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Harnessing neural stem cells for treating psychiatric symptoms associated with fetal alcohol spectrum disorder and epilepsy

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ABSTRACT

Brain insults with progressive neurodegeneration are inherent in pathological symptoms that represent many psychiatric illnesses. Neural network disruptions characterized by impaired neurogenesis have been recognized to precede, accompany, and possibly even exacerbate the evolution and progression of symptoms of psychiatric disorders. Here, we focus on the neurodegeneration and the resulting psychiatric symptoms observed in fetal alcohol spectrum disorder and epilepsy, in an effort to show that these two diseases are candidate targets for stem cell therapy. In particular, we provide preclinical evidence in the transplantation of neural stem cells (NSCs) in both conditions, highlighting the potential of this cell-based treatment for correcting the psychiatric symptoms that plague these two disorders. Additionally, we discuss the challenges of NSC transplantation and offer insights into the mechanisms that may mediate the therapeutic benefits and can be exploited to overcome the hurdles of translating this therapy from the laboratory to the clinic. Our ultimate goal is to advance stem cell therapy for the treatment of psychiatric disorders.

1. Fetal alcohol spectrum disorder

Fetal Alcohol Spectrum Disorder (FASD) results from intrauterine alcohol exposure, which can lead to a multitude of alterations during brain development and display further long-term negative cognitive, motor impairment and sensory ramifications. The occurrence of FASD is approximately 2% to 5% for births within the US, however this incidence is increased in communities with lower socioeconomic status. Although numerous mechanisms are believed to be involved in the FASD etiology, specific molecular regions of ethanol toxicity throughout development have yet to be fully characterized. Recent studies have examined the role of GABA-A and GABA-B, cell signaling, and cell death in altered gene expression (Riley et al., 2011; Muralidharan et al., 2013; Poulos et al., 2014). A number of stem cell centered therapies have been extensively developed within the last decade, leading to innovative clinical interventions within numerous specialties. Therefore, initial comprehension of the stem cells' therapeutic potential has enabled encouraging interventions over a variety of illnesses. These potential benefits may eventually forge a path to minimizing the occurrence and seriousness of this frequent and prevailing birth defect. However, stem cell therapy is known to present unique issues and restrictions for therapeutic use. This section will discuss current knowledge, as well as advantages and challenges regarding stem cell therapy for FASD.

Abbreviations: 5-HT1A, Serotonin receptor; 5-HTP, 5-hydroxytryptophan; AEDs, anti-epileptic drugs; ADHD, attention deficit hyperactivity disorder; APOE, Apolipoprotein E; ARND, alcohol-related neurodevelopmental disorder; BAL, blood alcohol concentration; CAMs, cellular adhesion molecules; CB, calbindin D-28; Cl^-, chloride; c-Myc, Myc family of b/HLH/LZ proteins; CNS, central nervous system; CR, calretinin; EPO, erythropoietin; ES, embryonic stem cells; FAE, fetal alcohol effects; FAS, fetal alcohol syndrome; FASD, fetal alcohol spectrum disorder; FGF-2, fibroblast growth factor-2; G9a, lysine dimethyltransferase; GABA, γ-amino-butyric acid; GD-7, gestational day 7; GVHD, graft-versus-host disease; H3K9, histone H3 lysine 9; hNT, human teratocarcinoma; MGE, medial ganglionic eminence; ILAE, International League Against Epilepsy; iPSC, induced pluripotent stem cells; K27, methylation of histone H3 on lysine 27; KA, kainic acid; MRI, magnetic resonance imaging; |MSCs, mesenchymal stem cells; NMDA, *N*-methyl-D-aspartate; NPC, neural progenitor cell; NPY, neuropeptide Y; NSCs, Neural stem cells; PET, position emission tomography; pFAS, partial fetal alcohol syndrome; p-gp, P-glycoprotein; PNPCs, FGF-2-responsive human precursor cells; PV, parvalbumin; ROS, reactive oxygen species; SBA, spina bifida aperta; SNRIs, serotonin-noradrenaline reuptake inhibitors; SRS, spontaneous recurrent seizures; SSRIs, serotonin reuptake inhibitors; SVZ, subventricular zone; TLE, temporal lobe epilepsy; VNS, vagus nerve stimulation

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1.1. Pathological manifestations of FASD

Exposure to alcohol during the critical prenatal period is widely recognized to result in severe long-term physiological deficiencies in the developing fetal central nervous system (CNS) and an assortment of disabilities designated as Fetal Alcohol Spectrum Disorder (FASD). As described by Riley, FASD is labeled as Alcohol-Related Neurodevelopmental Disorder (ARND), Fetal Alcohol Syndrome (FAS) and Partial Fetal Alcohol Syndrome (pFAS) (Riley et al., 2011). Additionally, FASD has been linked to a vast number of heath conditions and increased mortality rate, as well as a significant increase in health care expenses (Popova et al., 2012 and Burd et al., 2008).

The principal mechanisms mediating teratogenic effects of alcohol have been investigated using in vivo and in vivo models, along with epidemiological studies on humans. A recent investigation found evidence that alcohol impairs all stages of brain development (Muralidharan et al., 2013), principally during embryonic, rather than fetal, stage. The disturbance of neural precursors is likely to cause certain defects that do not occur within the fully formed brain. Conversely, numerous factors may lead to irregularities within the developing embryonic brain. In particular, since neurogenesis is a prenatal function, early damage of the brain tissue may create a cascade effect, resulting in a negative impact on typical CNS development. Accordingly, treatments intended to rectify faulty neurogenesis may be considered early on in pregnancy.

Embryonic development goes through a series of rapid growth during the first eight weeks of gestation with the formation of major organ systems. By twelve weeks of gestation, premature subdivisions of brain are completed, followed by extensive brain growth during the last trimester of pregnancy. This period of rapid neural maturation occurs within the first two years of life. Thus, the severity of the deleterious effects of alcohol later in life has been suggested to depend upon the timing of exposure during fetal development. For example, alcohol may impact the quality of the egg and sperm prior to conception, which may lead to spontaneous abortion. During the first three weeks of gestation, alcohol can interfere with primary neurulation leading to neural tube defects and ultimately to abnormalities in early brain development. This was demonstrated by exposing GD-7 mice to ethanol, which corresponds to 3-week gestation in humans, leading to central nervous system (CNS) defects typical of FASD (Godin et al., 2010).

Additionally, the fetus is at highest risk during the latter stages of the first trimester when extensive neural development occurs, leading to potential abnormalities. When pregnancies go full-term, potential signs of intrauterine alcohol exposure include facial irregularities and small size (Sulik, 2005). Later in life, in utero alcohol-exposure may lead to hyperactive behavior, poor coordination, learning disabilities such as delayed language and speech, mental retardation and a low IQ (Burd et al., 2008). Furthermore, individuals with FASD tend to experience aberrant social behaviors, such as trouble with the legal system, inappropriate sexual behavior, abnormal school experience and unemployment (Fast et al., 1999). However, depending on the severity of the in utero alcohol exposure, the effects of alcohol on brain growth may remain undetected (Riley and McGee, 2005).

1.2. Alcohol neurotoxicity

How does alcohol behave as a teratogen? The answer is complex due to alcohol's ability to trigger cell death through numerous mechanisms, resulting in various regions of the fetus to develop abnormally. Yet, mechanisms linked to malnutrition can be potentially a product of preventative effects of alcohol on the uptake of vitamin B6 and glucose from the gastrointestinal tract (Fisher et al., 1981) as well as the uptake of amino acids from placental tissue (Michaelis and Michaelis, 1994). In utero exposure to alcohol inhibits blood flow through the narrowing of blood vessels in the umbilical and placenta, therefore obstructing the distribution of oxygen and vital nutrients to the fetus (Goodlett and Horn, 2001). As a result, the maternal-fetal endocrine system is believed to be disrupted by alcohol, potentially resulting in the release of toxic free radicals. Free radicals production appears to be dose-dependent on the consumption of alcohol, and is generally linked to habitual alcohol ingestion within the first trimester. The damaging free radicals may cause accumulation of calcium inside of developing neurons, leading to a release of neurotransmitters, which can disrupt the movement of emerging nerve cells (Caillard et al., 2000).

Based on the observations that deficient brain development resulting in a variety of behavioral problems including social function, attention and cognition, minimizing and mending the impaired neural network is vital for the treatment of psychiatric diseases (Shirasaka et al., 2011). Global brain degeneration and underdevelopment of the basal ganglia and corpus callosum have been associated with the pathophysiology of FASD (Shirasaka et al., 2011). Although the specific mechanism of cell death in FASD still needs to be addressed, specific features are known. Alcohol travels through the maternal bloodstream and crosses the placenta to reach the fetus. Due to the fetus' slower metabolism relative to adults, the blood alcohol concentration (BAL) is elevated in the fetus. Subsequently, alcohol limits the ability of hemoglobin to bind to oxygen, leading to hypoxia and resulting in improper development of the CNS. Furthermore, alcohol inhibits the intake of vital vitamins and nutrients needed to prevent anemia.

Apoptosis is a key mechanism in FASD-related damage. Other mechanisms impairing cellular adhesion and hindered migration in FASD are believed to include L1. Throughout CNS development, axonal growth and movement of neurons are not only controlled by cell-to-cell interactions but also cell-to-substrate communication (Mattson et al., 2001). These networks are symbiotically controlled by cellular adhesion molecules (CAMs), including transporter proteins, in addition to L1, a part of the IgG superfamily. L1 belongs to the family of neural CAM expressed in the CNS. Hence, L1 mutations can affect neural movement, cellular adhesion and neurite extension (Greenberg, 2003). The study of L1 mutations has contributed to the elucidation of the role played by CAMs in CNS damage, suggesting a link between gene defects and clinical disorders, potentially increasing the understanding of specific gene functions, and elucidating the pathophysiology of FASD. Additionally, the semblance between FASD and L1 mutations has led researchers to investigate the potential function of L1 in FASD.

1.3. The role of neurotransmitters in FASD

1.3.1. GABA and neuropsychiatric disorders

In addition to norepinephrine and serotonin, the brain's primary inhibitory neurotransmitter γ-amino-butyric acid (GABA), has been involved in various psychiatric disorders, such as depression, schizophrenia and FASD. The two fundamental subtypes of postsynaptic GABA receptor complexes are GABA-A and GABA-B, and separate mechanisms activate each receptor (Olsen and DeLorey, 1999). The GABA-B receptor is activation by GABA resulting in neuronal membrane hyperpolarization and restriction of neurotransmitter discharge. Consequentially, GABA-B has been linked to the pathophysiology of a variety of diseases due to its anxiolytic and antidepressant characteristics. In addition to substrate sites for GABA, GABA-A receptors contain binding sites for barbiturates and benzodiazepines, which are also accompanied by chloride (Cl^-) ion channels. The binding to the GABA-A receptor/Cl^- channel complex results in a flood of Cl^- ions, which causes membrane hyperpolarization and finally, neuronal inhibition. Initial investigations of alcohol-caused CNS disorders concentrated on the deficiencies of memory and learning linked to GABA-A receptor activation. GABA-A does not only have a significant role in the metabolism of alcohol within the CNS, but it also releases a neurodegenerative reaction and its receptors are the most sensitive to the ramifications of alcohol during synaptogenesis (Cuzon et al., 2008 and Ikonomidou et al., 2000).