Dissecting Role of Sleep in Abnormal Neurocognitive Development in an Animal Model of Prenatal Alcohol Exposure

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It has been well established that human conditions with insufficient or restricted sleep have detrimental consequences, including cognitive, affective, cardiovascular and endocrine, and contribute to poor quality of life. Development of insomnia depends on genetic, epigenetic and environmental factors, and may have origins in early ontogenesis. Existing data suggest that poor sleep and increased behavioral arousal can result from prenatal adversities such as exposure to psychoactive substances or malnutrition. One of the major risk factors during the prenatal period is maternal alcohol consumption. It occurs in over 10% of pregnancies, leading to adverse consequences such as the Fetal Alcohol Spectrum Disorders (FASD) affecting 2-5% of births in the United States and Western European countries [1]. Prenatal exposure to alcohol is an established cause of abnormal sleep electroencephalogram (EEG) in infants that correlates with subsequent abnormalities of neurocognitive development, and a key predictor of disrupted sleep in older children [2-4]. A potential health impact of insufficient sleep can be profound and costly for the society, especially in such an already at risk pediatric population.

One may wonder whether long-term or persistent cognitive and behavioral components of FASD [5,6] may be secondary to, or exacerbated by, sleep deficits. To examine this hypothesis, the brain mechanisms underlying the disrupted control of sleep-wake behavior in victims of prenatal exposure to alcohol, as well the neurocognitive consequences of this disruption have to be elucidated. Due to the nature of these studies, especially those aiming to dissect the neural mechanisms of sleep abnormalities; they need to be conducted using animal models.

Indeed, animal models of prenatal or perinatal exposure to adverse factors allow one to control experimental conditions, provide invaluable insight into the mechanisms of structural damages, and link these mechanisms to altered functions. To select the right model, one should take into consideration that the timing and pattern of prenatal exposure to alcohol are critical for its effects. For example, earlier gestational exposures result in a higher likelihood of craniofacial malformations, whereas later exposures appear to affect primarily motor activity and cognitive functions [7-9]. In addition, so called binge exposures (mother having five or more drinks on one occasion) more severely affect brain functions, including the regulation of sleep, than continuously elevated blood alcohol concentrations [2]. Finally, detrimental effects of prenatal exposure to alcohol can be exerted both by its direct actions and indirectly, through the impaired maternal support. To analyze the direct effects of alcohol separately from the indirect ones, an elegant rat model has been designed [10]. Rats are born underdeveloped in comparison with humans who have a major period of rapid brain growth during the third trimester of pregnancy. In rats, this brain growth spurt occurs during the early postnatal period, thus making possible to administer alcohol via brief intragastric intubations directly to newborn rat pups. The dosage is adjusted daily based on the body weight of each pup, which allows one to precisely control alcohol exposure and its timing and reduce variability of the effects. The intubation technique for neonatal alcohol administration does not require preliminary surgery or prolonged isolation of pups from the mother, as does the related technique of artificial rearing, or “pup in a cup”.

In our laboratory, we used this model to test the hypothesis that exposure to alcohol during the period of brain growth spurt equivalent to the third trimester of human gestation leads to a long-lasting problems with sleep. We monitored cortical EEG and nuchal electromyogram (EMG) in adult rats treated with alcohol during this period and found that they had difficulty to initiate sleep and reduced amount of rapid eye movement (REM) sleep [11]. This prompted us to examine the neurochemical pathways involved in the regulation of sleep and wake behavior. It turned out that before reaching adulthood, alcohol-exposed animals had decreased expression of gamma-Aminobutyric acid (GABA) precursor, glutamate decarboxylase, in the sleep-controlling brain regions, and increased mRNA levels of the hypothalamic precursor of orexins. Orexin A and B are two excitatory neuropeptides produced by neurons that promote motor activity and whose activation plays a major role in the maintenance of wakefulness and motivated behaviors, including alcohol-seeking behavior [12-14]. Interestingly, orexins may play a role in development of anxiety [15], a commonly reported behavioral problem in FASD patients [6]. Therefore, it is plausible that abnormally high activity of orexin system may contribute to motor hyperactivity, disrupted sleep, cognitive deficits and anxiety in children and adults with FASD. To start testing this hypothesis, we used our model to determine whether early pharmacological intervention targeting orexin system could improve the behavioral outcomes. Following a short recovery period after the alcohol exposure, we treated immature rats with well characterized experimental compound SB-334867, an antagonist of the orexin 1 receptors, and then subjected them to behavioral tests. The results of these studies showed promising effects of this approach, such as improved spatial learning and memory and eliminated motor hyperactivity in alcohol-exposed animals [16]. Importantly, we treated rats with the orexin antagonist during a developmental stage that is equivalent to human infancy. Since our data suggest that pharmacological treatment after birth has a potential to alleviate severity of FASD symptoms, we believe that our finding obtained from this animal model is of clinical relevance. However, it provides us with only indirect evidence of the possible role of sleep in mediating the effects of the orexins on learning in alcohol-exposed animals. We
plan to address this gap in our knowledge in our future studies using this animal model.

The long-term goal of these studies should be to advance understanding of the cellular, molecular and epigenetic mechanisms of neurobehavioral abnormalities resulting from suboptimal prenatal environment. Characterization of mechanisms underlying the altered regulation of sleep following a socially relevant and common prenatal insult, exposure to alcohol, is a logical step on this path. Data from human victims of FASD and from animal models, including one that we use in our studies, strongly suggest that sleep deficits caused by prenatal exposure to alcohol are persistent, and may be at least a significant exacerbating factor for cognitive and behavioral abnormalities associated with FASD. Using of animal models allows researchers to determine whether there are openings for improvement of these neurobehavioral outcomes, and to evaluate them in preclinical studies.

References


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