Progress in Neuro-Psychopharmacology & Biological Psychiatry xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

The potential of neural stem cell transplantation for the treatment of fetal alcohol spectrum disorder

Stephen G. Poulos [a,*], William D. Richie [a], Rahn K. Bailey [a], Arthur Lee [a], Ike dela Pena [b], Paul R. Sanberg [b], Cesar V. Borlongan [b]

[a] Department of Psychiatry and Behavioral Sciences, Meharry Medical College, 1005 Dr Db Todd Jr Blvd, Nashville TN 37208 USA
[b] Center of Excellence for Aging and Brain Repair, Department of Neurosurgery and Brain Repair, University of South Florida College of Medicine, 12901 Bruce B. Downs Blvd. MDC 78, Tampa FL 33612 USA

ARTICLE INFO

Article history:
Received 7 March 2014
Received in revised form 13 May 2014
Accepted 26 May 2014
Available online xxxx

Keywords:
Fetal alcohol spectrum disorder
GABA
Neural stem cells
Neurodegeneration
Teratogenicity

ABSTRACT

Fetal alcohol spectrum disorder (FASD) is caused by intrauterine exposure to alcohol and can cause a full range of abnormalities to brain development, as well as long-term sequelae of cognitive, sensory and motor impairments. The incidence is estimated to be as high as 2% to 5% in children born within the US, however the prevalence is even higher in low socioeconomic populations. Despite the various mechanisms thought to explain the etiology of FASD, molecular targets of ethanol toxicity during development are not completely understood. More recent findings explore the role of GABA-A and GABA-B mechanisms, as well as cell death, cell signaling and gene expression malfunctions. Stem cell based therapies have grown exponentially over the last decade, which have lead to novel clinical interventions across many disciplines. Thus, early detailed understanding of the therapeutic potential of stem cell research has provided promising applications across a wide range of illnesses. Consequently, these potential benefits may ultimately lead to a reduced incidence and severity of this highly preventable and prevalent birth defect. It is recognized that stem cell derivations provide unique difficulties and limitations of therapeutic applications. This review will outline the current knowledge, along with the benefits and challenges of stem cell therapy for FASD.

Contents

1. Introduction . . . 0
2. Teratogenicity of alcohol . . . 0
3. Neurotransmitters and FASD . . . 0
3.1. GABA-A and GABA-B . . . 0
3.2. Neuropsychiatric disorders and GABA . . . 0
3.3. Synchronization of GABA . . . 0
4. Brain imaging and FASD . . . 0
5. Stem cell therapy in FASD . . . 0
5.1. The implications of neurodegeneration . . . 0
6. Neural stem cell transplantation in FASD . . . 0
6.1. Neural stem cell benefits . . . 0
6.1.1. Clinical difficulties with stem cell transplantation . . . 0
6.1.2. The role of neural stem cell transplant in psychiatry . . . 0
6.1.3. Timing of neural stem cell transplantation . . . 0

Abbreviations: FASD, fetal alcohol spectrum disorder; FAS, fetal alcohol syndrome; pFAS, partial fetal alcohol syndrome; ARND, alcohol-related neurodevelopmental disorder; GD-7, gestational day 7; GABA, γ-amino-butyric acid; PET, position emission tomography; PV, parvalbumin; MRI, magnetic resonance imaging; ROS, reactive oxygen species; NMDA, N-methyl-D-aspartate; G9a, lysine dimethyltransferase; H3K9, histone H3 lysine 9; K27, methylation of histone H3 on lysine 27; NSCs, neural stem cells; FAE, fetal alcohol effects; MSCs, mesenchymal stem cells; NPC, neural progenitor cell; hNT, human teratocarcinoma; c-Myc, Myc family of b/HLH/LZ proteins.

* Corresponding author at: Department of Psychiatry and Behavioral Sciences, Meharry Medical College, 1005 Dr Db Todd Jr Blvd, Nashville TN 37208, USA. Tel.: +1 615 327 6000.
E-mail address: spoulos@mmc.edu (S.G. Poulos).

http://dx.doi.org/10.1016/j.pnpbp.2014.05.016
0278-5846/

7. NSC transplantation for FASD: issues and considerations . . . 0
7.1. Limitations . . . 0
7.1.1. Side effects . . . 0
7.1.2. Technical difficulties in harvesting NSCs . . . 0
7.1.3. Efficacy of NSC transplantation . . . 0
8. Conclusion . . . 0
Conflicts of interest . . . 0
References . . . 0

1. Introduction

Intrauterine exposure to alcohol during the prenatal period is well known to cause serious long-term physiological defects to the developing fetal central nervous system and a full range of disabilities termed fetal alcohol spectrum disorders (FASD). As described by Riley, FASD is collectively termed fetal alcohol syndrome (FAS), partial fetal alcohol syndrome (pFAS), and alcohol-related neurodevelopmental disorder (ARND) (Riley et al., 2011). Furthermore, it has been associated with a wide array of health conditions and an increased mortality rate as compared to the general population, along with substantial health care costs involved in caring for affected individuals (Burd et al., 2008; Popova et al., 2012).

The mechanisms underlying the teratogenic effects of alcohol have been studied extensively using in vitro and in vivo models, as well as in epidemiological research involving human subjects. A recent study has found that alcohol interferes with all stages of brain development and causes distinct, specific patterns of focal abnormalities at various gestational stages (Muralidharan et al., 2013). Of note, many of these early aberrations mediating FASD would be occurring during embryonic, not fetal, stages. Equally important is that some of the defects are likely due to disruption of neural precursors and therefore would not be occurring within the brain per se. In this regard, there are many factors that can contribute to aberrations within the developing embryonic brain. For instance, since neurogenesis is a prenatal event, developmental disruptions outside of the brain may indirectly effect normal CNS development. Consequently, treatments aimed at correcting improper neurogenesis may possibly be initiated after identifying a positive pregnancy test.

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 development are complete which is followed by a second period of extensive brain growth during the last trimester of pregnancy. This period of rapid neural maturation is continued during 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, and the mice later developed central nervous system (CNS) defects typical of FASD (Godin et al., 2010).

Furthermore, during the late stages of the first trimester, alcohol can pose the highest risk due to the rapid neural growth that happens during this phase, a critical period indeed, for possible neural malformations. For pregnancies that do go to term, characteristics of in utero alcohol-induced abnormalities may include small for gestational age appearance, and facial abnormalities (Sulik, 2005). In later life, prenatal alcohol-exposed individuals may manifest poor coordination, hyperactive behavior, learning disabilities, developmental disabilities such as speech and language delays, mental retardation or even a low IQ score (Burd et al., 2008). Moreover, people with FASD often experience mental health problems as they get older, such as disrupted school experiences, trouble within the legal system, unemployment, and inappropriate sexual behavior (Fast et al., 1999). Lastly, depending on the amount of intrauterine alcohol exposure, the influence of alcohol on brain development in less severely affected individuals can remain unappreciated for several years or even decades (Riley and McGee, 2005).

2. Teratogenicity of alcohol

With what is understood about the effects of alcohol during fetal development, the next question becomes: how does alcohol act like a teratogen? The answer is complicated because alcohol can trigger cell death in a number of ways, causing different parts of the fetus to develop abnormally. Nevertheless, mechanisms associated with malnutrition may be due to inhibitory effects of alcohol on the uptake of glucose and vitamin B6 from the gastrointestinal tract (Fisher et al., 1981) as well as amino acid uptake across placental tissue (Michaelis and Michaelis, 1994). Intrauterine exposure to alcohol constricts blood vessels and interferes with blood flow in the placenta and umbilical blood vessels, which ultimately hinders the delivery of nutrients and oxygen to the entire fetus (Goodlett and Horn, 2001). Consequently, the maternal–fetal endocrine systems are also thought to be disrupted by alcohol which may trigger toxic free radical formation. The formation of toxic free radicals seems to be dose-dependent, and is usually associated with chronic, binge-like alcohol consumption during the first trimester. As described by Caillard, these damaged free radicals can result in the accumulation of calcium within neurons, resulting in a surge of neurotransmitters, which has the potential to interrupt the migration of developing nerve cells (Caillard et al., 2000).

Since it is well known that abnormal brain development can induce behavioral problems including cognition, attention and social functioning, maintaining and/or repairing a damaged neural network is a key strategy for the treatment of psychiatric diseases. Generalized brain atrophy and hypoplasia of the basal ganglia and corpus callosum have been implicated in the pathophysiology of FASD (Shirasaka et al, 2011). Though the exact mechanism of cellular death in FASD remains unclear, some aspects are well understood. Alcohol enters the bloodstream and reaches the developing fetus by crossing the placenta. Because a fetus metabolizes alcohol much slower than an adult does, the blood alcohol concentration (BAL) is higher in the fetus compared to an adult. Consequently, alcohol interferes with the amount of oxygen binding to hemoglobin and leads to hypoxia, rendering the developing CNS to develop improperly. Furthermore, it also hinders the absorption of nutrients and vitamins important for preventing anemia, which has a synergistic effect with oxygen saturation.

Indeed, apoptosis is certainly an important mechanism of cellular death in FASD. However, other means of altered migration and cellular adhesion mechanisms in FASD are thought to involve L1. During development of the CNS, migration of neurons and axonal growth are not only regulated by cell–cell interactions, but cell–substrate interactions as well (Mattson et al, 2001). These step-wise interactions are synergistically regulated by cellular adhesion molecules (CAMs), which collectively include transporter proteins, as well as L1, a member of the IgG superfamily. L1 is a type of neural CAM that is predominantly expressed within the CNS and when it is activated, neuronal migration, cellular

Please cite this article as: Poulos SG, et al, The potential of neural stem cell transplantation for the treatment of fetal alcohol spectrum disorder, Prog Neuro-Psychopharmacol Biol Psychiatry (2014), http://dx.doi.org/10.1016/j.pnpbp.2014.05.016