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HISTOSTRUCTURAL ALTERATIONS IN THE CEREBRAL ARCHITECTURE ASSOCIATED WITH THE PROGRESSION OF ALCOHOL INTOXICATION: AN EXPERIMENTAL ANALYSIS.

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The aim of this study is to evaluate the histological changes in the cerebellum of rat brains following chronic alcohol intoxication. Materials and Methods. We employed a classical approach for modeling chronic alcohol intoxication by administering 40% ethanol to rats (n=55) in a dosage of 2 ml per 100 g of body weight daily for three months. The cerebellar structure was then analyzed. Results. This study investigates the impact of chronic alcohol intoxication on the histological structures of the cerebellar cortex. The cerebellum, like the nervous system overall, possesses a significant cellular and functional reserve. However, teratogenic factors, including ethanol, notably influence the activity of cerebellar neurons, increasing it. Ethanol exposure during early pregnancy can lead to prenatal growth retardation, stillbirth, cleft palate, hydrocephaly, and reductions in fetal body size. There is evidence suggesting a correlation between blood ethanol levels and a reduction in the number of Purkinje cells. Chronic alcohol consumption results in cerebellar ataxia, alterations in upper limb movements, decreased reaction speeds, reduced attention concentration, impaired coordination accuracy, and disturbances in postural stability and balance. Conclusion. The cerebellum, especially during development, is particularly vulnerable to the toxic effects of alcohol. Recent research suggests that changes in the neurotransmission of gamma-aminobutyric acid (GABA)-dependent receptors may contribute to cerebellar dysfunction induced by ethanol. Ethanol exposure increases the release of GABA not only in Purkinje cells but also in the interneurons of the molecular layer and granule cells.

Key words: cerebellum, cerebellar cortex, chronic ethanol intoxication, rat model, histopathology.

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Introduction

The global research community continues to delve into the complexities of impact produced by alcohol on the central nervous system (CNS), a topic that remains a focal point of scientific inquiry due to its unresolved questions and profound implications. The specific mechanisms through which chronic ethanol intoxication (CEI) exerts its influence on the CNS, especially the cerebellum during prenatal and early postnatal development, have not been fully delineated yet.

Alcohol consumption is known to impair the functionality of brain centers, detrimentally affecting attention and memory. The cerebellum serves as a subcortical nexus for movement coordination within the CNS and plays a pivotal role in cognitive processing and sensory discrimination. This encompasses the modulation of a patient's excitability or lethargy, fluctuations in attention span, disruptions in tactile, proprioceptive, and vestibular perceptions, and challenges in postural maintenance. Recent studies have expanded the cerebellum recognized functions beyond movement control, implicating it in the formation and recollection of emotional experiences. Forebrain structures, namely the amygdala and hippocampus, are traditionally acknowledged for their essential roles in emotional memory formation. Nonetheless, novel findings utilizing functional magnetic resonance imaging have revealed that the cerebellar cortex exhibits increased activity in response to both positive and negative stimuli, with neutral stimuli failing to provoke a similar response. This research highlights a significant degree of connectivity between the cerebellum and the forebrain, particularly noting the cerebellum's receipt and processing of inputs from the anterior cingulate cortex, a crucial site for the perception and evaluation of sensations, and its subsequent relay of information to the amygdala and hippocampus. The detrimental effects of alcohol abuse on cerebellar function are well-documented, with persistent cerebellar disturbances observed in individuals with alcohol dependence, persisting even during periods of abstinence.

The cerebellum, mirroring the entire nervous system, harbors a substantial reserve of cellular and functional capacity. Investigations [1, 2] have revealed that only a minority of cerebellar neurons and glial cells are in an actively functional state at any given time. Exposure to extreme external factors, notably ethanol, markedly elevates the activity levels of cerebellar neurons. Certain studies [3] have posited a direct correlation between ethanol concentration in the bloodstream and a decrease in the population of Purkinje cells, which are characterized as large, pear-shaped, intricately branched neurons forming a dense synaptic network within the cerebellar cortex's molecular layer. These neurons project single axons through the granular layer into the cerebellar white matter, serving as critical

conduits for cerebellar signal transmission [4, 5, 6].

In recent investigations focused on chronic ethanol intoxication (CEI) and its impact on cerebral architecture, researchers identified significant alterations in the proportional dynamics among various brain tissue constituents. Detailed analyses of neuronal populations, specifically those within the pyramidal layer of the precentral gyrus cortex and the Purkinje cells in the cerebellar cortex, revealed evident atrophic transformations. The study highlighted that CEI is associated with vascular sclerosis and hyalinosis, in addition to a spectrum of neuronal changes encompassing dystrophy, atrophy, and hypertrophy. These morphological modifications are accompanied by disruptions in the quantitative relationships among brain tissue structures, leading to a reduction in the specific area of neurons due to ongoing atrophy and eventual cell death [7].

A body of literature suggests that prolonged alcohol consumption may precipitate neurotoxic effects through several mechanisms, including thiamine deficiency, the toxicity of metabolites, and neuroinflammation, which may culminate in severe neuropathological conditions such as Wernicke's encephalopathy or Korsakoff's psychosis, alongside a general acceleration of neurodegenerative processes [8]. Chronic ethanol exposure is also known to induce cerebellar ataxia, characterized by alterations in upper limb movements, decreased targeting accuracy, impaired postural stability and balance, and a reduction in the rapidity of foot tapping. Notably, the cerebellum, particularly during its developmental stages, shows increased susceptibility to ethanol toxic effects. Current research has illuminated that modifications in the neurotransmission of gamma-aminobutyric acid (GABA)-dependent receptors may serve as a critical pathway through which ethanol induces cerebellar dysfunction. This is evidenced by ethanol-induced augmentation of GABA release not only in Purkinje cells but also within interneurons of the molecular layer and granule cells [9].

The key role of cerebellum in the regulation of movement and oversight of motor skills underscores its integral contribution to both motor skill acquisition and cognitive processes related to movement control [10, 11]. Moreover, the cerebellum is instrumental in enhancing cognitive functions within the cerebrum [10, 12], including language development [10, 13, 14] and the generation of imaginative constructs, highlighting its comprehensive role in facilitating complex cerebral cognitive and motoric networks [10, 15].

Researchers have established that cerebellar atrophy resulting from chronic ethanol exposure precipitates coordination deficits in upper extremity function and engenders discernible aberrations in neuropsychological assessment outcomes [16]. Such deficits are clinically pertinent for the differential diagnosis of various neurological pathologies. Cognitive impairments in chronic ethanol intoxication (CEI) cases manifest as compromised memory consolidation, retrieval, and processing, as well as diminished analytical and synthesis capabilities, deterioration in motor skill retention and execution, and impaired verbal communication faculties.

Thus, this study focuses on elucidating the histostructural perturbations within the cerebellum attributable to sustained alcohol exposure.

The primary aim of this work is to delineate the histopathological alterations evident within the cerebellar anatomy of rodents subjected to chronic ethanol intoxication, utilizing a regimen of 40% ethanol administered orally in a dosage of 2.0 ml per 100 g of body weight, administered daily.

Methodological framework: The investigation encompassed the cerebellar architecture of adult Wistar rats of both sexes, with an average weight range of 180-220 grams. The study sample included 55 subjects and their 240 progeny, with observations recorded at key postnatal intervals - day 30, 60, and 90 - corresponding to established ontogenetic stages (Table 1). The animals were categorized into control and experimental cohorts, with the latter comprising males, non-gravid females (Group I), gravid females (Group II), and lactating females (Group III). These rats were administered ethanol intragastrically by a gavage technique to ensure precise dosing for a period of three months. Ethanol used was a 95% solution, which was subsequently diluted to a 40% concentration with potable water. Additionally, postpartum assessments included quantification of live births, litter size, and mortality rates within the initial 30-day neonatal period.

Table 1

Number of animals involved in the experiment modeling prenatal alcohol intoxication

	Control	Group I	Group II	Group III
30 days	40	20	25	20
60 days	40	20	20	20
90 days	40	15	20	15
Total	120	55	65	55

Brain tissues were obtained from the animals and subsequently preserved in a 10% neutral-buffered formalin solution. Tissue samples were then processed histologically using standardized

protocols and stained with hematoxylin and eosin to permit detailed microscopic analysis (Fig. 1). The animal-based component of this research adhered strictly to the ethical guidelines established by the First National Congress on Bioethics in Kyiv, Ukraine (2001), and complied with the stipulations of the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (Strasbourg, France, 1985). Experimental protocols were conducted within the controlled environment of the DDMU vivarium, ensuring the maintenance of all requisite standards for animal welfare.

Results

Chronic ethanol exposure in gestating rodent models was associated with a spectrum of teratogenic outcomes. Early gestational exposure to ethanol exerted a range of detrimental effects on embryonic development, as evidenced by fetal growth restriction, decreased fetal mass, higher rates of stillbirth, palatal dysgenesis, ventriculomegaly, and considerable diminution in overall fetal morphology. Notably, within the cohort subjected to ethanol exposure, the prevalence of stillbirth was markedly elevated as compared to the progeny of the control group, underscoring the profound teratogenicity of ethanol (Table 2).

Table 2

Rates of stillbirth and mortality in prenatally alcoholized offspring at different terms of postnatal ontogeny

Groups	Total offspring in litter, units	Stillborn, %	Mortality by 30 days, %	Mortality by 60 days, %	Mortality by 90 days, %	Total mortality, %
Control	12,4±0,1	0	0	0	0	0
Group II	5,4±0,1*	7,8	12,7	8,6	7,3	36,4
Group III	7,1±0,3*	2,1	5,1	3,3	1,1	11,6

*Note: * – p<0,05*

In the morphological assessment of cerebellar architecture in rodent models, neuronal anomalies were identified within the cerebellar cortex, manifesting as alterations in cellular morphology. Aberrant migration patterns were observed within the molecular layer, leading to atypical localization of neurons. The term “atypical” is conventionally employed within neuropathology to delineate cellular abnormalities discernible upon microscopic analysis, potentially affecting both the cytoplasmic and nuclear components of the cell.

Cell migration is acknowledged as a pivotal developmental process, instrumental in the ontogenesis of multicellular organisms and in reparative mechanisms following tissue injury, mediated by immune responses. Deviations from typical migration pathways during embryogenesis may precipitate organ heterotopy and other morphogenetic irregularities. Specifically, aberrant neuroblast migration within the cerebral cortex is implicated in the emergence of ectopic gray matter nodules embedded within white matter regions (Fig. 2). Such anomalous migratory events are implicated in the neuroblast compromised differentiation capacity.

Pathological cell migration is further correlated with disturbances in the cytoarchitectural organization of the cerebral cortex, implicating the laminar configuration and potentially leading to neural heterotopy within the white matter substrate. These developmental anomalies have also been documented within cerebellar structures.

Histopathologically, pericellular and perivascular lucencies were detected, suggestive of edematous processes within the cerebellar tissue. Concurrently, vascular distention was noted within the soft meningeal layers of the cerebellar molecular layer. A pervasive distribution of pericellular edema across the cerebellar expanse was observed, with regions of significant edema exhibiting neuronal wrinkling and hyperchromasia. Additionally, the presence of macrophagic infiltration within the granular layers denotes necrotic foci within the parenchyma (Fig. 3).

In a controlled study examining the effects of chronic ethanol intoxication in rodent models, there was a notable attenuation in motor function and the exhibition of complex behaviors. Subjects consistently exhibited signs of lethargy, mydriasis, and a lack of mobility. Detailed histological analysis revealed significant neurodegenerative alterations within the cerebellar cortex, specifically neuronal architecture and overall cortical cytoarchitecture. Diagnostic imaging identified discrete regions of pathology within the motor and sensory cortices of the cerebellum, characterized by a pronounced thickening of the molecular layer and a substantial disturbance in the structural integrity of the cerebellar white matter. Moreover, the cerebellar meninges displayed signs of ethanol-induced pathology, notably the vascular dilation within the soft meningeal layers.

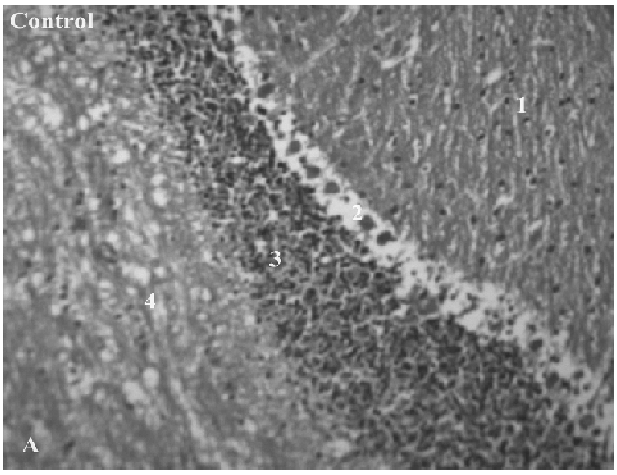

Fig. 1. Section of the cerebellum of a control group rat's brain.
Stained with hematoxylin and eosin.
Magnification: A – x400, B – x200, C – x200.
Notes: 1. Molecular layer. 2. Purkinje cell layer.
3. Granular layer. 4. White matter.

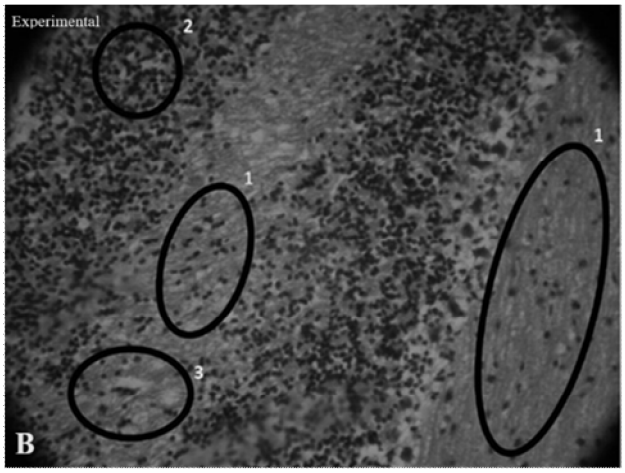

Fig. 2. Section of the cerebellum of a rat brain from the experimental group.
Stained with hematoxylin and eosin.
Magnification: A – x400, B – x200, C – x200.
Notes: 1. Migrating cells. 2. Necrotic islands.
3. Pericellular edema.

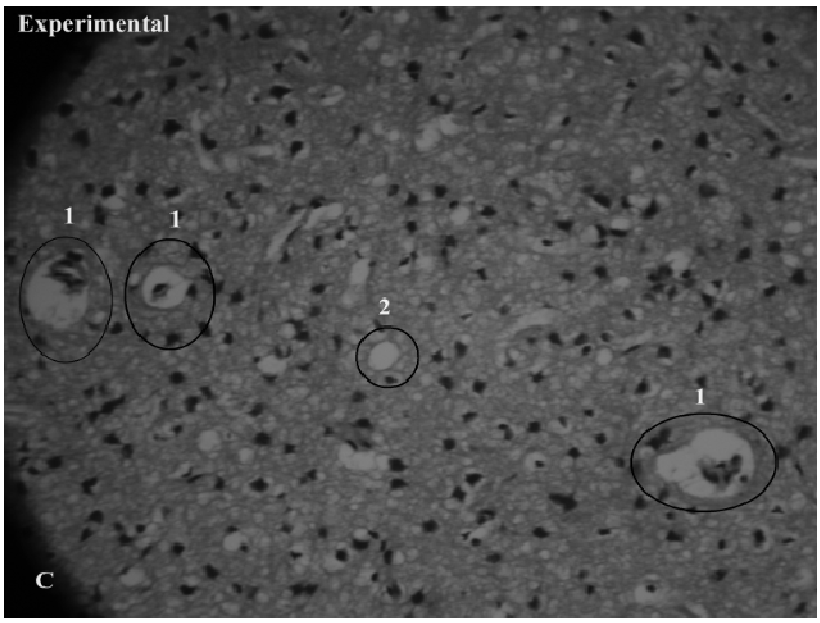

Fig. 3. Section of the cerebellum of a rat's brain from the experimental group.
Stained with hematoxylin and eosin. Magnification: A – x400, B – x200, C – x200.
Notes: Cerebellar edema in the rat: 1. Perivascular edema of the cerebellum of the rat's brain.
2. Acute immune inflammation in the molecular layer of the cerebellum of the rat's brain.

Exposure to ethanol during gestation in rodent models has been found to precipitate a spectrum of anatomical irregularities. In vivo experiments conducted on pregnant rats have established a correlation between early gestational ethanol exposure, immediately post-confirmation of pregnancy, and the onset of diverse congenital malformations. The research reveals that sustained ethanol exposure throughout pregnancy or lactation inflicts detrimental and toxicological impacts on fetal and neonatal development. Notably, early gestational ethanol intake was causatively associated with the manifestation of orofacial clefts in the progeny. Furthermore, a reduction in fetal encephalic mass and a heightened incidence of ventriculomegaly were also documented.

Discussion

Investigations led by Johnson-Greene, Adams, and Gilman delineate a spectrum of coordination dysfunctions attributable to alcohol-induced cerebellar degeneration. Our observational data concur, demonstrating across all test subjects an ensemble of neuromuscular disruptions, characterized by diminished muscle tone, expedited fatigue thresholds, apathy, lethargy, and a degradation of complex motor proficiency including limb coordination. Moreover, a compromised faculty for spatial navigation was evident.

Morphometric analyses of the cerebellum re-

vealed a diminution in cerebral mass both in the test subjects and their progeny, findings that are congruent with the investigations by Shormanov. Microscopic scrutiny of the cerebellum, particularly the anterior lobe, suggested these mass changes are affiliated with a reduction in Purkinje cell count, findings that are corroborated by Kovetsky and Konovalov research [17]. An observable downward trend was noted in cerebral mass metrics within the ethanol-exposed cohort.

Shormanov et al. documented a triad of degenerative, atrophic, and hypertrophic neuronal alterations within the cerebral cortex and the cerebellum. Our study echoes these findings, exhibiting not only alterations in interneuronal density but also neuropathological lesions characterized by necrotic islands, contributing to cellular demise and pericellular edema. Shormanov highlights cerebrovascular alterations such as sclerosis and hyalinosis, alongside meningeal pathology, which may elucidate the noted upsurge in hydrocephalus among ethanol-impacted fetuses. In mature test subjects, angiopathy was observed in the form of dilated vessels within the meningeal layers.

Pathomorphological cerebral modifications subsequent to chronic ethanol exposure were discerned extending beyond the meninges and vasculature to neuronal and glial cells. In the cerebellar dentate nucleus, beyond the observed neuronal depletion, cells exhibiting cytoplasmic vacuolization, karyopyknosis, and karyorrhexis were identified, paralleling the observations of Kovetsky, Konovalov, Hungund, and Mahadik [17, 18].

Conclusions

Our findings elucidate the nuanced and stratified responses of cerebellar cortical neurons to ethanol exposure, highlighting layer-specific susceptibilities. In particular, neuronal responses to ethanol are heterogeneous across the cerebellar cortex, suggesting a complex interplay of alcohol's effects on cellular function. Quantitative alterations in the interneuronal density of granular layer and morphological variations in neuronal integrity were observed indicating ethanol differential impact on cerebellar microarchitecture. Ethanol exposure precipitated cellular edema and morphological distortions in neurons, such as cytoplasmic wrinkling, underscoring the cytotoxic effects of alcohol. A chronic regimen of ethanol administration induced notable deficits in motor coordination and intricate behavioral expressions in subjects, implicating ethanol in the disruption of cerebellum-mediated motor control. Functional aberrations in the cerebellar cortex as a result of ethanol exposure have the potential to undermine cognitive processing, suggesting a prolonged impact on mental agility and occupational proficiency post intoxication. The study evidences ethanol-associated compromise in cerebrovascular integrity, manifesting as altered permeability, which may contribute to the pathophysiology of alcohol-induced cerebellar damage. The protracted impact of ethanol manifests in enhanced histopathological changes within the cerebellum, including perivascular and pericellular edema coupled with neurodegenerative outcomes such as neuronal apoptosis and microcavity formation.

Prospects for further research

Investigations are poised to advance into the degree and character of cerebellar dysfunctions stemming from enduring alcoholism, contributing to a broader understanding of ethanol's neurotoxicity.

Clinical implications

The findings obtained have significant implications for various fields including neurochemistry, toxicology, psychopharmacology, psychiatry, neurology, addiction medicine, and forensic medicine. These findings could potentially inform therapeutic approaches and forensic assessments.

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Реферат

ГІСТОСТРУКТУРНІ ЗМІНИ МОЗОЧКА ГОЛОВНОГО МОЗКУ ПРИ ХРОНІЧНІЙ АЛКОГОЛЬНІЙ ІНТОКСИКАЦІЇ В ЕКСПЕРИМЕНТІ.
Назарова Д.І., Крамар С.Б., Кожушко Г.Ю., Кожушко В.В., Барабашова Ю.П.
Ключові слова: головний мозок, мозочок, кора мозочка, хронічний алкоголізм, щури.

Метою даного дослідження було вивчення ступеню гістоструктурних змін мозочка головного мозку щура при хронічній алкогольній інтоксикації.

Матеріал та методи. В роботі використана класична методика моделювання хронічної алкогольної інтоксикації з дослідженням структури мозочка головного мозку щурів (n=55), яким протягом 3-х місяців вводили 40% етанол із розрахунку 2 мл на 100 г маси тіла на добу.

Результати. Мозочок, як і нервова система в цілому, містить значний клітинний та функціональний резерв. Дослідники підкреслюють, що відносно невелика кількість нервових клітин та клітин глії мозочка знаходяться в активному функціональному стані. Вплив тератогенних чинників, яким є етанол, суттєво впливають на активність нервових клітин мозочка, підвищуючи її, на ранніх стадіях вагітності впливають на пренатальну затримку росту та ваги плода, на випадки мертвонародження, розщеплення піднебіння, гідроцефалії та значне зменшення розмірів тіла плодів. Деякі дослідження вказують, що рівень та концентрація етанолу в крові корелює з редукцією кількості клітин Пуркіньє. Регулярне вживання алкоголю призводить до мозочкової атаксії та до змін у рухах верхніх кінцівок, знижує швидкості реакції при рухах, знижує концентрацію уваги, точність координації, викликає порушення постуральної стійкості і рівноваги. Мозочок, під час свого розвитку, особливо вразливий до токсичного впливу алкоголю. Нещодавні з'ясовано, що зміни нейротрансмісії рецепторів, яка залежить від гамма-аміномасляної кислоти, є потенційним механізмом дисфункції мозочка, яка індукується етанолом. Під впливом етанолу збільшується кількості гамма-аміномасляної кислоти, яка вивільняється, не тільки у клітинах Пуркіньє, але й в інтернейронах молекулярного шару та клітинах-зернах.

Висновки. Хронічна алкоголізація протягом місяця призводить до змін рухової активності і складних форм поведінки експериментальних тварин. Зміни функцій кори мозочка головного мозку під впливом етанолу, які виявлені в ході експерименту, можуть бути основою когнітивних порушень і призводити до зниження психічної стійкості та працездатності у віддаленому періоді інтоксикації. Найбільш виразні патологічні зміни спостерігаються у молекулярному і зернистому шарах мозочка. У результаті хронічної алкогольної інтоксикації відмічаються порушення проникності судин. Хронічна алкоголізація призводить до посилення гістологічних змін, до розвитку периваскулярного та перицелюлярного набряку мозкової тканини в комплексі з нейродегенеративними проявами (загибель нейронів кори півкуль і мозочка, утворення мікропорожнин).