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Signaling Pathways Regulating Cell Motility: A Role in Ethanol Teratogenicity?

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Abstract

This article summarizes the proceedings of a symposium presented at the 2005 annual meeting of the Research Society on Alcoholism in Santa Barbara, California. The organizer and chair was Tara A. Lindsley. The presentations were (1) Ethanol and Neuron Migration in the CNS, by Michael W. Miller; (2) Ethanol and L1-mediated Neurite Outgrowth, by Yoav Littner and Cynthia F. Bearer; and (3) Ethanol and Axon Guidance, by Tara A. Lindsley.

Keywords

Alcohol; Fetal Alcohol Syndrome; Neural Cell Adhesion Molecule; L1 Cell Adhesion Molecule; Reelin; Brain-Derived Neurotrophic Factor; Heterotopia; Neurite Outgrowth; Axon Guidance; Microarray

THE REGULATION OF motile behavior is critical for key events during nervous system development, including neuron migration, the outgrowth of axons and dendrites, and guidance of growing axons to their synaptic targets. The migration of the whole neuron and its growth cones is similar in that both utilize intracellular signaling from specific membrane receptors that triggers cytoskeletal rearrangements. The emerging picture from recent cell biological studies is that many of these signaling pathways appear to converge on key regulatory molecules upstream of actinbased motile apparatus, even though the extracellular ligands and their receptors involved are distinctly different.

The speakers presented findings from recent studies showing that prenatal ethanol exposure can disrupt whole-cell migration and growth-cone motility in a variety of experimental model systems. The goals of this symposium were to present evidence that disrupted

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neuronal migration and neurite growth and guidance contributes to the pathogenesis of fetal alcohol spectrum disorders (FASD) and to explore the possibility that these effects of ethanol might ultimately be linked mechanistically through common signaling pathways linking receptor activation to cytoskeletal reorganization.

ETHANOL AND NEURONAL MIGRATION IN THE CNS

Michael W. Miller

Neuronal migration is a process that is essential for the proper development of the central nervous system (CNS). Although there is an element of “two steps forward, one step back,” neuronal migration is ostensibly a unidirectional process (e.g., Edmondson and Hatten, 1987; Leavitt et al., 1999; Rakic et al., 1966). The movement is an active, energy-requiring process that is highly ordered and it is organized and promoted by environmental factors.

Migration is the process by which postmitotic neurons move from the proliferative zone(s) to their residence wherein the young neurons differentiate and integrate into the neural network. Most studies of CNS migration have used the cerebral cortex as a model. As such, cortical neurons arise from progenitors cycling in 3 proliferative zones. Two zones which are located deep in the cerebral wall are the ventricular zone (VZ) and the subventricular zone (SZ). The VZ and SZ give rise to neurons which migrate to the infragranular (deep) laminae (layers V and VI) and supragranular (superficial) laminae (layer II/III), respectively (Miller, 1992; 2006). These migrations are radial; that is, the neurons migrate along a pathway that is perpendicular to the ventricular and pial surfaces. Cellular processes, known as radial glial fibers, span the cerebral wall from the proliferative zones to the pial surface. These radial glia are used as guides for radial migration. A minority of cortical neurons, local circuit neurons, are generated in the third proliferative zone, the medial ganglionic eminence (de Carlos et al., 1996; Faireén et al., 1998; Marin and Rubenstein, 2001; Peretto et al., 1999). These neurons take a distinctively different pathway, migrating tangentially across the cerebral wall and then migrate radially with the derivatives of the VZ and SZ.

Neuronal migration can be disrupted by genetic mutations/deletions. Two of these are of particular note. They are *dcx* and *lis*1 deficiencies (Guerrini and Carrozzo, 2001; Kato and Dobyns, 2003; Olson and Walsh, 2002). $dcx^{-/-}$ people do not have the ability to produce the transcript for double cortin and their brains have a characteristic band of heterotopic neurons between the subcortical white matter and the remnant of the proliferative zones. People who are $lis1^{-/-}$ have a lissencephalic cortex which particularly deep (2 to 3 times wider than normal).

Exposure to environmental agents, e.g., ethanol, can cause defects that are reminiscent of $dcx^{-/-}$ and $lis1^{-/-}$ genetic mutations. Children with fetal alcohol syndrome (FAS) have smaller brains that have (1) fewer gyri (i.e., they tend to be more lissencephalic) and (2) the gyri can be covered with sheets of heterotopic neural cells (Clarren et al., 1978). Ethanol-induced heterotopias can be replicated in animal models (Kotkoskie and Norton, 1988; Mooney et al., 2004). Using these models, it has been determined that the heterotopias contain radial glial cells which are continuous through the length of the cerebral wall and into the heterotopia. In addition, heterotopias have postmitotic neurons that migrated

through breachesin the marginal zone. The marginal zone is composed of Cajal-Retzius neurons, cells that elaborate reelin (Frotscher, 1998; Gierdalski and Juliano, 2002; Sarnat and Flores-Sarnat, 2002). Reelin is the signal that causes migrating neurons to stop their migration in the underlying superficial plate. Cajal-Retzius neurons are displaced to the periphery of the heterotopia, thereby permitting migrating neurons to continue their migration through the breach and into the heterotopia (Mooney et al., 2004).

Ethanol can cause neurons to complete their migrations to ectopic sites within the cortical parenchyma (Miller, 1986, 1988, 1992). This can result from ethanol-induced premature retraction of the radial glia from their pial contacts (Guerri, 2006; Miller and Robertson, 1993; Valles et al., 1996). The consequence is that migrating neurons are without their glial guides and only migrate to the termini of the glial guides, which are abnormally in deep cortex. Defects can also result from an ethanol-induced retardation in neuronal migration (Miller, 1993; Siegenthaler and Miller, 2004, 2006). For example, in control tissues (organotypic slice cultures and in vivo), the rate of migration is 6.0 μm/h, whereas in corresponding ethanoltreated samples, the rate is significantly slower, 3.0 to 3.5 mm/h. Thus, even in the absence of a premature loss of the glial guides and because of the retarded migration, the late-migrating neurons are unable to complete their migrations to superficial cortex and become marooned in ectopic sites.

A key player in the regulation of neuronal migration is transforming growth factor (TGF)-β1. Transforming growth factor-β ligands (TGF-β1 and TGF-β2) are endogenously expressed in developing cortex by cells involved in neuronal migration, including radial glia (Miller, 2003). Likewise, TGF-β receptors are expressed by radial glia and migrating neurons. Exogeneous TGF-β1 affects the rate of migration in a concentration-dependent manner (Siegenthaler and Miller, 2004, 2006). Maximal effect, a doubling of the rate of neuronal migration occurs at a concentration of 10 ng/mL; interestingly, greater concentrations are inhibitory. Ethanol blocks the stimulatory effect of TGF-β1on neuronal migration.

Transforming growth factor-β1 promotes the expression of cell adhesion proteins (CAPs) including neural cell adhesion molecule, L1, and integrins (Luo and Miller, 1999; Miller and Luo, 2002; Minñana et al., 2000; Siegenthaler and Miller, 2004a, 2004b). Transforming growth factor-β1 affects CAP expression in a concentration-dependent manner; increasing TGF-β1 amounts induce progressively more CAP. The implication is that there is an optimal amount of CAP expression to facilitate neuronal migration. Too much TGF-β1, and hence too much CAP, leads to inhibition of the migration, likely because the extracellular environment is too sticky for the migrating neurons. Likewise, ethanol induces CAP expression in amounts that are equivalent to that stimulated by high concentrations of TGF-β1. Therefore, this may be a mechanism by which ethanol retards neuronal migration. Microarray studies show that changes in protein expression follow earlier changes in CAP transcripts (Miller et al., 2006).

In summary, ethanol can induce defects in neuronal migration that include neurons migrating to incorrect places within cortex or beyond the limits of cortex. The results are heterotopias. Contributions to these defects are alterations in cell adhesion, in the physical

structures guiding neuronal migration, and in factors that regulate neuronal migration. Thus, there is no single cause to ethanol-induced defects in neuronal migration. It is striking that ethanol-induced changes are reminiscent of those evident in people who are *dcx*$^{-/-}$ or *lis*1 $^{-/-}$. The implication is that genetic and environmental alterations lead to similar consequences.

ETHANOL AND L1-MEDIATED NEURITE OUTGROWTH

Yoav Littner and Cynthia F. Bearer

Fetal alcohol syndrome was first described by Lemoine et al. (1968) leading to the recognition of alcohol as a teratogen. Despite significant efforts to educate the public, the incidence of FAS has not been declining. Moreover, the rate of binge drinking during pregnancy is still increasing, resulting in an enormous burden for society. With an incidence of 1/3,000 live births (Abel and Sokol, 1991), FAS is the leading known cause of mental retardation. Also, it is clear nowadays that even at minimal exposure to alcohol, infants can present with neurodevelopmental defects Stratton et al., 1996). This spectrum of outcomes is more prevalent than FAS and estimated to affect 1% of all newborns (Sampson et al., 1997).

In 1994, Charness and colleagues, described similarity in neuroanatomical pathology found in patients with FAS and patients with mutation in L1 cell adhesion molecule (L1) suggesting that L1 is a target for ethanol toxicity (L1CAM Mutation Web Page; Charness et al., 1994). L1 is a transmembrane glycoprotein and a member of the immunoglobulin super family, which has a critical role in the development of the CNS. It is expressed on axonal shafts and growth cones of developing neurons generating intracellular signals, which promote neurite outgrowth. Charness et al. (1994) reported that physiologic concentrations of ethanol inhibit L1–L1 homophilic binding. In addition, our lab (Bearer et al., 1999) and Watanabe's lab (Watanabe et al, 2004) found that ethanol inhibited L1-mediated neurite outgrowth.

There are several potential sites for inhibition of L1 function. The first is at the site of sorting of L1 to the leading edge of the growth cone (Bearer et al., 1999; Charness et al., 1994; Ramanathan et al., 1996). Kamiguchi and colleagues found that endocytosis, as well as Ll targeting to the growth cone, are dependent on a tyrosine-sorting signal within the cytoplasmic domain of L1. Disruption of this signal leads to absence of Ll within the neurite and failure of Ll to undergo endocytosis (Kamiguchi et al., 1998a; Kamiguchi and Lemmon, 1998). Using confocal microscopy on dorsal root ganglion cells from embryonic chicks that were grown on Ll in media containing 100 mM ethanol, our lab found no effect of ethanol on the presence of Ll in the growth cone, or on the surface of the growth cone. Thus, ethanol has no effect on the tyrosine-sorting signal.

The second possible site for ethanol inhibition of L1 function is at the activation of ERK1/2 and p60^{src} by L1. L1 clustering followed by its endocytosis has been shown to activate signal transduction including mitogenactivated protein kinase (MAPK) and p60^{src} (Schaefer et al., 1999). If endocytosis is blocked, no Ll-mediated MAPK activation occurs (Schaefer et al., 1999). In addition, inhibition of MAPK reduces Ll-mediated neurite outgrowth by 50%

(Schmid et al., 2000). Our lab found that treatment with 25 mM ethanol for 1 hour inhibited the activation of ERK1/2 as well as the phosphorylation of $p60^{src}$.

A third possible site for ethanol inhibition of L1 function is at the endocytosis of L1. As mentioned before, Ll targeting to the growth cone and endocytosis is dependent on a sorting signal containing a tyrosine at position 1,176 (Kamiguchi et al., 1998a, 1998b; Kamiguchi and Lemmon, 1998). This tyrosine is phosphorylated in cells unexposed to L1 and becomes dephosphorylated after cellular contact with L1. The dephosphorylated tyrosine is required for binding of AP-2 and endocytosis of L1. Using a mouse monoclonal antibody, 74-5H7, which recognizes only the dephosphorylated tyrosine in L1 at position 1,176, we showed delayed dephosphorylation of Y1176 in cells treated with 25 mM ethanol. Hence, ethanol can delay L1 endocytosis by the same pathway, or L1 is endocytosed by a different pathway (Long and Lemmon, 2000) in the presence of ethanol.

The above-mentioned observations suggest that the ethanol effect on L1 function occurs between the expression of L1 at the leading edge of the growth cone and its subsequent endocytosis. We hypothesize that ethanol may change the phosphorylation status of L1. Possible sites are the other 3 tyrosine residues of the cytoplasmic domain of L1: Y1151, which is the binding site for actin and Y1211 or Y1229—both of them are ankyrin-binding sites.

To investigate the effect of ethanol on tyrosine phosphorylation of L1, we used postnatal day 6 rat cerebellar granule neurons treated with ethanol at 25 mM for 1 hour. Neurons were triggered by addition of clustered anti-L1 monoclonal antibodies and at indicated times were washed and lysed. Cell lysates were immunoprecipitated with anti-phosphotyrosine antibodies and immunoblotted with a polyclonal antibody to the cytoplasmic domain of L1. Phosphorylation was assayed by Western blot analysis. Our results show an inhibitory effect of ethanol on L1 tyrosine phosphorylation at baseline before L1 activation as well as complete inhibition of tyrosine phosphorylation following L1 activation. As Y1176 is only phosphorylated at baseline, i.e., there is no immunoreactivity with 74-5H7 in resting cells, the anti-phosphotyrosine antibody used in these experiments does not immunoreact with phosphor-Y1176. Hence the changes seen here with ethanol must occur at 1 or more of the other 3 tyrosines in the cytoplasmic domain of L1 and may result in increased binding to either ankyrin or actin. Future directions that our laboratory is currently investigating are: identifying the site of tyrosine phosphorylation affected by ethanol and defining the effect of duration, dosing, and reversibility of ethanol treatment on L1 tyrosine phosphorylation.

ETHANOL AND AXON GUIDANCE

Tara A. Lindsley

It is clear from studies in a variety of animal and cell culture models that prenatal alcohol disrupts the outgrowth of axons and dendrites in the developing hippocampus. The resulting morphologic abnormalities alter functional properties of synaptic circuitry that are linked to cognitive and behavioral problems that characterize FASD in humans (reviewed in Berman and Hannigan, 2000; Lindsley, 2006; Pentney and Miller, 1992). Using rat hippocampal pyramidal neurons in culture our laboratory previously showed that exposure to 22 to 87

mM ethanol in the medium during the initial stages of axon development has a number of dose-dependent effects. It delays initial axon outgrowth but accelerates subsequent axon growth rate by reducing retractions during periodic pauses in elongation (Lindsley et al., 2003). The periodicity of growth cone elongation is interesting, because pauses are associated not only with the rate of growth, but also with responses to attractive and repulsive guidance cues (Ming et al., 2002; Song and Poo, 1999). In recent experiments we observed that the same conditions of ethanol exposure that alter axon growth dynamics also dramatically increase the extent of growth cone lamellipodia and filopodia. Taken together, these data suggest that ethanol exposure might disrupt the way axons respond to guidance cues. The objective of the current study was to determine whether exposure to ethanol altered axon turning induced by a known guidance factor.

Although direct evidence is lacking, some effects of prenatal alcohol exposure reported in the literature are consistent with faulty axon guidance. For example, Jim West's lab and others reported that adult rats prenatally exposed to ethanol have an abnormally targeted infrapyramidal tract with axons extending far into the statum oriens of CA3 (Sakata-Haga et al., 2003; West et al., 1981). The mechanisms controlling mossy fiber axon guidance are not fully understood, however, evidence points to a role for brain-derived neurotrophic factor (BDNF) in attractive guidance (Goodman et al., 1996; Ip et al., 1993) and semphorin 3F in repulsive guidance and axon pruning (Sahay et al., 2003). Indeed, there are striking similarities between the abnormal mossy fiber trajectories of prenatal ethanol-exposed rats and mossy fiber phenotype of mice deficient in the axon guidance molecule semaphorin 3F (Sahay et al., 2003) or members of the holoreceptor for semaphorin, neuropilin-2, and plexin A3 (Chen et al., 2000, 2001).

Axon turning in response to a stable, microscopic gradient of BDNF in hippocampal neuron cultures exposed to 47 or 87 mM ethanol for 20 to 36 hours in the medium was assessed using repetitive pulsatile ejection of picoliters of BDNF-containing Krebs–Ringer saline from a micropipette (Lohof et al., 1992). When the gradient was applied at a 45° angle with respect to the direction of growth, and the pipette was placed 100 μm away from the growth cone, the axons of control neurons turned attractively toward the source of BDNF as they grew. However, when axons of neurons maintained in 87 mM ethanol-containing medium were exposed to the same gradient of BDNF, nearly all exhibited marked repulsive turning. Neurons maintained in medium with 43 mM ethanol had varied responses, with an equal proportion of growth cones turning attractively and repulsively. When a membranepermeable cAMP agonist that activates PKA (Sp-cAMPS, 20 mM) was added to the bath of ethanol-treated neurons 30 minutes before they were exposed to the BDNF gradient, the switch to repulsive turning was significantly reduced and growth-cone turning response was similar to control neurons. The net extension of axonal growth cones during the 90-minute period of the assay was not significantly affected by any of the conditions tested. Control neurons and neurons exposed to ethanol showed no significant turning response when the pipette solution contained Krebs–Ringer without BDNF.

The results of these experiments provide the first direct evidence that ethanol can disrupt not only growth-cone motility associated with axon growth, but motility associated with axon guidance. This is not surprising given that both growth and guidance signals are transduced

by intracellular signaling pathways that regulate cytoskeletal reorganization. Our findings are consistent with the modulation of signal transduction pathways by ethanol and suggest that ethanol-induced reductions in growth-cone cAMP levels may contribute to altered turning response to BDNF.

CONCLUSION

The presentation by Miller reviewed evidence that prenatal ethanol exposure can delay and misdirect the essential process of postmitotic neuron migration in the developing cortex, resulting in defects reminiscent of certain genetic mutations characterized by lissencephaly and heterotopias. Recent studies demonstrated that ethanol blocks the stimulatory effect of TGF-β1 on migration of cortical neurons in organotypic slice cultures and in vivo and induces expression of several CAPs known to be involved in neuronal migration, incuding nCAM and integrin subunits α_3, α_v, and β_1. These cell adhesion molecules not only mediate adhesion per se, but also trigger cytoplasmic signaling cascades that modulate neuronal motility. Transforming growth factor-β1 and ethanol both signal via the ras/faf/MAPK pathway.

The presentation by Littner and Bearer reviewed evidence that ethanol inhibits L1-mediated neurite outgrowth in cerebellar granule neuron cultures. Ongoing studies to determine the cellular sites for ethanol inhibition of L1 function were presented. Results of these studies indicate that ethanol inhibits L1-mediated neurite outgrowth by disrupting events downstream of L1 activation. This includes altered regulation of tyrosine phosphorylation at 1 or more sites known to interact with cytoskeletal proteins and inhibition of extracellular signal-regulated kinases (ERK1/2) which are downstream in an L1 signaling pathway from PI3 kinase, Rac1 GTPase and mitogen-activated protein kinase kinase (MEK).

The presentation by Lindsley described new studies using hippocampal pyramidal neuron cultures that are aimed at determining whether exposure to ethanol during axon growth affects growth-cone turning in response to the neurotrophin BDNF, which normally acts as an attractive guidance factor for these neurons. Their results indicate that neurons exposed to ethanol reverse direction of turning in response to BDNF and that experimental manipulation of cAMP levels can prevent this effect of ethanol.

In summary, the experimental findings highlighted in this symposium indicate that developmental events dependent on cell motility are sensitive to disruption by ethanol exposure. Thus, altered cellular motility may underlie some neuropathologic abnormalities in children with FASD, a possibility that warrants further study. Evidence presented here, which reflect observations from several distinct model systems, is consistent with multiple intracellular targets of ethanol impacting cytoskeletal organization and cell motility. However, despite apparent progress made in the identification of ligands and receptors that could play a role in altered cell motility induced by ethanol exposure, additional studies are clearly required to identify the direct molecular targets of ethanol and distinguish them from the countless intermediates that may be indirectly affected via complex interconnected signaling cascades or during compensatory responses occurring with prolonged ethanol exposure.

Receptors for neuron migration, process outgrowth, and steering are numerous; however, there is a growing awareness that the integration of these signals and the directional specificity of motile behavior resides in the signaling intermediates that serve as a link between diverse receptors upstream and common cytoskeletal regulators downstream (Song and Poo, 2001). These potentially important targets of ethanol include widely recognized second messengers like Ca^{2+}, cyclic nucleotides, and the Rho family GTPases. Indeed, results published during the preparation of this symposium summary demonstrated the central role of Ca^{2+}, cAMP, and cGMP in the inhibition of cerebellar granule cell migration by acute ethanol exposure (Kumada et al., 2006). Future studies should attempt to take into account overlapping signaling pathways with shared signaling intermediates for neuronal migration, axon growth and axon guidance that have also been identified as targets of ethanol in neurons and nonneuronal cells.

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