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Review

Antiepileptic drugs and the developing brain

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Abstract. Epilepsy is the most common neurological disorder in young humans. Antiepileptic drugs (AEDs) which are used to treat seizures in infants, children and pregnant women can cause cognitive impairment, microcephaly and birth defects. Ion channels, neurotransmitters and second messenger systems constitute molecular targets of AEDs. The same targets regulate brain processes essential both for propagation of seizures and for learning, memory and emotional behavior. Thus, AEDs can influence brain function and brain development in undesired ways. Here we review mechanisms of action of AEDs, examine clinical evidence for their adverse effects in the developing human brain, and present studies on cognitive and behavioral effects in animal models. Furthermore, we discuss mechanisms responsible for adverse effects of AEDs in the developing mammalian brain, including interference with cell proliferation and migration, axonal arborization, synaptogenesis, synaptic plasticity and physiological apoptotic cell death.

Key words. Antiepileptic drugs; development; apoptosis; neurodegeneration; synaptogenesis.

Introduction

Epilepsy is a brain disorder characterized by recurrent seizures, affects 1–2% of humans worldwide and displays its highest incidence in the first year of life [1]. Antiepileptic drugs (AEDs) are used to prevent epileptic seizures but are also beneficial in other neurological and psychiatric conditions, such as bipolar disorder, migraine, movement disorders (dystonia, restless leg syndrome), myotonia and neuropathic pain [2].

The selection of an AED for treatment of epilepsy in infancy, childhood and adolescence is based on the syndromic diagnosis of the patient's seizure disorder. The broad spectrum of new-generation AEDs have expanded the choice of available agents for most syndromes (table 1). Appropriate selection of an AED is based on the established efficacy for a specific syndrome, on relative toxicity and tolerability of AEDs, and on age-specific organ toxicities [3, 4].

AEDs interact with ion channels, metabolic enzymes and neurotransmitter transporters in the brain, modify bursting properties of neurons, inhibit spread of epileptic activity and reduce synchronization [5]. In addition, they can interfere with neuronal migration, differentiation and plasticity, and in the developing rodent brain, they can induce neuronal cell death [6].

In this article we review mechanisms of action of AEDs, and present clinical and experimental evidence describing their adverse effects in the developing mammalian brain.

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Table 1. Pediatric epilepsy syndromes and treatments.

Syndrome	Treatment
Neonatal seizures	phenobarbital, phenytoin, anecdotal reports for topiramate and levetiracetam
Infantile spasms	adrenocorticotropic hormome (ACTH), vigabatrin, valproic acid
Lennox-Gastaut syndrome	valproic acid, lamotrigine, topiramate
Childhood and juvenile absence epilepsy	ethosuximide, valproic acid, lamotrigine
Rolandic epilepsy	sulthiame, carbamazepine, gabapentin
Juvenile myoclonic epilepsy	valproic acid, lamotrigine, topiramate
Partial seizures	carbamazepine, oxcarbazepine, lamotrigine, topiramate, phenytoin
Generalized tonic-clonic seizures (GTC)	oxcarbazepine, phenytoin, topiramate, lamotrigine valproic acid, carbamazepine

Table 2. Molecular targets of antiepileptic drugs.

Drug	GABA system	Glutamate receptors	Sodium Channels	Calcium channels
Benzodiazepines	+			
Phenobarbital	+	+		+
Vigabatrin	+			
Tiagabine	+			
Valproate	+		+	+
Topiramate	+	+	+	+
Gabapentin	+			+
Phenytoin			+	
Carbamazepine			+	
Oxcarbazepine			+	
Lamotrigine			+	+
Zonisamide			+	+
Levetiracetam	+			+
Ethosuximide				+
Felbamate	+	+	+	+

Mechanisms of action of AEDs

Voltage-gated ion channels are the main targets of AED action. These channels determine the excitability of neurons and regulate neurotransmitter release. AEDs which act on voltage-gated ion channels inhibit epileptic bursting, synchronization and seizure spread. Blockade of sodium or calcium channels as well as facilitation of potassium channels lead to anticonvulsant action in animal seizure models [7].

Voltage-gated sodium channels consist of multiple subunits and undergo conformational change as soon as a neuron is depolarized to action potential threshold. This conformational change converts the channels to an open conducting state and permits sodium flux for only a few milliseconds. Channels rapidly inactivate and can only be reactivated following repolarization. Rapid changes between open and closed states of sodium channels are essential both for normal brain function and for epileptic discharges. Phenytoin, carbamazepine, oxcarbazepine, zonisamide and lamotrigine primarily act by modulating voltage-dependent sodium channels. Blockade of sodium channels can also be achieved with valproate, felbamate and topiramate (table 2). These drugs block high-frequency repetitive spike firing without affecting physiological neural activity. This translates into an antiepileptic effect without causing generalized impairment of brain function. Although these drugs do not alter excitatory or inhibitory synaptic responses, they do reduce transmitter output at synapses [8, 9].

Voltage-gated calcium channels are divided into high voltage-activated (HVA) and low voltage-activated families. HVA channels (L-, R-, P/Q- and N-types) can only gate following strong membrane depolarization, and regulate calcium entry and neurotransmitter release from presynaptic nerve terminals. Gabapentin and several other AEDs inhibit HVA channels (table 2) [10–18]. Gabapentin binds to the $\alpha 2\delta$-1 and a2δ-2 subunits and inhibits HVA calcium currents in a concentration-dependent fashion [19–21]. This effect probably leads to reduction in excitatory transmission [22, 23].

Low-voltage calcium channels (T-type) regulate neuronal firing and influence bursting and intrinsic oscillations [24]. Abnormal oscillatory behavior is thought to underlie generalized absence seizures [25]. T-type calcium channels generate low-threshold calcium spikes and trigger a burst of action potentials mediated by sodium channels in thalamic reticular neurons [26]. Ethosuximide, an AED that is effective against absence seizures, valproic acid and zonisamide inhibits T-type calcium channels [27, 28].

Interaction with neurotransmitter systems

Several AEDs enhance synaptic inhibition or decrease synaptic excitation. These effects are mediated by interaction with neurotransmitter receptors and neurotransmitter-regulated channels and can also suppress bursting and seizure spread. Two major neurotransmitter systems constitute targets of AED action, the inhibitory GABAergic system and the excitatory glutamatergic system. Many AEDs enhance inhibition mediated by $GABA_A$ (γ-amino-

butyric acid A) receptors. Blockade of glutamate receptors [including those of the NMDA (*N*-methyl-D-aspartate), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid), kainate and group I metabotropic receptors] exhibit anticonvulsant action in animal models. Other neurotransmitter systems which have been shown to modulate seizure threshold include the glycine system, monoamines, neuropeptides, galanin, neuropeptide Y, adenosine, serotonin and histamine [5].

GABA-mediated inhibition

Inhibitory synapses are important for controlling activity of excitatory neurons and for inhibiting synchronized epileptiform discharges [29]. Enhancement of GABA-mediated inhibition is a major mechanism of action of AEDs.

GABA activates chloride-permeable $GABA_A$ receptors and slower metabotropic G-protein-coupled $GABA_B$ receptors. Compounds which block $GABA_A$ receptors are potent proconvulsants. Mutations in $GABA_A$ receptor subunits have been associated with epilepsy syndromes such as GEFS+, childhood absence epilepsy, Dravet's syndrome and juvenile myoclonic epilepsy [30–34].

Benzodiazepines are used as first-line drugs in the treatment of status epilepticus. They allosterically modulate $GABA_A$ receptors containing the γ2 subunit and the α1 subunit [35, 36]. Enhancement of tonic $GABA_A$ receptor currents is important for benzodiazepine action [37].

Barbiturates such as phenobarbital also allosterically modulate $GABA_A$ receptors. At clinically relevant concentrations, phenobarbital shifts the relative proportion of openings to favor the longest-lived open state and increases the overall probability that the channel is open [38]. Barbiturates act on calcium and sodium channels as well [13]. Felbamate and topiramate might also partly act through positive modulation of $GABA_A$ receptors [39–41].

Vigabatrin (γ-vinyl GABA) is an irreversible inhibitor of the GABA-degrading enzyme GABA transaminase [42] and leads to elevations of GABA levels in the brain [43]. It is assumed that elevation of extracellular GABA alters the dynamics of inhibition and reduces the fading of inhibitory mechanisms during repetitive activation of neurons [44]. Such fading, which is dependent on $GABA_B$ receptors and on trafficking of $GABA_A$ receptors [45, 46], is an important factor that permits localized epileptiform activity to develop into a seizure.

Tiagabide is a selective competitive inhibitor of the high-affinity plasma membrane GABA transporter GAT1 [47]. Tiagabine prevents GABA uptake and prolongs inhibitory postsynaptic potentials [48–50].

Glutamate-mediated excitation

Ionotropic glutamate receptors are glutamate-gated cation channels that mediate fast excitatory neurotransmission in the central nervous system (CNS) [51]. Antagonists at glutamate NMDA, AMPA and kainate receptors are potent anticonvulsants in animal seizure models [52].

Several AEDs can influence ionotropic glutamate receptors. Felbamate inhibits NMDA receptors at clinically relevant concentrations [53, 54] and is modestly more potent as an antagonist of NMDA receptors containing NR2B subunits [55, 56].

AMPA and kainate receptors mediate seizure spread and seizure-induced brain damage [57]. Kainate receptors also modulate glutamate release from excitatory afferents and suppress GABA release from inhibitory interneurons [58]. Topiramate selectively inhibits AMPA and kainate receptors [59, 60].

Susceptibility of the developing brain to environmental agents

Short- and long-term deleterious effects resulting from any interference with normal brain development differ in their extent and quantity depending on the nature of interference and the timing of the insult [61]. In the past several decades, studies in rodents have provided substantial information on brain development [61–66]. Although there are variations in the rates of brain growth among mammals, comparisons of brain development between species are possible [66, 67]. The developmental ages of human and rat embryos or fetuses are comparable when anatomical features and histological landmarks are similar in appearance in the two species, even though their exact chronological ages are different [66]. In the CNS, structures are built by cell proliferation, migration and a sequence of steps called differentiation [61]. Normal function requires a specific number of cells with the proper characteristics in the correct location [61]. With autoradiography, the neurogenesis of individual neuronal populations has been determined in rodent brain, and extrapolations were made to the human brain [61, 66]. These studies clearly indicate that different brain areas develop at different times during gestation, and within a single brain region, subpopulations of neurons develop at different rates and at different times. Cerebellar Purkinje cells, for example, develop early (embryonic days 13–15 in the rat, corresponding to gestational weeks 5–7 in humans), whereas granule cells are generated much later (postnatal days 4–19 in the rat, corresponding to gestational weeks 24–40 in humans) [66]. Many agents, such as X-ray irradiation, cause brain damage by interfering with cell proliferation, and if the insult occurs during the stage of formation of a certain neuronal subpopulation, those cells will not be formed.

Cell migration is another important process during brain development by which neurons reach their final location. Such physical contact between the cells is important for

the construction of complex circuits, and any interference with cell migration has deleterious effects on the developing brain [62]. During development, migration occurs in waves associated with different cell types [68]. Neurons must subsequently form connections, and this occurs during the process of synaptogenesis. The developmental period of synaptogenesis is critical for the formation of the basic circuitry of the nervous system, although neurons are able to form new synapses throughout life [68]. Furthermore, evidence exists that neurotransmitters can modulate proliferation of neural stem cells, neuroblasts and glioblasts, regulate migration and induce differentiation [69–72]. Thus, pharmacological agents that interfere with neurotransmission during development may cause permanent defects in the CNS.

Neurogenesis produces about twice as many neurons in a given structure as the number of neurons that survive in the adult organism. This initial excess of neurons is short lasting and followed by a process known as apoptosis or programmed cell death [73]. Apoptosis is regulated by growth factors and cytokines as well as by neurotransmitters and is executed by a number of intracellular proteins [74–77]. Any compound that interferes with these processes may trigger apoptotic degeneration of neurons that would not otherwise have been deleted from the developing brain, or may, in contrast, promote survival of unnecessary cells [78].

Pruning, defined as a loss of synapses, also occurs physiologically in the developing brain [78]. Such trimming of connections is a more extensive process than cell death and occurs late in childhood and adolescence [78]. Any interference with this process would be expected to affect the number of synaptic connections. Most of the developmental processes discussed so far have focused on neurons. However, it is well established that glial cells (astrocytes, oligodendrocytes and microglia) play a most relevant role in brain function as well as in brain development.

An important period of brain development is the so-called brain growth spurt, a transient period when the brain is growing most rapidly [63]. This occurs in the first 2 postnatal weeks in the rat and in the third trimester of gestation and first 2 years of life in humans [64].

Clinical evidence for adverse effects of AEDs in humans

AEDs are among the most common causes of fetal malformations. These include neural tube defects, orofacial clefts and digital anomalies, growth retardation, developmental delay and microcephaly [79–84]. Teratogenic effects have been associated with the use of phenytoin, carbamazepine, valproate and phenobarbital. Increasing maternal blood levels and combinations of AEDs impose an increased risk for harm to human infants [84].

The neonatal brain is vulnerable to teratogenic agents, which have an impact on neuronal migration and synaptic organization. However, specific cognitive dysfunction may be difficult to detect in children below the age of 5 years [85], as brain maturation is incomplete and developmental tests have poor predictability for future intellectual functioning [86]. Despite these difficulties, it has been shown that AEDs may have adverse effects on human intellect when given to treat seizures in pregnant women, infants and toddlers. Long-lasting neurobehavioral effects in humans following in utero exposure to phenobarbital such as impaired cognitive development [87] and lower IQ scores [88] have been reported. Despite the developmental neurotoxicity of phenobarbital, its embryotoxicity and teratogenic effects appear to be less than those of other anticonvulsants in animal models [83].

Valproic acid is a clear animal and human teratogen [89, 90]. The nervous system appears to be very sensitive to the developmental toxicity of valproic acid. Neural tube defects, specifically spina bifida, occur at a high rate upon in utero exposure to this compound [91].

Similar to valproic acid, in utero exposure to carbamazepine has been associated with an increased risk of spina bifida, with an incidence of about 1% [81, 92]. Carbamazepine has been found to be teratogenic in humans, and the pattern of malformations (facial dysmorphic features, microcephaly, growth retardation) resembles that of other anticonvulsants [81, 93].

There is evidence that phenytoin is a developmental toxicant in animals and humans. The fetal hydantoin syndrome in humans is characterized by facial dysmorphologies, growth retardation and other anomalies [94, 95], and similar effects have also been seen in rodents [96]. Microcephaly, learning disabilities and decreased IQ scores have also been reported in humans [97–99].

The majority of studies investigating the effects of prenatal antiepileptic drug exposure were performed in children below age 5. In many studies a trend towards lower developmental scores was reported, although in few studies no adverse effects could be shown [100].

In a longitudinal study, children exposed to carbamazepine and phenytoin had lower developmental and language scores, compared with controls. In children receiving carbamazepine, a deficit in language development was not evident until an age beyond 3 years, suggesting that specific cognitive deficits may first become apparent when the child is older [101].

Inconsistent results have also been obtained in studies that have investigated the long-term effects of AED exposure in children older than 5 years [99, 102–105]. Some studies have reported specific cognitive deficits in visuospatial functioning [87, 106], spelling and linguistic abilities [101, 107, 108].

Intrauterine exposure to phenytoin, phenobarbital, polytherapy, valproate and carbamazepine is associated with

lower intellectual functioning [107–110]. Carbamazepine appears to be the least developmentally neurotoxic compound among the major AEDs. Although in one study mild mental retardation has been reported in children exposed in utero to carbamazepine [111], no neurologic or IQ differences were found by other investigators [87, 107].

In humans, in utero exposure to valproic acid has been associated with developmental delay, mental retardation, cognitive impairment and other behavioral deficits [112, 113]. In a recent retrospective study exploring neuropsychological effects of exposure to anticonvulsant medication in utero, Vinten et al. reported that an in utero exposure to valproate was harmful to later neuropsychological development. Children exposed to valproate had a significantly lower IQ compared with children exposed to other antiepileptic drugs or not exposed at all. The same children were more likely to have an IQ below 69 and more likely to have memory impairment when compared with other groups [114].

In addition, postnatal exposure to AEDs during the first years of life may be harmful for cognitive development. In several studies it was shown that therapy with barbiturates during the first 3 years of life may cause cognitive impairment that persists into adulthood [88, 115–117].

Adverse effects of AEDs in animal studies

Phenobarbital is the oldest synthetic antiepileptic drug available. The effect of exposure of animal fetuses or pups to phenobarbital on brain growth and behavior has been studied extensively [118–120]. Perinatal exposure to phenobarbital can reduce brain weight [121], and causes a reduction of Purkinje and granule cells in the cerebellum [122] and pyramidal and granule cells in the hippocampus [123]. Neurochemical studies have indicated that phenobarbital profoundly disrupts cholinergic neurotransmission in the hippocampus [124].

Administration of phenobarbital to rat pups results in significant decreases in brain weight and DNA, RNA, protein and cholesterol concentrations and reduced neuronal number [125, 126]. Results of behavioral studies are consistent with morphological and neurochemical changes, as perinatal exposure of rodents to phenobarbital causes decrements in various spatial learning tasks [124, 127]. Compared with controls, rats receiving phenobarbital have increased aggression and activity levels [125, 128, 129]. Prenatal exposure to phenobarbital resulted in deficits in the hippocampal eight-arm maze, spontaneous alternations and water maze behaviors in adulthood [126], and affected operant conditioning [130, 131]. Similar effects were reported in kindled rats when AEDs were administered in doses that protected against kindled seizures [132].

When phenobarbital was administered to developing animals that had undergone kainic acid-induced status epilepticus, it exhibited a clear-cut anticonvulsant effect. Young animals develop spontaneous seizures following status epilepticus and reorganization, and phenobarbital was effective in reducing these spontaneous seizures. However, animals receiving phenobarbital performed worse in the water maze than animals receiving saline, although saline treated animals has significantly more spontaneous seizures. For cognitive testing phenobarbital had been withdrawn. Thus it appears that phenobarbital can have adverse effects on cognition when administered following an acute insult, such as status epilepticus [128].

Concerning phenytoin and carbamazepine, there are no experimental data which convincingly demonstrate adverse effects of these compounds on cognition when they are given at an early age. In a study of active avoidance, carbamazepine at low doses protected against impairment of learning rate caused by repeated application of convulsant shock [133] and had no effect on learned taste aversion [134].

Animal studies have shown that perinatal administration of phenytoin causes a reduction in brain weight [135] and a number of behavioral deficits (seen at subteratogenic doses), which include, in particular, deficits in spatial learning tasks and activity change (hyperactivity) [136–138]. In rodents, incidence and severity of teratogenic effects of carbamazepine were less than those observed with other AEDs and occurred mostly at high doses [139].

Impaired learning has been ascribed to benzodiazepines [133, 140]. Pereira et al. reported profound effects of diazepam on shuttle avoidance behavior and attributed this to its interfering effects on memory [140]. Holley et al. suggested that the effects of benzodiazepines on memory and learning could be related to an effect on attention [141]. This is a matter of concern that is unique to the developing brain, and $GABA_A$ receptor activation could be of relevance to benzodiazepines as well as barbiturates and general anesthetic agents. Our group has found that phenytoin, valproic acid, vigabatrin, diazepam and clonazepam induce apoptotic neurodegeneration in the developing rat brain at plasma concentrations relevant for seizure control in humans [142, fig. 1]. Jevtovic-Todorovic et al. administered midazolam, nitrous oxide and isoflurane to 7-day-old infant rats and described widespread apoptotic neurodegeneration and impaired long-term potentiation in hippocampal slices obtained from these animals 3 weeks later [143]. Persistent deficits in memory and learning were evident when the rats were tested using the Morris water maze or the radial arm maze.

Neural tube defects have been seen with valproic acid in mice [144], and strain differences in susceptibility suggest an underlying genetic predisposition [145]. Most mechanistic studies have focused on the major malformations induced by valproic acid [146]. At therapeutically relevant

concentrations, valproic acid alters the expression of certain homeobox genes, which suggests that teratogenicity may be at least in part mediated by changes in Hox gene expression [145]. Concentrations of valproic acid within its therapeutic range inhibit histone deacetylase, which is involved in the repression of gene expression and plays an important role in embryonic development [147, 148]. Inhibition of histone deacetylase can prevent cell proliferation and may be responsible for the ability of valproic acid to reduce proliferation of C6 glioma cells [149]. This antiproliferative effect of valproic acid may be relevant for its teratogenicity, as alterations of normal proliferation rate of the tissues involved with neuronal tube closure may result in an embryo with a neural tube defect [150]. The effect of valproic acid as an inhibitor of the detoxifying epoxide hydrolase could also be relevant to the teratogenic effect of this AED [151].

Exposure to subteratogenic doses of valproic acid may cause microencephaly and behavioral changes (deficits in spatial learning tasks and altered locomotor activity) in rodents [150]. Valproic acid may be more toxic to the developing brain than other anticonvulsants [112], and neural tube defects may only be the tip of the iceberg, because valproate carries particular risks to the learning and development of children [101]. In utero exposure of rats to valproic acid causes cerebellar anomalies associated with autism, and an association between exposure to valproic acid and autistic-type behaviors has been suggested in humans [112, 152].

Bolanos et al. compared the cognitive function in rats that received phenobarbital or valproic acid following kainic acid-induced status epilepticus [153]. A convulsant dose of kainic acid was administered to rats on postnatal day P35, which corresponds to prepubescence in children. From P36 to P75, rats received daily injections of phenobarbital, valproic acid or saline, and spontaneous seizure frequency was monitored. Following tapering of the drugs, the rats were tested in the water maze, on visuospatial memory and using a handling test (a measure of emotionality). Rats receiving phenobarbital or saline were significantly impaired in learning in the water maze and also had increased emotionality in the handling test, whereas rats receiving valproic acid had no deficits in the water maze and did not differ from non-status epilepticus rats in their emotionality scores. However, rats receiving valproic acid had no spontaneous seizures following the status epilepticus compared with frequent spontaneous seizures in the rats receiving saline or phenobarbital.

Topiramate interacts with AMPA and kainate subtypes of glutamate receptors, and because of these effects concerns have been raised about the impact of its long-term use on cognitive function. Cha et al. evaluated effects of topiramate on cognitive function in the immature brain. They administered topiramate, 80 mg/kg, or saline for 4 weeks following a series of 25 neonatal seizures or status epilepticus induced by lithium-pilocarpine in P20 rats [154]. Animals were tested in the water maze for spatial learning, and the brains were examined for cell loss and sprouting of mossy fibers. There was a trend for improved visuospatial performance in the water maze following topiramate therapy in rats with neonatal seizures. Neonatal rats without seizures exposed to 4 weeks of topiramate did not differ from untreated controls in water maze performance or histologic examination.

In weanling rats subjected to status epilepticus, topiramate-treated rats performed better in the water maze than rats receiving saline, a finding indicative of a possible neuroprotective effect. These findings demonstrate a mild beneficial effect of topiramate on cognitive function. In addition, long-term administration of high-dose topiramate in the normal developing rat brain does not appear to impair cognitive performance.

Work by Cha et al. (2002) and Koh and Jensen (2001) suggests that topiramate might be neuroprotective in the developing brain, an effect similar to that of NBQX, a specific AMPA receptor antagonist in a neonatal hypoxia model of neonatal seizures in rats [154–156].

Cilio et al. treated P35 rats subjected to kainic acid-induced status epilepticus with twice-daily doses of gabapentin [157]. After tapering of the drugs, the rats were tested in the water maze and open field, a test that measures activity level. In animals treated with gabapentin, there was a reduced incidence of spontaneous recurrent seizures and reduced hyperactivity compared with saline-treated controls. No differences in performance in the water maze or emotional response to painful injection were found between the gabapentin-treated and saline-treated animals. This study demonstrates that gabapentin has a beneficial effect following status epilepticus but does not contribute to impairment or enhancement of learning in animals.

Treatment with tiagabine has been reported to impair performance in the Morris water maze test in adult rats [158]. No comparable studies have been performed in developing animals.

Levetiracetam is structurally related to nootropic agents, which may produce cognitive enhancement in certain models of learning and memory. The structural analogs piracetam [159] and etiracetam [160] seem to have a positive effect on learning and memory. Verloes et al. found that levetiracetam antagonized the amnestic effects of scopolamine in passive avoidance learning in mice [161]. In water maze testing in rats, levetiracetam did not affect the latency for locating the platform at any dose tested in amygdala-kindled rats, whereas all reference antiepileptic drugs tested in the experiment (valproic acid, carbamazepine and clonazepam in normal rats, valproic acid in amygdala-kindled rats) significantly increased latencies at comparable doses [162].

Very little is known about the effect of zonisamide on behavior or learning and memory. No adverse effects of zonisamide were reported in spontaneous alternation behavior and active avoidance in mice, but impaired acquisition of step-down passive avoidance behavior was reported [163]. No studies have so far evaluated the behavioral effects of zonisamide in developing animals.

Neurotoxicity of antiepileptic drugs in the developing brain

Physiological cell death, a process by which redundant or unsuccessful neurons are deleted by apoptosis (cell suicide) from the developing CNS, has been recognized as a regular phenomenon in the developing brain. In recent studies it has been shown that compounds which are used as sedatives [76, 77], anesthetics [143] or anticonvulsants [142] in medicine trigger widespread apoptotic neurodegeneration throughout the developing brain when administered to immature rodents during the period of the brain growth spurt. Such compounds include drugs which alter physiologic synaptic activity, i.e. antagonists of NMDA receptors (ketamine, nitrous oxide), agonists of γ-aminobutyric acid subtype A ($GABA_A$) receptors (barbiturates, benzodiazepines, propofol) and/or sodium channel blockers (phenytoin, valproate).

The brain growth spurt period occurs at different times relative to birth in different species. In rats and mice it occurs postnatally, but in humans it extends from the sixth month of gestation to several years after birth [164]. Thus, there is a period in pre- and postnatal human development that lasts for several years, during which immature neurons might be prone to commit suicide if exposed to AEDs.

Possible neurotoxicity of AEDs was systematically studied in infant rodents [142]. Phenytoin (10–50 mg/kg) produced widespread and dose-dependent neurodegeneration in infant rats within the medial septum, nucleus accumbens, thalamic and hypothalamic nuclei, subiculum, globus pallidus, piriform and entorhinal cortices, the amygdala and layers II and IV of the frontoparietal, cingulate and retrosplenial cortices. By electron microscopy it was determined that the cells degenerating in the brains of phenytoin-treated rats displayed ultrastructural changes similar to those described in neurons undergoing programmed cell death, a prototypic example of apoptosis [165]. The threshold dose for triggering an apoptotic response was 20 mg/kg, which resulted in phenytoin plasma concentrations ranging between 10–15 μg/ml over 4 h.

Phenobarbital (20–100 mg/kg) and diazepam (5–30 mg/kg) caused widespread apoptotic neurodegeneration in the brains of rats on P7 with a similar distribution pattern. Neurotoxic effects were reproduced by clonazepam (0.5–4 mg/kg) in 7-day-old rats [142] (fig. 1). The threshold doses for triggering apoptotic brain damage were 40 mg/kg for phenobarbital, 10 mg/kg for diazepam and 0.5 mg/kg for clonazepam. Analysis of plasma concentrations revealed that when concentrations of phenobarbital were maintained at 25–35 μg/ml over a 12-h period, significant apoptotic neurodegeneration occurred [142]. Valproate (50–400 mg/kg on P7) or vigabatrin (50, 100 or 200 mg/kg twice daily on 3 consecutive days starting on P5) elicited apoptotic neurodegeneration in the developing rat brain in a dose-dependent manner.

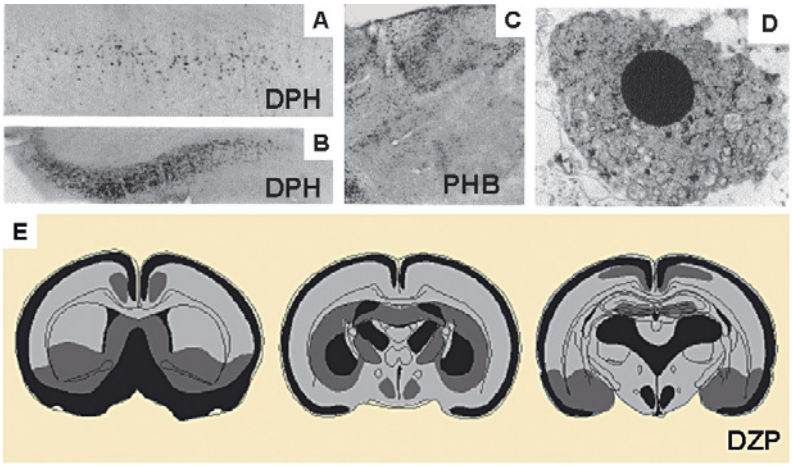

Figure 1. AEDs induce apoptotic neurodegeneration in the infant rat brain. (*A–C*) Low-magnification light microscopic overviews of silver-stained transverse sections and electron micrograph depicting neurodegenerative changes in the brains of P8 rats following treatment with phenytoin (DPH; *A, B* in parietal cortex and subiculum) and phenobarbital (PHB; *C*, in the thalamus). In *D* an electron micrograph (×1800) is shown illustrating late stages of apoptotic neurodegeneration within the thalamus 24 h following administration of diazepam. In *E* the distribution pattern of apoptotic neurodegeneration, as seen in the brains of 8-day-old rats following administration of diazepam 24 h earlier, is depicted. Darker shades indicate higher densities of degenerating cells.

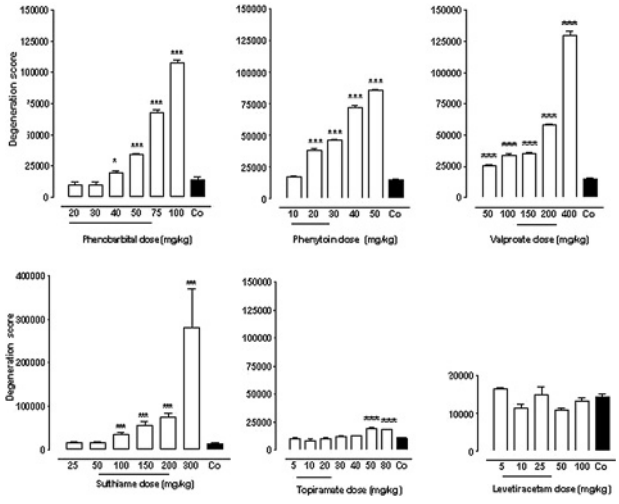

Figure 2. Proapoptotic effect of phenobarbital, phenytoin, valproic acid, sulthiame, topiramate and levetiracetam in 7-day-old rats in comparison. Bars represent degeneration scores (mean ± SEM) as determined using a stereological dissector [166]. Lines underneath the x-coordinates depict reported ED_{50} (mean effective concentration) dose range of the given drug in various rodent seizure models. Statistical comparisons were performed between drug-treated and vehicle-treated groups (n=7–9 per group). *P < 0.05; ***P < 0.001, Student's *t*-test (adapted from [166, 167]).

Additional experiments were performed to determine how the apoptotic response to AEDs might differ as a function of developmental age. These experiments revealed that there is a time window from P0-P14 when various neuronal populations in the rat forebrain show transient sensitivity to AEDs.

Developmental neurotoxicity of topiramate, levetiracetam and sulthiame were tested in a similar way. Topiramate elicited a neurotoxic effect in infant rat brain beginning at a dose of 50 mg/kg, which is higher than the effective anticonvulsant doses in infant rodent seizure models [166]. Thus, it was concluded that topiramate has a rather beneficial profile, since it shows no detectable toxicity at anticonvulsant doses. Interestingly, levetiracetam showed no neurotoxicity in the infant rat brain at all doses tested [167, fig. 2].

Other groups have reported that phenytoin can affect the cerebellar system and the hippocampus. Indeed, neonatal exposure of mice to phenytoin leads to cerebellar damage, characterized by apoptotic death, delayed migration of granule cells and altered development of Purkinje cells [168, 169]. *In vitro* experiments have confirmed that phenytoin induces apoptotic cell death of cultured cerebellar granule cells [170], degeneration of Purkinje cells [171] and toxicity in cerebral cortical cell cultures [172].

Further studies elaborated several mechanisms responsible for AED-induced apoptotic death in the developing rodent brain. One mechanism includes changes in gene expression in the developing brain, i.e. depressed synthesis of brain derived neurotrophic factor, neurotrophins 3 and 4, as well as reduced levels of the active phosphorylated forms of extracellular signal regulated kinase (ERK1/2) and protein kinase B (AKT). ERK1/2 and AKT are key players in two major survival promoting pathways, the MEK-ERK1/2 and the phosphatidylinositol 3-kinase-AKT pathways, which are activated by tyrosine kinase receptors upon binding of growth factors [142, 173]. Ras activation results from binding of growth factors to the respective receptors and initiates signaling via the MEK and PI3 kinase pathways. SynRas transgenic mice, which postnatally overexpress activated Ras in neurons and display higher levels of phosphorylated ERK1/2 in the cortex, were less susceptible to the proapoptotic effect of MK801 or phenobarbital [173]. Such changes, which have also been described in *in vitro* systems following blockade of NMDA receptors [174], reflect an imbalance between neuroprotective and neurodestructive mechanisms in the brain. During a developmental period of ongoing physiological elimination of cells in the brain, such an imbalance will likely promote apoptotic death. Interestingly, 17β-estradiol counteracted inactivation of the ERK1/2 and AKT pathways and, by doing so, conferred protection against apoptotic neuronal deletion following treatment with AEDs [142, 175].

Influence of AEDs on other developmental processes

AEDs not only induce widespread apoptotic neurodegeneration in the developing brain, but can also impair cell proliferation and differentiation, synaptogenesis and synaptic plasticity, cell migration and axonal arborization. A disruption of these developmental processes may potentially account for neurological deficits seen in humans exposed to AEDs pre- or postnatally. Unfortunately, the effect of AEDs on these processes in the developing brain has not been systematically analyzed.

Cell proliferation and differentiation

Glutamate and GABA neurotransmitter systems are implicated in neuronal proliferation and migration during CNS development. The application of a single dose of diazepam (5 mg/kg) at P11 induced a significant reduction of mitotic activity in rodent cerebral cortex and anterior pituitary gland [176]. The sodium channel blocker valproate, on the other hand, promoted neuronal differentiation in human fetal forebrain stem cell cultures [177]. Increased numbers of immature granule cells in the dentate gyrus resulted from treatment of mice with 35 mg/kg/d phenytoin from P5 to P14 [178]. Reactive astrogliosis has previously been observed, along with microglial activation, in rats given 250 mg/kg/d vigabatrin for a period of 8 weeks beginning at age P28 [179].

Synaptogenesis and synaptic plasticity

Concerns have been expressed that AEDs may disrupt synaptogenesis and synapse remodeling due to inhibition of excitatory neurotransmission [180, 181]. Results of published studies are, however, somewhat contradictory. NMDA receptors are involved in the refinement of synaptic circuitry and the pruning of synaptic connections during brain development [182]. Pharmacological inhibition of NMDA receptor activity in 5- or 15-day-old rats for 2 weeks through intracranial application of 2-amino-5-phosphonovaleric acid (APV) or phencyclidine (PCP) has been associated with decreased brain weight, cortex layer depth and total number of synapses [183]. Withdrawal from these NMDA antagonists led to similar results initially, but was later (P36) displaced by a transitory rebound with increased molecular layer depth and total number of synapses.

Chronic exposure of cultured mouse spinal cord neurons to phenobarbital led to reduced cell survival and decreased length and number of dendrite branches [184, 185]. Morphologically immature dendritic development of Purkinje cells was observed in immature mice following administration of 35 mg/kg/d phenytoin from P5 to P14 [186]. Phenytoin application to mouse cerebellar granule cells *in vitro* resulted in cell loss, decreased numbers of neurites, rarefied branching and decreased levels of cytoskeletal protein microtubule-associated protein 2 (MAP2) [187]. Such inhibition of MAP2 expression has been associated with decreased neurite formation *in vitro* [188]. The application of AMPA receptor antagonists to hippocampal slice cultures prepared from 6-day-old rats similarly decreased CA1 pyramidal cell spine density and length; pharmacological NMDA receptor blockage did not reduce the density of spines but induced a change of spine appearance [189]. Intracerebral infusion of the NMDA antagonist APV led to a disruption of experience-dependent synaptic modifications in the cortex of immature kittens [190], and blocking of glutamatergic transmission decreased dendritic filopodial motility *in vitro* [180].

In contrast to these findings, Lüthi et al. demonstrated a substantial increase in synapse number in slice cultures prepared from newborn rats, a more complex dendritic arborization and an increased density of presynaptic buttons of CA1 and CA3 pyramidal cells *in vitro* upon pharmacological blockage of NMDA receptors for 14 days [182]. Similarly, infusion of APV to 14-day-old ferrets led to an increase in the number of branch points and density of dendritic spines of lateral geniculate nucleus compared with control animals [191].

Neuronal migration and axon arborization.

The relationship between neurotransmitter receptor activity and neuronal morphology has been studied in cultured dentate granule neurons from embryonic rat hippocampus. Here, NMDA receptor antagonist MK801 blocked branching of neuronal processes [192]. Phenytoin (35 mg/kg/d), administered daily from P2 to P4, inhibited migration of granule cells in murine cerebella; purkinje cells in brains studied at P7–P21 had poor and immature arbors in the treated group [169]. A temporary block of NMDA and non-NMDA glutamate receptors in immature rats also disrupted the topographic refinement of thalamocortical connectivity and columnar organization, i.e. the topographic organization of synaptic connections [193]. On the other hand, exposure of embryonic E14 rat cortical or striatal primordial stem cells to 6 days of valproate increased neurite outgrowth [194], and topiramate increased neurite outgrowth in immature rodent E18 hippocampal and cortical neurons *in vitro* [195].

Myelination

Based on animal studies concerns were raised that prolonged vigabatrin administration may induce intramyelinic edema (IME) [196, 197]: treatment of rodents with 30 mg/kg/d vigabatrin was associated with IME changes 1 year following the initiation of treatment, whereas a dose of 100–300 mg/kg/d triggered IME already within 6 months [196]. However, a progression of IME lesions to demyelination has not been reported, and microvacuolation has been described as reversible after cessation of treatment [196]. Monkeys treated with high doses of vigabatrin (300 mg/kg/d) for up to 16 months demonstrated only occasional mild microvacuolation; monkeys treated with 50–100 mg/kg/d for 6 years showed no pathology [196]. Moreover, the phenomenon of IME has not been documented in humans. Other groups have reported a reduction in myelination in immature rat brains at P20 and P40 following subcutaneous vigabatrin injections of 40 mg/kg/d from P12 to P16 and 25 mg/kg/d from P12 to P26, respectively [197, 198]. Similarly, long-lasting myelin abnormalities have been reported following administration of phenobarbital to immature mice [199]. Phenobarbital, phenytoin and valproate administration to dams resulted in a decrease of brain myelin in their offspring [200].

Relevance for the clinic

The information presented raises concerns with regard to current clinical practice employing AEDs for seizure control in pregnant women, infants and children. They call for the design of novel AEDs, adjunctive neuroprotective therapies and generation of new clinical data by means of well-designed clinical trials to guide clinical practice. Measures that promote neurotrophin signaling in the brain may offer a novel adjunctive neuroprotective approach. The finding that β-estradiol ameliorated pheno-

barbital neurotoxicity is encouraging in that respect [175]. Preterm infants, which are prematurely deprived maternal β-estradiol and are frequently treated with AEDs (especially phenobarbital), are expected to be at high risk for AED neurotoxicity. β-Estradiol replacement therapy in premature infants has been introduced in some centers with the goal to improve bone mineralization [201]. We thus speculate that maintaining *in utero* β-estradiol plasma levels may be an effective measure to protect premature infants from AED neurotoxicity.

Our studies demonstrated that topiramate is an antiepileptic drug with a favorable therapeutic index in terms of the separation between anticonvulsant activity and neurotoxic/proapoptotic effects in the developing rat brain [166]. Even more encouraging was the finding that levetiracetam does not demonstarate a proapoptotic effect [167]. These findings suggest that it may possible to design age-specific antiepileptic therapies and avoid or minimize neurotoxic side effects in the vulnerable age groups. Whether such data apply to humans remains an open question which will need to be addressed by means of carefully designed clinical studies and use of appropriate brain-imaging techniques.

1 Hauser W. A. (1994) The prevalence and incidence of convulsive disorders in children. Epilepsia **35:** Suppl. **2:** S1–S6
2 Rogawski M. A. and Löscher W. (2004) The neurobiology of antiepileptic drugs for the treatment of nonepileptic conditions. Nat. Med. **10:** 685–692
3 Brodie M. J. and Dichter M. A. (1996) New antiepileptic drugs. N. Engl. J. Med. **334:** 168–175
4 Sankar R. (2004) Initial treatment of epilepsy with antiepileptic drugs. Neurology **63:** S30–S39
5 Rogawski M. A. and Löscher W. (2004) The neurobiology of antiepileptic drugs. Nat. Rev. Neurosci. **5:** 553–564
6 Olney J. W., Jevtovic-Todorovic V. and Ikonomidou C. (2004) Do pediatric drugs cause developing neurons to commit suicide? Trends Pharmacol. Sci. **25:** 135–139
7 Tatulian L., Delmas P., Abogadie F. C. and Brown D. A. (2001) Activation of expressed KCNQ potassium currents and native neuronal M-type potassium currents by the anti-convulsant drug retigabine. J. Neurosci. **21:** 5535–5545
8 Leach M. J., Marden C. M. and Miller A. A. (1986) Pharmacological studies on lamotrigine, a novel potential antiepileptic drug: II. Neurochemical studies on the mechanism of action. Epilepsia **27:** 490–497
9 Prakriya M. and Mennerick S. (2000) Selective depression of low-release probability excitatory synapses by sodium channel blockers. Neuron **26:** 671–682
10 Brown J. P. and Gee N. S. (1998) Cloning and deletion mutagenesis of the alpha2 delta calcium channel subunit from porcine cerebral cortex. Expression of a soluble form of the protein that retains [3H]gabapentin binding activity. J. Biol. Chem. **273:** 25458–25465
11 Marais E., Klugbauer N. and Hofmann, F. (2001) Calcium channel $\alpha_2\delta$ subunits – structure and gabapentin binding. Mol. Pharmacol. **59:** 1243–1248
12 Bryans J. S., Davies N., Gee N. S., Dissanayake V. U. K., Ratcliffe G. S., Horwell D. C. et al. (1998) Identification of novel ligands for the gabapentin binding site on the $\alpha_2\delta$ subunit of a calcium channel and their evaluation as anticonvulsant agents. J. Med. Chem. **4:** 1838–1845
13 Ffrench-Mullen J. M. H., Barker J. L. and Rogawski, M. A. (1993) Calcium current block by (–)-pentobarbital, phenobarbital and CHEB but not (+)-pentobarbital in acutely isolated CA1 neurons: comparison with effects on GABA-activated Cl^- current. J. Neurosci. **13:** 3211–3221
14 Stefani A., Spadoni F., Siniscalchi A. and Bernardi G. (1996) Lamotrigine inhibits Ca^{2+} currents in cortical neurons: functional implications. Eur. J. Pharmacol. **307:** 113–116
15 Wang S.-J., Huang C.-C., Hsu K.-S., Tsai J.-J. and Gean P.-W. (1996) Inhibition of N-type calcium currents by lamotrigine in rat amygdalar neurones. Neuroreport **7:** 3037–3040
16 Zona C., Niespodziany I., Marchetti C., Klitgaard H., Bernardi G. and Margineanu D. G. (2001) Levetiracetam does not modulate neuronal voltage-gated Na^+ and T-type Ca^{2+} currents. Seizure **10:** 279–286
17 Niespodziany I., Klitgaard H. and Margineanu D. G. (2001) Levetiracetam inhibits the high-voltage-activated Ca^{2+} current in pyramidal neurones of rat hippocampal slices. Neurosci. Lett. **306:** 5–8
18 Lukyanetz E. A., Shkryl V. M. and Kostyuk P. G. (2002) Selective blockade of N-type calcium channels by levetiracetam. Epilepsia **43:** 9–18
19 Martin D. J., McClelland D., Herd M. B., Sutton K. G., Hall M. D., Lee K. et al. (2002) Gabapentin-mediated inhibition of voltage-activated Ca^{2+} channel currents in cultured sensory neurones is dependent on culture conditions and channel subunit expression. Neuropharmacology **42:** 353–366
20 Sutton K. G., Martin D. J., Pinnock R. D., Lee K. and Scott R. H. (2002) Gabapentin inhibits high-threshold calcium channel currents in cultured rat dorsal root ganglion neurones. Brit. J. Pharmacol. **135:** 257–265
21 Sarantopoulos C., McCallum B., Kwok W. M. and Hogan Q. (2002) Gabapentin decreases membrane calcium currents in injured as well as in control mammalian primary afferent neurons. Reg. Anesth. Pain. Med. **27:** 47–57
22 Dooley D. J., Mieske C. A. and Borosky S. A. (2000) Inhibition of K^+-evoked glutamate release from rat neocortical and hippocampal slices by gabapentin. Neurosci. Lett. **280:** 107–110
23 Shimoyama M., Shimoyama N. and Hori Y. (2000) Gabapentin affects glutamatergic excitatory neurotransmission in the rat dorsal horn. Pain **85:** 405–414
24 Perez-Reyes E. (2003) Molecular physiology of low-voltage-activated T-type calcium channels. Physiol. Rev. **83:** 117–161
25 Huguenard J. R. (1996) Low-threshold calcium currents in central nervous system neurons. Annu. Rev. Physiol. **58:** 329–358
26 Suzuki S. and Rogawski M. A. (1989) T-type calcium channels mediate the transition between tonic and phasic firing in thalamic neurons. Proc. Natl Acad. Sci. USA **86:** 7228–7232
27 Coulter D. A., Huguenard J. R. and Prince D. A. (1989) Characterization of ethosuximide reduction of low-threshold calcium current in thalamic relay neurons. Ann. Neurol. **25:** 582–593
28 Sankar R. and Holmes GL. (2004) Mechanisms of action for the commonly used antiepileptic drugs: relevance to antiepileptic drug-associated neurobehavioral adverse effects. J. Child Neurol. **19:** Suppl. **1:** S6–14
29 Miles R. and Wong R. K. (1987) Inhibitory control of local excitatory circuits in the guinea-pig hippocampus. J. Physiol. (Lond.) **388:** 611–629
30 Wallace R. H., Marini C., Petrou S., Harkin L. A., Bowser D. N., Panchal, R. G. et al. (2001) Mutant $GABA_A$ receptor γ2-subunit in childhood absence epilepsy and febrile seizures. Nat. Genet. **28:** 49–52
31 Baulac S., Huberfeld G., Gourfinkel-An I., Mitropoulou G., Beranger A., Prud'homme J. F. et al. (2001) First genetic evidence of $GABA_A$ receptor dysfunction in epilepsy: a mutation in the γ2-subunit gene. Nat. Genet. **28:** 46–48
32 Kananura C., Haug K., Sander T., Runge U., Gu W., Hallmann K. et al. (2002) A splice-site mutation in GABRG2 associated

with childhood absence epilepsy and febrile convulsions. Arch. Neurol. **59:** 1137–1141
33 Harkin L. A., Bowser D. N., Dibbens L. M., Singh R., Phillips F., Wallace R. H. et al. (2002) Truncation of the $GABA_A$-receptor $\gamma 2$ subunit in a family with generalized epilepsy with febrile seizures plus. Am. J. Hum. Genet. **70:** 530–536
34 Cossette P., Liu L., Brisebois K., Dong H., Lortie A., Vanasse M. et al. (2001) Mutation of GABRA1 in an autosomal dominant form of juvenile myoclonic epilepsy. Nat. Genet. **31:** 184–189
35 Rudolph U., Crestani F., Benke D., Brunig I., Benson J. A., Fritschy J. M. et al. (1999) Benzodiazepine actions mediated by specific γ-aminobutyric $acid_A$ receptor subtypes. Nature **401:** 796–800
36 Crestani F., Martin J. R., Möhler H. and Rudolph U. (2000) Mechanism of action of the hypnotic zolpidem *in vivo*. Br. J. Pharmacol. **131:** 1251–1256
37 Bai D., Zhu G., Pennefather P., Jackson M. F., MacDonald J. F. and Orser B. A. (2001) Distinct functional and pharmacological properties of tonic and quantal inhibitory postsynaptic currents mediated by γ-aminobutyric $acid_A$ receptors in hippocampal neurons. Mol. Pharmacol. **59:** 814–824
38 MacDonald R. L. and Olsen R. W. (1994) $GABA_A$ receptor channels. Annu. Rev. Neurosci. **17:** 569–602
39 Rho J. M., Donevan S. D. and Rogawski M. A. (1997) Barbiturate-like actions of the propanediol dicarbamates felbamate and meprobamate. J. Pharmacol. Exp. Ther. **280:** 1383–1391
40 White H. S., Brown S. D., Woodhead J. H., Skeen G. A. and Wolf H. H. (1997) Topiramate enhances GABA-mediated chloride flux and GABA-evoked chloride currents in murine brain neurons and increases seizure threshold. Epilepsy Res. **28:** 167–179
41 Gordey M., DeLorey T. M. and Olsen R. W. (2000) Differential sensitivity of recombinant $GABA_A$ receptors expressed in Xenopus oocytes to modulation by topiramate. Epilepsia **41:** S25–S29
42 De Biase D., Barra D., Bossa F., Pucci P. and John R. A. (1991) Chemistry of the inactivation of 4-aminobutyrate aminotransferase by the antiepileptic drug vigabatrin. J. Biol. Chem. **266:** 20056–20061
43 Löscher W. and Horstermann D. (1994) Differential effects of vigabatrin, γ-acetylenic GABA, aminooxyacetic acid and valproate on levels of various amino acids in rat brain regions and plasma. Naunyn Schmiedeberg's Arch. Pharmacol. **349:** 270–278
44 Jackson M. F., Esplin B. and Čapek, R. (2000) Reversal of the activity-dependent suppression of GABA-mediated inhibition in hippocampal slices from γ-vinyl GABA (vigabatrin)-pretreated rats. Neuropharmacology **39:** 65–74
45 Kang J. and Macdonald R. L. (2004) The GABAA receptor gamma2 subunit R43Q mutation linked to childhood absence epilepsy and febrile seizures causes retention of alpha1beta2-gamma2S receptors in the endoplasmic reticulum. J. Neurosci. **24:** 8672–8677
46 Naylor D. E., Liu H. and Wasterlain C. G. (2005) Trafficking of GABAA receptors, loss of inhibition and a mechanism for pharmacoresistance in status epilepticus. J. Neurosci. **25:** 7724–7733
47 Suzdak P. D. and Jansen J. A. (1995) A review of the preclinical pharmacology of tiagabine: a potent and selective anticonvulsant GABA uptake inhibitor. Epilepsia **36:** 612–626
48 Thompson S. M. and Gahwiler B. H. (1992) Effects of the GABA uptake inhibitor tiagabine on inhibitory synaptic potentials in rat hippocampal slice cultures. J. Neurophysiol. **67:** 1698–1701
49 Engel D., Schmitz D., Gloveli T., Frahm C., Heinemann U. and Draguhn A. (1998) Laminar difference in GABA uptake and GAT-1 expression in rat CA1. J. Physiol. (Lond.) **512:** 643–649
50 Jackson M. F., Esplin B. and Čapek, R. (1999) Activity-dependent enhancement of hyperpolarizing and depolarizing γ-aminobutyric acid (GABA) synaptic responses following inhibition of GABA uptake by tiagabine. Epilepsy Res. **37:** 25–36
51 Dingledine R., Borges K., Bowie D. and Traynelis S. F. (1999) The glutamate receptor ion channels. Pharmacol. Rev. **51:** 7–61
52 Rogawski M. A., Gryder D., Castaneda D., Yonekawa W., Banks M. K. and Lia H. (2003) GluR5 kainate receptors, seizures and the amygdala. Ann. N. Y. Acad. Sci. **985:** 150–162
53 Subramaniam S., Rho J. M., Penix L., Donevan S. D., Fiedling R. P. and Rogawski M. A. (1995) Felbamate block of the N-methyl-D-aspartate receptor. J. Pharmacol. Exp. Ther. **273:** 878–886
54 Kuo C. C., Lin B. J., Chang H. R. and Hsieh C. P. (2004) Use-dependent inhibition of the N-methyl-D-aspartate currents by felbamate: a gating modifier with selective binding to the desensitized channels. Mol. Pharmacol. **65:** 370–380
55 Kleckner N. W., Glazewski J. C., Chen C. C. and Moscrip T. D. (1999) Subtype-selective antagonism at N-methyl-D-aspartate receptors by felbamate: insights into the mechanism of action. J. Pharmacol. Exp. Ther. **289:** 886–894
56 Harty T. P. and Rogawski M. A. (2000) Felbamate block of recombinant N-methyl-D-aspartate receptors: selectivity for the NR2B subunit. Epilepsy Res. **39:** 47–55
57 Meldrum B. S. (1996) Excitatory amino acid receptors and their role in epilepsy and cerebral ischemia. Ann. N. Y. Acad. Sci. **757:** 492–505
58 Lerma J., Paternain A. V., Rodriguez-Moreno A. and López-Garcia J. C. (2001) Molecular physiology of kainate receptors. Physiol. Rev. **81:** 971–998
59 Gryder D. S. and Rogawski M. A. (2003) Selective antagonism of GluR5 kainate-receptor-mediated synaptic currents by topiramate in rat basolateral amygdala neurons. J. Neurosci. **23:** 7069–7074
60 Kamiski R. M., Banerjee M. and Rogawski M. A. (2004) Topiramate selectively protects against seizures induced by ATPA, a GluR5 kainate receptor agonist. Neuropharmacology **46:** 1097–1104
61 Rodier P. M. (1980) Chronology of neuron development: animal studies and their clinical implications. Dev. Med. Child Neurol. **22:** 525–545
62 Rodier P. M. (1994) Vulnerable periods and processes during central nervous system development. Environ. Health Perspect. **102** (Suppl. 2): 121–124
63 Dobbing J. and Sands J. (1993) The quantitative growth and development of the human brain. Arch. Dis. Child. **48:** 757–767
64 Dobbing J. (1974) The later development of the brain and its vulnerability. In: Scientific Foundations of Pediatrics, pp. 565–577, Davis J. A. and Dobbing J. (eds.), Saunders, Philadelphia
65 Smart J. L. (1991) Critical periods in brain development. In: The Childhood Environment and Adult Disease (Ciba Found. Symp. 156), pp. 109–128, Wiley, Winchester, PA
66 Bayer S. A., Altman J., Russo R. J. and Zhang X. (1993) Timetables of neurogenesis in the human brain based on experimentally determined patterns in the rat. Neurotoxicology **14:** 83–144
67 Passingham R. E. (1985) Rates of brain development in mammals including man. Brain Behav. Evol. **26:** 167–175
68 Rodier P. M. (1995) Developing brain as a target of toxicity. Environ. Health Perspect. **103** (Suppl. 6): 73–76
69 Emerit M. B., Riad M. and Hamon M. (1992) Trophic effects of neurotransmitters during brain maturation. Biol. Neonate **62:** 193–201
70 Retz W., Kornhuber J. and Riederer P. (1996) Neurotransmission and the ontogeny of human brain. J. Neural Transm. **103:** 403–419

71 Levitt P., Harvey J. A., Friedman E., Simansky B. and Murphy E. H. (1997) New evidence for neurotransmitter influences on brain development. Trends Neurosci. **20:** 269–274
72 Nguyen L., Rigo J. M., Rocher V., Belachew S., Malgrange B., Rogister B. et al. (2001) Neurotransmitters as early signals for central nervous system development. Cell Tissue Res. **305:** 187–202
73 Johnson E. M. and Deckwerth T. L. (1993) Molecular mechanisms of developmental neuronal death. Annu. Rev. Neurosci. **16:** 31–46
74 Henderson C. E. (1996) Programmed cell death in the developing nervous system. Neuron **17:** 579–585
75 Ikonomidou C., Bittigau P., Koch C., Genz K., Hoester F., Felderhoff-Mueser U. et al. (2001) Neurotransmitters and apoptosis in the developing brain. Biochem. Pharmacol. **62:** 401–405
76 Ikonomidou C., Bosch F., Miksa M., Bittigau P., Vöckler J., Dikranian K. et al. (1999) Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain. Science **283:** 70–74
77 Ikonomidou C., Bittigau P., Ishimaru M. J., Koch C., Genz K., Price M. T. et al. (2000) Ethanol-induced apoptotic neurodegeneration and fetal alcohol syndrome. Science **287:** 1056–1060
78 Webb S. J., Monk C. S. and Nelson C. A. (2001) Mechanisms of postnatal neurobiological development: implications for human development. Dev. Neurophychol. **19:** 147–171
79 Speidel B. D. and Meadow S. R. (1972) Maternal epilepsy and abnormalities of the fetus and newborn. Lancet **308:** 839–843
80 Strickler S. M., Dansky L. V., Miller M. A., Seni M. H., Andermann E. and Spielberg S. P. (1985) Genetic predisposition to phenytoin-induced birth defects. Lancet **2:** 746–749
81 Jones K. L., Lacro R. V., Johnson K. A. and Adams J. (1989) Pattern of malformations in the children of women treated with carbamazepine during pregnancy. N. Engl. J. Med. **320:** 1661–1666
82 Buehler B. A., Delimont D., van Waes M. and Finnell R. H. (1990) Prenatal prediction of risk of the fetal hydantoin syndrome. N. Engl. J. Med. **322:** 1567–1572
83 Holmes L. B., Harvey E. A., Coull B. A., Huntington K. B., Khoshbin S., Hayes A. M. et al. (2001) The teratogenicity of anticonvulsant drugs. N. Engl. J. Med. **344:** 1132–1138
84 Zahn C. A. (1998) Neurologic care of pregnant women with epilepsy. Epilepsia **39** (Suppl. 8): S26–S31
85 Zigler E., Balla D. and Hodapp R. M. (1984) On the definition and classification of mental retardation. Am. J. Ment. Defic. **89:** 215–230
86 Willerman L. and Fedler M. F. (1977) Intellectually precocious preschool children: early development and later intellectual accomplishments. J. Genet. Psychol. **131:** 13–20
87 Van der Pol M. C., Hadders-Algra M., Huisies H. J. and Touwen B. C. (1991) Antiepileptic medication in pregnancy: late effects on the children's central nervous system development. Am. J. Obstet. Gynecol. **164:** 121–128
88 Reinisch J. M., Sanders S. A., Mortensen E. L. and Rubin D. B. (1995) In utero exposure to phenobarbital and intelligence deficits in adult men. JAMA **274:** 1518–1525
89 Winter R. M., Donnai D., Burn J. and Tucker S. M. (1997) Fetal valproate syndrome: is there a recognizable phenotype? J. Med. Genet. **24:** 692–695
90 Wyszynski D. F., Nambisan M., Surve T., Alsdorf R. M., Smith C. R., Holmes L. B. (2005) Antiepileptic drug pregnancy registry. Increased rate of major malformations in offspring exposed to valproate during pregnancy. Neurology **64:** 961–965
91 Lindhout D. and Schmidt D. (1986) In utero exposure to valproate and neural tube defects. Lancet **1:** 1392–1393
92 Rosa F. W. (1991) Spina bifida in infants of women treated with carbamazepine during pregnancy. N. Engl. J. Med. **324:** 674–677
93 Matalon S., Schechtman S., Goldzweig G. and Ornoy A. (2002) The teratogenic effect of carbamazepine: a meta-analysis of 1255 exposures. Reprod. Toxicol. **16:** 9–10
94 Hanson J. W. (1976) Fetal hydanthoin syndrome. Teratology **13:** 185–188
95 Hansen D. K. (1991) The embryotoxicity of phenytoin: a review of possible mechanisms. Proc. Soc. Exp. Biol. Med. **197:** 361–368
96 Finnell R. H. and Chernoff G. F. (1984) Variable patterns of malformation in the mouse fetal hydanthoin syndrome. Am. J. Med. Genet. **19:** 463–471
97 Adams J., Vorhees C. V. and Middaugh L. D. (1990) Developmental neurotoxicity of anticonvulsants: human and animal evidence on phenytoin. Neurotoxicol. Teratol. **12:** 203–214
98 Van Overloop D., Schnell R. R., Harvey E. A. and Holmes L. B. (1992) The effects of prenatal exposure to phenytoin and other anticonvulsants on intellectual function at 4 to 8 years of age. Neurotoxicol. Teratol. **14:** 329–335
99 Dessens A. B., Cohen-Kettenis P. T., Mellanbergh G. F., Koppe J. G., van de Poll N. E. et al. (2000) Association of prenatal phenobarbital and phenytoin exposure with small head size at birth and with learning problems. Acta Paediatr. **89:** 533–541
100 Rovet J., Cole S. and Nulman I. (1995) Effects of maternal epilepsy on children's neurodevelopment. Child Neuropsychol. **1:** 150–157
101 Adab N., Jacoby A., Smith D. and Chadwick D. (2001) Additional educational needs in children born to mothers with epilepsy. J Neurol. Neurosurg. Psychiatry **70:** 15–21
102 Mawer G., Clayton-Smith J., Coyle H. and Kini U. (2002) Outcome of pregnancy in women attending an outpatient epilepsy clinic: adverse features associated with higher doses of sodium valproate. Seizure **1:** 512–518
103 Gaily E., Kantola-Sorsa E. and Granstrom M. L. (1988) Intelligence of children of epileptic mothers. J. Pediatr. **113:** 677–684
104 Gaily E., Kantola-Sorsa E. and Granstrom M. L. Specific cognitive dysfunction in children with epileptic mothers. Dev. Med. Child Neurol. **32:** 403–414
105 Hanson J. W., Myrianthopoulos N. C., Harvey M. A. and Smith D. W. (1976) Risks to the offspring of women treated with hydantoin anticonvulsants, with emphasis on the fetal hydantoin syndrome. J. Pediatr. **89:** 662–668
106 Koch S., Titze K. and Zimmermann R. B. (1999) Long-term neuropsychological consequences of maternal epilepsy and anticonvulsant treatment during pregnancy for school-age children and adolescents. Epilepsia **40:** 1237–1243
107 Scolnick D., Nulman I. and Rovet J. (1994) Neurodevelopment of children exposed in utero to phenytoin and carbamazepine monotherapy. JAMA **271:** 767–770
108 Leavitt M. D., Yerby M. S., Robinson N., Sells C. J. and Erickson D. M. (1982) Epilepsy in pregnancy: developmental outcome of offspring at 12 months. Neurology **42:** 141–143
109 Losche G., Steinhausen H. C., Koch S. and Helge H. (1994) The psychological development of children of epileptic parent. The differential impact of intrauterine exposure to anticonvulsant drugs and further influential factors. Acta Paediatr. **83:** 961–966
110 Adab N., Kini U., Vinten J., Ayres J., Baker G., Clayton-Smith J. et al. (2004) The long term outcome of children born to mothers with epilepsy. J. Neurol. Neurosurg. Psychiatry **75:** 1575–1583
111 Ornoy A. and Cohen E. (1996) Outcome of children born to epileptic mothers treated with carbamazepine during pregnancy. Arch. Dis. Child. **75:** 517–520
112 Moore S. J., Turnpenny P., Quinn A., Glover S., Lloyd A. J., Montgomery T. et al. (2000) A clinical study of 57 children with fetal anticonvulsant syndromes. J. Med. Genet. **37:** 489–497
113 Kozma C. (2001) Valproic acid embryopathy: report of two siblings with further expansion of the phenotypic abnormalities and a review of the literature. Am. J. Med. Genet. **98:** 168–175

114 Vinten J., Adab N., Kini U., Gorry J., Gregg J. and Baker G. A., for the Liverpool and Manchester Neurodevelopment Study Group* (2005) Neuropsychological effects of exposure to anticonvulsant medication in utero. Neurology **64:** 949–954

115 Farwell J. R., Lee Y. J., Hirtz D. G., Sulzbacher S. I., Ellenberg J. H. and Nelson K. B. (1990) Phenobarbital for febrile seizures – effects on intelligence and on seizure recurrence. N. Engl. J. Med**. 322:** 364–369

116 Sulzbacher S., Farwell J. R., Temkin N., Lu A. S. and Hirtz D. G. (1999) Late cognitive effects of early treatment with phenobarbital. Clin. Pediatr. Phila. **38:** 387–394

117 Thorp J. A., O'Connor M., Jones A. M., Hoffman, E. L. and Belden B. (1999) Does perinatal phenobarbital exposure affect developmental outcome at age 2? Am. J. Perinatol. **16:** 51–60

118 Fishman R. H. and Yanai J. (1983) Long-lasting effects of early barbiturates on central nervous system and behavior. Neurosci. Biobehav. Rev. **7:** 19–28

119 Diaz J., Schain R. J. and Bailey B. G. (1977) Phenobarbital-induced brain growth retardation in artificially reared rat pups. Biol. Neonate **32:** 77–82

120 Yanai J., Rosselli-Austin L. and Tabakoff B. (1979) Neuronal deficits in mice following prenatal exposure to phenobarbital. Exp. Neurol. **64:** 237–244

121 Schain R. J. and Watanabe K. (1975) Effect of chronic phenobarbital administration upon brain growth in the infant rat. Exp. Neurol. **49:** 509–515

122 Fishman R. H. B., Ornoy A., Yanai J. (1983) Ultrastructural evidence of long-lasting cerebellar degeneration after early exposure to phenobarbital in mice. Exp. Neurol. **79:** 212–222

123 Bergman A., Feigenbaum J. J. and Yanai J. (1982) Neuronal losses in mice following both prenatal and neonatal exposure to phenobarbital. Acta Anat. **114:** 185–192

124 Roger-Fuchs Y., Newman M. E., Trombka D., Zabalke E. and Yanai J. (1992) Hippocampal cholinergic alterations and related behavioral deficits after early exposure to phenobarbital. Brain Res. Bull. **29:** 1–6

125 Diaz J. and Schain R. J. (1978) Phenobarbital: effects of long-term administration on behavior and brain of artificially reared rats. Science **199:** 90–91

126 Yanai J., Fares F., Gavish M., Greenfeld Z., Katz Y., Marcovici G. et al. (1989) Neural and behavioral alterations after early exposure to phenobarbital. Neurotoxicology **10:** 543–554

127 Pick C. G. and Yanai J. (1985) Long-term reduction in eight arm maze performance after early exposure to phenobarbital. Int. J. Dev. Neurosci. **3:** 223–227

128 Mikati M. A., Holmes G. L., Chronopoulos A., Hyde P., Thurber S., Gatt A. et al. (1994) Phenobarbital modifies seizure-related brain injury in the developing brain. Ann Neurol. **36:** 425–433

129 File S. E. and Wilks L. J. (1990) Changes in seizure threshold and aggression during chronic treatment with three anticonvulsants and on drug withdrawal. Psychopharmacology (Berl.) **100:** 237–242

130 Picker M., Thomas J., Koch C. and Poling A (1985) Effects of phenytoin, phenobarbital, and valproic acid, alone and in selected combinations, on schedule-controlled behavior of rats. Pharmacol. Biochem. Behav. **22:** 389–393

131 Krafft K., Lyon D. O. and Poling A. (1982) Effects of phenytoin on schedule-controlled performance of rats. Psychopharmacology (Berl.) **78:** 93–95

132 Renfrey G., Schlinger H., Jakubow J. and Poling A. (1989) Effects of phenytoin and phenobarbital on schedule-controlled responding and seizure activity in the amygdala-kindled rat. J. Pharmacol. Exp. Ther. **248:** 967–973

133 Rostock A., Hoffmann W., Siegemund C. and Bartsch R. (1989) effects of carbamazepine, valproate calcium, clonazepam and piracetam on behavioral test methods for evaluation of memory-enhancing drugs. Methods Find. Exp. Clin. Pharmacol. **11:** 547–553

134 Smith D. F. (1983) Lithium and carbamazepine: effects on learned taste aversion and open field behavior in rats. Pharmacol. Biochem. Behav. **18:** 483–488

135 Hatta T., Ohmori H., Murakami T., Takano M., Yamashita K. and Yasuda M. (1999) Neurotoxic effects of phenytoin on postnatal mouse brain development following neonatal administration. Neurotoxicol. Teratol. **21:** 21–28

136 Vorhees C. V. (1987) Fetal hydanthoin syndrome in rats: dose-effect relationships of prenatal phenytoin on postnatal development and behavior. Teratology **35:** 287–303

137 Vorhees C. V. and Minck D. R. (1989) Long-term effects of prenatal phenytoin exposure on offspring behavior in rats. Neurotoxicol. Teratol. **11:** 295–305

138 Schilling M. A., Inman S. L., Morford L. L., Moran M. S., Vorhees C. V. (1999) Prenatal phenytoin exposure and spatial navigation in offspring: effects on reference and working memory and on discrimination learning. Neurotoxicol. Teratol. **21:** 567–578

139 Vorhees C. V., Acuff K. D., Weisenburger W. P. and Minck D. R. (1990) Teratogenicity of carbamazepine in rats. Teratology **41:** 311–317

140 Pereira M. E., Rosat R., Huang C. H., Godoy M. G. and Izquierdo I. (1989) Inhibition by diazepam of the effect of additional training and of extinction on the retention of shuttle avoidance behavior in rats. Behav. Neurosci. **103:** 202–205

141 Holley L. A., Turchi J., Apple C. and Sarter M. (1995) Dissociation between the attentional effects of infusions of a benzodiazepine receptor agonist and an inverse agonist into the basal forebrain. Psychopharmacology (Berl) **120:** 99–108

142 Bittigau P., Sifringer M., Genz K., Reith E., Pospischil D., Govindarajalu S. et al. (2002) Antiepileptic drugs and apoptotic neurodegeneration in the developing brain. Proc. Natl. Acad. Sci. USA **99:** 15089–15094

143 Jevtovic-Todorovic V., Hartman R. E., Izumi Y., Benshoff N. D., Dikranian K., Zorumski C. F. et al. (2003) Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. J. Neurosci. **23:** 876–882

144 Paulson R. B., Sucheston M. E., Hayes T. G. and Paulson G. W. (1985) Teratogenic effects of valproate in the CD-1 mouse fetus. Arch. Neurol. **42:** 980–983

145 Faiella A., Wernig M., Consalez G. G., Hostick U., Hoffman C., Hustert E. et al. (2000) A mouse model for valproate teratogenicity: parental effects, homeotic transformation, and altered HOX expression. Hum. Mol. Genet. **9:** 227–236

146 Finnell R. H., Gelineau-van Waes J., Eudy J. D. and Rosenquist T. H. (2002) Molecular basis of environmentally induced birth defects. Annu. Rev. Pharmacol. Toxicol. **42:** 181–208

147 Phiel C. J., Zhang F., Huang E. Y., Guenther M. G., Lazar M. A. and Klein P. S. (2001) Histone deacetylase is a direct target of valproic acid, a potent anticonvulsant, mood stabilizer and teratogen. J. Biol. Chem. **276:** 26724–26731

148 Gottlicher M., Minucci S., Zhu P., Kramer O. H., Schimpf A., Giavara S. et al. (2001) Valproic acid defines a novel class of HDAC inhibitors inducing differentiation of transformed cells. EMBO J. **29:** 6969–6978

149 Martin M. L. and Regan C. M. (1991) The anticonvulsant valproate teratogen restricts the glial cell cycle at a defined point in the mid G1 phase. Brain Res. **554:** 223–228

150 Vorhees C. V. (1987) Behavioral teratogenicity of valproic acid: selective effects on behavior after prenatal exposure to rats. Psychopharmacology **92:** 173–179

151 Ingram J. L., Peckham S. M., Tisdale B. and Rodier P. M. (2000) Prenatal exposure of rats to valproic acid reproduces the cerebellar anomalies associated with autism. Neurotoxicol. Teratol. **22:** 319–324

152 Bolanos A. R., Sarkisian M., Yang Y., Hori A., Helmers S. L., Mikati M. et al. (1998) Comparison of valproate and phenobarbital treatment after status epilepticus in rats. Neurology **51:** 41–48

153 Cha B. H., Silveira D. C., Liu X., Hu Y. and Holmes G. L. (2002) Effect of topiramate following recurrent and prolonged seizures during early development. Epilepsy Res. **51:** 217–232

154 Koh S and Jensen F. E. (2001) Topiramate blocks perinatal hypoxia-induced seizures in rat pups. Ann. Neurol. **50:** 366–372

155 Buehler B. A., Rao V. and Finnell R. H. (1994) Biochemical and molecular teratology of fetal hydantoin syndrome. Neurol. Clin. **12:** 741–748

156 Jensen F. E., Blume H., Alvarado S., Firkusny I. And Geary C. (1995) NBQX blocks acute and late epileptogenic effects of perinatal hypoxia. Epilepsia **36:** 966–972

157 Cilio M. R., Bolanos A. R., Liu Z., Schmid R., Yang Y., Stafstrom C. E. et al. (2001) Anticonvulsant action and long-term effects of gabapentin in the immature brain. Neuropharmacology **40:** 139–147

158 Schmitt U. and Hiemke C. (2002) Tiagabine, a gamma-aminobutyric acid transporter inhibitor impairs spatial learning of rats in the Morris water-maze. Behav. Brain Res. **133:** 391–394

159 Bryant R. C., Petty F. and Byrne W. L. (1973) Effects of piracetam (SKF 38462) on acquisition, retention and activity in the goldfish. Psychopharmacologia **29:** 121–130

160 Wolthuis O. L. (1981) Behavioural effects of etiracetam in rats. Pharmacol. Biochem. Behav. **15:** 247–255

161 Verloes R., Scotto A. M., Gobert J. and Wülfert E. (1988) Effects of nootropic drugs in a scopolamine-induced amnesia model in mice. Psychopharmacology **95:** 226–230

162 Lamberty Y., Margineanu D. G. and Klitgaard H. (2000) Absence of negative impact of levetiracetam on cognitive function and memory in normal and amygdala-kindled rats. Epilepsy Behav. **1:** 333–342

163 Hori M., Ito T., Oka M., Noda Y., Matsuno Y., Furukawa K. et al. (1987) General pharmacology of the novel antiepileptic compound zonisamide. First communication: Effects on central nervous system. Arzneimittelforschung **37:** 1124–1130

164 Dobbing J., Sands J. and Gratrix C. A. (1979) Cell size and cell number: a reconsideration of organ growth and catch-up potential. Proc. Nutr. Soc. **38:** 99A

165 Ishimaru, M. J., Ikonomidou C. , Tenkova T. I., Der T. C., Dikranian K., Sesma M. A. et al. (1999) Distinguishing excitotoxic from apoptotic neurodegeneration in the developing rat brain. J. Comp. Neurol. **408:** 461–476

166 Glier C., Dzietko M., Bittigau P., Jarosz B., Korobowicz E. and Ikonomidou C. (2004) Therapeutic doses of topiramate are not toxic to the developing brain. Exp. Neurol. **185:** 403–409

167 Manthey D., Asimiadou S., Stefovska V., Kaindl A. M., Fassbender J., Ikonomidou C. et al. (2005) Sulthiame but not levetiracetam exerts neurotoxic effect in the developing rat brain. Exp. Neurol. **193:** 497–503

168 Ohmori H., Yamashita K., Hatta T., Yamasaki S., Kawamura M., Hogashi Y. et al. (1997) Effects of low-dose phenytoin administered to newborn mice on developing cerebellum. Neurotoxicol. Teratol. **19:** 205–211

169 Ohmori H., Ogura H., Yasuda M., Nakamura S., Hatta T., Kawano K. et al. (1999) Developmental neurotoxicity of phenytoin on granule cells and Purkinje cells in mouse cerebellum. J. Neurochem. **72:** 1497–1506

170 Yan G. M., Irwin R. P., Liu S. Z., Weller M., Wood K. A. and Paul S. M. (1995) Diphenylhydanthoin induces apoptotic cell death of culture rat cerebellar granule neurons. J. Pharmacol. Exp. Ther. **274:** 983–990

171 Blank N. K., Nishimura R. N. and Seil F. J. (1982) Phenytoin neurotoxicity in developing mouse cerebellum in tissue culture. J. Neurol. Sci. **55:** 91–97

172 Neale E. A., Sher P. K., Granbard B. I., Habig M., Fitzgerald S. C. and Nelson P. G. (1985) Differential toxicity of chronic exposure to phenytoin, phenobarbital or carbamazepine in cerebral cortical cell cultures. Pediatr. Neurol**. 1:** 143–150

173 Hansen H. H., Briem T., Dzietko M., Sifringer M., Rzeski W., Zdzisinska B. et al. (2004) Mechanisms leading to disseminated apoptosis following NMDA receptor blockade in the developing rat brain. Neurobiol. Dis. **16:** 440–453

174 Hardingham G. E. and Bading H. (2003) The Yin and Yang of NMDA receptor signalling. Trends Neurosci. **26:** 81–89

175 Asimiadou S., Bittigau P., Felderhoff-Mueser U., Manthey D., Sifringer M., Pesditschek S. et al. (2005) Protection with estradiol in developmental models of apoptotic neurodegeneration. Ann. Neurol., in press

176 Pawlikowski M., Stepien H., Mroz-Wasilewska Z. and Pawlikowska A. (1987) Effects of diazepam on cell proliferation in cerebral cortex, anterior pituitary and thymus of developing rats. Life Sci. **40:** 1131–1135

177 Laeng P., Pitts R. L., Lemire A. L., Drabik C. E., Weiner A., Tang H. et al. (2004) The mood stabilizer valproic acid stimulates GABA neurogenesis from rat forebrain stem cells. J. Neurochem. **91:** 238–251

178 Ogura H., Yasuda M., Nakamura S., Yamashita H., Mikoshiba K. and Ohmori H. (2002) Neurotoxic damage of granule cells in the dentate gyrus and the cerebellum and cognitive deficit following neonatal administration of phenytoin in mice. J. Neuropathol. Exp. Neurol. **61:** 956–967

179 Jackson G. D., Williams S. R., Weller R. O., van Bruggen N., Preece N. E., Williams S. C. et al. (1994) Vigabatrin-induced lesions in the rat brain demonstrated by quantitative magnetic resonance imaging. Epilepsy Res. **18:** 57–66

180 Wong W. T. and Wong R. O. (2001) Changing specificity of neurotransmitter regulation of rapid dendritic remodeling during synaptogenesis. Nat. Neurosci. **4:** 351–352

181 Bashir Z. I., Bortolotto Z. A., Davies C. H., Berretta N., Irving A. J., Seal A. J. et al. (1993) Induction of LTP in the hippocampus needs synaptic activation of glutamate metabotropic receptors. Nature **363:** 347–350

182 Luthi A., Schwyzer L., Mateos J. M., Gahwiler B. H. and McKinney R. A. (2001) NMDA receptor activation limits the number of synaptic connections during hippocampal development. Nat. Neurosci. **4:** 1102–1107

183 Brooks W. J., Petit T. L. and LeBoutillier J. C. (1997) Effect of chronic administration of NMDA antagonists on synaptic development. Synapse **26:** 104–113

184 Serrano E. E., Kunis D. M. and Ransom B. R. (1988) Effects of chronic phenobarbital exposure on cultured mouse spinal cord neurons. Ann. Neurol. **24:** 429–438

185 Bergey G. K., Swaiman K. F., Schrier B. K., Fitzgerald S. and Nelson P. G. (1981) Adverse effects of phenobarbital on morphological and biochemical development of fetal mouse spinal cord neurons in culture. Ann. Neurol. **9:** 584–589

186 Ogura H., Yasuda M., Nakamura S., Yamashita H., Mikoshiba K. and Ohmori H. (2002) Neurotoxic damage of granule cells in the dentate gyrus and the cerebellum and cognitive deficit following neonatal administration of phenytoin in mice. J. Neuropathol. Exp. Neurol. **61:** 956–967

187 Kempermann G. and Volk B. (1995) Phenytoin inhibits expression of microtubule-associated protein 2 and influences cell-viability and neurite growth of cultured cerebellar granule cells. Brain Res. **687:** 194–198

188 Caceres A., Mautino J. and Kosik K. S. (1992) Suppression of MAP2 in cultured cerebellar macroneurons inhibits minor neurite formation. Neuron **9:** 607–618

189 McKinney R. A., Capogna M., Dürr R., Gahwiler B. H. and Thompson S. M. (1999) Miniature synaptic events maintain dendritic spines via AMPA receptor activation. Nat. Neurosci. **2:** 44–49

190 Bear M. F., Kleinschmidt A., Gu Q. and Singer W. (1990) Disruption of experience-dependent synaptic modifications in striate cortex by infusion of an NMDA receptor antagonist. J Neurosci. **10:** 909–925
191 Rocha M. and Sur M. (1995) Rapid acquisition of dendritic spines by visual thalamic neurons after blockade of N-methyl-D-aspartate receptors. Proc. Natl. Acad. Sci. USA **92:** 8026–8030
192 Brewer G. J. and Cotman C. W. (1989) NMDA receptor regulation of neuronal morphology in cultured hippocampal neurons. Neurosci. Lett. **99:** 268–273
193 Fox K., Schlaggar B. L., Glazewski S. and O'Leary D. D. (1996) Glutamate receptor blockade at cortical synapses disrupts development of thalamocortical and columnar organization in somatosensory cortex. Proc. Natl. Acad. Sci. USA **93:** 5584–5589
194 Laeng P., Pitts R. L., Lemire A. L., Drabik C. E., Weiner A., Tang H. et al. (2004) The mood stabilizer valproic acid stimulates GABA neurogenesis from rat forebrain stem cells. J. Neurochem. **91:** 238–251
195 Smith-Swintosky V. L., Zhao B., Shank R. P. and Plata-Salaman C. R. (2001) Topiramate promotes neurite outgrowth and recovery of function after nerve injury. Neuroreport **12:** 1031–1034
196 Cohen J. A., Fisher R. S., Brigell M. G., Peyster R. G. and Sze G. (2000) The potential for vigabatrin-induced intramyelinic edema in humans. Epilepsia **41:** 148–157
197 Sidhu R. S., Del Bigio M. R., Tuor U. I. and Seshia S. S. (1997) Low-dose vigabatrin (gamma-vinyl GABA)-induced damage in the immature rat brain. Exp. Neurol. **144:** 400–405
198 Qiao M., Malisza K. L., Del Bigio M. R., Kozlowski P., Seshia S. S. and Tuor U. I. (2000). Effect of long-term vigabatrin administration on the immature rat brain. Epilepsia **41:** 655–665
199 Fishman R. H., Ornoy A. and Yanai J. (1989) Correlated ultrastructural damage between cerebellum cells after early anticonvulsant treatment in mice. Int. J. Dev. Neurosci. **7:** 15–26
200 Patsalos P. N. and Wiggins R. C. (1982) Brain maturation following administration of phenobarbital, phenytoin and sodium valproate to developing rats or to their dams: effects on synthesis of brain myelin and other subcellular membrane proteins. J. Neurochem. **39:** 915–923
201 Trotter A. and Pohlandt. F. (2000) The replacement of oestradiol and progesterone in very premature infants. Ann. Med. **32:** 608–614