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Neurobiology of Neuronal Network Alteration in Intellectual Disability Related to Fetal Alcohol Spectrum Disorders

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Abstract

The molecular and cellular mechanisms by which alcohol produces its deleterious effects on neuronal networks are only now beginning to be understood. This review focused on alcohol-induced neurobiological alterations on neuronal network components underlying information processing, for further understanding of intellectual disability related to FASD. Abnormal neurodevelopmental events related to alcohol-damaged fetal brain included neurogenesis inhibition, aberrant migration, impaired differentiation, exacerbated apoptosis, impaired axon outgrowth and branching altering synaptogenesis and synaptic plasticity, abnormal GABAergic interneurons triggering synaptic inhibitory/excitatory imbalance, reduced myelinogenesis causing injured white matter in prefrontal lobe and atrophied corpus callosum compromising interhemispheric information transfer, the whole compromising neuronal network scaffolding which may lead to biased information processing with deficits in executive function. What added to these abnormalities are smaller gray matter and reduced hippocampus, resulting in cognition and memory failures. As a whole, these developmental disorders may underlie intellectual disability related to FASD. In rodents, these neuronal network components matured mainly during the second and third trimesters equivalents of human gestation. Transferability of results from animal to human was also discussed. It was hoped that the understanding of alcohol-induced neuronal networks failure mechanisms during the developing brain may lay a foundation for prospective new treatments and interventions.

Keywords

Fetal Alcohol Spectrum Disorders, Intellectual Disability, Neuronal Network, Axogenesis, Synaptogenesis, Myelinogenesis

1. Introduction

Alcohol is a potent teratogen in humans and embryonic exposure to alcohol alters the course of normal brain development [1] [2] [3]. Prenatal alcohol exposure is a leading cause of central nervous system (CNS) developmental disorders *i.e.* intellectual disability [4] [5]. The term "fetal alcohol spectrum disorders" (FASD) refers to a pattern of birth defects found in children born from alcoholic mothers [6] [7]. FASD has four criteria: 1) maternal drinking during pregnancy; 2) a characteristic pattern of facial abnormalities; 3) intrauterine growth retardation paired to a microencephaly; 4) brain damage often manifested by intellectual disability and behavioral disorders including attention deficit, cognition, and learning inabilities [6] [8] [9]. Evidence converged on the proposal that intellectual disability was primarily due to deficiencies in neuronal network connectivity in the major cognitive centers in the brain, which secondarily would result in impaired information processing [10]. Clinical and experimental studies on individuals with FASD reported marked deficits in executive function, *i.e.* alterations in complex tasks processing requiring precise timing and involving working memory suggesting central information processing failure [11] [12] [13]. Indeed, neuropsychological studies showed that FASD was associated with executive function impairment, *i.e.* deficits in planning, fluency, and set-shifting [14]. Assessing other executive function domains, deficits in attentional vigilance and response inhibition were also associated with FASD [15]. Studies examining specific domains of cognitive functioning such as language, visual perception, memory and learning, social functioning, and number processing in individuals with FASD have revealed an inverse correlation between decreased performance and increased task complexity [11] [16] [17] [18]. Indeed, recent studies showed the development of executive function to be delayed in children between 4 and 6 years of age [19].

The above findings converge on the conclusion that FASD-affected children have a generalized deficit in the processing and integration of information which is an emerging topic of investigation [11] [18] [20]. Although intellectual disability has been largely regarded as a brain disorder that can't be cured, our increased understanding of the abnormalities and mechanisms underlying this affection may provide an avenue for the development of improver therapies [10] [18]. Indeed, there is no effective treatment for FASD, because of a lack of complete characterization of the cellular and molecular mechanisms underlying this condition [21]. In addition, the molecular and cellular mechanisms by which alcohol produces its deleterious effects on the neuronal network are only now beginning to be understood [22]. In this review, we discuss the neurobiology of alcohol toxicity on neuronal network components underlying information processing in intellectual disability, with a focus on axogenesis, dendrogenesis, myelinogenesis alterations, and interneurons abnormalities. But at first, we will dwell on the anatomical and structural alterations that can compromise information processing.

2. Brain Morphological and Anatomical Alterations

FASD models studied in humans showed the developing brain to be a major target for alcohol toxicity. Volumetric measures were done as biomarkers for prenatal alcohol exposure. These brain measurements showed in FASD-affected children gross morphological and anatomical abnormalities including microencephaly (brain weight decreases), reduced volumes of frontal cortex and cerebellum, alterations in the shape and volume of the corpus callosum, smaller volume of the hippocampus and basal ganglia [23] [24] [25] [26]. Neuroimaging and postmortem assessment studies in children with FASD showed structural damage in different brain organs. Thus, the severity of fetal brain white matter atrophy and degeneration was correlated with heavy daily alcohol exposures during pregnancy [27]. A recent study showed substantial reductions of frontal lobe matters white and gray which were critical for executive function, higher-order learning and social behavior [28]. In addition, the corpus callosum, one of the main targets of developmental alcohol exposure, was significantly atrophied in adult males with heavy fetal alcohol exposure [26] [29]. Atrophy of the corpus callosum impaired inter-hemispheric communication, compromising the exchange of sensory, motor and cognitive information [30].

Similar studies in animal models of in utero alcohol exposure have also shown growth retardation with microencephaly and high vulnerability in different developmental stages of the central nervous system such as proliferation: reduction in number and atrophy of pyramidal neurons in the hippocampal and cortical layers; cell migration: increased number of angular and ectopic pyramidal cells in the hippocampus; cell differentiation: impaired axogenesis, dendrogenesis, and myelinogenesis; cell function: impaired psychomotor development and visual system [1] [3] [31] [32] [33] [34] [35]. For example, in rats prenatally exposed to alcohol, ectopias in the cerebral cortex, aberrant distribution of hippocampal mossy fibers, the fusion of cerebellar folia and hydrocephalus were found [36] [37] [38]. In addition, prenatal alcohol exposure altered functional connectivity in the medial prefrontal cortex (mPFC) whose alteration disrupted executive function [39] [40]. According to Sakata-Haga *et al.* [41], abnormal development of the dorsal hippocampus induced by prenatal alcohol exposure may be associated with the deficit of spatial memory seen in rat offspring.

Several pathological pathways allowed explaining cognitive dysfunction associated with FASD. However, human studies were limited, despite their necessity in understanding FASD. Conversely, experimental results from animal models provide useful insights on the cellular and molecular mechanisms underlying FASD pathology, including inhibition of proliferation, aberrant migration, impaired differentiation, and exacerbated apoptosis.

2.1. Proliferation Inhibition

After the closure of the neural tube, the ventricular zone of the neural tube or germinal zone or matrix (on the surface of the future lateral ventricle) is the seat

of intense mitotic activity. It thickens to form the neuroepithelium. During corticogenesis, there is an intense multiplication of neuroblasts in the ventricular zone, which migrate along the radial glial fibers to form the cortical plate where the neuroblasts compile and differentiate into specialized neurons of the cerebral cortex forming the gray matter [42]. By cytostasis, alcohol inhibited the rat progenitors cell proliferating in the basal layer surrounding the primitive ventricle generating the majority of the cortical layers cells [43]. According to Miller [44], gestational alcohol exposure in rats disrupted more severely the late-generated neurons in the deep cortex (layers VI-V) than the first-generated neurons in the superficial cortex (layers III-II). Consequently, developmental binge-pattern alcohol exposure produced dysregulated pyramidal neurons in layer VI of the adult mice medial prefrontal cortex, leading to attention deficits associated with FASD [45].

Moreover, pregnant mice exposed to alcohol between gestational days (GD) 12.5 and 14.5, corresponding to the emergence of the subventricular zone and cerebral cortical pre-plate and the generation of layer V and VI neurons [46], have shown ventricular dilation and decreased thickness of the developing cortical plate in the fetal brain [47]. In ex vivo models of the murine cortical neuroepithelium, ethanol exposure did increase asymmetric cell proliferation [48]. In the mice exposed to alcohol at gestational day 12.5 and after micro-dissection of the dorsal telencephalon of the exposed fetal brain, Salem *et al.* [49] used a single-cell RNA sequencing approach to characterize 38 distinct neural subpopulations across 8 lineage subtypes, and showed that prenatal alcohol exposure increased the proportion of cells assigned to S-phase altering cell cycle and neural maturation and disrupted gene co-expression networks. In 15 days rat embryon, stem cells cultures derived from different embryonic brain regions were exposed to high alcohol concentration resulting in both gliogenesis and neurogenesis proliferations alterations, but the most profound effect was observed on glial phenotype [50]. According to Rubert *et al.* [51] in utero ethanol exposure impaired cell proliferation and decreased neurons and astrocytes generated in rat embryonic cerebral cortex. Thus, telencephalic cultures obtained at embryonic day 12 on ethanol-treated rats displayed a reduction in the proportion of actively dividing radial glie progenitor cells, and showed a reduced number of multipotent stem cells in cultures.

Collectively, these observations explain that developmental binge-pattern alcohol exposure-inhibited basal neuroblasts proliferation is susceptible to influence laminar thickness, neuron density, its subtype, size, shape, connectivity, resulting in impeded cortico-cortical development and functioning associated with FASD (Robertson *et al.* 2016) [52].

2.2. Aberrant Migration

Migration from the ventricular and germinal layers proceeds radially toward the medial/dorsal neocortex and tangentially into other regions of the forebrain

[53]. During the radial migration, the forming cerebral cortex, the so-called cortical plate becomes thicker and more stratified as more cells migrate from the ventricular zone [54]. On the one hand, using an established mouse model of FASD with binge-type prenatal alcohol exposure, Delatour *et al.* [55] reported aberrant radial migration of neuroblasts during embryonic corticogenesis. Alcohol-induced blocking of neuronal migration desynchronized cortical development and compromised normal neural network establishment [56]. For instance, heterotopias of cortical neurons, presumably due to defects of cortical migration, have been observed [57]. In addition, there is growing evidence linking prenatal alcohol exposure to GABAergic interneuronal migration defects predicting a subsequent cortical dysfunction [58]. Indeed, during the human cerebral cortex development, fine interactions between pyramidal cells and migrating GABA interneurons are required to orchestrate correct positioning of interneurons: The microcircuitry of the cerebral cortex depends upon precise interrelationships between inhibitory γ-aminobutyric acid (GABA) interneurons and excitatory (glutamatergic) pyramidal neurons [59]. In a rat model of fetal alcohol spectrum disorder, abnormal increases of GABA/glutamate ratio were observed in the medial prefrontal cortex [40] showing a neurobiological substrate of attention-deficit/hyperactivity disorders associated with FASD. Consequently, abnormal regulation of neuronal proliferation and migration during corticogenesis may impair the development of cortical microcircuitry leading to executive function deficits associated with FASD [14]. On the other hand, tangential migration was affected by prenatal alcohol exposure impairing neural crest migration and destabilizing cytoskeletal formation, causing disturbances to cell adhesion and motility; their directional migratory capacity was also lost [60] [61]. Both migrations of early and late generated neurons were delayed in rats following prenatal alcohol exposure [56]. According to Bâ *et al.* [1] [31], developmental alcohol exposure induced sparse pyramidal cells in the hippocampal CA3 field of the exposed pups, predicting aberrant migration; that effect of alcohol-induced disorganization of hippocampus CA3 field was counteracted by thiamine co-treatment during developmental alcohol exposure [1] [31], suggesting a role of thiamine in alleviating alterations of cognitive processes, whose regulation involves the hippocampus [2].

2.3. Impaired Differentiation

Studies showing the effects of alcohol on human cell differentiation during brain development are relatively scarce. However, a few can be cited. Using in vitro culture of human embryonic stem cells, Taléns-Visconti *et al.* [62] demonstrated that alcohol exposure impaired neurons progenitors survival, affected the differentiation of neuroblasts and glioblasts into neurons and astrocytes respectively, disrupted the actin cytoskeleton, and affected the expression of different genes associated with neural differentiation. In addition, alcohol exposure has altered cell-cycle regulatory gene expression and delayed cell differentiation of human

embryonic stem cells [63].

However, animal cells culture models yielded useful information on the effects of alcohol-induced impaired cellular differentiation. Differentiating neurons of the mouse fetal brain, pretreated with alcohol during the proliferation phase, exhibited reduced neurite branching and an increased length of primary neurites, indicating a persistent destabilization of neuronal maturation [64]. According to Serio *et al.* [65], alcohol altered differentiation-related gene expression and cell lineage specifications. For instance, using the fetal cerebral cortical neuroepithelial cells culture obtained from GD12.5 mouse, Camarillo and Miranda [64] showed that isolated alcohol-treated neural progenitors exhibited abnormal morphological transformation into radial glial-like cells. In addition, alcohol was demonstrated to inhibit the rat neuroectoderm differentiation which was correlated with epigenetic changes, such as the hypomethylation of several genes involved in neural development [66]. Moreover, Liu *et al.* [67] found that alcohol gestational exposure in mice caused neural tube defects through the alteration of DNA methylation (both hypomethylation and hypermethylation). Alcohol-mediated changes in DNA methylation, for-runner signs of DNA mutation were associated with impaired differentiation and subsequent cellular death, commonly found in neurodegenerative diseases [68]. These data help explain the increased incidence of neurodevelopmental disorders associated with fetal alcohol syndrome disorders.

Some preliminary attempts to explain the mechanisms of alcohol's action on neuronal differentiation have suggested the teratogen to anticipate embryonic stem cells differentiation by activating the nuclear transcriptional program controlled by the metabolite all-trans-retinoic acid of vitamin A [69]. This may induce eye opening precocity in alcohol exposed rats pups [35] since it is well known that vitamin A (retinol) is the key molecule triggering the visual cycle for phototransduction [35].

Similarly, Bâ [3] reported that alcohol and related thiamine deficiency exert efficient neurotoxic actions on differentiation processes. Indeed, our investigations compared developmental neurotoxicity evoked by three patterns of maternal thiamine deficiency (pre, peri and postnatal), with two patterns of maternal chronic alcohol intake (alcohol alone and alcohol + thiamine cotreatment), on seven neurodevelopmental abilities in rat pups [3]. The results showed that both developmental thiamine deficiencies and ethanol exposure produced two waves of neurofunctional alterations, peaking at P15 (postnatal day 15) and P25, respectively. The first peak of vulnerability was a prenatal event; it may interfere with the periods of intense cellular proliferation and migration. The second peak represented both perinatal and postnatal events; it may interfere with the periods of cellular differentiation, synaptogenesis, axonogenesis and myelinogenesis. Alcohol + thiamine cotreatment failed to reduce the first peak, but neutralized essentially the second peak. The results suggested that alcohol interferes with thiamine during cellular differentiation and membrane developmental processes

mainly. Indeed, among the three conditions of thiamine-deficient diet, only perinatal thiamine deficiency exhibited a closer relationship with developmental alcohol exposure. Together, these observations suggested that the critical period for alcohol–thiamine antagonism occurred perinatally and affected primarily cellular differentiation [3] [34].

2.4. Exacerbated Apoptosis

Inhibition of neuroblasts proliferation can generate apoptosis. Excessive cell apoptosis was also found in the cerebra of prenatal alcohol exposed fetuses [70] [71] for review of detailed apoptotic mechanisms]. Ikonomidou *et al.* [72] reported a regional vulnerability of the rat brain to alcohol-induced neuroapoptosis. Each brain region owns its time window during which neurons showed vulnerability to alcohol-induced apoptosis, and the timing of this vulnerability period was different from one region to another. Neuronal populations showing the early vulnerability to alcohol-induced apoptosis peaked at embryonic day 19 (E19) in hypothalamus and thalamus regions, and then peaking at postnatal day 3 (P3) in Subiculum, hippocampus and caudate regions. There was also a late vulnerability to alcohol-induced apoptosis peaking at P7 in cerebral cortices (frontal, parietal, temporal and cingulate) [72]. In addition, alcohol- induced apoptosis is cellular type- dependent [71]. In mice primary cells cultures exposed to alcohol, neurons showed a great vulnerability to alcohol-induced neuroapoptosis relative to astrocytes [73]. Investigations on rat hippocampus ontogeny revealed that the magnitude of alcohol-induced cell killing responses was significantly greater in the CA1 field than in CA3 and DG, which did not differ [74] [75] [76]. Similarly, alcohol killed more easily cerebellar granule cells compared to Purkinje cells, in neonatal-exposed rats [77]. According to Dikranian *et al.* [78], exposure of infant rats or mice to alcohol on a single occasion during synaptogenesis can kill Purkinje cells, and many other neuronal populations at all levels of the developing neuraxis, and in each case the mechanism of cell death was apoptosis. The ability of brief exposure to alcohol to cause widespread neuroapoptosis in the developing rodent brain resulted in long term learning/memory deficits that persisted through adolescence into adulthood [79].

Current literature reports several mechanisms of cell death induced by fetal brain exposure to alcohol. One mechanism points to mitochondria as a potential link between prenatal alcohol exposure and the brain damage that is characteristic of FASD. Indeed, mitochondria-linked cellular apoptosis is also reported in an animal model of prenatal acute exposure to alcohol [80]. For instance, rat primary cerebellar neuron cultures exposed to alcohol have significantly reduced expression of mitochondrial genes encoding mRNA for several electron transport chain protein complexes [81], impairing mitochondrial function and ATP production, increasing oxidative stress and DNA damages, thereby leading to apoptosis [71] [82]. In a mouse model, extended gestational exposure to alcohol resulted in an increased fraction of immature mitochondria in the fetal brain

and reduced activities of respiratory chain complexes I and IV, as well as ATP synthase triggering cellular death [71] [83].

Thiamine deficiency is also a trigger agent for developmental alcohol exposure-induced apoptosis. Results of our previous studies on the rat model of FASD suggest that alcohol provoked cellular atrophy and death by induction of B1 vitamin (thiamine) deficiency (TD) [1] [84]. It appeared that alcohol and TD trigger two different mechanisms of mitochondrial permeability transition (MPT) pore opening to induce cellular death: Alcohol promotes neuroapoptosis while TD triggers both neuroapoptotic and necrotic cellular deaths [71]. The term "mitochondrial permeability transition (MPT)" refers to an abrupt increase in the permeability of the outer/inner mitochondrial membrane. Due to osmotic forces, MPT causes a massive influx of water into the mitochondrial matrix, triggering the structural collapse of the organelle. Alcohol induces mitochondrial permeability transition (MPT) by cytosolic factors like Bcl-2 family proteins which open MPT pores in the mitochondrial outer membrane, resulting in rapid mitochondrial swelling and subsequent collapsus triggering apoptic cellular death [71]. Both pro-(Bak, Bax and Bid) and anti-apoptotic (Bcl-2, Mcl-1, Bcl-XL, A1 and Bcl-w) Bcl-2 family proteins may physically bind each other, forming channel-like proteins by the spatial disposition of pore-forming domains [85], that are ion-conducting channels directly involved in the permeabilization of the mitochondrial outer membrane induced by alcohol [71] [86]. Conversely, TD activates the translocation of CyP-D from the mitochondrial matrix to the mitochondrial inner membrane to form the MPT pore, which specifically triggers the necrotic cell death induced by both Ca^{2+} overload and ROS overproduction generated by TD. These two neurotoxicants can act synergistically to cause extensive cell death and tissue necrosis associated with FASD [71].

Finally, alcohol exerts direct cytotoxic effects on cellular membrane promoting apoptosis. Bâ *et al.* [1] [31] reported that histological studies of hippocampal sections of gestational alcohol-exposed rats pups showed more angular than pyramidal-shaped cells in the CA3 field compared to the control or saccharose groups. That breaking in cell membrane curvature was counteracted by thiamine administration during developmental alcohol exposure, showing that thiamine is involved in membrane stabilizing processes [87]. A direct mechanism by which ethanol induces cell death could be explained by the long-lasting effects of ethanol on cellular membrane leading to the peroxydation of its polyunsaturated fatty acids components. Ethanol probably interacts with phospholipid bilayers at the lipid-water interface, disorders the lipid chains by desaturation [88], and fluidizes the membrane lipids following an increased double-bond number in the membrane long-chain fatty acids [89] [90]. Thus, the lipoperoxidation process alters the polyunsaturated structure of long-chain phospholipid fatty acids leading to an impairment of membrane structure and function [91] and subsequent cellular death. These actions might explain developmental ethanol exposure-induced breaking of cell membrane curvature [1].

Altogether, the observed widespread loss of neurons, or their progenitors, from the developing brain would be a sufficient mechanism to explain neuronal networks failure in FASD-affected children. Thus, immature fetal brain exposed to alcohol undergoes massive neuron death [92]. According to Olney [93], within only a few hours after alcohol enters the developing brain, millions of brain cells that were on a healthy survival track, suddenly become derailed and commit suicide. The apoptotic response induced by alcohol depends on how rapidly the dose is administered and on how long the blood alcohol levels are elevated above a toxic threshold in the range of 180 to 200 mg/dl, *e.g.* binge-like drinking [72]. Loss of neurons reduces dendritic tree complexity and size, signifying there will be fewer axons to establish appropriate synaptic contacts [93]. The resulting deranged circuitry may be reconstituted by neural plasticity in the developing brain networks. However, Granato and Dering [92] suggested that developmental alcohol-induced massive cellular death was compensated by a maladaptive rearrangement of synaptic plasticity representing the main pathogenetic mechanism of the alcohol-induced damage to the developing brain. Such a circuitry reorganization is a dare for the brain of a fetus whose mother heavily abuses alcohol multiple times, both early and late, during pregnancy, thereby compromising the efficiency of neuronal computational networks weaving in FASD-affected children [93].

Overall, the results obtained in human and animal studies establish the anatomical, morphological, and neuropathological bases that may lead to the intellectual disability associated with FASD. However, cerebral functioning deficits in FASD require further investigation on the dendrites and axons growths, interneurons and myelinogenesis which implement synaptic connectivity and neuronal network during developmental alcohol exposure.

3. Axogenesis Alterations

In the developing nervous system, axons project through considerable distance to their targets in order to assemble neural circuits that control behavior [94]. Indeed, during embryonic development, each differentiating neuron sends out an axon that motility is guided by a growth cone located at its tip [95]. Migration and pathfinding of neuronal growth cones during neurite extension is critically dependent on dynamic microtubules [96].

Evidence of alcohol-induced altered axogenesis was reported in previous studies using a Golgi-like retrograde labeling of cortical projections neurons. On the one hand, Granato *et al.* [97] showed a disruption of cortico-cortical associative projections in rats exposed to alcohol during early postnatal life. In addition, prenatal exposure to alcohol caused multifaceted and permanent changes in the rat thalamo-cortical circuits [98], showing aberrant thalamo-cortical terminations in cortical layer Va and underlying the establishment of anomalous thalamo-cortical relationships [99]. On the other hand, prenatal alcohol exposure has reduced the size of the forelimb representation area in the rat motor cortex

[100]. Such a rewiring of the cortical network was likely to affect its functional features. However, molecular mechanisms of alcohol-induced alterations of neural circuitry ontogeny that ultimately underlies behavioral disturbances, as intellectual disability described in FASD, remain poorly understood and are the focus of our investigations on axogenesis. Most of the results obtained on alcohol-induced axogenesis disorders have been obtained on animal models of FASD. The study of alcohol effects on axogenesis focused on growth cones and their guidance molecules.

Axons, more specifically their highly dynamic tips known as growth cones, are chemoattracted by molecules and guidepost cells that could be utilized by the axons to orient towards the targets; the axons were guided along their routes in the developing nervous system [101]. For instance, during the formation of corpus callosum (CC), that large bundle which connects the two hemispheres of the brain, a spatiotemporal callosal axons guidance by guidepost cells and molecules is genetically programmed [102]; this is necessary for information inter-hemispheric transfer and processing and decision-making [103]. In developing CC, the guidepost molecules like Sema3C and Netrin-1, those receptors on growing axons are NRP1 and DCC respectively, attract both cingulate and callosal pioneering axons to the midline [101] [102]. Once callosal axons have been attracted to the midline by Sema3C/NRP1 signaling, Slit/Robo signaling repels the axons into the opposite cortex where they continue to their proper target [101] [103]. Aberrant axon guidance mimics some cellular, molecular, and behavioral phenotypes of FASD. Several studies indicate that alcohol exposure disrupts Sema3C/NRP1, Netrin-1/DCC and Slit/Robo signaling and functions, impairing growth cone responsiveness to guidance cues that could contribute to diverse CC abnormalities, including aberrant callosal axon growth as Probst bundles seen alongside severe FASD with complete or partial CC agenesis ([104]; see more details in a recent review of Mathews *et al.* [103]). While molecular guides posted at appropriate times are disorganized by in utero alcohol exposure, what about axonal growth cones' responsiveness to alcohol?

The interpretation given by previous studies on the alterations of growth cone responsiveness to alcohol is its simple intercalation inside the plasma membrane [105]. However, a growing body of evidence indicates that alcohol can act as a typical pharmacological agent that engages a ligand-receptor type interaction with a transmembrane multidomain protein, such as the L1 neural cell adhesion molecule (L1CAM), [106] [107]. Indeed, one mechanism of alcohol teratogenicity is the disruption of the functions of the L1 cell adhesion molecule (L1CAM), [61]. These functions include enhancement of neurite outgrowth, trafficking through lipid rafts, and signal transduction [108] [109]. L1, a transmembrane glycoprotein, is a cell adhesion molecule (CAM) and a member of the immunoglobulin (Ig) superfamily, predominantly expressed on axonal shafts and growth cones of developing neurons [110] [111]; it promotes axon outgrowth [112], fasciculation [113], and branching [114]. The transmembrane multido-

main protein complex structure of the L1CAM comprises six extracellular Ig domains, five fibronectin III, a short transmembrane domain and an intracellular domain [107]. According to Arevalo *et al.* [107], a three-dimensional structure of the extracellular domain of L1CAM shows the spatial disposition of four Ig domains (Ig1, Ig2, Ig3, Ig4) in a horseshoe structure facilitating multiple facets of interactions with several molecules, including alcohol, other L1CAM family members, integrins and extracellular matrix proteins [115] [116]. The cytoplasmic domain of L1CAM binds cytoskeletal anchoring proteins and transduces signals across the plasma membrane [117] [118] [119]. L1CAM is internalized in the central domain of growth cones where it can initiate MAP kinase signaling cascades [117] [118] [120] and then is recycled and re-inserted in the growth cone periphery [121]. Mutations in the human L1CAM gene can result in neurological syndromes showing common characteristics with FASD, including hydrocephalus, intellectual disability, and agenesis of the corpus callosum [122] [123]. These brain abnormalities are similar to those found in patients with FASD, suggesting that prenatal alcohol exposure targets L1CAM cellular adhesion function and/or intracellular signal-transducing [107] [124] [125] [126]. However, the effects of alcohol on L1CAM are controversial. Previous studies reported that alcohol either did inhibit cell-cell adhesion [124] [127] and disrupted L1CAM-mediated outgrowth [125] [126], or did not inhibit L1CAM-mediated adhesion [125] [128]. On the one hand, Hoffman *et al.* [129] reported that alcohol did not alter axonal polarization, L1CAM-dependent axon outgrowth or branching, or L1CAM recycling in axonal growth cones of developing rat cortical neurons. Even L1CAM would play a more important role in axon branching than outgrowth, and that alcohol inhibition on L1CAM would depend on neuronal context [129]. In addition, alcohol had no effect on L1 distribution to the growth cone or its ability to be expressed on the cell surface as determined by confocal microscopy [130]. On the other hand, Sepulveda *et al.* [104] have determined that even low concentrations of alcohol could render axonal growth cones less motile and insensitive to several guidance cues, but remarkably, this sensitivity would be substrate dependent. Alcohol likely would inhibit L1CAM-mediated neurite outgrowth by retarding L1CAM trafficking/signaling through a lipid raft compartment [108] [130]. Structure-activity analysis of various alcohol straight-chain, branched-chain, and cyclic alcohols revealed surprisingly strict structural requirements allowing alcohol inhibition of L1CAM-mediated cell-cell adhesion [131]. The efficiency of alcohol inhibition on L1CAM did increase as a function of carbon chain length [124] [127]. These findings suggest that ethanol and other small alcohols could inhibit L1-mediated cell-cell adhesion by binding within a well defined, hydrophobic pocket of a target protein [132]. Actually, the molecular mechanisms of alcohol binding on L1CAM seem to be outlined. Recent issues locate alcohol binding site within a hydrophobic pocket bordered by Glu-33 and Tyr-418 whose proximity derives from allosteric positioning between the Ig1 and Ig4 domains of L1CAM [107] [132]. Dou *et al.* [132] suggest that alcohol

binding within a pocket bordered by Glu-33 and Tyr-418 inhibits L1 adhesion by disrupting the Ig1-Ig4 interaction. Consequently, during the neural processes of migration and morphogenesis, L1CAM appeared to be involved in the organization and function of synaptic networks, which determine neuronal plasticity. Alcohol induces functional disturbance of L1 cell adhesion molecule and compromises synaptic networks organization causing deficits on cognition and learning related FASD. However, developmental alcohol intoxication could also cause a failure in neuronal network building through dendrogenesis worsening.

4. Dendrogenesis Alterations

Dendrite growth is a postsynaptic neuronal process which plays a key role in synapse formation and dendritic anomalies are the most consistent anatomical correlates of intellectual disability [133]. The study of animal models of FASD showed the significance of dendritic pathology in FASD-associated synaptic circuitry failure. The dendritic tree of pyramidal neurons, with its long and extensively ramified branches, must be considered the main computational device of the neocortex [134]. Severe dendritic changes are the reflections of generalized cortical dysfunction and profound cognitive impairment [135]. Dendritic spines are specialised membrane protrusions of neuronal dendrites that receive the majority of excitatory synaptic inputs [136]. The degree of dendritic spine loss and abnormality is related to the severity of intellectual disability [137]. Over the course of normal development, long, thin spines commonly found in immature networks are replaced in later stages by shorter, more stubby spines [138]. In normal children, the spines that appear on the dendrites of cortical neurons are short and thick, whereas in children with intellectual disabilities these spines become abnormally long and thin [137].

Maternal binge-type alcohol intake induces both permanent spine and dendritic tree dysmorphogenesis in the rat pup's CA1 pyramidal neurons, which is likely to change their firing patterns [139]. Cytoarchitecture of dendritic microstructure was analyzed using the Golgi method. On the one hand, in rats prenatally exposed to alcohol, the spine distribution in proximal apical dendrites of layer V pyramidal cells of the parietal cortex exhibited a persistent predominance of long, thin and entangled spines, and a decreased number of normal stubby and mushroom-shaped spines [140]. On the other hand, postnatal binge-like alcohol exposure decreases basilar dendritic tree complexity in pyramidal neurons of the rat prefrontal cortex layer II/III [141] and reduces spine density [142]. Another method using transmission electron microscopy to analyze DiI diolistic labeling of dendritic spines of pyramidal cells in the mouse visual cortex observed that prenatal alcohol exposure induces persistent ultrastructural changes including decreased dendritic spines density, increased spines length, decreased numbers of synaptic vesicles and narrowed synaptic cleft, the whole affecting visual functions [143].

Moreover, Yanni and Lindsley [144] utilized quantitative morphometric anal-

ysis by double-immunofluorescent staining of MAP2 and synapsin I, to examine the effects of alcohol on the subsequent development of dendrites and synapses respectively in rat hippocampal pyramidal neurons cultures. They found decreases in total dendritic length per cell, dendrite number per cell, length of individual dendrites and synapse number per innervated dendrite. Consequently, alcohol produces a decrease in the number of synapses which correlates with reduced dendritic length, promoting a compensatory spines elongation. However, a computational model has been used to infer rules governing dendritic growth of layer II/III associative pyramidal neurons in a rat model of fetal alcohol spectrum disorders. Basal dendrites were studied in adult rats exposed to alcohol during the first postnatal week. Results suggest that alcohol exposure during early postnatal life affects mainly the branching of dendrites rather than their elongation [145]. In addition, by employing a mouse model of FASD, Delatour *et al.* [55] showed that prenatal ethanol exposure also altered the density and morphology of spines along the apical dendrites of cerebral cortical pyramidal neurons. Indeed, in cultured rat hippocampal neurons exposed to chronic alcohol exposure, network activity assessed by imaging of [Ca(2+)]i variations, was markedly reduced with a significant reduction in the density of mature dendritic spines; this decrease of network activity was associated with a reduction in rates of miniature excitatory postsynaptic currents mEPSCs [146]. Dual whole-cell recordings from the soma and distal apical dendrites were performed in cortical pyramidal neurons of young adult rats exposed to alcohol during the first week of postnatal life [147]. Following the injection of depolarizing current into the dendrites, layer V pyramidal neurons from alcohol-treated animals displayed a lower number and a shorter duration of dendritic spikes, attributable to a downregulation of calcium electrogenesis. As a consequence, the mean number of action potentials recorded at the soma after dendritic current injection was also lower in alcohol-treated animals [147].

Furthermore, dendritic spine formation, morphology and synaptic functions are governed by the actin cytoskeleton. It has been reported that alcohol exposure affects the levels, assembly and cellular organisation of the actin cytoskeleton in the primary culture of rat hippocampal neurons [148]. In addition, immunocytochemistry labelling of doublecortin, a microtubule protein expressed early in differentiating neurons, showed its reduction in newly generated cells of the adult rat hippocampus after four weeks of alcohol drinking. Morphological analyses of doublecortin-positive cells revealed that four weeks of alcohol treatment reduced the size of the dendritic tree including the total length of apical dendrites, number of nodes and endings [149]. Together, these changes may be related to the dysfunction in the memory and learning processes present in FASD-affected children.

5. Synaptogenesis and Synaptic Plasticity Alterations

Synaptogenesis is a process that concerns the most elementary part of the con-

struction of the central nervous system (CNS), *i.e.* the CNS wiring. Synapse formation is the postnatal quintessential process by which neurons form specific connections with their targets to enable the development of functional circuits [150]. It is the stage of development that will bring a neuron A into contact with a neuron B. The area of contact is called a synapse, which defines the pre- and post-synaptic elements. A circuit generally refers to a set of interconnected neurons performing a specific function. Dendrites and axon terminals can be in a state of perpetual movement and reciprocal adjustment throughout our lives, a phenomenon that contributes to the synaptic plasticity underlying learning [151]. Thus learning and environmental experience constantly modify neural circuits forming the functional units of the neural network [152]. Changing synaptic strength is widely believed to be a cellular mechanism underlying the storage of information in the brain [153]. The most appropriate cellular model for studying learning would be the assessment of relevant neuronal activity, *i.e.* long-term potentiation (LTP), that would result in lasting changes in synaptic weights, *i.e.* synaptic plasticity, distributed throughout brain networks [151] [153]. At this level of analysis, too, the main results obtained on alcohol-induced disorders of synaptogenesis have been obtained in animal models of FASD.

Ultrastructural studies showed a delayed synaptogenesis and immature appearance of the presynaptic grid in the cerebellum of rat prenatally exposed to alcohol [154]. Within a single synaptic junction, prenatal alcohol exposure has affected the expression levels of synaptic proteins such as synapsin 1 and of other proteins of the pre-synaptic (GAP-43, synaptophysin, synaptotagmin) or post-synaptic machinery (MAP 2 and neurogranin), [54].

Behavioral studies indicated that rats pups exposed to alcohol during gestation showed impaired contextual fear conditioning and reduced memory performance which was consistent with a decrease in LTP as compared to controls [21]. In addition, irreversible cognitive deficits induced by alcohol exposure during fetal life have been ascribed to a lower NMDA-dependent synaptic LTP in the rat hippocampus. In humans, adolescent alcohol exposure caused altered synaptic remodeling and neurogenesis in key brain regions leading to adult psychopathology such as anxiety and alcoholism [155].

Physiological studies showed that long-term potentiation (LTP) is a form of synaptic plasticity, and occurs via N-methyl-D-aspartate type glutamate receptor (NMDAR) dependent mechanisms [140] [156] [157]. Indeed, NMDA receptors are presumed to be the most sensitive targets of alcohol in immature neurons and are implicated in different types of learning and memory [158]. Altered NMDAR function following developmental alcohol exposure has been observed in the rat hippocampus [159]. According to Puglia and Valenzuela [160] prenatal alcohol exposure in rat, equivalent to the third trimester of human pregnancy, inhibited both glutamatergic transmission and LTP induction in the hippocampus, which could alter synapse refinement and ultimately contributed to the pathophysiology of fetal alcohol spectrum disorder. Whole-cell patch-clamp re-

cordings in hippocampal slices from neonatal rats showed that alcohol decreased glutamate release via inhibition of N-type voltage-gated Ca^{2+} channels [158]. In addition, in the mouse model of neonatal alcohol exposure, electrophysiological recordings showed that alcohol inhibited NMDA receptor excitatory postsynaptic currents (EPSCs) in pyramidal neurons and interneurons in the cortex [159]. Moreover, in the rat experimental model of FASD, Granato *et al.* [135] demonstrated that the generation of Ca^{2+} spikes in the apical dendrites of layer 5 pyramidal neurons was strongly impaired. Calcium spikes were required to induce synaptic plasticity [148] [161]. A derangement of dendritic Ca^{2+} signaling predicted dendritic channelopathies [162], compromising synaptic plasticity, a prelude to intellectual disability. These observations suggest that developmental alcohol intoxication inhibits glutamate release to block LPT via Ca^{2+} signaling disorder, thereby impairing synaptic plasticity processes underlying learning and memory.

Moreover, the literature reported more details on the role of NMDAR subunits regulating the effects of alcohol on the NMDA receptors-induced synaptic plasticity. Thus, NMDA receptors were durably down-regulated into adulthood following early alcohol exposure [163] [164]. In addition, Kervern *et al.* [165] reported that perinatal alcohol exposure in rats increased GluN2B subunit expression in the synaptic compartment; blocking GluN2B containing NMDA receptor prevented LTP. These results corroborate the findings of Ster *et al.* [166] showing that a greater proportion of synaptic GluN2B subunit-containing receptors is typical for less mature synapses. As a consequence of increased expression of GluN2B subunits, Ster *et al.* [166] observed increased proportions of immature filopodia-like dendritic protrusions at the expense of thin-type dendritic spines in CA1 pyramidal cells, accompanied by a decrease in dendritic arborization. Consequently, increased GluN2B containing NMDA receptor in the synaptic compartment is responding to the effects of alcohol-induced aberrant synapses.

We have described the effects of alcohol on glutamate receptors involved in synaptic plasticity. Glutamate is the most prevalent neurotransmitter released by excitatory neurons in the central nervous system (CNS) while gamma-amino butyric acid (GABA) is one of the main CNS inhibitory neurotransmitters. GABA interneurons have been involved in the neural network scaffolding and refinement. What are the effects of developmental alcohol intoxication on these GABA interneurons?

6. GABAergic Neurons Abnormalities

GABA is present at approximately one third of all synapses in the central nervous system and shapes neural network dynamics via GABAergic interneurons [167]. During mammalian brain development, GABAergic interneurons, which constitute approximately 20% - 30% of the neurons in the cerebral cortex, originate mostly from proliferative zones that produce largely distinctive interneuron

populations [168].

Interneurons generated in proliferative zones migrate tangentially to the subcortical regions and radially into the developing cortical layers [169] [170]. After reaching their final destinations in the cortical and subcortical brain tissues, interneurons undergo further diversification through four main classes of cortical interneuron defined by the markers PV, SST, RELN and VIP each sending axonal projections to target different cellular compartments of excitatory pyramidal neurons [171]. PV+ cells directly target the neuronal soma of pyramidal neurons to reduce neuronal firing, whereas SST+ and RELN+ cells target mainly the distal dendrites to regulate the integration of excitatory synaptic inputs. VIP+ neurons, by contrast, target both SST+ and PV+ inhibitory neurons and thus mediate disinhibition of pyramidal neurons [168] [172]. These molecularly and functionally defined interneurons integrate into the developing cortex in coordination with glutamatergic neurons to establish Excitatory/Inhibitory balance in cerebral cortex circuits [173] [174]. In a fully developed brain, the GABAergic network modulates neural circuit activity through two major modes of inhibition: phasic and tonic. Phasic inhibition is mediated mainly by action potential-induced presynaptic GABA release, which triggers chloride currents passing through ionotropic GABA type A receptors at postsynaptic sites to provide temporally precise inhibition that rises and decays within hundreds of milliseconds [171]. As a result, GABAergic signaling may be involved in developmental disorders affecting neural plasticity, stress reactivity, sensory processing, memory formation and attention [167] [171].

Alcohol developmental exposure suggests subtle defects of neuronal networks related to the aberrant GABAergic interneurons. The cerebral cortex is targeted by in utero alcohol toxicity. Prenatal alcohol exposure in animal models resulted in excitatory-inhibitory imbalance in the neocortex due to alterations in the GABAergic interneuron differentiation and migration. Indeed, Skorput *et al.* [175] reported that gestational exposure to alcohol increased the density of migrating GABAergic cortical interneurons in mice pups; this effect persisted in young offspring with GABAergic transmission increased shifting the inhibitory/excitatory balance toward favoring inhibition. Thus, excitatory-inhibitory imbalance may underlay intellectual disability in individuals with fetal alcohol spectrum disorders (FASD) [55] [176]. During differentiation of human pluripotent stem cell-derived neurons, alcohol significantly altered the expression of genes inducing GABAergic interneuron specification, pointing to incomplete neuronal differentiation as an underlying mechanism of intellectual disability in FASD [176]. Indeed, gestational exposure to alcohol has been reported to alter the disposition of tangentially migrating GABAergic cortical interneurons in mice. By limiting alcohol exposure in utero to the gestational window when tangential migration was at its height, Skorput *et al.* [175] reported that the aberrant tangential migration of GABAergic interneurons persisted as an enduring interneuronopathy in the medial prefrontal cortex, later in adult mice prenatally ex-

posed to alcohol. Behavioral testing on the same offsprings exhibited impaired reversal learning in a modified Barnes maze, indicative of decreased prefrontal cortex-dependent behavioral flexibility, and heightened locomotor activity in open field test [175]. In addition, prenatal alcohol-exposed rat pups showed impaired arousal which was mediated or modulated by GABAergic mechanisms [177]. Impairment of excitatory synaptic transmission contributed to indelible abnormal formation of neuronal circuits in both developing hippocampus [178] [179] and cortex in vitro, which were suggestive of mechanisms leading to intellectual disability in fetal alcohol spectrum [175] [180].

Furthermore, the function of neurons in the cerebellar cortex is tightly controlled by GABAergic inhibitory inputs provided by specialized interneurons: Purkinje cells. These Purkinje cells form a singular layer inserted between the granule and molecular layers interface. These highly specialized GABAergic interneurons provide powerful inhibitory input to deep cerebellar nuclei neurons, regulating their activity [181]. The cerebellum is also one of the main targets of in utero alcohol toxicity. Within the cerebellum, Purkinje cells (PCs) are highly sensitive to alcohol. PCs constitute the sole output of the cerebellar cortex and thus have a central functional role in information integration [182]. Children with fetal alcohol spectrum disorder (FASD) show many symptoms associated specifically with cerebellar deficits. Thus, developmental alcohol exposure impaired the development of cerebellar circuitry following the loss of PCs, which could result in modifications of the structure and function of other brain regions that receive cerebellar inputs, thereby inducing cerebellar degeneration and motor coordination [183]. PCs from rat pups treated with alcohol on postnatal days 4 - 6 showed a significantly increased number of inhibitory postsynaptic potentials resulting in important hyperpolarization current [184]. Servais *et al.* [182], using a mouse model of FASD, reported that Purkinje cells prenatally exposed to alcohol presented decreased modulator capacity of voltage-gated calcium current and increased inhibitory firing rates which contributed to ataxia and motor learning deficits observed in fetal alcohol syndrome. Their results showed that calcium dysregulation-related neuronal dysfunction is central to the pathogenesis of the neurological manifestations of fetal alcohol syndrome.

7. Myelinogenesis Alterations

Oligodendrocytes are responsible for the formation of myelin sheath by wrapping axons allowing rapid and efficient saltatory propagation through the nodes of Ranvier. It has been recently demonstrated that once myelinated, the long-term integrity of axons depends on the glial supply of metabolites and neurotrophic factors. In rodents, oligodendrocyte maturation occurs mainly after birth and is a process extremely susceptible to stress [185]. A failure of oligodendrocytes to assure axon insulation and functionality might cause the reduction of neuronal connectivity and information processing speed producing a brain with a fundamentally altered organization, which then translates to alterations in adult cog-

nitive function [186].

Experimental rodent models of FASD have shown increased oligodendrocyte precursor cells apoptosis and altered oligodendrocyte differentiation [187]. Cantacorps *et al.* [188] reported that maternal binge-like alcohol consumption in mice caused myelin damage in the brains of offspring *i.e.* myelin-associated glycoprotein, myelin basic protein and myelin proteolipid protein levels were reduced, and that such effects may underlie the persistent cognitive and behavioural impairments observed in FASD. A FASD rat model showed white matter atrophy associated with neurodegeneration due to targeting of myelin and oligodendrocytes [189]. In a mouse model of FASD, Newville *et al.* [190] reported acute oligodendrocyte loss with persistent white matter injury impairing neural transmission and cognitive development. In addition, alcohol inhibited de novo sphingolipid biosynthesis, reducing white matter myelination, including the corpus callosum, in the rat brain and promoting cognitive impairment [189] [191]. Moreover, the nuclear transcription factor Nfia controls gliogenesis, cell proliferation and neuronal survival by regulating the expression of target genes. Microarray analysis revealed that a significant number of the Nfia-target genes (Aldh1a, Folh1, Gjb6, Fgf1, Neurod1, Sept4, and Ntsr2) expressions were altered in mice offspring by maternal binge alcohol consumption [192].

Myelin is a specialized membrane that has a very high dry mass of lipids (70% - 85%) compared with proteins (15% - 30%), [193]; white matter in the brain and spinal cord is a compilation of myelinated axons. Regulation of myelin is considered as a new form of neural plasticity due to its profound impacts on the computation of neural networks [28]. In adult men, neuroimaging studies have found that chronic alcohol exposure was associated with white matter damage [194], with frontal lobes being particularly affected [195]. White matter microstructure was often probed through the use of fractional anisotropy (FA) values, as a measure of white matter integrity [28]. Fractional anisotropy (FA) allowed measuring the degree to which water motion is restricted along the tract length (axial diffusion), with axonal walls and myelin sheaths serving as barriers to the flow of water across the tract (radial diffusion), [196]. According to Rice and Gu [28], while alcoholism ratings increased, white matter fractional anisotropy (FA) values decreased. Axonal and myelin loss increased both water axial and radial diffusivities following intracellular structures loss, thereby decreasing FA values (resistance to water molecules motion and diffusion) in alcohol-injured white matter. Following that investigation method, McEvoy *et al.* [196] reported 12 major white matter tracts to be altered in heavy drinkers and such microstructural abnormalities impaired cognitive performance [194] [196] [197]. White matter structural deficits are also often found in children with FASD. Using diffusion tensor imaging for white matter microstructural evaluation in FASD-affected children, Fan *et al.* [198] reported decreased FA values in cerebellar peduncles which forms large bundles of myelinated nerve fibers connecting the cerebellum to the brainstem; these values showed a close correlation with impaired myelina-

tion and poorer eyeblink conditioning. Similarly, Sowell *et al.* [199] showed disorganization and reduced density of myelinated axon tracts, leading to atrophy and degeneration of white matter in children with FASD, thereby impairing executive function [200]. Indeed, prenatal alcohol exposure did increase oligodendrocyte cytotoxicity *i.e.* excessive apoptosis, reduced differentiation and delayed maturation of oligodendrocytes in human fetal brain [201]. Thus, alcohol exposure caused demyelination in different brain regions, often accompanied by deficits in cognition and emotion [28]. The white matter damages found in several regions were dose-dependent [187]. Multiple regression models indicated that cortical white matter impairment partially mediated adverse effects of prenatal alcohol exposure on information processing speed and eyeblink conditioning [198].

Most of the adverse effects of alcohol on the fetal brain have been studied in animal models. Whether the obtained results can be transferred from animal to human is questionable.

8. Comparative Studies of Human and Animal Models of FASD

FASD-related research conducted in humans has developed a lot of renewed techniques to examine associations of regional brain tissue excesses or deficits with degrees of prenatal alcohol exposure (**Table 1**). Frequently, morphometric methods were used for structural imaging analyses of alcohol adverse effects on the human fetal brains [202]. For instance, a recent method used, *i.e.* magnetic resonance imaging (MRI) pushed forward the study of brain developmental abnormalities by allowing for in vivo measurements of the teratogenic effects of alcohol [203], thereby providing more information about the brain damage associated with FASD. Thus, increases or reductions in brain volumes represent a neurobiological signature of fetal alcohol spectrum disorders. However, these techniques are limited because of ethical problems associated with the manipulation of human fetal brain organs in vitro, when assessing the degree of alcohol intoxication. Conversely, rodent models have been essential in identifying structural insults and behavioral deficits of prenatal and postnatal alcohol exposures. However, experimental models outcomes are extremely diverse based on alcohol level, pattern, timing, and method of alcohol exposure, as well as the histological and behavioral domains assayed and paradigm used [18]. Indeed, **Table 1** shows a battery of technical investigations deployed for tissues analyses in developmental alcohol-exposed animals, including cells culture, histology, biochemistry, neurochemistry, immunocytochemistry, etc. used in studies of axogenesis, dendrogenesis, interneurons, myelinogenesis, or in the diagnosis of localized lesions. These technical investigations are not suitable for the human fetal brain, thereby complicating the translation of animal results to the human. While animal models show quantifiable alcohol intake and degree of alcohol intoxication on fetal brain tissues, reliable history of mother binge-like drinking

Table 1. Comparison of human and animal models of FASD.

	Animal					Human				
Tissues, structures, and nuclei	**Alcohol exposure pattern and timing**	**Equivalent of human gestation**	**Structural or functional alterations**	**Behavioral disorders diagnosed later in life**	**Authors**	**Exposure timing**	**Age (years)**	**Structural or functional alterations**	**Behavioral disorders diagnosed later in life**	**Authors**
Axogenesis	Ethanol exposure during the last week of fetal life; during the first postnatal week in rats	Second and third trimesters	Thinner thalamic-recipient zone of sensorimotor cortex; aberrant thalamo-cortical terminations in layer Va; disruption of cortico-cortical associative projections	Dysfunction of thalamo-cortical relationships and altered information integration	Minciacchi *et al.* 1993 [99]; Granato *et al.* 2003 [145]	–	–	–	–	–
Dendrogenesis	Postnatal binge-like alcohol exposure on PD 4-9 in rats	Third trimester	Altered basilar dendritic complexity of layer II/III neurons in the medial PFC; decrease in both length and number of intersections connected to the neuronal soma.	Inefficient innervations of the soma and basilar dendrites by thalamic projections and thereby reducing performance on prefrontal-dependant behavioral tasks	He *et al.* 2005 [149]; Hamilton *et al.* 2010 [141]	–	–	–	–	–
	Postnatal binge-like alcohol exposure on PD 4-9 in rats	Third trimester	Decreased spine density in layer II/III neurons of medial PFC; Reduced dendrite number of nodes and endings	Functional deficits in this cortical area	He *et al.* 2005 [149]; Whitcher and Klintsova 2008 [142]	–	–	–	–	–
	Chronic alcohol exposure from pregestational stage until weaning in rats	First, second and third trimesters	Higher proportion of stubby or wide spines, but decreased percentage of thin spines	Thin spines may propagate the synaptic potentials more efficiently than stubby or wide spines, causing altered electrical excitability	Tarelo-Acuña *et al.* 2000 [139]	–	–	–	–	–
Interneurons	Binge-type ethanol exposure on GD13-GD16 in mice, rat model of fetal alcohol spectrum disorder	Second and third trimesters	Aberrant migration and loss of GABAergic interneurons, indelible abnormal cortical and hippocampal circuits, disturbances of GABA/glutamate ratios in medial prefrontal cortex (mPFC)	Synaptic excitatory-inhibitory imbalance causing attention-deficit/hyperactivity disorders	Skorput *et al.*, 2015 [175]; Delatour *et al.* 2020 [55]; Tang *et al.* 2019 [40]	–	–	–	–	–
Synaptogenesis and synaptic plasticity	Binge-type ethanol exposure on GD13.5-GD16.5 and P7 in mice	Second and third trimesters	Delayed synaptogenesis, Impaired synaptic connectivity and plasticity	Impaired fear conditioning, reduced memory performance	Lovinger and Abrahao, 2018 [156]; Bird *et al.* 2020 [159]; Almeida *et al.* 2020 [54]	Adolescent alcohol exposure	–	Altered synaptic remode-ling and neurogenesis in key brain regions	Anxiety, high levels of emotion and impulsive behavior, arresting the development of executive function	Kyzar *et al.* 2016 [155]
Myelinogenesis	Maternal binge-like alcohol consumption in during gestation and lactation in mice	Second and third trimesters	Oligodendrocyte precursor cells apoptosis and altered differentiation, myelin damage in both prefrontal cortex and hippocampus; white matter injury	Impaired cognitive functions and motor coordination	Newville *et al.* 2017 [190]; Cantacorps *et al.*, 2017 [188]	Prenatal alcohol exposure	10 years 12.2 - 21.4 weeks gestation	Poorer myelination in cerebellar peduncles Dysmyelination, Disruption of white matter integrity	Visual-motor Deficits Changes in executive function	Fan *et al.*, 2015 [198]; Sowell *et al.* 2008 [199]; Gautam *et al.* 2014 [200]; Darbinian *et al.* 2021 [201]
White matter	Binge model of early prenatal alcohol exposure in sheep; and posnatal in mouse	First trimester and third trimesters	Lesions in the temporal, parietal, and occipital white matte; white matter atrophy in the corpus callosum and mPFC	Cognitive impairment; Long-lasting effects on neurobehavioral functions	Watari *et al* 2006 [210]; Rice and Gu 2019 [28]	In utero exposure to alcohol	Shortly after birth; age range 6 - 17	White matter atrophy, particularly in frontal lobes; Brain white matter microstructure damaged	Persistent impaired cognitive and executive functions	Gautam *et al.* 2014 [200]; Darbinian and Selzer 2022 [187]

Continued

Cerebral cortex	Chronic alcohol exposure on GD 10 to 21 in rats, and throughout gestation in mice and rats	Second and third trimesters	Delayed pyramidal neurons migration and cortical stratification, thinning and Heterotopias in the cerebral cortex, altered development of the frontal lobe and impaired functional connectivity in the mPFC	Information integration and processing disorders, impaired executive functions	Miller 1993 [56]; Fukui and Sakata-Haga 2009 [38]; Tang *et al.* 2019 [40]	In utero alcohol exposure	Preadolescent children with FASD	Smaller volume of grey matter, thinner cortex, reduced functional connectivity between cortical and deep grey matter structures	Impaired executive function with cognitive/ behavioral deficits	Donald *et al.*, 2015 [26]; Robertson *et al.* 2016 [52]; Kingdon *et al.* 2016 [14]; Rice and Gu 2019 [28]
Lateral ventricule	Chronic alcohol exposure on GD 10 to 21 in rats; Binge-like exposure from GD12 to 15	Second trimester	Dilation of the lateral ventricles, hypoplasia of the septum	Hydrocephalus	Sakata-Haga *et al.* 2004 [37]; Sudheendran *et al.* 2013 [47]	Binge-like exposure during pregnancy	Gestational age: 5 - 12 weeks.	Abnormalities in the formation of the lateral ventricle walls; ventriculo-megaly	?	Konovalov *et al.* (1997) [215]; Lebel *et al.* (2011) [203]
Corpus callosum	Binge model of early prenatal alcohol exposure in sheep	First trimester	Loosely bundled corpus callosum; enhanced corpus callosum and optic radiation white matter	Impaired information processing	Watari *et al.* 2006 [210];	Prenatal alcohol exposure	Under 5 years to adulthood	Alterations in the shape and volume of the corpus callosum, corpus callosum atrophy	Impaired executive function, visual and logical memories	Bookstein *et al.* 2002 [30]; Donald *et al.* 2015 [26];
Hypothalamic-pituitary adrenal axis	Binge-like prenatal ethanol exposure on GD7 in mice	Second trimester	Elevated corticosterone and adrenocorticotropic hormone (ACTH) levels	Increased anxiety-like behavior	Wieczorek *et al.* 2015 [214]	–	–	–	–	–
Hippocampus	Binge alcohol exposure on GD 10 to 21 in rats/on P1 throughout P8 in mice and rat	Second and third trimester	Aberrant distribution of mossy fibers, apoptosis, more cornered and ectopic pyramidal cells in the hippocampus in CA1, CA3 and GD	Defect of spatial memory	Bâ *et al.* 1999 [1]; Sakata-Haga *et al.* 2003 [41]; Smith *et al.* 2015 [76]	Binge-like drinking throughout pregnancy	Children with FASD	Small hippocampi; hippocampus more deformed at the head and tail	Cognitive deficits	Autti-Rämö *et al.* 2002 [23]; Joseph *et al.*, 2014 [180]; Glass *et al.* 2014 [24]; Cardenas *et al.* 2014 [25]
Cerebellum	Chronic alcohol exposure on GD 10 to 21 in rats/ P4-9 in mice	Second and third trimester	Fusion of cerebellar folia and disruption of the cortical structure, losses of Purkinje and granule cells	Delayed motor development and ataxia	Sakata-Haga *et al.* 2001 [36]; Fukui and Sakata-Haga 2009 [38]	Prenatal alcohol exposure	Children (13 years)	Smaller cerebellar volumes; hypoplastic cerebellar hemispheres	Impaired basic fine motor skills, attention deficits	Autti-Rämö *et al.* 2002 [23]; Cardenas *et al.* 2014 [25]; Donald *et al.*, 2015 [26].
Brain weight	Binge-like alcohol exposure on postnatal day (PD) 4 trough 10 in rats	Third trimester	Reduced weight of the whole brain, forebrain, and cerebellum	Microencephaly and related disorders	Bonthius and West 1988 [32]	Binge-like drinking during first, second, and third trimesters	Infants	Reduced brain weight, reduced brain volume, reductions in frontal, temporal, parietal and occipital lobes.	Microencephaly and related disorders	Lebel *et al.* (2011) [203]; Feldman *et al.*, 2012 [204].

Effects of maternal chronic alcohol intake and/or binge-like drinking during equivalents of the first, second and/or third trimesters of human gestation on fetal brain main tissues, structures and nuclei are presented in animals models. Generally, studies have investigated abnormal aspects of nuclei in both human and animal models. Consequences of fetal brain structural alterations on behavioral disorders diagnosed later in life are shown in both models. However, quantifications of alterations on fine structures like axogenesis, dendrogenesis, interneurons and myelinogenesis are missing in human models, which are perhaps unattainable for ethical consideration and technical difficulties to perform in vitro studies, complicating the study of human fetal brain computational networks failure related to FASD. GD = Gestational Day; PD = Postnatal Day.

and critical doses of such exposure have yet to be specified in human studies where the most clinically significant and consistent consequences occur following heavy exposure. Thus, the use of human models remained very inflexible, due to the difficulty of verifying drinking patterns, number of binge episodes, the maximum number of daily intakes, evidence of a threshold and timing of exposure [204]. To address these weaknesses in human studies, animal gestation ages were fractioned into first, second or third trimester equivalents of human gestation for a best understanding of FASD (**Table 1**). Therefore, the effects of

alcohol exposure can be different throughout gestation [144]. During the first trimester equivalent of human gestation, alcohol exposure induced increased apoptosis [1] [57] [71] [81], impeded neural tube and crest development, leading to microcephaly [205], and hydrocephaly [206]. During the second trimester, alcohol exposure impaired neuronal proliferation and migration [3] [207] [208] leading to differentiation failure, cellular atrophy and ectopias [1] [35] [209]. During the third-trimester equivalent of human gestation, alcohol exposure affects synaptogenesis, axogenesis, dendrogenesis and myelinogenesis [3] [210], leading to permanent functional deficits of the CNS [3] [31] [35], including learning and memory disorders [211].

Another concern is that humans seldom expose themselves or fetuses to pure alcohol, meaning that FASD in humans could very well be driven in part by co-exposures, making the experimental models unreliable for fully understanding human disease. Adiong *et al.* [212] reported some aspects of these recurrent questions from clinical studies: "An increasing number of my patients are asking about the safety of consuming non-alcoholic beer and other alcohol-free versions of alcoholic beverages during pregnancy and breastfeeding, as they believe that these drinks might be a 'safer' alternative to regular alcoholic beverages. What are recommendations on mothers' risks regarding these products? Authors' answer to the asked questions: "Such drinks might contain higher alcohol levels than what is indicated on their labels. As there is no known safe level of alcohol intake in pregnancy, abstinence from non-alcoholic beverages would eliminate any risk of fetal alcohol spectrum disorder" [212]. Indeed, women predominantly assessed the risk of their drinking in terms of the kinds of alcoholic beverages consumed rather than alcohol content [25]. Both studies on human and animal models confirmed that even low to moderate levels of exposure can have deleterious consequences for the fetus [24] [213]. Consequently, women should continue to be advised to abstain from alcohol consumption from conception throughout pregnancy and even during breastfeeding [204].

9. Conclusion

This study points out neuronal network scaffolding impairment as a key mechanism underlying intellectual disability in FASD-affected children. Alcohol-induced aberrances underlying FASD occurs ostensibly during gestation and early postnatal periods with perduring effects in adulthood. Several hypotheses have led regarding potential cellular and molecular mechanisms to explain cognitive dysfunction associated with FASD. These mechanisms involve windows of vulnerability to alcohol intoxication that are proliferation, migration, differentiation, apoptosis, and synaptogenesis, the alteration of which compromises developing neural circuits and networks in the fetal brain. Protecting these potentially sensitive windows of brain vulnerability against alcohol cytotoxic effects may lend novel insights into intellectual disability understanding and its medication in FASD.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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