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Review

Cognitive outcomes of prenatal antiepileptic drug exposure

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SUMMARY

Antiepileptic drugs (AEDs) have been known to have teratogenic effects for a little over 50 years. While early reports focused on fetal malformations, there has been an increasing amount of data over the last few decades exploring the cognitive outcomes of offspring exposed to AEDs in utero. Although the challenges of confounding factors and varied methodologies have led to inconsistent results, the negative impact of some of the agents, such as valproate, have become clear. Further studies are needed to evaluate the cognitive effects of prenatal exposure to many AEDs which have not been tested, to clarify the effects of existing AEDs which have yielded mixed results, and to better understand the effects of polytherapy. Research in animal models is warranted to screen AEDs for their effects on cognition in exposed offspring and to further our understanding of the underlying mechanisms by which AEDs exert their harmful effects on the developing brain. And finally, new AEDs without these harmful effects and agents which can prevent or reverse the negative consequences imparted by AED therapy on cognition should be sought.

Contents

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Animal studies

Cognitive and behavioral effects of prenatal AED exposure in animal models

There have been numerous animal studies demonstrating poor behavioral, cognitive, and motor functioning in offspring that were prenatally exposed to antiepileptic drugs (AEDs). The early studies included phenobarbital (Rogel-Fuchs et al., 1992), valproate (Schneider and Przewlocki, 2005) and phenytoin (Vorhees, 1987). In the 1980s and 1990s, Vorhees published a series of studies examining the behavioral effects on the offspring of maternal rats that had received phenytoin during days 7–18 of gestation, the prime period of organogenesis, at serum levels comparable to the therapeutic range for humans. The offspring were found to have abnormal circling, impaired learning, hyperactivity, delayed development of air righting reflex and abnormal reference memory-based spatial learning (Vorhees, 1987; Schilling et al., 1999; Weisenburger et al., 1990). More recently, studies have been conducted in which the maternal rat was exposed to phenytoin for the duration of the pregnancy and pre-weaning period to more closely resemble a human mother's experience of taking the medication throughout pregnancy and nursing. Higher order learning in which rats transitioned from appetitive (positive reinforcement) to aversive conditioning was impaired (Mowery et al., 2008), and the authors suggested a mechanism of impaired hippocampal development, which has been seen histologically in mice and rats exposed to phenytoin and other AEDs perinatally (Ogura et al., 2002; Vorhees et al., 1990).

Cognitive and behavioral effects of prenatal AED exposure in primates

Evaluation of infant monkeys with exposure to therapeutic maternal levels of phenytoin during gestation demonstrated significantly increased hyperexcitability during recognition testing which required attention to presented stimuli. Infant monkeys with prenatal phenytoin or phenytoin and stiripentol exposure demonstrated higher degrees of hyperexcitability marked by vocalizations, struggling, biting, inconsolability, and inattention to stimuli. In contrast, hyperexcitability was not seen in infant monkeys with prenatal exposure to carbamazepine or stiripentol alone (Phillips and Lockard, 1993, 1996).

Effects of AED exposure on early development at the cellular level

On the cellular level, several groups have demonstrated increased apoptosis and impairment of neurogenesis and synaptogenesis with some AEDs. Bittigau et al. (2002, 2003) found evidence of apoptosis in nearly every region of forebrain examined in postnatal rats 24 h after exposure to benzodiazepines, phenytoin, phenobarbital, or valproate. The effects were dose dependent and were found to occur predominantly during a specific phase of development, between postnatal days 0 to 14, through a mechanism hypothesized to be due to impaired signaling of cell survival pathways. Evaluation specifically of the limbic system in rats with postnatal exposure revealed diffuse apoptosis with phenobarbital, apoptosis in the nucleus accumbens with phenytoin, and no increase in apoptosis with carbamazepine (Forcelli et al., 2011). There have been additional AEDs that were not found to cause apoptosis in the developing rat brain, including carbamazepine, lamotrigine, levetiracetam, and topiramate (Glier et al., 2004; Katz et al., 2007; Kim et al., 2007a,b; Manthey et al., 2005). In combination, however, potentiation of the apoptotic effect in phenytoin was seen when combined with carbamazepine or topiramate, while levetiracetam did not alter the degree of apoptosis seen with phenytoin. Thus, not all AEDs result in apoptotic effect, and even amongst AEDs, the effect on apoptosis varies.

In mice exposed to phenytoin on postnatal days 5–14, which is comparable to a portion of the third trimester in human development, a thinner granule cell layer was seen in the dentate gyrus, and Purkinje cells were immature and abnormally arranged in the cerebellum, which is not only important for motor control, but likely for cognitive processing as well. The average brain weight was significantly lower in 56-day-old mice in the group treated with phenytoin, and was most pronounced in the cerebellum, which was only 71% that of the control mice cerebellar weight. Impairments in spatial learning were also demonstrated in the phenytoin treated group, in the absence of motor deficits (Ogura et al., 2002). Carbamazepine has also been shown to dramatically decrease neuronal numbers both in the hippocampus and cortex in mice exposed in utero; however, no changes were observed in their ability to perform cognitive tests at 5 weeks of age (Åberg et al., 2013). Decreased neuronal membrane order in the hippocampus has been shown in rats with prenatal exposure to phenytoin, during the same day 7–18 of gestation for which cognitive deficits were noted above in section "Cognitive and behavioral effects of prenatal AED exposure in animal models". In a paralleled experiment using valproic acid, the synaptic membrane order was decreased not only in the hippocampus but also in the neocortex (Vorhees et al., 1991). Prenatal exposure to valproate and vigabatrin in rats has been noted to increase cortical and hippocampal dysplasias in the offspring, further reinforcing the evidence for impaired neurogenesis (Manent et al., 2007).

Not only is there structural evidence, but more recent work has confirmed that synaptic deficits result from the exposure as well. Abnormal function has been demonstrated at the synaptic level with a single exposure on postnatal day 7 to phenytoin, phenobarbital and lamotrigine but not to levetiracetam in rats examined up to postnatal day 18 (Forcelli et al., 2012). Interestingly, while lamotrigine has previously been shown to have apoptotic effects at supratherapeutic levels but not within the therapeutic range (Katz et al., 2007), a delay in synaptic maturation was seen with the single dose of therapeutic range which improved over time (Forcelli et al., 2012). We are only in the beginning stages of understanding how AEDs exert their harmful effects on the developing brain, and animal studies have begun to shed light on the potential underlying mechanisms.

Human studies: a historical perspective

Recognition of the teratogenic effects of AEDs

The gravity of teratogenicity from medication exposure during pregnancy was brought to the forefront with the unfortunate thalidomide incident of the late 1950s and early 1960s. A medication that was reported to be safe, thalidomide was prescribed to pregnant women to combat morning sickness and resulted in numerous birth defects of which phocomelia was the most notorious (Franks et al., 2004). AEDs did not come under scrutiny for their