Title

Chapter 28 Fetal Alcohol Spectrum Disorder Targeted Effects of Ethanol on Cell Proliferation and Survival

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Publication Date

2013

DOI

10.1016/b978-0-12-397267-5.00139-4

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Keywords: Alcohol; Apoptosis; Death, Fetal alcohol syndrome; Fetal programming; Insulin-like growth factor; Neural stem cell; Platelet-derived growth factor; Proliferation; Somatosensory; Teratology; Transforming growth factor

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CHAPTER

139

Fetal Alcohol Spectrum Disorder

Targeted Effects of Ethanol on Cell Proliferation and Survival

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OUTLINE

139.1 INTRODUCTION

Developmental disorders arise from genetic and environmental causes. Often, either the genetic or environmental factor takes precedence and defines the disorder, for example, Huntington's chorea or mercury poisoning, respectively. In other situations, the effects of the two contributors are not mutually exclusive. In fact, the effect of a genetic or environmental alteration alone may be masked, and a disorder may result only when a genetically susceptible organism is exposed to an environmental factor. One such developmental disorder is fetal alcohol spectrum disorder (FASD).

Besides genetic and environmental contributions, another major factor defining developmental disorders such as FASD is fetal programming. On the basis of this concept, nutrition or exposure to a substance during fetal development can cause alterations over the lifespan. These consequences often can be quiescent for years and then have powerful effects that shape the behavior of adolescent or adult humans; for example, fetal exposure to substances can shape lifelong mental health status (Salisbury et al., 2009; Schlotz and Phillips, 2009). Taken more broadly, fetal programming can be part of a cycle that promotes the continued pathological situation. In the case of alcohol use, this has been referred to as the "alcoholism generator" (Miller and Spear, 2006). Accordingly, fetal exposure increases the likelihood of ethanol use in adolescents and reduces the age of initiation of ethanol consumption. These behaviors contribute to an increased incidence of alcoholism/alcohol abuse in adults, which in turn begets children who are exposed to ethanol in utero.

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139.2 CLINICAL CONSEQUENCES OF ALCOHOL EXPOSURE

p0115 The effects of ethanol on a fetus are extensive, devastating, ~~and~~ often permanent and~~,~~ when clustered, are referred to as FASD. Depending upon the population, 2% or more of all neonates have FASD (Centers for Disease Control and Prevention, 2009). Defects can include a stereotypical set of craniofacial malformations such as narrow palpebral fissures, a deficient philtrum, and a flattened nasal bridge (Jones et al., 1973; Lemoine et al., 1968). Based on rodent studies, these features occur when the exposure is restricted to or includes the period of gastrulation (Sulik, 2005; Sulik et al., 1981).

p0120 Prenatal alcohol exposure has profound effects on the nervous system in humans, including learning/memory deficits and hyperactivity (Coles, 2006; Fryer et al., 2006). In fact, prenatal alcohol exposure is the leading known cause of mental retardation (Abel and Sokol, 1992; Stratton et al., 1996). Careful examination of the brains of children with FASD shows profound changes. Postmortem and imaging studies show that their brains are smaller, can be covered with sheets of neuroglial heterotopias, and exhibit abnormal gyral patterns and dysmorphic corpora callosa (e.g., Bookstein et al., 2002; Clarren et al., 1978; Jellinger et al., 1981; Pfeiffer et al., 1979; Riley et al., 1995; Swayze et al., 1997; Wisniewski et al., 1983). Quantitative magnetic resonance imaging studies show that ethanol induces microencephaly, as evidenced by the reduced size of specific nuclei, for example, the basal ganglia (Mattson et al., 1996) and cerebellum (Sowell et al., 1996).

139.3 ANIMAL MODELS OF ETHANOL INTAKE

p0125 When interpreting the data on fetal ethanol effects, it is important to appreciate the various animal models of FASD because each has strengths and weaknesses, Au3 as discussed in a number of excellent reviews (e.g., Cudd, 2005; Kelly et al., 2009; Schneider et al., 2011). For the purposes of this review, it is important to consider three features of a chosen model when determining its utility and appropriateness: the timing, duration, and amount of ethanol exposure. That is, the method of choice is based on the focus of the study and on determining the variables that require controls.

p0130 The timing and duration of ethanol exposure are critical because neural development is a constantly changing and asynchronous process among the multitude of brain components. Grossly, the brain increases in size steadily during gestation and then transiently exhibits a relative burst during what is described as the brain growth spurt (Dobbing and Sands, 1979). In primates, this spurt occurs during the third trimester of gestation, and in rodents, it occurs during the first 2 postnatal weeks. Much of this growth results from the early morphogenesis of neuronal processes and the production of glia. Another major event that contributes to early brain growth and can shape the response to ethanol neurotoxicity is the timing and duration of neuronal production. Neurons in most components of the rodent brain are generated prenatally, but in some brain regions (e.g., the hippocampus, thalamus, and cerebellum), ~~neuronal~~ populations are produced postnatally (e.g., Altman and Bayer, 1990; Altman and Das, 1965, 1966; Mooney and Miller, 2007a; Rao and Jacobson, 2005). The complexity of the effect of ethanol on select brain structures results from the incidence and different length periods of this neuronogenesis. These periods may be discrete or may Au4 overlap; thus, individual or multiple brain structures may be vulnerable to ethanol at a particular time during gestation.

p0135 The amount of exposure, that is, the dose of ethanol, is also a critical variable (Bonthius and West, 1988a,b, 1990). Dose can be defined by the peak exposure and Au5 the time over which this exposure is maintained. For example, the size of the cerebellum and the density of Purkinje neurons are adversely affected by ethanol when ethanol is administered in a larger bolus over a short period of time than when it is delivered more slowly over a more protracted period, even if the total amount of ethanol exposure is equalized.

p0140 Prenatal administration of ethanol has generally relied on one of three methods: (1) pair-feeding of a liquid diet, (2) intragastric gavage of the dam, and (3) delivery via intraperitoneal injection of the dam. Integral to these models is the use of controls that account for caloric and nutritional intake and for stress. (1) In the pair-feeding approach, animals in the ethanol-exposed group are given an ethanol-containing liquid diet at the same time each day, and the same volume as an isocaloric, non-ethanol-containing diet is given to the pair-fed control animal. The pair-feeding model is the most biologically relevant to the human situation; however, it leads to variability in blood ethanol concentrations over the diurnal cycle (Miller, 1992). Often, changes in pair-fed controls have been compared with animals fed chow and water ad libitum, but this diet differs from the liquid ethanol-containing and control diets. Therefore, it is advisable to provide the controls fed ad libitum free access to the liquid control diets (Eade et al., 2010; Youngentob et al., 2007). (2) In the gavage model, an ethanol-containing liquid is delivered to pregnant dams directly into their stomachs (Kelly and Lawrence, 2008). This can lead to stress, the effects of which can be minimized by frequent and equivalent handling of all the subjects. (3) In the injection model (usually used with

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mice), pregnant dams are administered a diluted solution of ethanol or an equivalent volume of saline. This can produce quick increases in peak ethanol exposure; however, it also has the complication of stress. The latter two models should include careful monitoring of nutritional intake.

p0145 Administration of ethanol in the early postnatal period is a bit more complicated. Using one approach, referred to as the pup-in-a-cup method (Diaz and Samson, 1980; West et al., 1981), each 4-day-old rat pup has a permanent gavage tube implanted directly into its stomach and an ethanol-containing solution of artificial milk or a nonethanol control solution is delivered directly. The liquid is usually provided every 2 h, but this schedule can be manipulated. This method allows for careful delivery and monitoring of the ethanol, but the pups are stressed and do not have maternal interactions. Comparisons to suckling control pups can partially obviate these confounding variables. An alternative method is to provide the ethanol or control solution via intragastric gavage (Kelly and Lawrence, 2008). Following gavage, the pups are returned to their dam. This method minimizes the stress inherent in the pup-in-a-cup method, but it does have some inherent stress that can affect maternal–pup interactions, and it is labor intensive.

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139.4 CELL NUMBERS

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p0150 Research on the effects of ethanol on the rodent brain, specifically the cerebral cortex, is more advanced than similar research on humans (Miller, 2006a). The cerebral cortex has been extensively studied and is profoundly affected by prenatal ethanol exposure. It is smaller and exhibits multiple abnormalities such as neurons that are in the wrong place (i.e., ectopic neurons), dysmorphic and dysfunctional neurons, and alterations in synaptogenesis and myelinogenesis. These developmental problems lead to permanent alterations. For example, (1) the numbers of neurons in cortex and other structures in the mature brain are reduced (e.g., Bonthius et al., 1992; Marcussen et al., 1994; Miller, 1995a,b, 1999; Miller and Muller, 1989; Miller and Potempa, 1990; Mooney and Miller, 2007a), (2) surviving neurons form aberrant connections (e.g., Al-Rabiai and Miller, 1989; Clamp and Lindsley, 1998; Miller, 1987, 1997; Miller and Al-Rabiai, 1994; Miller et al., 1990; West et al., 1981), and (3) cortical metabolism is reduced (e.g., Miller and Dow-Edwards, 1988, 1993; Vingan et al., 1986). These changes are downstream from primary defects in early development, for example, neuronal production and survival. This review focuses on these two processes, which are primary determinants of the numbers of neurons in a specific brain structure.

139.4.1 Cell Proliferation

s0030

p0155 In the rodent, the proliferation of most CNS neurons occurs prenatally and, in some structures (e.g., the cerebellum, thalamus, and hippocampus), it extends into the first couple of weeks postnatally. In most cases, this proliferation takes place within zones that line or are proximal to the ventricles. The principal exceptions to this pattern are the external granule layer of the cerebellum and the subgranular zone (SGZ) of the dentate gyrus, which are seeded by cells lining the fourth and lateral ventricles, respectively (Chizhikov et al., 2006; Rao and Jacobson, 2005). Cell proliferation is defined by the cycling behavior of the cells (i.e., how quickly cells pass through the four phases of the cell cycle) and the numbers of cells that are actively cycling, which is known as the growth fraction.

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139.4.1.1 Cell cycle

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139.4.1.1.1 CEREBRAL CORTEX

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p0160 Ethanol has a profound effect on the cell cycle kinetics and growth fraction for proliferating populations. Ad libitum consumption of ethanol by pregnant rat dams during the last 2 weeks of gestation (achieving peak blood ethanol concentrations of ~150 mg dl^{-1}) affects cell proliferation in the brains of the developing fetuses. The cycling of cells in the cortical ventricular zone (VZ) is retarded (Kennedy and Elliott, 1985; Miller, 1989; Miller and Nowakowski, 1991). On the other hand, ethanol has no effect on the numbers of cells that are actively cycling. Ethanol has a similar effect on VZ cells in organotypic slices of the dorsal telencephalon (Siegenthaler and Miller, 2005a) and cultures of dissociated neuroblastoma cells (Luo and Miller, 1999a) and neural stem cells (Hicks et al., 2010). In each of these cases, ethanol has a consistent effect of prolonging the length of the cell cycle. T, this occurs principally through lengthening of the G1 phase of the cell cycle, though other phases, notably S, are vulnerable.

Au8

p0165 The changes in the cell cycle kinetics appear to result from activation of specific cell cycle checkpoints. Ethanol induces a strong genomic response, which leads to the down- or upregulation of many transcripts associated with passage through G1 (Hicks et al., 2010). Inhibition of the G1/S checkpoint is a consequence of the silencing of genes that is necessary for the progression of cells through G2 and M. Methylation and another epigenetic event, acetylation, are key mechanisms underlying gene silencing and are targets of ethanol (Haycock, 2009; Hicks et al., 2010; Liu et al., 2009; Moonat et al., 2010; Oberlander et al., 2008; Pandey et al., 2008; Zhou et al., 2011). The occurrence of methylation is environmentally affected by the presence of an ambient growth factor (Hicks et al., 2010). Such findings are consistent with

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evidence that ethanol toxicity can be offset by choline supplementation (Thomas et al., 2004, 2010).

p0170 The response of VZ cells to ethanol differs from that of cycling cells in non-VZ proliferative populations, for example, the subventricular zone (SZ). The SZ gives rise to cortical neurons largely in the superficial cortex (Miller, 1989; Nieto et al., 2004; Pontious et al., 2008; Tarabykin et al., 2001) and neurons in the olfactory bulb (Lledo et al., 2008; Whitman and Greer, 2009). Exposure to moderate amounts of ethanol *in vivo* (wherein the blood ethanol concentration is $\sim$150 mg dl^{-1}) increases SZ cell proliferation (Miller and Nowakowski, 1991). This results from an increase in the growth fraction and not from a change in the cell cycle kinetics of SZ cells. The net outcome is that there is a latent surge in the generation of cortical neurons, particularly those that are normally destined for the superficial cortex (Miller, 1986, 1988a, 1997). A similar growth-promoting effect is also evident for neural progenitors in the SGZ of the dentate gyrus; however, this effect is dose-dependent, with high doses of ethanol depressing neural production (Miller, 1995a).

s0045 **139.4.1.1.2 THALAMUS**

p0175 The ventrobasal (VB) nucleus of the thalamus is a special CNS site; it has two nonoverlapping periods of neuronal generation (Altman and Bayer, 1979, 1989; Mooney and Miller, 2007b). The second (postnatal) period of neuronogenesis uniquely occurs within the brain parenchyma per se. This second period is even more intriguing because it occurs concurrent with a number of desynchronous developmental events within the VB. Such events include the elaboration of neurites particularly by the prenatally generated neurons, the formation of synapses, the generation of projections to the cortex, and the innervation of the VB by cortical axons.

p0180 Prenatal exposure to ethanol has a latent effect on the proliferating cells in the VB of young pups (Mooney and Miller, 2010). Specifically, the length of the cell cycle is shorter in ethanol-exposed animals than in controls, and this has a direct, albeit transient, effect on the number of neurons generated daily. This change is consistent with the notion that ethanol exposure initiates a sequence of fetal programming, that is, ethanol causes effects in the fetus that have long-term consequences, which become evident in the more mature animal. The proliferation and survival of the postnatally generated VB neurons are regulated by neurotrophins, for example, nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF; Mooney and Miller, 2011). Prenatal exposure to ethanol affects the expression of NGF, and it only alters postnatal VB neuronogenesis in the presence of the dyadic effector NGF.

s0050 **139.4.1.1.3 BRAINSTEM**

p0185 Early exposure to ethanol also affects the generation of neurons in the brainstem. This includes neurons in the trigeminal brainstem nuclear complex (Miller, 1999; Miller and Muller, 1989), which are derived from cells lining the fourth ventricle. This effect has been refined by restricting the exposure to ethanol to a single episode on a single day. As might be predicted, exposure on a day of neuronogenesis (when neuronal precursors pass through their last mitotic division) is sufficient to reduce the neuronal number in some cranial nerve nuclei (Mooney and Miller, 2007a). It is surprising, however, that these nuclei are equally vulnerable to exposure on a day of gastrulation [e.g., gestational day (G) 7 or G8] and refractile to ethanol toxicity during the 3–4 days between gastrulation and neuronogenesis. These patterns are consistent with the notion that cycling stem cells are vulnerable to ethanol and that these effects are programmed at an early time.

p0190 Most cerebellar neurons are derived from an auxiliary proliferative zone, the external granular layer (EGL; Rao and Jacobson, 2005). The EGL gives rise to the granule neurons that populate the internal granular layer. The generation of cerebellar granule neurons is negatively affected by ethanol (Bauer-Moffett and Altman, 1977; Kornguth et al., 1979). This alteration results from an ethanol-induced lengthening of the cell cycle of their precursors in the external granule layer (Borges and Lewis, 1983) and by the dysregulation of cyclins and cyclin-dependent kinases (Li et al., 2002).

s0055 ### *139.4.1.2 Fetal programming*

p0195 Prenatal exposure to ethanol has many long-term consequences, and at least two of them can be attributed to fetal programming. They relate to the two systems that exhibit postnatal neurogenesis: (1) the SGZ of the dentate gyrus and (2) the anterior SZ and olfactory system. Postnatal neurogenesis is highly responsive to environmental perturbations.

s0060 **139.4.1.2.1 DENTATE GYRUS**

p0200 The dentate gyrus has captured the interest of neuroscientists because of its apparent role in learning and memory, notably spatial navigation. Increased neuronogenesis (the production of new neurons) correlates with improved learning and memory (Deng et al., 2010; Eisch et al., 2008; Leuner and Gould, 2010). For example, rats that exercise on a running wheel have increased neuronal production and improved learning in a spatial learning task in a Morris water maze (van Praag et al., 2005). The numbers of neurons generated and the behavioral improvement are positively correlated to the amount of running. Furthermore, training on hippocampal-dependent associative learning tasks doubles the number of neurons in the rat dentate gyrus (Gould et al., 1999). This contrasts with

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training on hippocampal-independent tasks wherein there is no effect on the number of neurons in the dentate gyrus. Some pathological situations, such as traumatic brain injury (e.g., stroke), can stimulate neuronal production (Dash et al., 2001). This can lead to improved recovery and learning outcome (Chang et al., 2005; Chou et al., 2006; Kleindienst et al., 2005; Lu et al., 2005; Nakatomi et al., 2002; Wang et al., 2004).

p0205 SGZ neuronogenesis is reduced in a number of situations. The antiproliferative agent methylazoxymethanol (MAM) can eliminate the postnatal generation of neural cells in the dentate gyrus. Animals treated with MAM have impaired performance in hippocampal-dependent memory tasks, for example, conditioned fear (Shors et al., 2001). Recovery of neuronogenesis correlates with a return in ability to acquire trace memories. Postnatal neuronogenesis is highly responsive to environmental perturbations. Inflammation and stress can cause a decrease in neuronogenesis and degradation in memory (Ekdahl et al., 2003; Monje et al., 2002, 2003). Different psychiatric states can affect neural stem cell proliferation in the adult dentate gyrus. Postmortem samples from schizophrenic patients reveal depressed proliferation, whereas proliferation in patients with bipolar disorder is unaffected (Reif et al., 2006). Furthermore, SGZ neurogenesis decreases with aging (Jin et al., 2005; Kuhn et al., 1996) as does the ability to learn new tasks and to recall memories. Ablation of proliferating SGZ cells by irradiation compromises spatial discrimination, navigation, and learning (Clelland et al., 2009).

p0210 Ethanol exposure has fascinating effects on neuronal generation in the dentate gyrus in rats of all ages. Exposure of adolescents and adults to high doses of ethanol reduces SGZ neurogenesis (Crews et al., 2006; Nixon and Crews, 2002). This corresponds to ethanol-induced reductions in learning and memory. Moreover, at least in nursing rats, the effects of ethanol are dose-dependent (Miller, 1995a). Whereas exposure to high doses reduces neuronogenesis, low doses can promote neuronal production. Exposure to other substances of abuse (e.g., opiates and cocaine) also depresses neuronal generation and reduces the ability to learn and remember new behaviors (Domínguez-Escribà et al., 2006; Eisch et al., 2000). Note that all of these substances of abuse appear to target the proliferation of new cells rather than their differentiation and survival. Possibly the most intriguing findings are that prenatal exposure to ethanol alters SGZ neurogenesis in adolescents and adults (Domínguez-Escribà et al., 2006; Klintsova et al., 2007; Redila et al., 2006). The implication is that such fetal programming is transmitted via proliferating neural stem cells.

s0065 **139.4.1.2.2 OLFACTORY SYSTEM**

p0215 The olfactory system is affected by ethanol. Exposure to ethanol during the first 2 postnatal weeks leads to a reduction in the numbers of granule and mitral cells in the olfactory bulb (Bonthius et al., 1992). This reduction persists into adulthood despite replacement from cells generated in the anterior SZ. There is no direct evidence that ethanol affects the proliferation of cells in the anterior SZ; however, studies do show that prenatal exposure to ethanol can shape the olfactory behavior of adolescents (Eade et al., 2009, 2010; Youngentob et al., 2007). Not only is there an enhanced neurophysiological response to ethanol odor among rats exposed to ethanol in utero, but such animals are also more likely to follow an ethanol-exposed peer than a water-exposed rat. In addition, ethanol-exposed animals show an increased avidity for bitter-tasting substances including ethanol and quinine (Youngentob and Glendinning, 2009; Youngentob et al., 2007). Together, these findings show that animals exposed to ethanol prenatally are programmed to prefer the odor and taste of ethanol. Human studies also show a link between prenatal exposure to ethanol and later use/abuse of the drug (Molina et al., 2007; Pepino and Mennella, 2007). Indeed, this is the basis for the 'alcoholism generator' (Miller and Spear, 2006).

Au9

139.4.1.3 Cell fate

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p0220 Cell fate is defined by many events; one appears to be cell migration. Prenatal exposure to ethanol disrupts the migration of cortical neurons *in vivo* (Miller, 1986, 1988a, 1993) and *in situ* (Siegenthaler and Miller, 2004). *In vivo* studies show that late-generated neurons that normally reside in layer II/III of the cortex often terminate their migration in layers V and VI after ethanol exposure (Miller, 1986, 1988a, 1997). ~~Even some~~ early-generated neurons destined for layer V ~~may~~ end up in the superficial cortex (Miller, 1986, 1987, 1988a; Miller et al., 1990). Despite these defects, the neurons retain their connectional phenotype. That is, many of the late- and early-generated neurons are callosal or corticospinal projection neurons, respectively, regardless of whether they are distributed in their correct position or in an ectopic location. Interestingly, this disruption is remarkably similar to the pattern that occurs when cortical precursors from a later time in cortical neuronogenesis are transplanted into the proliferative zones of younger fetuses (McConnell, 1988). The implication from this heterochronic transplantation experiment is that cells that are generated late in cortical histogenesis are predominantly neuronal progenitors, and the fates of these cells are largely immutable regardless of their ultimate laminar residence. By extension, it also appears that ethanol does not affect cell fate when the exposure includes the time when cells pass through their final mitotic cycle, that is, their birth date (Miller, 1987, 1997). Note that a study of cultured neural stem cells also shows that ethanol has no effect on the diversity or numbers of progeny (Hicks et al., 2010).

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p0225 Some *in vivo* data support the notion that cell fate can be altered by ethanol exposure. Prenatal exposure to ethanol alters the fates of hematopoietic progenitors in the bone marrow of mouse neonates, and lymphocyte development is delayed (Wang et al., 2006, 2009). Presumably, this contributes to the immunosuppression and vulnerability of children with FASD (Sliwowska et al., 2006; Zhang et al., 2005).

p0230 Numerous studies of cultured precursors concur that ethanol can affect cell fate. For example, the diversity of cells generated by precursors in neurospheres can be reduced by ethanol (Santillano et al., 2005), and the differentiation of cultured neural stem cells is affected by ethanol (Tateno et al., 2005). Accordingly, ethanol induces precursors to become glia (astrocytes and oligodendrocytes) and reduces neuronal differentiation. This occurs in the absence of an effect on cell viability. A study of human brain-derived neural stem and progenitor cells shows that ethanol alters the expression profile of glia- and neuron-committed precursors (Vangipuram and Lyman, 2010). The concept of ethanol-induced cell fate switching is also addressed by the cell and in ovo culture studies by Vernadakis and colleagues. The embryonic chick telencephalic wall contains proliferating pluripotential cells, that is, neural stem cells (Kentroti and Vernadakis, 1992, 1995). Ethanol can cause the selective elimination of cells with a particular lineage (i.e., after lineages are determined Kentroti and Vernadakis, 1996); however, other evidence shows that ethanol causes cells to switch their neurochemical phenotypic lineage (Brodie and Vernadakis, 1992; Kentroti and Vernadakis, 1992).

p0235 Ethanol can affect the differentiation of cycling and recently postmitotic cells via targeted alterations of genetic expression (Hashimoto-Torii et al., 2011; Hicks et al., 2010; Liu et al., 2009; Miller et al., 2006; Zhou et al., 2011). This is exemplified by altered expression of genes associated with cell proliferation (e.g., cyclins and cyclin-dependent kinases), growth factor function (e.g., transforming growth factor (TGF) β1, insulin-like growth factor (IGF) I, epidermal growth factor (EGF) receptor), and extracellular matrix molecules (e.g., integrins, L1, and neural cell adhesion molecule), as well as mRNAs underlying cell determination and morphogenesis such as *Wasf1*, *SatB2*, *Bhlhb5*, *ID2*, *NR4A3*, *FoxP1*, neurogenin, *Sox5*, and *Bhlhe22*. One mechanism by which the profile of expressed transcripts is altered is the ethanol-induced selective hyper- and hypomethylation of CpG islands of genes associated with neural development such as *Bub1*; cyclins A2, B1, and F; securin; IGF-I; and EGF-containing fibulin-like extracellular matrix protein I (Hicks et al., 2010; Liu et al., 2009; Zhou et al., 2011). The changes in methylation are particularly notable for cells treated with TGFβ1.

139.4.1.4 Growth factor regulation of cell proliferation s0075

139.4.1.4.1 INSULIN-LIKE GROWTH FACTOR I s0080

p0240 The behavior of neural stem cells can be affected by pro- and antimitogenic growth factors. IGF-I is a key promitogenic player in brain development (Rubin and Baserga, 1995). Reduction or elimination of IGF-I (e.g., via pharmacological blockade or gene knockout or knockdown) leads to smaller fetuses and microencephaly. One of the contributing effects of IGF-I toward brain growth is its ability to promote cell proliferation as exemplified by a shortened doubling time for cultured neural cells (Resnicoff et al., 1994). IGF-I initiates its action by binding to and activating specific membrane-bound receptors that sequentially lead to the activation of extracellular signal-regulated kinase (ERK) 1/2.

p0245 Microencephaly and reductions in overall body growth caused by prenatal exposure to ethanol correlate with reductions in plasma IGF-I (Breese et al., 1993; de la Monte et al., 2005; Lynch et al., 2001; Mauceri et al., 1993; Singh et al., 1994; Soscia et al., 2006). Some studies also show that IGF-2 is altered (Singh et al., 1994), whereas others show that IGF-2 expression is unchanged (Breese and Sonntag, 1995). A further contributor to the brain and body growth reduction is a ~~reduction~~ in IGF-I transcript and protein in pregnant dams. The acute changes during gestation have long-term consequences (Breese et al., 1993). Despite being normal during the first 3 postnatal weeks, IGF-I concentrations eventually fall in weanling and adolescent rats. The dynamism of ethanol-induced changes has also been examined in the chick (Lynch et al., 2001). IGF-I expression is unaffected before day 6, drops transiently on day 6, and then rises 2 days later. This increase appears to be a response to a reduction in the availability of IGF-binding protein. Supplementation of IGF-I in the rat can partially offset ethanol-induced alterations (McGough et al., 2009) and alleviate the behavioral effects of ethanol such as on motor coordination. On the other hand, IGF-I does not mitigate ethanol-induced hyperactivity and spatial learning deficits.

p0250 Ethanol inhibits the effects of IGF-I to promote cell proliferation (Resnicoff et al., 1994). This is associated with a reduction in receptor phosphorylation and the association of phosphatidylinositol-3 kinase with insulin receptor substrate 1. Thus, central IGF signaling mechanisms are altered by ethanol. Apparently, these changes lead to altered feedback regulation. Impaired insulin and IGF-I signaling leads to a general depression of the transcription of genes for insulin, IGF-I and IGF receptors (de la Monte et al., 2005). The outcome of these changes is the inhibition of glucose transport and the associated production of ATP.

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s0085 **139.4.1.4.2 PLATELET-DERIVED GROWTH FACTOR**

p0255 Like IGF, platelet-derived growth factor (PDGF) is a potent promitogenic factor. PDGF ligands and receptors are expressed by cells in the immature brain (Reddy and Pleasure, 1992; Valenzuela et al., 1997) and cycling neural cells (Luo and Miller, 1997, 1999b). Moreover, PDGF ligands affect the behavior of cycling neural cells (Luo and Miller, 1997, 1999b). This is mediated by an acceleration of the cell cycle, presumably by shortening the G1 phase.

p0260 Of the two high-affinity receptors for PDGF, ethanol targets the α isoform (Luo and Miller, 1999b). It upregulates the expression and inhibits the activation of the PDGFα receptor. PDGF signals through a receptor-activated Ras-Raf-ERK1/2 pathway in proliferating neural cells. Ethanol affects the PDGF-initiated activation of each mediator in the Ras-Raf-ERK1/2 cascade with the ultimate effect being a change in the pattern of ERK1/2 phosphorylation. Interestingly, ethanol causes the upregulation of ERK1/2, which changes the PDGF-promoted phasic stimulation into a tonic activation.

s0090 **139.4.1.4.3 TRANSFORMING GROWTH FACTOR β1**

p0265 Antimitogenic factors are a counterbalancing set of proteins. These are critical for limiting cell proliferation and restraining the expansion of neural precursor populations. A prime example of an antimitogenic factor is TGFβ1. TGFβ1 reduces neural generation, not by slowing the cell cycle but by moving cells out of a proliferative population (Hicks et al., 2010; Siegenthaler and Miller, 2005b). That is, TGFβ1 reduces the growth fraction by promoting cell cycle exit. This is transduced through a p21-mediated mechanism. Furthermore, TGFβ1 facilitates this cell cycle exit and promotes the migration of postmitotic cells away from the proliferative populations (Siegenthaler and Miller, 2004).

p0270 TGFβ1 binds to a heterodimerized receptor with serine/threonine kinase activity (Danielpour and Song, 2006; ten Dijke and Hill, 2004). When activated, the receptor phosphorylates Smad2/3, which translocates to the nucleus and promotes transcription. In cortical proliferative zones, TGFβ1 also activates ERK1/2 either directly or through crosstalk with activated Smad2/3 (Powrozek and Miller, 2009). TGFβ1 activation of ERK1/2 is a sustained response, not unlike that initiated by ethanol (Luo and Miller, 1999a).

p0275 Ethanol inhibits the TGFβ1-mediated inhibition of cell proliferation in various populations of neural precursors: astrocytes and C6 glioma cells (Miller and Luo, 2002a), B104 neuroblastoma cells (Luo and Miller, 1999a), and neuronal progenitors (Miller and Luo, 2002b). The principal mechanism involves ethanol-mediated interference with the TGFβ1-induced reduction in the growth fraction. Concomitantly, it may cause the death of neural cells through a TGFβ1-mediated mechanism (Hicks and Miller, 2011; Kuhn and Sarkar, 2008). Prenatal exposure to ethanol affects the expression of TGFβ receptors in the fetal cerebral wall (Miller, 2003), which has downstream effects on the two signaling pathways triggered by TGFβ1 (Powrozek and Miller, 2009). These two pathways rely on Smad2/3 and ERK1/2. Not only do these pathways interact, but ethanol can affect this interplay. In fact, it appears that ethanol mimics, and presumably acts through, TGFβ1.

139.4.2 Neuronal Death/Survival s0095

p0280 Neuronal death is a normal process of neural development. Neurons can die via a number of processes: apoptosis, necrosis, excitotoxicity, and autophagy. Apoptosis is the most common mode during development; it is characterized by morphological and biochemical changes (Danial and Korsmeyer, 2004; Kerr, 2002; Kerr et al., 1972; Mooney and Henderson, 2006; Wyllie, 1997). Morphological changes include chromatin condensation, membrane blebbing, endonucleolytic DNA cleavage, and formation of apoptotic bodies. Biochemical changes include activation of caspase 3, fragmentation of the nuclear DNA, and the consequent generation of polyadenylated strands of DNA.

p0285 Neuronal death is time dependent, and it can affect proliferating and postproliferative cells. Though the proliferative behavior of both stem and progenitor cells can be affected by ethanol (Miller, 2006b; Zawada and Das, 2006), there is an apparent difference in the susceptibility of these two types of precursors to ethanol-induced death. Stem cells (which are commonly in the VZ) may be vulnerable to ethanol; however, neural progenitors (e.g., those in the SZ) appear to be impervious to ethanol-induced death (Camarillo and Miranda, 2008; Hicks and Miller, 2011; Prock and Miranda, 2007; Santillano et al., 2005). Interestingly, these data run counter to studies showing that ethanol has no apparent effect on the survival of stem cells (Tateno et al., 2005). Such findings are in accord with the evidence that hypoxic ischemia has little effect on stem cells but compromises the viability of progenitors (Romanko et al., 2004).

p0290 The survival of postproliferative cells has most thoroughly been studied in the cerebral cortex. In the cortex, the period of naturally occurring neuronal death (NOND) takes place primarily during the second postnatal week (e.g., Ferrer et al., 1990; Finlay and Slattery, 1983; Heumann and Leuba, 1983; Heumann et al., 1978; Miller, 1995c). Indeed, the pattern of NOND follows the inside-to-outside sequence of cortical neuronal

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generation. That is, it is defined by the neuronal time of origin so that neurons in the deep cortex (e.g., layer V) die before those in the superficial cortex (layer II/III; Miller, 1988b, 1995c).

p0295 Developmental exposure to ethanol can induce neuronal death in various brain regions, and this death appears to be generalized. For example, in the principal sensory nucleus of the trigeminal nerve, all constituent neurons appear to be equally vulnerable (Miller, 1995b, 1999). Likewise, there is no discernible pattern to incidence of death among Purkinje and granule neurons within a cerebellar lobule (Pierce et al., 1999). Patterns of biochemical changes indicate that ethanol-induced neuronal death also occurs in neocortex (Kuhn and Miller, 1998; Miller, 1996; Mooney and Miller, 2001; Olney et al., 2002a,b). Based on anatomical studies of the expression of 'death markers' (e.g., caspase 3 immunolabeling and TUNEL), it appears that the cerebral cortex is different in that select subpopulations are particularly vulnerable to ethanol exposure during the period of NOND, notably neurons in layers II/III and V (Ikonomidou et al., 2000; Olney et al., 2002a,b; Young et al., 2003).

p0300 Ethanol can affect multiple mechanisms of neuronal death (Mooney and Henderson, 2006). Three are described here: (1) intrinsic, (2) extrinsic, and (3) caspase 3-independent pathways.

s0100 ### 139.4.2.1 *Intrinsic pathway*

p0305 The intrinsic pathway is a mitochondrial-dependent pathway that is typically activated in response to an apoptotic signal such as DNA damage or reactive oxygen species (ROS; Green and Reed, 1998; Miller et al., 2000; Mooney and Henderson, 2006; Soengas et al., 1999). Proapoptotic proteins are released from the mitochondrial intermembrane space. Permeabilization of the mitochondrial outer membrane is mediated by Bcl proteins and promotes binding of p53 to proapoptotic Au10 proteins, for example, Bcl-XS or Bax (Chipuk et al., 2004). Bax upregulation may allow insertion of Bax homodimers into the mitochondrial membrane, thereby altering its permeability and permitting intermembrane substances to leak into the cytoplasm. These substances cause activation of caspase 3, which represses DNA repair and initiates DNA fragmentation and cell death.

p0310 Exposure to ethanol alters the *in vivo* expression of Bcl proteins (Mooney and Miller, 2003). Changes may be rapid, as in the case of the transcripts (Inoue et al., Au11 2002; Moore et al., 2000), or delayed, as detected by changes in protein expression (Mooney and Miller, Au12 2001; Heaton, 2003b). Ethanol also increases the expression of active caspase 3 (Carloni et al., 2004; Han et al., 2005; Ikonomidou et al., 2000; Mooney and Miller, 2003; Nowoslawski et al., 2005; Olney et al., 2002a,b) and induces production of ROS, which then causes DNA damage (Heaton et al., 2003a,b; Kotch et al., 1995; Maffi et al., 2008; Ramachandran et al., 2001, 2003). Interestingly, Bax is apparently required for ethanol-induced cell death, but caspase 3 is not (Young et al., 2003, 2005). Mice deficient in *Bax* do not exhibit argyrophilic (degenerating) cells in response to acute ethanol exposure, whereas caspase 3-null animals do.

139.4.2.2 *Extrinsic pathway* s0105

p0315 The extrinsic pathway is activated by binding the Fas ligand (FasL) to its cell surface receptor Fas. This binding causes receptor oligomerization, and the recruitment of the Fas-associated death domain (Fadd) and its association with procaspases 8 and 10 (Benn and Wolff, 2004). The Fadd-caspase 8/10 complex forms the death-inducing signaling complex, which cleaves and activates caspase 3. As with the intrinsic pathway, active caspase 3 inactivates poly-ADP-ribose polymerase (PARP) and allows DNA fragmentation. In addition, active caspase 8 cleaves the Bcl family protein, Bid. Truncated Bid (tBid) translocates to the mitochondria where it can activate the intrinsic pathway by promoting insertion of Bax homodimers into the mitochondrial membrane. Ethanol alters expression of FasL and Fas (Cheema et al., 2000; de la Monte and Wands, 2002; Hicks and Miller, 2011) and can increase caspase 8 activity (Vaudry et al., 2002).

139.4.2.3 *Caspase 3-independent pathway* s0110

p0320 As with the intrinsic pathway, the caspase 3-independent pathway is mitochondria-dependent. Following its release from the mitochondrial intermembrane space, apoptosis-inducing factor can either directly upregulate DNase activity or can cleave and inactivate PARP. The effect of this is the repression of DNA repair and promotion of cell degeneration. Although there is little direct evidence that ethanol activates the caspase 3-independent pathway, inhibiting caspase activity does not prevent ethanol-induced cell death (D'Mello et al., 2000; Keramaris et al., 2000; Au13 Miller, 1997; Selznick et al., 2000; Stefanis et al., 1999). This implies that a caspase 3-independent pathway is able to be activated, regardless of whether it is the main pathway affected by ethanol. It is noteworthy that both the intrinsic and extrinsic pathways are upstream of p53 activation (Mooney and Henderson, 2006); ethanol affects p53 expression (Kuhn and Miller, 1998) and p53-mediated cell death (Miller et al., 2003).

139.4.2.4 *Growth factor targets* s0115

p0325 Neurotrophins play critical roles in normal brain development (e.g., Bibel and Barde, 2000). Developmental expression of neurotrophins is necessary for neuronal survival, process outgrowth, and synaptogenesis. Two neurotrophins particularly important for brain development are NGF and BDNF. Although NGF is not

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expressed by cortical progenitors *in vitro* or in the VZ *in vivo*, which suggests that it is not required for cell proliferation or the initiation of migration (Barnabé-Heider and Miller, 2003; Fukumitsu et al., 1998; Maisonpierre et al., 1990), it is highly expressed in the early postnatal period, suggesting a role in postmitotic development (Das et al., 2001; Heaton et al., 2003b).

p0330 BDNF is present in cortical progenitor cells *in vivo* and *in vitro* (Barnabé-Heider and Miller, 2003; Fukumitsu et al., 1998; Maisonpierre et al., 1990) and remains evident in the cerebral cortex through adulthood (Climent et al., 2002; Das et al., 2001; Heaton et al., 2003b; Itami et al., 2000; Pitts and Miller, 2000; Vitalis et al., 2002).

p0335 Developmental exposure to ethanol alters the expression of neurotrophins and their receptors, although there is no consensus as to the effect (e.g., Climent et al., 2002; Heaton et al., 1999, 2000b, 2003a,b; Light et al., 2001; Seabold et al., 1998). Prenatal and postnatal exposure to ethanol increases NGF expression in the cortex and striatum (Heaton et al., 2000a, 2003a,b). Cortical BDNF expression (Climent et al., 2002) is reduced during the first 2 postnatal weeks by prenatal exposure to ethanol, whereas postnatal exposure to ethanol increases cortical BDNF expression (Heaton et al., 2003b).

p0340 For neurotrophins to have an effect on brain development, they must bind to and activate receptors. Thus, the expression, both amount and location, of receptors may provide greater insight into the role of the neurotrophin systems in development. Cortical expression of trkA and trkB is upregulated following prenatal exposure to ethanol (Climent et al., 2002; Gottesfeld et al., 1990; Valles et al., 1994). Exposure to ethanol in the early postnatal period also upregulates cortical p75 expression (Toesca et al., 2003) as does ethanol treatment of cultured cortical neurons (Seabold et al., 1998). Evidence suggests that p75 can mediate apoptotic death or mediate the protective effect of a neurotrophin (Blochl and Blochl, 2007; Casaccia-Bonnefil et al., 1996, 1999; Seabold et al., 1998). Thus, the changes in receptor expression may be in response to ethanol-induced reductions in neurotrophin concentrations and subserve a protective mechanism.

p0345 Exogenous neurotrophins can ameliorate ethanol-induced cell death. Animals that overexpress NGF are less vulnerable to ethanol-induced neurotoxicity (Heaton et al., 2000a). The addition of NGF or BDNF to cultured cells reduces ethanol-induced cell death (Bhave et al., Au14 1999; de la Monte et al., 2002; Heaton et al., 1992, 1993, 1994; Miller et al., 2003; Seabold et al., 1998). The ability of NGF to protect cortical neurons against ethanol-induced death is both site-specific and age-dependent. NGF fails to protect against ethanol-induced death in cultures of cortical neurons (Seabold et al., 1998), or in slice cultures from 16-day-old rat fetuses (Mooney and Miller, 2007a). In contrast, NGF is neuroprotective in slice cultures taken from a 3-day-old rat brain. This neuroprotection is seen only in the more mature lower cortical plate and not in the upper cortical plate, which largely contains migrating neurons. The implication is that the neuroprotection depends upon the maturity of the neurons.

p0350 NGF-induced neuroprotection is correlated with receptor activity. Ethanol inhibits the NGF-induced phosphorylation of trkA in the primary neurons taken from 16-day-old fetuses but does not affect p-trk expression in slices from 3-day-old pups. Activation, that is, phosphorylation, of trkA is generally associated with neuronal survival. Thus, an ethanol-induced reduction in p-trk expression may be predictive of an inability of NGF to protect against ethanol-induced death.

p0355 In addition to altering expression of neurotrophin ligands and receptors, exposure to ethanol alters downstream signaling. Trk receptors can signal survival via the MAPK and PI3K pathways, and p75 may also signal survival via PI3K. Activation of both pathways is age-dependent. Growth factor-dependent activation is downregulated in the presence of ethanol (Climent et al., 2002; Kalluri and Ticku, 2002). Ethanol inhibits endogenous phospho-MAPK expression (Kalluri and Ticku, 2002). Ethanol also alters growth factor-induced phosphorylation of the MAPK pathway in cortical cells (Climent et al., 2002; Luo and Miller, 1999a,b) and PI3K/Akt in cerebellar cells (de la Monte and Wands, 2002; Li et al., 2004). Interestingly, the ethanol-induced reduction in growth factor-stimulated PI3K/Akt activation in cerebellar neurons occurs in the absence of a change in receptor or ligand expression (de la Monte and Wands, 2002). The effect of ethanol on pathway activation is cell type dependent. For example, ethanol inhibits the BDNF-mediated increase in expression of phosphorylated jun-*N*-terminal kinase (p-JNK) and phosphorylated Akt (p-Akt) in cultured mouse cerebellar granule cells (Li et al., 2004). In contrast, in a human neuroblastoma cell line (TB8 cells), ethanol inhibits the BDNF-mediated increase in p-Akt but not p-JNK expression, suggesting that different pathways are activated by BDNF in these cells.

139.5 BEHAVIORAL CONSEQUENCES s0120

p0360 Social interactions are crucial for the survival of humans and other mammalian species. In humans, peer relationships are sources of knowledge about behavioral patterns, attitudes, values, and consequences in different situations (Deutsch and Gerard, 1955). In the same way, peer-directed social activity of rodents seems crucial for establishing social organization in a group or between partners and for developing the ability to express and understand intraspecific communication signals (Vanderschuren et al., 1997).

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p0365 A secure and consistent social milieu is important not only for humans but for laboratory rodents as well, with social deprivation being stressful (Hall, 1998). Rats exhibit numerous social behaviors including play fighting, contact behavior, and social investigation. Abnormal social behaviors have been reported in rats following a number of developmental insults, including neonatal lesions of the amygdala (Daenen et al., 2002), neonatal exposure to Borna disease virus (Lancaster et al., 2007), and ethanol exposure during development (Kelly et al., 2000; Thomas et al., 1998). Developmental exposure to ethanol alters play fighting behavior (Lawrence et al., 2008; Lugli et al., 2003; Meyer and Riley, 1986; Royalty, 1990), as well as the amount ~~of~~ and type of active social interaction in adolescents and adults (Kelly and Dillingham, 1994; Lugli et al., 2003). Prenatal exposure to ethanol alters social behavior in a sex-dependent fashion (Meyer and Riley, 1986), with males showing less play behavior and females demonstrating more play fighting. Interestingly, a single exposure to ethanol on G12 alters the social behavior of adolescent and adult rats, and many of the changes are sex-specific, that is, they are detected only in males (Mooney and Varlinskaya, 2011; Mooney et al., 2009).

139.6 SUMMARY

s0125

p0370 Early developmental exposure to ethanol has multiple consequences including targeted effects on cell proliferation and survival. In general, ethanol reduces cell proliferation and compromises neuronal survival, but the scope of the changes are defined by the site, the exposure, the maturity of the cells, and the growth factor availability and receptivity. The culmination of these changes affects the total numbers of neurons in the brain. Interestingly, the numbers of neurons in structures within a ~~single functional~~ system (e.g., the somatosensory system) may be differentially altered. For example, the numbers of neurons in the rat trigeminal brainstem nuclei (Miller, 1999; Miller and Muller, 1989) and the somatosensory cortex (Miller and Potempa, 1990; Powrozek and Zhou, 2005) are 30–50% fewer in ethanol-exposed animals; however, no detectable effect is evident in the thalamus (Livy et al., 2001; Mooney and Miller, 1999, 2010). This breakdown in the numerical matching of neuronal populations within a system of interconnected structures implies that the assemblage of neurons within each structure occurs either autonomously or asynchronously. The consequences of such differential effects are functional changes (Miller and Au15 Dow-Edwards, 1993; Vingan et al., ~~1988~~; Xie et al., 2010) that likely underlie ethanol-induced dysfunction such as motor incoordination and cognitive deficits (Coles, 2006; Fryer et al., 2006).

p0375 Two intriguing contributors to postnatal responses and responsivity are genetic–environmental interactions and fetal programming. It is becoming clearer that ethanol has targeted effects on genomic expression and epigenetic modifications (e.g., Haycock, 2009; Hicks et al., 2010; Pandey et al., 2008). Overlying these interactions, and possibly a result of them, is the effect of early exposure to ethanol on fetal programming (Miller and Spear, 2006). Such programming may be mediated through neural stem cells. The mechanism and the scope of this programming are at present unknown, ~~but~~ understanding them will not only provide key insights into normal brain ontogeny but also likely ~~be~~ critical for developing strategies to modify neural development and outcome and ultimately preventing or offsetting developmental disorders such as FASD. Au16

Acknowledgments

s0130

p0380 The authors thank the National Institutes of Health (AA06916, AA18693, and AA178231, SMM; ES14901, PJL; AA06916, AA07568, and AA178231, MWM), Autism Speaks (SMM), University of California at Davis MIND Institute (PJL), and the Department of Veterans Affairs (MWW) for their support.

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DNRS, 978-0-12-397267-5

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Date:9/8/12 Time:15:31:04 Page Number: 17