The effect of acute and chronic exposure to ethanol on the developing encephalon: a review

Os efeitos da exposição aguda e crônica ao etanol sobre o desenvolvimento do encéfalo: uma revisão

Tales Alexandre Aversi-Ferreira [1]
Guilherme Nobre Lima do Nascimento [2]

[1,2] Laboratório de Bioquímica e Neurociências (LABINE). Departamento de Morfologia (DMORF). Instituto de Ciências Biológicas-ICB III. Universidade Federal de Goiás. Campus II (Samambaia). Goiânia, GO, Brasil. CEP: 74.001-970.
E-mail: aversiferreira@hotmail.com

Abstract

Objectives: to compare the acute and chronic effects of ethanol on the neural development, by analysis of the ontogenetic neural structure of mammals.

Methods: searches were performed in the following electronic databases: MEDLINE, SciElo, PubMed, LILACS, CAPES periodical, and the Open Journal System. The descriptors used were: "chronic ethanol toxicity", "chronic alcohol toxicity", "acute ethanol toxicity", "acute alcohol", "neural ontogenic development", "neuronal migration disturbances", "neural structure". The following inclusion criteria were used: articles published between 2003 and 2007, some classic articles in the field and an important neuropsychology textbook.

Results: the analysis of papers revealed that, although several studies of the chronic effects of ethanol exposure on the mammalian nervous system have been conducted, only a few have investigated the acute effects of ethanol on specific days of gestation, and these studies have revealed important disorders relating to the cerebral tissue.

Conclusions: it should be recommended that women refrain from the consumption of ethanol during gestational phase to protect the fetus' health. Furthermore, the acute consumption of ethanol by women nearing the eighth or ninth week of gestation has been shown to be potentially harmful to the nervous tissue of the fetus.

Key words *Ethanol, Neural ontogenic development, Brain, Public health*

Resumo

Objetivos: comparar os efeitos agudo e crônico do etanol sobre o desenvolvimento do sistema nervoso através da análise da estrutura ontogênica neural dos mamíferos.

Métodos: pesquisas foram feitas nas bases eletrônicas: MEDLINE, SciElo, PubMed, LILACS, CAPES periodical, Open Journal System. Os descritores usados foram: "toxidade crônica ao etanol", "toxidade crônica ao álcool", "toxicidade aguda ao etanol", "toxicidade aguda ao álcool", "desenvolvimento ontogênico neural", "distúrbios da migração neuronal", "estrutura neural".Foram considerados critérios de inclusão: artigos publicados no periódo de 2003 e 2007, alguns artigos clássicos da área, e um livro básico em neuropsicologia.

Resultados: constatou-se que muitos estudos sobre os efeitos crônicos do etanol sobre o sistema neural de mamíferos foram feitos, mas poucos estudos foram realizados sobre os efeitos agudos do etanol em dias específicos da gestação, e esses revelaram importantes desordens sobre o tecido neural.

Conclusões: o consumo de etanol não é recomendado para mulheres na fase gestacional para preservar a saúde do feto, e o consumo agudo de etanol entre mulheres próxima à oitava e nona semanas de gestação têm demonstrado ser potencialmente perigoso para o tecido neural do feto.

Palavras-chave *Etanol, Desenvolvimento neural ontogênico, Encéfalo, Saúde pública*

Introduction

Despite the advances in study of the nervous system in recent years, many questions regarding how this system works and how its physiology is influenced by its morphology have still not been investigated. Studies of cell migration from the primitive neural tube have contributed to understanding how these cortical layers are constructed in adult individuals.[1,2]

The organization and connections of cells in the nervous system depend on the development of the neural neocortex during its embryogenesis.[2] One way of knowing the functions of the nervous system is to study the effects of drugs on its morphology, construction and hence physiology.

In mammals, especially humans, the neocortex has a complex structure and its various connections still remain unknown or little understood.

Cell migration

The development of the central nervous system involves a series of programmed cellular and molecular events, including the pattern of migration of neurons and axonal growth; health care for the mother is, therefore, essential for the future health of the offspring.[1]

The adult cerebral neocortex is composed of six horizontal layers[1], which are divided into individual neuron columns; both are essential for the normal functions in the adult brain.

Migration involves the displacement of a neuron cell body from the proliferative zone to its final destination in the mature brain[2]. These events are regulated in such a way as to produce a neuronal density that is approximately the same from one area to another in the human brain and in the brain of several species of mammal.[3]

The regulation of the migration of neurons involves different cell populations, including Cajal-Retzius neurons, sub-plate neurons, neuronal precursors or radial glia, and multiple molecular mechanisms such as cell cycle control, cell-cell interactions - usually mediated by cell adhesion molecules (CAMs), which include cadherins, selectins, integrins, mucins, and members of the IgG superfamily - release of neurotransmitters, growth factor availability, platelet-activating degradation factor and signal transduction pathways,[4-6] and the state of array or disarray of microtubules on the cytoskeleton.[7]

In the incipient development of the nervous system, the telencephalic vesicles have three distinct layers: 1) the germinal layer, 2) the plate layer, and 3) the marginal layer.

The germinal layer (ventricular zone or ependimal layer) forms the neural tube. In this layer, the precursor neuron cells are divided near the tube light and undergo differentiation. Then, after the birth the neuron, it migrates to the surface location of the neural tube in order to construct the plate layer that includes neuroblasts and glia.

The ventricular zone includes three distinct neurons and glial precursor populations: 1) proliferative cells from the ventricular pseudostratified epithelium or proliferative fractions; 2) cells from the quiescent fraction located in the ventricular pseudostratified epithelium, and 3) secondary proliferative populations.[3]

In this ventricular pseudostratified epithelium, the neuroblast undergoes cell division and differentiation in intensive synthesis of genetic materials that is especially important for the metabolism of division. All the future neurons begin to migrate from the ventricular pseudostratified epithelium to form the adult cortical structure.

The marginal layer will be the molecular layer in the adult brain.

Generation, migration and differentiation occur mainly during the pre-natal period, but in some areas of the nervous system, this phenomenon occurs in the post-natal period, for example in the cerebellum,[8] hippocampus[9] and in the sub-ventricular zone.[2,10,11]

Most neurons in the developing vertebrate nervous system are generated at sites that are significantly different from their location in the adult brain.[7]

The histological neuronal sequences in the embryo begin with the generation of neurons (neurogenesis) in the ventricular pseudostratified epithelium on the edge of the ventricle cavity.[3,12,13]

In the ventricular and sub-ventricular zones, in the telencephalon, precursor neuron cells form a secondary proliferative population from the pseudostratified epithelium. In the intervening time, these cells migrate from embryonic stages E_{11} to E_{17}, during which they complete 11 cell cycles in the case of rats.[3]

After E_{14}, many histological modifications have already occurred. First of all, the cortical layer, along with the molecular layer, includes the cortical plate and sub-plate, emerging from the surface of the cortical wall. Thus, the intermediate zone penetrates between the ventricular zone and the cortical layer. Finally, the sub-ventricular zone is indistinct because it is joined to the ventricular zone.[3,13]

The various neuroblast groups migrate at

different stages, some before others, subsequent to axon elongation, following precursors with specific functions that establish the future neuron identification, its functional properties and future connections in order to define the distinctive layers in the adult neocortex. This process is called lamination.

The lamination process is associated with the birth of neurons that use the radial glia to reach their final destination.[7,12-14] Neurons migrate to find their specific *locus* and to compete with other neurons for synaptic connections.

Nervous systems under development produce so many neurons that most of them survive with many connections and form the best encephalon organization for all of them.

The first neurons to migrate are formed from the deep neocortex layers, whereas the last neurons migrate to form the most superficial layers.[15,16] Horizontal and vertical stratification of the brain neocortex is very important for normal brain physiology.

Disorders relating to the migration of neurons lead to a variety of congenital malformations. The complexity and multiplicity of mechanisms involved probably accounts for the clinical, radiological and genetic heterogeneity observed in neuronal migration disorders.[6]

The migration process from ventricular and subventricular zones should not be disrupted, since this will result in anatomical and functional disorders,[17-21] as well as metabolic problems.[22]

When problems have occurred with neuron migration, the layers might present inverted natural orders, with neuronal depopulation of the inner layer.[20] Diseases such as epilepsy are associated with migration disorders.[18]

Genetic abnormalities or epigenetic factors may generate disorders of the glial cells and in relation to neuron-glia in the critic development period, these problems generate various molecular, structural and functional abnormalities.[12,23]

Disorders relating to the migration of neurons lead to fetal malformations that affect millions of epidermic precursor neurons from the ventricular and sub-ventricular zones to the germinal layer. These factors produce important changes in the cytoarchitecture, lamination and neural physiology, mainly in the cerebral neocortex, which is infected, intoxicated, exposed to radiation or genetically disrupted.[21]

Indeed, other problems with the migration of neurons may be generated by the disabling of the radial glia. The radial glia is the support for the neuron movement and conducts these cells to the correct site in the adult brain for the construction of normal circuits for the formation of synapses.[7,12]

Retardations in migration may lead to desynchronization of cortical development and this is harmful for circuit formation in the adult brain.[7]

The consumption of drugs, especially ethanol, may generate a number of disturbances in the migration of neurons, especially when consumed by the mother at specific periods in the development of the embryo or fetus.[24-27] Some of these drugs are illegal, but others, such as nicotine and ethanol, are freely available.

The migration of neurons and the effects of ethanol

Prenatal exposure to ethanol is a cause of several abnormalities in the development of the brain cortex, and the abnormal development may result in functional disturbances in adults.[6,7,18,19,21]

Ethanol retards the migration of neurons,[7,28] and this makes the normal construction of the brain cortex morphology difficult. Neuron location depends on spatial and temporal factors and ethanol intoxication disrupts the various necessary factors through which the neuron is recognized in its final destination; this location is very important for adequate neuron functioning in the adult brain, since this position facilitates the formation of synapses.[24]

Although several studies on the chronic effects of ethanol exposure on the mammalian nervous system have been conducted,[7,29] only a few studies have investigated the acute effects of ethanol on specific days of gestation.[24-27] These latter studies have revealed important disorders in the cerebral tissue.

Studies of neural disturbances caused by the chronic consumption of ethanol have detected ectopy, heterotopy and a reduction in neurons in various regions of the brain.[7,21] Aversi-Ferreira *et al*.[24-27] demonstrated that only a single day of exposure to ethanol is sufficient to generate important alterations in the neural structure of newborn rats. These authors injected ethanol on the E_{12} day of gestation in female rats, studied its effects on the offspring and found generalized ectopy and heterotopy, a reduction in neurons in the lobes of the neocortex,[25,26] layers in the pre-frontal zone[24] and evident deviation of the neurons' tangential route from the ventricular zone to the olfactory bulb;[24,27] however, the cerebellum remained unaltered, probably because the neuron cells in this structure were born on different days from those of the neocortex.[28-30]

The objective of this work was to demonstrate that the acute consumption of ethanol on specific days of ontogenic development is as dangerous as chronic consumption during gestation.[24-27,30] Therefore the acute consumption of ethanol, as well as the chronic effects, especially by pregnant women, may be a public health problem, since there are only a few papers on this topic in the literature associating acute and chronic effects of ethanol on the encephalon.

Methods

Searches were performed in the following electronic databases: MEDLINE, SciElo, PubMed, LILACS, CAPES periodical, and the Open Journal System. The descriptors used were: "chronic ethanol toxicity", "chronic alcohol toxicity", "acute ethanol toxicity", "acute alcohol", "neural ontogenic development", "neuronal migration disturbances", "neural structure". Only one textbook was used for this paper; an important neuropsychology textbook.[31]

Criteria for inclusion were: indexed papers published between 2003 and 2007 (Table 1); classic indexed papers on older and more diverse areas.
Exlusion criteria included: papers on the nervous system that did not mention the main ideas addressed in this review and texts with the same content as the most recent papers used here. Papers on the toxicity of alcohol in general but not on the nervous system were also excluded.

The objective of this paper was to compare the acute and chronic effects of ethanol on neural development, with reference to the ontogenetic neural structure of mammals. This constitutes an important contribution to understanding the effects of ethanol on the encephalon.

Results

The results are summarized on Table 1. In this table, some papers appear twice under more than one category.

Chronic ethanol toxicity or chronic alcohol toxicity

Twenty-nine papers on chronic ethanol (alcohol) toxicity were analyzed and none of them mentioned the acute effect of ethanol on the nervous system. Miller[7,32-34] has reported the chronic effects of ethanol on the neural structure, emphasizing neocortical migration, the generation of neurons, callosal projection neurons,[33] postnatal development alterations and glia and astrocyte transformation caused by the chronic effects of ethanol. These papers are very important because they focus the main phase of degeneration caused by ethanol on neural development. In general, these papers deal with problems caused by fetal alcohol syndrome.

Liesi[28] reported that the migration of neurons fails after exposure to ethanol, but other authors focused on the disruption caused by ethanol on the second messenger and protein phosphorilation,[35] alterations in the expression of genes;[36,37] alterations in the growth factors;[38,39] and Bleich *et al*.[40] reported that the homocysteine is a neurotoxin that occurs in chronic alcoholism.

Many studies have been conducted on the disruption of several parts of the neural structure, but there is no references to the neocortex, except for Diaz-Granados *et al*.[41] The other neural structures studied were substantia nigra;[42] the neural crest;[43] and the hypothalamic-pituitary-adrenal axis.[44]

Ethanol influences cholinergic development,[45,46] generates glial alterations[23,47] and reduces the density of Purkinje cells.[48] These data are a result of chronic studies on the effect of ethanol on the nervous system, especially the neuron cells. Ikonomidou *et al*.[49] reported that the deleterious effects of alcohol on the developing human encephalon are poorly understood and that the vulnerability of the brain to ethanol coincides with the synaptogenesis period and concluded that apoptosis is associated with the blocking of NMDA (N-methyl-D-aspartate) receptors and also excessive stimulation of GABA (gamma aminobutyric acid) receptors.

Acute ethanol toxicity or acute alcohol toxicity

Five papers on the acute effects of ethanol on the nervous system produced by Aversi-Ferreira[24-27,30] were found. These works studied the effects of ethanol on the neocortex,[24-26] olfactory bulbs[27] and cerebellum[30] on the same day on which female rats were exposed to ethanol, which was the 12th day of intrauterine life in rats, and these papers reported that the ingestion of ethanol on specific days of gestation, called the neuron birth day, generates the same problems as those observed in fetal alcohol syndrome, which is caused by the chronic consumption of ethanol, namely ectopy and heterotopy, a reduction in neurons in the neocortex lobes,[25,26] layers in the pre-frontal zone[24] and evident deviation

Table 1

General data from papers used in this work.

General data and associated reference numbers of papers	Textbooks and papers used in this work	Type of papers
Chronic ethanol toxicity and chronic alcohol toxicity.[7,17,22,23,28,29,32-49]	29	Original
Chronic ethanol toxicity and chronic alcohol toxicity.[65-69]	29	Review
Acute ethanol toxicity or acute alcohol toxicity.[24-27,30]	5	Original
Nervous system ontogenetic development.[1-4,8,9,12-16, 50-59]	21	Original
Neuron migration disorders.[5,6,18-21,60]	7	Original
Nervous system structure.[10,11,31,61--63]	7	Original
Reviews.[65-69]	5	Review

of the neurons' tangential route from the ventricular zone to the olfactory bulb.[27] At the time of writing, these are the only works that focus on the acute effects of ethanol on the nervous system.

The ontogenetic development of the nervous system

Twenty-one works on the ontogenetic development of mammals were analyzed. Recently, many neuroscientists have contributed to the development of the new cytoarchitecture neocortex theory to explain the ontogeny of mammals. This theory was used to explain the disturbances generated by the consumption of ethanol during ontogenetic development. Marin-Padilla[1] proposes a unified theory of nervous development through the ontogenesis of the pyramidal cell. In other works,[50-53] this unified theory focused on the first neocortical layer presented by Cajal-Retzius cells at the outset of development. Generally-speaking, pyramidal cells elongate their apical dendrites from subcortical zone to layer I and the Cajal-Retzius cells play an important role in this elongation, which is the reelin secretion associated with radial glia,[54] the in-and-out movement of neurons and pyramidal cell morphology, which depends on thalamic control.

Other researchers have focused on the radial glia and have ascertained the principal days for neuron birth and the populations of neuron-generating cells.[3,55-58] Supér *et al*.[12] have reported the preplate function of the neocortex development and evolution, and Brittis *et al*.[59] have used immunohistochemistry to establish the differentiation pattern of neuron migration in the central nervous system.

Disorders of the migration of neurons

Seven papers reporting problems with the migration of neurons problems were consulted in an attempt to explain various aspects of disorders involving the migration of neurons caused by the consumption of ethanol. Veléz-Domínguez[21] reported heterotopy, ectopy and nodular alterations of neuron populations that undergo migration problems. Redecker *et al*.[20] reported problems caused by excitotoxicity. Dobyns *et al*.[60] reported problems arising from nodular heterotopy in which ethanol is one of the causes. Luhman *et al*.[19] reported many neuron migration disorders in in vitro experiments. Chevassus-au-Louis *et al*.[18] reported that the neocortical heterotopy of neurons on layer I is associated with relationships with the hippocampus and neocortex.

The structure of the nervous system

Seven papers on the structure of the nervous system in addition to one classic text on neuroscience (neuropsychology) were consulted.[31,61-64] These papers are important in explaining the loss of neural functions when neuron migration disorders occur and also in explaining future neurological problems. Caviness Jr.[61] wrote a classic paper on the architectonic map of the neocortex in normal rats, and this paper has become a standard reference for understanding of the structure of the cortex and interpreting the results obtained from studies involving the brains of rats. Luria[31] reported important features of the structure and physiology of the brain.

Reviews

Five review papers on several fields were analyzed[65-69] and the main conclusions will be reported here. Chen *et al*.[65] report that studies of brain anomalies are very important for research on the effect of alcohol on the nervous system and on the development of several regions of the brain,

since these regions are not uniformly vulnerable to alcohol.

Calhoun & Warren[66] in a recent review study considered Fetal Alcohol Syndrome (FAS) as an objective medical diagnosis. Pollard[67] reported that the developing brain is extremely vulnerable to the effects of drugs, principally because of the absence of a protective fetal blood-brain barrier. Spadoni *et al*.[68] and Chen *et al*.[65] reported that certain areas of the brain are considerably vulnerable to the effects of ethanol. Spadoni *et al*.[68] and Harper[69] considered neuroimaging to be an important technique for the diagnosis of fetal alcohol spectrum disorders because this technique has shown that prenatal exposure to alcohol causes permanent alterations in the structure of the brain. Harper[69] also reported that ethanol dependence and abuse is a social problem whose consequences are a public health problem. All these reviews deal with the loss of neurons in various regions of the brain associated with the chronic effects of ethanol and loss of neurons.

Discussion

The association between structural, physiological and behavioral data on the nervous system and the consumption of drugs demonstrates the high degree of severity of the impact of the latter on this system.

The comparison of results on the acute[24-27,30] and the chronic effect of ethanol[32,33-39,41-45] on the nervous system demonstrates the same problems, principally in cases where the acute consumption has occurred at the birth of the neuron near to E_{12}. Chronic consumption of ethanol causes human fetal alcohol syndrome (FAS), and is characterized by retardation, microencephaly, neurological abnormalities, facial dysmorphology, and other congenital anomalies;[32-34] the acute consumption of ethanol causes similar effects.[24-27]

Aversi-Ferreira *et al*.[24-27] demonstrated that only a single day of exposure to ethanol is sufficient to generate disorders in the nervous system of newborn rats. These authors injected ethanol on the E12 day of gestation, which is the day when neurons are born in the brain cortex in female rats and studied its effects on the offspring. They found generalized ectopy and heterotopy, a reduction in the number of neurons in the neocortex lobes,[25,26] layers in the prefrontal zone,[24] and evident deviation of the neurons' tangential route from the ventricular zone to the olfactory bulb.[24,27] These data are consistent with those found for FAS in cases of the chronic consumption of ethanol.

Therefore, further studies need to be conducted to verify possible behavioral deviation in the offspring.

Studies on the effect of ethanol on the nervous system have, in fact, demonstrated a high degree of severity of the impact of this drug on the nervous system in cases of both chronic[32-39,41-45] and acute consumption.[24-27] These points should be considered when warning society of the dangers of ethanol consumption, especially among females who suspect they may be pregnant, since it has been observed that acute ethanol consumption brings about significant disturbances in the offspring in rats. Moreover, Caviness Jr.[61] has reported that humans and rats have the same neural substrate and structure and the connections are identical to all species of mammal.

These observations strongly suggest the need for more studies of ethanol and its effects on the tissues and cellular and molecular structures involved in the process of cell migration in the nervous system. Days of gestation other than E12 should also be studied, because only a few references[24-27,30] on this subject were found in the current literature.

The reviews analyzed here[65-69] did not provide information on the acute effects of ethanol, but reported the same anatomical, physiological and structural problems caused by fetal alcohol syndrome, as Aversi-Ferreira *et al*.[24-27,30] have demonstrated for acute ethanol consumption.

Ikonomidou *et al*.[49] reported that the deleterious effects of alcohol on the developing human encephalon are poorly understood, and further studies are required in order to understand the effects of ethanol on the nervous system.

Studies on the acute effect of ethanol on the nervous system are scarce, especially where specific days in the development of the brain are concerned. The few studies on the chronic effects of ethanol on the nervous system focus on anatomical aspects and do not explain how ethanol acts on the neuron or cell structures.

Conclusions

In short, the consumption of ethanol should be prohibited for women during the gestational phase in order to preserve the fetus' health. The acute consumption of ethanol on specific days is a serious public health problem because acute exposure to ethanol among women near the eighth or ninth week of gestation has been shown to be potentially harmful to the nervous tissues of the fetus.

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