing mode of action observed in mature neurons and cannot activate calcium signaling (Rivera et al., 1999; Galanopoulou, 2008b). The timing of $GABA_A$-receptor switch differs among regions, and at least in the SNR, also between sexes, being delayed in males.

The mechanisms available to terminate seizures in otherwise normal healthy brain may not be available to terminate seizures in a brain that has already experienced seizures. SE in developing rats does not produce neuronal injury in the SNR. Nevertheless, ongoing studies indicate that the development of the $SNR_{anterior}$ is distorted if infant rats experience three episodes of SE (3SE) prior to PN6, irrespective of gender, by preventing the emergence of the $SNR_{anterior}$ GABA-sensitive anticonvulsant region at PN30. However, in the SNR, 3SE accelerate the developmental increase of KCC2 mRNA; accelerate the $E_{GABA}$ switch with sex-specific features, occurring earlier in females than in males; induce changes in $GABA_A$-receptor subunit expression, and alter the responsiveness of $SNR_{anterior}$ neurons to $GABA_A$ agents. If 3SE are induced in PN14–16 male rats (a period during which the $E_{GABA}$ switch naturally occurs), the $SNR_{anterior}$ $GABA_A$-sensitive anticonvulsant region develops normally. The switch of the $GABA_A$ signaling (depolarizing vs. hyperpolarizing) is sex related; in fact it appears earlier in the female neonatal rat hippocampus than in males. Therefore, the effect of precocious repeated SE episodes result in different effects: in males, 3KA-SE result in precocious deprivation of the differentiating and trophic effects of early depolarizing $GABA_A$ response; in females, 3 KA-SE cause a transient, aberrant reappearance of depolarizing $GABA_A$ responses (Galanopoulou, 2008a). This effect is similar to the reported effects of seizures and SE in adults, but it is transient.

Understanding the spectra of SE-induced changes on the networks involved in the control of seizures as a function of age and sex may lead to the identification of neuro-protective/disease-modifying treatments specific for the developing central nervous system (CNS) to ameliorate the outcome after SE is terminated. This understanding will require translational studies such as the ongoing study of febrile SE and data from experimental models. The latter have provided some evidence regarding the age-specific efficacy of treatment regimens to stop ongoing SE. Hasson et al. (2008) have shown that it is possible to stop 1 h–long SE in 2- and 3-week-old rats using high doses of pentobarbital or diazepam. Diazepam works faster but may be less effective; a combination of diazepam followed by low dose pentobarbital is very efficacious with lower morbidity. These treatments are ineffective in rats. However, in PN9 rats the administration of bumetanide (a NKCC1 blocker) can augment the efficacy of phenobarbital (Dzhala et al., 2005). Another important observation is that topiramate may prevent epileptogenesis in PN15 PN28 rats, even though it does not stop SE (Suchomelova et al.,

2006). The search for potential treatments, both acute and chronic, should be tailored according to specific age, sex, etiology of SE, and genetic/epigenetic predisposition.

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