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Developmental neurotoxicity and anticonvulsant drugs: A possible link

A. Verrotti [a], A. Scaparrotta [b], M. Cofini [a], F. Chiarelli [b], G.M. Tiboni [b,*]

[a] Department of Pediatrics, University of Perugia, Italy
[b] Department of Medicine and Aging Sciences, University "G. d'Annunzio" of Chieti-Pescara, Italy

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ABSTRACT

In utero exposure to antiepileptic drugs (AEDs) may affect neurodevelopment causing postnatal cognitive and behavioral alterations. Phenytoin and phenobarbital may lead to motor and learning dysfunctions in the pre-exposed children. These disorders may reflect the interference of these AEDs with the development of hippocampal and cerebellar neurons, as suggested by animal studies. Exposure to valproic acid may result in inhibition of neural stem cell proliferation and/or immature neuron migration in the cerebral cortex with consequent increased risk of neurodevelopmental impairment, such as autistic spectrum disorders. A central issue in the prevention of AED-mediated developmental effects is the identification of drugs that should be avoided in women of child-bearing potential and during pregnancy. The aim of this review is to explore the possible link between AEDs and neurodevelopmental dysfunctions both in human and in animal studies. The possible mechanisms underlying this association are also discussed.

1. Introduction

Antiepileptic drugs (AEDs) used during pregnancy may have a role in neurocognitive and behavioral alterations in children born to epileptic mothers [1]. A relationship between in utero exposure to AEDs and major anatomic congenital malformations has been established over several years. Growing evidence also suggests that developmental and cognitive functioning of children can be affected by fetal exposure to AEDs [2], but existing data are conflicting and/or insufficient. Despite the increased risk of birth defects with fetal exposure to AEDs, therapy is often continued throughout pregnancy because of the possible adverse effects on mother and child caused by recurrent seizures [3]. It is important to underline in this context, that AEDs are not limited to the treatment of epilepsy or seizures, but are also extended to the treatment of pain and psychiatric disorders [4,5].

Neurotoxicity is defined as a structural change or a functional alteration of the nervous system, caused by exposure to a biological, chemical or physical agent [6]. While the effects of AEDs on cognition are poorly defined, intrauterine exposure to these agents has been associated with mental retardation, impairment of language, psychomotor impairment and behavioral difficulties [7–12]. In addition, fetal exposure, especially to valproic acid (VPA), has been associated with autistic spectrum disorders (ASD) including childhood autism, Asperger syndrome, atypical autism and other or unspecified pervasive developmental disorders [13,14].

Animal studies have shown that in utero AEDs-exposure can induce both anatomical and behavioral anomalies. Although the mechanism(s) are still undefined, evidence suggests the potential role of several factors, including folate deficiency, ischemia, neuronal suppression, detrimental effects of reactive intermediates and AED-induced neuronal apoptosis with related dysfunction in the remaining neurons [15].

The aim of this paper is to provide a review of the developmental neurotoxicity of AEDs in animals and in humans.

A PubMed search indexed for MEDLINE was undertaken to identify studies in adults, children and animals using the terms

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AEDs, antiepileptic drugs; ASD, autistic spectrum disorders; ATP, adenosine triphosphate; CBZ, carbamazepine; CNS, central nervous system; DNT, developmental neurotoxicity; ED, effective dose; ETHO, ethosuximide; EGL, external granular layer; FHS, fetal hydantoin syndrome; GBP, Gabapentin; GABA, gamma-aminobutyric acid; GD, gestational day; HDAC, histone deacetylase; IQ, Intelligence Quotient; LTG, lamotrigine; LEV, levetiracetam; MRIs, magnetic resonance images; mRNA, messenger RNA; M/P, milk-to plasma; MME-EST, multiple molecular endpoint embryonic stem cell test; NMDA, N-methyl-D-aspartate; NT2/D1, Ntera2/clone D1; PBA, phenobarbital; PHT, phenytoin; PND, postnatal day; RT, reproductive toxicity; 5-HT, serotonin; TH, tyrosine hydroxylase; TPM, topiramate; TNF-α, tumor necrosis factor-α; VPA, valproic acid.

* Corresponding author at: Department of Medicine and Aging Sciences, University "G. d'Annunzio" of Chieti-Pescara, Via Dei Vestini, 66013 Chieti, Italy.
Tel.: +39 0859172390.
E-mail address: tiboni@unich.it (G.M. Tiboni).

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"*antiepileptic drugs and neurotoxicity*" and "*antiepileptic drugs and children neurodevelopment*" as key words. The date of our last search was January 2014 and the time period covered was approximately 40 years. Only English language articles were reviewed. References of the selected article were consulted for possible relevant articles.

2. Animal studies

Animal studies indicate that exposure to AEDs causes developmental toxicity (DNT) and neurotoxicity, and that all major antiepileptic drugs such as phenytoin (PHT), phenobarbital (PBA), VPA and carbamazepine (CBZ) cause impaired behavioral development following prenatal exposure [6].

Although animal models are important to assess the potential toxicity of foreign agents on the developing central nervous system (CNS), extrapolation of animal data to the human remains a complex process. Both humans and rats are considered "altricial" species, with an immature CNS at birth. Major developmental events that occur postnatally in both the human and the rat include myelination, synapse formation and neuronal and synapting pruning, although differences between the two species have been described. For example, in humans about 20% of the granule cell population in the dentate gyrus is formed after birth, compared with >80% in rats. At birth, the peripheral nerves, the pons and the cerebellar peduncles are fairly well myelinated in humans, whereas only limited myelination occurs prenatally in rats. However, as these developmental processes occur earlier in human development, differences in maturation timelines are not expected to substantially impact on the significance of the rat data in the detection of potential toxicants to human postnatal brain development. The concept that the rat model is appropriate in the evaluation of toxic effects on postnatal brain development is also supported by the notion that most of the brain regions and structures develop postnatally in both humans and rats [16].

In humans, rats and dogs locomotor capabilities develop postnatally, with a gradual rostrocaudal maturation, leading to lifting of the shoulders prior to the pelvis. Both rats and dogs appear to be useful in the assessment of motor development in juvenile toxicity studies [17]. It is estimated that the rat brain at postnatal days (PND) 1–10 corresponds to that of the third trimester in humans, and that rat neurodevelopment at PND 7 is equivalent to that of the human brain at birth [18].

2.1. Phenytoin

PHT is associated with the fetal hydantoin syndrome (FHS), first described by Hanson and Smith in 1975. Following the first reports, many investigators have carried out experimental animal studies searching potential links between PHT and DNT [19].

PHT is a developmental toxicant for animal brain, causing a reduction in brain weight [20], affecting the cerebellar system and the hippocampus [21], and resulting in a number of behavioral deficits such as deficits in spatial learning tasks and activity change (hyperactivity) [6,22–24].

Neonatal exposure of mice and rat to PHT results into cerebellar damage such as apoptotic death and delayed migration of granule cells, associated with altered development of Purkinje cells [25–28], while early postnatal exposure affects the hippocampus, cortical areas, amygdala and thalamus with a dose-dependent increase in apoptotic neuronal death [6,29]. Ohomori and colleagues examined correlations between dosage of PHT and neurotoxic effects on cerebellar development from histologic and morphometric prospectives, administering low-dose PHT orally to newborn mice. Following low-dose PHT treatment on postnatal days 2–4, they observed pyknotic cells in the external granular layer (EGL) as early as day 5 of age in the vermis, associated with thickening of the EGL on postnatal day 14, and reduced cerebellar weight. In addition, they noticed degenerative changes in Purkinje cells [25]. These findings were confirmed by Ogura and colleagues, demonstrating that neonatal administration of PHT in mice interferes with the development of granule cells in the hippocampus and the cerebellum and causes spatial learning deficits in later life [30].

A very recent study has shown that endogenous catalase plays an important gender-dependent neuroprotective role in utero and in aged mice, associated with a reduction of the neurodevelopmental effects of PHT. Low levels of catalase in the developing brain following in utero exposure to PHT were found to increase vulnerability to postnatal neurodevelopmental deficits, pointing to an important mechanistic role played by reactive oxygen species [31].

Regarding PHT neurobehavioral effects, animal studies found that rats exposed to PHT in utero exhibit heightened locomotor movement, primarily pivoting, during early postnatal development. In particular, they become more active than controls on days 9 and 4, with increasing hyperactivity as they grow older [19,23].

Other investigators reported that rats exposed prenatally to PHT showed impaired acquisition of the air-righting reflex, which attained full proficiency in the control rats at 3 weeks of age [19,32,33].

Neurological abnormalities are often first manifest around postnatal days 40–50, in the form of excessive abnormal circling movements. This behavior is most conspicuous in confined, such as when the animal is first returned to its home cage or in the narrow channels of a maze: the affected rats show episodic bouts of repetitive circling [19]. A more recent study evaluating the persistence of PHT-induced circling in Sprague–Dawley rats suggested that early postnatal exposure to PHT may exacerbate the long-term behavioral effects of gestational exposure [34]. Prenatal PHT exposure also affects the startle response, another complex reflex: the offspring exhibit a significant reduction in startle amplitude to either anacoustic or tactile stimuli as an adult, but no change in the latency of their maximum response [19,23].

The impairment of the offspring learning ability is one of the most striking effects of prenatal exposure. The existing studies have utilized the Morris hidden platform maze, a test of spatial navigation, which is sensitive to hippocampal damage, and a complex multiple-T water maze, namely the Cincinnati maze, a test known as "dead-reckoning" navigation, which relies upon the use of proximal cues and vector estimation [19]. The exposed animals took significantly longer to navigate to the hidden platform than controls, making many more errors. In particular, those exhibiting abnormal circling behavior were the most severely affected and showed little improvement in performance across trials, while those without abnormal circling showed impaired learning but they eventually succeeded in learning the maze [19,33].

In summary, locomotor response can influence spatial performance in maze-like paradigms. More specifically, alterations in circling behavior may influence the evaluation of other characteristic motor, learning, and memory disorders following a prenatal exposure to PHT [34].

2.2. Phenobarbital

Several animal studies have shown that PBA clearly causes DNT. Schain and Watanabe in 1975 hypothesized that chronic administration of PBA caused delay in the brain development of infant rats and administration during the first 3 weeks of life caused a delay in body and brain growth during this period [35]. Perinatal exposure to PBA can cause a reduction of pyramidal and granule cells in the hippocampus [36] as well as Purkinje and granule cells in the cerebellum [37] and can reduce brain weight [6,35]. Data from mice exposed to PBA prenatally and neonatally