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Prenatal alcohol exposure and autonomic nervous system dysfunction: A review article

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Abstract: Alcohol is a recognized teratogen that affects various aspects of fetal development. Tissue that is particularly susceptible to its teratogenicity is neuronal tissue. The effect of prenatal alcohol exposure (PAE) on the central nervous system has been extensively studied, yet the knowledge on the influence of PAE on the autonomic nervous system is scarce. The purpose of this article is to review the current state of knowledge about the impact of PAE on the autonomic nervous system.
Studies conducted on the PAE animal model have shown that prenatal alcohol exposure is associated with significant alterations in the autonomic nervous system, but the mechanisms and consequences are not yet clearly defined. It was established that PAE causes decreased heart rate variability (HRV) in fetal cardiotocography. Several studies have revealed that later, in infancy and childhood, reduced parasympathetic activity with or without compensating sympathetic activity is observed. This may result in behavioral and attention disorders, as well as an increased predisposition to sudden infant death syndrome.
Both animal and human studies indicate that the relationship between PAE and autonomic dysfunction exists, however large, well-designed, prospective studies are needed to confirm the causal relationship and characterize the nature of the observed changes.

Key words: prenatal alcohol exposure, heart rate variability, autonomic nervous system, fetal alcohol spectrum disorders.

Introduction

Although the first reports of the teratogenic potential of alcohol date back to biblical times, it has been widely studied since 1973, when the first report on fetal alcohol syndrome was published [1, 2]. Initially, it was thought that the effects caused by prenatal alcohol exposure (PAE) were limited to facial dysmorphism, microcephaly and growth restriction. Further research demonstrated that brain damage resulting from PAE occurs at the cellular and molecular level and does not always cause visible changes in brain size or structure [3]. Nonetheless, among patients with fetal alcohol spectrum disorder (FASD), various brain domains such as learning, memory, attention, behavior and executive function are affected [4].

There are several mechanisms in which alcohol affects the central nervous system. A rat model of early postnatal alcohol exposure mimics human prenatal exposure in the third trimester of pregnancy due to differences in developmental stages when the consequences are most critical for nervous system formation [5]. In vitro and in vivo studies have shown that alcohol induces oxidative stress by suppressing the synthesis of antioxidants and increasing the synthesis of free radicals, which enhances fetal cells' apoptosis [6]. Besides, alcohol alters stem cell proliferation in the cerebral cortex, as well as further differentiation of neural cell lines, to some extent due to the inhibited activity of neurotrophic factors [7, 8]. Alcohol also affects neuromediators, and its toxic effect on glutaminergic and serotonergic neurons is well documented [9, 10]. In the in vitro studies, it was demonstrated that alcohol impairs glucose uptake in neurons by suppressing the expression of genes encoding GLUT-1 protein, which affects cell growth [11]. There is also evidence that alcohol can inhibit cell adhesion, affecting the synthesis of adhesion molecules [12]. As a result, synaptogenesis, dendritic arborization and neuronal migration are disturbed. Recently, the importance of epigenetic changes resulting from PAE as a potential teratogenic mechanism has been emphasized. Alcohol-induced DNA and histone methylation leads to significant changes in the expression of genes responsible for cell proliferation, differentiation, apoptosis, as well as intracellular signaling pathways [13]. With an altered expression of microRNA, all this causes pathology throughout the entire genome. Nevertheless, brain structures are characterized by different susceptibility to the neurotoxic effect of alcohol [14]. Each group of neurons is stimulated by different trophic factors, but these factors are not evenly affected by ethanol which leads to a wide range of its negative effects. The brainstem is at particular risk of being damaged by alcohol. Moreover, the susceptibility of nervous system structures changes over time [14, 15].

Although the teratogenic effect of alcohol on the neurons in the central nervous system was studied from both clinical and pathophysiological perspective, there is little knowledge of the potential damage to the autonomic nervous system caused by PAE.

The purpose of this article is to review the current state of knowledge about the effects of alcohol on the peripheral autonomic nervous system.

Animal models

Prenatal alcohol exposure (PAE) impairs the central and peripheral nervous system causing neurodevelopmental behavioral and physiological changes. Rodents exposed to alcohol in utero reveal hyperactivity similar to isolated individuals. Moreover, the proliferation of Schwann cells and astrocytes, as well as oligodendrocytes maturation, are disturbed [15, 16]. Since these changes were confirmed by histopathological assessment of adult animals, they are considered permanent.

Essential mechanisms involve the preterm maturation of adrenergic receptors and delayed maturation of cholinergic receptors [17]. Zimmerberg *et al.* observed an increased number of B1 adrenergic receptors in brown adipose tissue, which may reflect insufficient levels of neurotransmitters and delayed onset of sympathetic stimulation in a rat exposed to alcohol during the prenatal period [18]. If the increase in neurotransmitter concentration caused by delayed maturation does not reduce the number of receptors, overactivity may persist. Alcohol alters sympathetic nervous system development in heart, thymus and spleen. Sympathetic neurons are responsible for the stress response that allows individuals to adapt to a changing environment. For the first 2 weeks after birth, the sympathetic nervous system dominates the control of heart rate due to earlier maturation. During the further development of the autonomic nervous system, a vagal influence on the heart gradually increases, but PAE appears to change the parasympathetic tone and even lead to bradycardia [5]. Ethanol is also a neurobehavioral teratogen affecting the hypothalamic-pituitary-adrenal axis by increasing activity and exaggerating the stress response. Fetal alcohol exposure has been shown to decrease beta-endorphin stress response as well. It is reflected by significant differences in the heart rate variability parameters from day 1 to 6, however, these findings diminish over time.

PAE is associated with cognitive and attention deficits. The orientation reflex consists of numerous physiological and behavioral reactions that allow adaptation to the new environmental stimulus. PAE reduces the orientation response and its evaluation early in life may be predictive of disturbances in adolescence and adulthood. Therefore, habituation assessment of newborns is a tool used to determine the risk of intellectual disorders. The orienting response just after birth, in contrast to the heart rate, is under the control of the vagus nerve, which means that new stimuli cause the heart rate deceleration. Two weeks after delivery, sympathetic nervous activity increases, as a result of which new stimuli begin to accelerate the heartbeat. In utero alcohol exposure causes prolonged latencies of orienting response. It may be an indicator of central data processing disturbances. PAE animals do not

disclose physiological novelty preference which may indicate an alteration of working memory [19].

PAE causes a reduction in the number of motoneurons in hypoglossal nerve nuclei, which is suspected to increase the risk of sudden infant death syndrome and obstructive sleep apnea[16]. In addition, offspring of pregnant rodents treated with ethanol gain weight at a slower pace [18]. However, lower body weight does not explain neuronal changes as corresponding findings were not observed in the experimental group with food restriction [5]. The immune system is also affected by alcohol exposure, which leads to increased susceptibility to bacterial infection and carcinogenesis [20]. One of the underrated mechanisms is sympathetic dysregulation, which affects the anti-inflammatory response of the spleen and its leukocytes. This disturbed neuroimmunological communication may result in an inappropriate response to inflammation. Impaired neurotransmission involves the serotonergic system, especially in the digestive tract. Due to reduced synthesis of serotonin, there is an increased occurrence of gastrointestinal disorders such as constipation or chronic diarrhea [21].

In conclusion, numerous studies have shown that prenatal alcohol exposure is associated with significant disturbances in the functioning of the autonomic nervous system, but the mechanisms and consequences, due to their complexity, are not yet clearly defined.

Human studies

Reduced heart rate variability in fetuses exposed to alcohol has been described in several case reports. Although various authors point to altered maturation of the fetal autonomic nervous system as the underlying cause, in all cases fetal cardiotocography was performed during maternal intoxication so a direct effect of alcohol cannot be excluded [22–24]. On the other hand, all fetuses were exposed to high doses of alcohol throughout pregnancy and fetal alcohol syndrome was diagnosed after delivery, so chronic PAE may also contribute to the observed effect.

In the neonatal period, it was observed that children with PAE have a significantly lower heart rate and that after an acute stress stimulus (heel lance) data analysis of HRV spectrum shows a reduced change in low-frequency power and low-frequency power/high-frequency power ratio without a decrease in respiratory sinus arrhythmia (RSA) in those individuals. According to the authors' interpretation, the fact that high-frequency power has not changed significantly may be due to the increased variability of the HFP signal, as well as the design of the study and the equipment used. However, they concluded that their findings strongly suggest that infants with PAE may disclose reduced parasympathetic activity without accompanying increased sympathetic activity [25]. Fifer at al. demonstrated that infants with PAE have decreased HRV and do not respond adequately to tilting (no increase in HR

during head-up tilt and no decrease in HR during head-down tilt), which indicates autonomic dysfunction. According to the authors, infants with PAE may therefore be at risk of sudden infant death syndrome (SIDS) [26].

There is evidence that the influence of PAE on the autonomic regulation is not limited to infancy and persists in childhood and adolescence. Suess at al. studying the influence of prenatal opiates exposure demonstrated that concomitant PAE was the main cause of autonomic dysfunction. A greater decrease in RSA was observed in children exposed to opiates and alcohol compared to the group exposed only to opiates or none of the factors. Contrary to expectations, there was no difference between the effects of opiates in combination with alcohol and alcohol alone, however, the authors suggest that the PAE in the latter group might have been mild as opposed to the group with co-exposure [27]. Chandran *et al.* demonstrated a significant increase in low-frequency power and low/high-frequency power ratio among children with PAE indicating a sympathetic predominance [28]. To the best of our knowledge, no studies on the effects of PAE on the functioning of the autonomic nervous system in adults have been so far performed.

Summary

Studies on the animal model of PAE, as well as studies on humans, confirm the thesis that prenatal exposure to alcohol deeply affects the autonomic function of the nervous system. Current evidence suggests a significant link between reduced parasympathetic activity and PAE. The unclear impact of PAE on sympathetic neuronal function is still under discussion. Therefore, large, well-designed, prospective studies are needed to further investigate the causal relationship and characterize the nature of the observed changes. Finally, it seems important to investigate the relationship between autonomic dysfunction and behavioral or cognitive changes in patients with FASD, since it has been established that imbalance in parasympathetic/sympathetic activity serves as an indicator of impaired social, linguistic, cognitive and attention skills [29–31].

Conflict of interest

None declared.

Authors contribution

K.D., M.J. and K.G. conceived the presented idea, K.D. and M.J. developed the search strategy and performed the literature search, K.D., M.J. and K.S. wrote the manuscript, K.G. revised the manuscript and supervised the search process; all authors approved the final version of the manuscript.

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